Intercontinental collaborative experience with abdominal, retroperitoneal, and pelvic schwannomas

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Abstract

Background

Schwannomas are rare tumours that pose a significant management challenge in the abdomen, retroperitoneum and pelvis. No data are available to inform management strategy.

Methods

A collaborative international cohort study, across specialist sarcoma units, was conducted to include adults with histopathologically-confirmed schwannomas within the abdomen, retroperitoneum, or pelvis presenting between 2000 and 2017.

Results

Of 485 patients across 12 centres, 38 (7·8%) were discharged without follow-up, 199 (41·0%) underwent early resection, and 248 (51·1%) patients underwent radiological monitoring. Of these, 96/248 patients eventually underwent surgery (38·7%), giving an overall resection rate of 60·8% (295/485). At baseline, the median tumour volume was 90·1cm^3 (interquartile range: 26·5–262·0). The average growth rate was 10·5% per year (95% CI: 9·4% - 11·6%), and was consistent across the short- (within 2 years of diagnosis) and long-term (beyond 2 years, rho: 0·405, p=0·021). A decision to operate was more common in symptomatic patients (p<0·001) and rapidly growing tumours (>20% per year, p=0·025). R0/R1 resection was achieved in 91·6%. Kaplan-Meier long-term recurrence rates after R0/R1 resection were 2% and 7% at 3 and 5 years, respectively.

Discussion

Specific recommendations include: indications for early surgery, prediction of growth from radiological monitoring, promotion of selective sub-macroscopic resection, and cessation of postoperative imaging surveillance.

Introduction

Schwannomas are rare, usually benign nerve sheath tumours, typically composed of well-differentiated Schwann cells.[1,2] The majority are solitary, sporadic, and represented by several different subtypes. A number are associated with genetic syndromes, such as neurofibromatosis type 2 or schwannomatosis.[3] A decision to resect is considered on a case-by-case basis. There are no existing data to support superiority of early surgical intervention over a strategy of radiological monitoring. Furthermore, for patients that do undergo surgery, it is unclear if post-operative radiological surveillance is of benefit. Establishing evidence-based guidelines for management of these rare soft tissue tumours is challenging.

The Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG) represents an international collaboration of specialist sarcoma centres across the globe. The collective experience of this alliance captures the majority of patients with rare soft tissue tumours that undergo surgery worldwide.[4] The primary aim of this study was to evaluate clinical, radiological, and histopathological features of abdominal, retroperitoneal, and pelvic schwannomas within this intercontinental collaborative group, to better understand the natural history of schwannomas, and make evidence-based recommendations for future management. The principle objectives were to identify a practical method of predicting growth, stratify those that can be managed conservatively or surgically, and determine postoperative imaging surveillance.

Methods

Study design and approvals

A retrospective, international, multi-centre cohort study was undertaken according to a pre-specified protocol across high-volume specialist sarcoma units from North America, Europe, and Australia. All contributing centres were part of the Transatlantic Australasian Retroperitoneal Sarcoma Working Group. Institutional Review Board approval and data sharing agreements were obtained according to local institutional policy in each centre prior to data collection. Ethical approval was obtained in countries where Local Research Ethics Committees deemed it a requirement. No specific funding was received for study conduct or data interpretation. This study was reported according the STROBE guidelines for observational studies.

Patients and settings

All adult patients (aged over 18 years) presenting with a primary abdominal, retroperitoneal and pelvic schwannoma from 1 January 2000 to 31 August 2017 were eligible for inclusion. Only confirmed schwannomas based upon biopsy or final histology of a resected specimen were included for analysis. Specialist sarcoma units have significant existing expertise in histopathological analysis of schwannomas, quality assuring patient inclusion. However, histological specimens were not further centrally reviewed for the purpose of this study. Patients undergoing radiological monitoring or resection were included.

Data were extracted from Electronic Health Records, inpatient and outpatient clinical notes, imaging archives and clinical letters in each centre, depending on local availability and infrastructure. Data extraction included baseline demographics, mode and outcomes of diagnostics and imaging studies at presentation, choice and outcomes of management strategy (operative and non-operative), and mode and outcomes of surveillance imaging. Data were collated in each centre before being submitted for central analysis, fully-anonymised, using encrypted email accounts, in-line with Data Transfer Agreements between each collaborating centre and the coordinating centre (University Hospitals Birmingham UK). Follow-up continued for each patient until the end of the data collection period, death, or loss to follow-up, whichever was earliest.

The primary outcome measure was tumour growth rate, assessed using volumetric assessment of sequential radiological scans (Computed Tomography (CT) or Magnetic Resonance Imaging (MRI)). The secondary outcome measures were the rate of surgical management, defined as a total or partial resection of the tumour through an abdominal incision, and for patients undergoing surgery: the high-grade post-operative complication rate, a composite measure including re-intervention, re-operation, single or multiple organ failure or death (grade 3 to 5); [5] the overall post-operative complication rate, defined as all deviations from the normal post-operative course (grade 1 to 5); the RO/R1 resection rate, defined as the absence of macroscopic residual disease at the circumferential resection margin; and the recurrence rate, defined as radiological evidence of residual or recurrent disease at the resection site.

Data management

Estimation of tumour volume

For the calculation of volume, we assumed that schwannomas would approximate the shape of a triaxial ellipsoid. As such, we estimated the volume from the reported tumour axial (x), coronal (y) and sagittal (z) dimensions using the formula $V=4/3\ \pi$ (xyz).

Z-score sensitivity analysis (tumour growth)

Whilst the majority of scans reported both the x and y-dimensions of the tumour, a considerable proportion (21.2%) did not report data on the z-dimension. Analysis of those tumours where all three dimensions were reported found that the average of the x- and y-dimensions correlated with the z-dimension (Spearman's rho=0.920), with an average difference of <1cm (mean=0.88). As such, missing z-dimensions were replaced with the average of the x- and y-dimensions to maximise the included sample size. To test the effect of this assumption on the primary outcome of the tumour growth rate, a sensitivity analysis was performed excluding those with missing z-dimensions to measure the influence of this assumption on the conclusions of the analysis.

Inter-scan intervals

A minimum interval of 60 days between consecutive scans was set, in order to prevent artificial inflation of the sample size. Where a patient had a CT and MRI scan within a

60-day period, the MRI was excluded. Where both scans were of the same type (e.g. two CT scans), the earlier one within the 60-day period was excluded.

Statistical methods

Initially, the tumour volumes recorded at the first available scan ('baseline scan') for each patient were compared across a range of factors. Upon visualising the data in a density plot, the distribution of tumour size was found to be highly positively skewed; hence a non-parametric approach was used, with comparisons made by Mann-Whitney or Kruskal-Wallis tests, and data summarised using medians and interquartile ranges (IQRs).

The change over time in tumour volume was assessed using a general linear model. Since it followed a skewed distribution and preliminary analysis suggested that changes in tumour volume was non-linear, values were $\log_{10}$-transformed. The timing of each scan, relative to the first scan for that patient, was set as a continuous covariate. The patient ID was set as a categorical factor, allowing each patient to have a different intercept, to account for the inter-patient variability in baseline tumour volume. The coefficients from the resulting model were then anti-logged, and converted into percentage increases in tumour volume per year.

As well as assessing the tumour growth rate for the cohort as a whole, the model was also repeated for each patient in whom at least three scans were available. The resulting gradients were then compared across a range of factors, using Mann-Whitney and Kruskal-Wallis tests, to identify predictors of tumour growth rates.

Rates of surgery were analysed using a time-to-event approach, in order to account for the timing of surgery, and the different durations of follow up across the cohort. The start of follow up was set to the earliest recorded date for each patient, be this the point of referral, provisional diagnosis or the first CT/MRI scan. Those that did not undergo surgery were censored on the 31st August 2017. The timing of surgery was visualised using a Kaplan-Meier curve, whilst Cox regression models were used to compare the rates of surgery across a range of factors. In those that underwent R0/R1 resections, and entered post-operative surveillance, a similar analysis was then used to estimate the rates of tumour recurrence.

Predictors of post-operative complications were then assessed. Categorical variables were analysed using Fisher's exact tests for dichotomous variables, or Chi-square tests for those with more than two categories. Ordinal variables were analysed using Mann-Whitney tests. The analysis was then repeated to identify predictors of high-grade complications (Clavien-Dindo grade 3 to 5).[5]

All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY), with an alpha level of 5% ($P<0.05$) used throughout. Cases with missing data were excluded on a per-analysis basis. The numbers of patients included in each analysis were reported in the tables, to allow for such exclusions to be identified.

Results

Patient demographics

Data were available (see ***Table 1***) for a total of 485 patients (56.1% female), with a median age at diagnosis of 54 years (IQR: 41 – 64 years). Data were included from 12 centres across North America, Europe and Australia (***Supplementary Table 1***). The mode of presentation was approximately equally split between incidental findings (51.2%) and symptomatic patients (48.8%), with the majority of tumours in the retroperitoneum (50.5%). The type of schwannoma was poorly recorded, only being available in 110 cases (22.7%), with the majority of these being cellular (50.0%) or ancient (42.7%). No schwannomas displayed malignant transformation within this cohort. Ten patients reported a genetic predisposition (neurofibromatosis type II and schwannomatosis). Diagnosis was most commonly made by pre-operative core biopsy (64.4%, N=313).

Brief overview of management

The breakdown of the approaches to tumour management is reported in ***Figure 1***. In 38 (7.8%) patients, only a single scan was performed after presentation, hence these patients were assumed to have been discharged at diagnosis. Surgery was performed within six months of the initial consultation for 199 (41.0%) patients, who were classified as the early surgery group. The remaining 248 (51.1%) underwent radiological monitoring, of whom 96 (38.7%) were eventually treated surgically.

Scan data

Of the 485 patients in the cohort, a total of 424 (87.4%) had data for at least one scan during the study period from which a tumour volume could be estimated, with a total of 1201 scans performed between 1 January 2000 and 31 August 2017. After excluding 109 scans that were within 60 days of a subsequent scan, a total of 1092 scans in these 424 patients were available for analysis. Of these, 188 patients contributed only a single scan, and so were excluded from longitudinal analysis of tumour growth. The remaining 236 patients contributed a total of 904 scans to the analysis (median: 3, IQR: 2-5 scans), over a median of 20 months (IQR: 6 – 47 months) of follow up.

Initial tumour size

In baseline scans, the median tumour volume was 90.1cm^3 (IQR: 26.5 – 262.0). Tumours were significantly larger in male patients, with a median of 112.7cm^3, compared to 73.5cm^3 in females (p=0.005, ***Table 3***). Tumour size also differed significantly by location (p<0.001), with pelvic tumours being the largest, and abdominal tumours the smallest (median 124.7 vs. 20.9cm^3). Cellular schwannomas were significantly larger than ancient schwannomas (median: 264.9 vs. 66.7cm^3, p=0.002). ASA grade at referral was inversely associated with tumour size, with a median of 151.3cm^3 for ASA1, compared to 87.0cm^3 for ASA3-4 (p=0.001). No significant associations between tumour size and either age (p=0.254) or type of presentation (p=0.767) were detected.

Tumour growth

Longitudinal analysis of tumour growth was based on the 236 patients (904 scans) with more than one scan during the study period. Including all scans in a single model, we found that tumour volume increased significantly over time (p<0.001), with an estimated gradient of 10.5% per year (95% CI: 9.4% - 11.6%). Due to the large sample size, it was difficult to clearly demonstrate this effect graphically; hence three approaches were used. ***Figure 2a*** displays the percentage change from the first scan to all subsequent tumour measurements, along with the trend line produced by the regression model. ***Figure 2b*** shows the pooled average tumour volume within intervals of the follow up period. ***Figure 3*** shows the individual trajectories of tumour volume in those patients with more than five scans, split by the size of the tumour at baseline.

In 192/904 (21.2%) scans included in the analysis, the z-dimension of the tumour was unavailable, and so was estimated based on the x and y dimension. A sensitivity analysis in which these scans were excluded returned similar results, with an estimated growth rate of 11.0% per year (95% CI: 9.8% - 12.2%, p<0.001) over 712 included scans.

The rate of tumour growth was also estimated at a patient level for the 146 patients with data available for at least three scans. Using this approach, the average tumour growth rate was found to be similar to utilising all scans in a single model (described above), at a median of 10.0% per year (IQR: 1.4% - 18.9%). Tumour volume was found to be relatively stable over time (i.e. ±2% per year) in a small number of patients (n=18, 12.3%), and to decline over time in 25 (17.1%) patients. However, the majority of

patients saw an increase in tumour size, with 69 (47.2%) having a gradient between 3-20% per year, and 34 (23.2%) growing by >20% per year. None of the factors considered were found to be significantly predictive of growth rate (***Table 3***).

Short and long-term growth rates of tumours were then compared. Growth rates were estimated separately for the first two years of follow up, and over subsequent scans for each patient. A total of 32 patients had at least three scans in both periods, and were included in the analysis. For these, the growth rate over the first two years was found to be significantly correlated with the subsequent growth rate (rho: 0.405, p=0.021, ***Figure 4a***). Bland-Altman analysis (***Figure 4b***) found no significant difference between the short- and long-term growth rates, with a mean difference of 2.7 (standard deviation: 22.9) percentage points per year (p=0.505). However, there was considerable variability within the pairs of growth rates, with a 95% prediction interval of approximately ±45 percentage points per year.

The tumours were then divided into those with slower (≤10% per year, N=16) and faster (>10% per year, N=16) growth rates over the initial two years of follow up. Of those with faster growth initially, 56% (9/16) retained a >10% growth rate over the subsequent period of follow up, compared to 25% (4/16) of those with a slower initial growth rate.

Decision to operate

The entire cohort of N=485 had a median of 59 months of follow-up (Kaplan-Meier estimate of potential follow-up), during which time 295 patients underwent surgery. Of these, N=199 were classified as early surgery, occurring within six months of diagnosis, after a median of 67 days (IQR: 36-107). For those patients that entered radiological monitoring (N=248), N=96 were eventually treated surgically, giving Kaplan-Meier estimated surgery rates of 20.4%, 31.3% and 37.9% at 1, 3 and 5 years after diagnosis, respectively (***Figure 5***). For those that underwent surgery, the reason for operating was recorded for 276 (93.6%), with the most common reasons being due to the patient being symptomatic (40.2%) or due to an uncertain diagnosis (35.5%). Of those in whom surgery was not performed, reasons were recorded in 180 (94.7%) patients, with the decision most commonly due to a patient being asymptomatic and stable (42.8%) or

asymptomatic with a risk of major nerve injury (23.9%). A further breakdown of these reasons is reported in ***Supplementary Table 2***.

Factors associated with decision to operate

Surgery was found to be significantly more common in patients with symptomatic vs. incidental presentation, with crude rates of 68.9% vs. 52.7%, respectively ($p<0.001$). Tumours with major nerve involvement were significantly less likely to be resected (55.2% vs. 76.2%, $p=0.001$). There was a trend towards a higher rate of surgery in abdominal tumours (66.1% vs. 54.3% in pelvic tumours, $p=0.052$) and in patients with a younger age at presentation (72.2% vs. 56.3% in <40 vs. 65+ years, $p=0.051$), although neither of these comparisons reached statistical significance. A significant association between surgery and the tumour growth rate was also detected ($p=0.003$). Those tumours with the fastest increases in volume (>20% per year) had the highest rate of surgery at 41.2%, compared to 5.6% in stable (±2% per year) tumours ($p=0.025$, ***Table 4***).

Intra-operative factors and post-operative outcomes

Further details of the 295 patients that underwent surgery are reported in ***Supplementary Table 3***. Post-operative complication data were available for 221 patients, of whom 61 (27.6%) developed complications. The complication grade could be derived for 52 of these patients, with 18 (8.5% of patients undergoing surgery) found to have high-grade (grade 3-5) complications. Associations between a range of factors and complication rates are reported in ***Table 5a/b***. This analysis found significantly higher complication rates in faster growing tumours ($p=0.033$), in those originating from a named nerve ($p=0.003$), with a major nerve resection/transection ($p=0.002$), and in cases with vascular resection ($p<0.001$). Analysis of the rates of high-grade complications found only vascular resection to be significant ($p=0.001$). Post-operative length of stay was recorded in 283 (95.9%) operated patients, with a median of 6 days (IQR: 4 – 9), and 23 (7.8%) patients staying longer than two weeks. Moderate to severe long-term impairment was induced by major nerve division (seven femoral and 11 lumbosacral) and one operative death occurred after attempted repair of a post-operative enterocutaneous fistula.

Resection margin

Preoperative cross-sectional imaging was recorded in 294 patients, of whom an R0/R1 resection was predicted in 273 (92.9%). The final resection status was unavailable in two of these patients, with 262 (96.7%) of the remainder ultimately achieving an R0/R1 resection, and nine (3.3%) having an unplanned R2 resection. Of the 24 patients where an R2 resection was predicted, the final resection status was recorded in 16, of whom a single patient (6%) received an unplanned R0/R1 resection.

Post-operative surveillance

Of the 263 patients who underwent an R0/R1 resection, 124 (47.1%) entered a post-operative surveillance programme. Of these, 57 (45.6%) received only a single surveillance scan, with a maximum of ten scans, over a median surveillance period of 19 months (IQR: 7 – 39). Residual disease was detected at the first post-operative scan in four (3.2%) patients. After excluding these, a total of four patients developed recurrence during post-operative surveillance at 12, 12, 24 and 57 months, giving Kaplan-Meier estimated long-term recurrence rates of 2% and 7% at 3 and 5 years, respectively.

Of the 24 patients who had an R2 resection, 12 had data available for post-resection surveillance. The first scan was performed a median of 7 months (IQR: 5 – 15) after resection, with the median tumour volume being 41.2 cm^3 (IQR: 2.1 – 163.2). Multiple scans were available for ten patients, who contributed a total of 39 scans, with a maximum of six scans per patient and a maximum follow up time of 48 months. No significant post-resection tumour growth was detected in this cohort (p=0.536), with an average estimated growth rate of 2.8% per year (95% CI: -6.1%, 25.9%).

Discussion

The growth characteristics of schwannomas were previously unknown, leading to a great deal of uncertainty in optimal clinical management. All existing literature on schwannomas is confined to case studies or small single-centre case series.[2,6-11] The inclusion of all eligible schwannomas in a single growth model found tumour volume to increase significantly over time. This steady expansion has significant consequences if the tumour is critically placed against anatomical structures. Surgical morbidity in the near term needs to be considered against the potential longevity of the patient, possible heightened complexity of future resection, and preservation of function.

On an individual basis, there is a huge variability in size at presentation and subsequent rate of expansion. Tumours of all sizes at presentation appeared to retain the ability to grow with a highly individualised trajectory, ranging from largely stable with some exhibiting a prolonged period of stability to growing at >20% per annum. For those patients without clear indication for immediate resection, the unpredictability of tumour growth at presentation impacts informed decision-making regarding timing of surgery. Practical guidance is therefore required, and this can only be based upon serial cross-sectional images to obtain an indication of the tempo of tumour growth over time. In patients without a clear indication for immediate resection, the future growth trajectory can be cautiously predicted after three scans over a two-year period. No other factors had a bearing on tumour growth, including anatomical location and interestingly, histological subtype, with the classically indolent ancient schwannoma expanding at a similar rate to the main cohort.

The spectrum of disease, in terms of anatomical location, size at presentation and growth characteristics was broad. Pelvic tumours tended to be the largest, where occult expansion can occur until eventually constrained by bony contours or discovered coincidentally. Histological sub-characterisation was not widely described; however, of the two major subtypes, cellular schwannomas were found to be significantly larger at presentation than ancient schwannomas. Interestingly, size at presentation was found to be negatively correlated with ASA grade, perhaps due to the greater propensity for more co-morbid patients to undergo cross-sectional imaging and therefore discover asymptomatic lesions at an earlier stage.

Symptomatic presentation was one of the main drivers for resection, although patients with major nerve involvement were significantly less likely to undergo surgery, presumably due to concerns regarding associated morbidity. Those exhibiting rapid expansion (>20% increase) and younger patients were most likely to undergo resection. Abdominal schwannomas also tended towards higher rates of resection, compared to pelvic lesions. Difficulty in establishing a preoperative diagnosis with biopsy, due to surrounding structures, may also have contributed to increased levels of resection for abdominally placed tumours.

For the uninitiated, the benign nature of schwannomas can falsely reassure the operating surgeon and patient that resection will be a relatively straightforward endeavour. However, these tumours are hard, unyielding, vascular, and firmly adherent to surrounding critical structures. Operative morbidity is high, where risk factors for complications were faster-growing tumours, involvement of a major nerve, or division of a named artery. Surprisingly, location of the tumour was not associated with a higher risk of complication. Large schwannomas in the pelvis are classically associated with significant morbidity and blood loss, and the equivalence of operative risk is likely to reflect selective resection practice.

Anticipated (planned) and all R2 resections were associated with a higher complication rate. If more aggressive surgery were performed to avoid incomplete resections entirely, the overall complication rate may have been even higher, from expected division of major nerves and vessels. Moderate to severe long-term impairment was seen to be induced by major nerve division. Planned R2 resection, where an R0/R1 resection would necessitate major nerve or artery division, would seem a reasonable option to minimise long-term morbidity. Preoperative planning with the aid of cross-sectional imaging can be used to counsel patients on the likelihood of an R0/R1 or R2 resection and the potential implications that this may have.

In the majority of contributing institutions, post-resection surveillance was offered to patients as a default policy, along similar lines to comparable sarcoma resections. With such a low incidence of recurrence, post-operative surveillance imaging should not be routinely recommended. If imaging is thought to be required, consideration of a one-off baseline scan to exclude residual disease at three months post resection may be of

value. The value of post-operative surveillance remains debatable with an average estimated growth rate of 2.8% per year. No further operative intervention was performed following R2 resection during the period of the study. A pragmatic approach is recommended with surveillance balanced with the patient's wishes and the knowledge that further attempts at resection risks the morbidity that the incomplete resection was designed to avoid at the first operation.

Limitations

As with any retrospective study, selection and measurement biases were evident. Selection bias was minimised by including all operated and non-operative patients referred to sarcoma services during the time window, although the burden of disease that was not referred to these centres (e.g. locally managed, not detected) remains unmeasured. Not all data fields were complete for each patient, leading to a moderate level of data absence for some fields. This was a particular issue for the z-dimensions of tumours, which was not recorded in over a fifth of scans. However, this was mitigated by estimating the volume based on the remaining dimensions, with sensitivity analysis indicating that this had minimal impact on the analysis of tumour growth.

Although patients were often followed up for prolonged periods, there was inevitable attrition bias due to patients moving or being lost to follow-up. Histological sub-classification of schwannomas was not universally performed, which prevented comment on the growth characteristics of some of the rarer subtypes, such as melanocytic schwannomas.

Recommendations for surgical management of abdominal, retroperitoneal, and pelvic schwannomas:

1. Early indications for surgery include symptomatic tumour at presentation, diagnostic uncertainty and existing evidence of rapid expansion or patient preference after adequate counselling.
2. Where a clear indication for surgery at presentation exists, then surgery should proceed with adequate patient counselling, and consideration given to a planned R2 resection if major nerves or vessels would otherwise need to be sacrificed.

3. In the absence of an indication for early surgery, diagnosis of a schwannoma should be confirmed on biopsy and the patient enrolled in to a programme of radiological monitoring for at least 2-years in order to predict individualised tumour growth characteristics. After identification of growth characteristics, multi-disciplinary discussion should then occur to consider future resectability and likely induced morbidity of surgery, coupled with patient age, wishes and specific tumour location.
4. Post-operative surveillance imaging for patients with R0/R1 resected schwannomas holds little benefit beyond a baseline scan and should not be routinely recommended.
5. Post-operative surveillance imaging after R2 resection should be considered on a pragmatic basis.

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Table 1 – Patient demographics

Factor	Total N	Statistic
Age at Diagnosis (Years)	485	54 (41 - 64)
Gender (Female)	485	272 (56.1%)
ASA (At Referral)	321	
1		133 (41.4%)
2		114 (35.5%)
3		70 (21.8%)
4		4 (1.2%)
Presentation	467	
Incidental		239 (51.2%)
Symptomatic		228 (48.8%)
Location of Schwannoma	479	
Abdominal		62 (12.9%)
Pelvis		175 (36.5%)
Retroperitoneal		242 (50.5%)
Type of Schwannoma	110	
Ancient		47 (42.7%)
Cellular		55 (50.0%)
Cystic		2 (1.8%)
Melanocytic		5 (4.5%)
Plexiform		1 (0.9%)
Major Nerve Involvement	306	67 (21.9%)

Data are reported as N (%), or as median (IQR), as applicable. "Total N" represents the number of patients for whom data were recorded for the stated factor.

Table 2 – Factors associated with initial tumour size

	Total N	Initial Tumour Volume (cm^3)*	p-Value
Age at Diagnosis (Years)			0.254
< 40	97	91.2 (27.0 - 253.8)	
40 - 54	121	90.3 (24.6 - 235.3)	
55 - 64	99	110.2 (31.6 - 364.7)	
65+	107	67.3 (21.2 - 198.5)	
Gender			**0.005**
Female	243	73.5 (20.6 - 217.6)	
Male	181	112.7 (36.3 - 402.2)	
ASA (at Referral)			**0.001**
1	119	151.3 (49.4 - 335.1)	
2	97	65.4 (25.7 - 197.3)	
3-4	64	87.0 (20.4 - 167.2)	
Presentation			0.767
Incidental	211	89.8 (36.3 - 224.1)	
Symptomatic	203	92.1 (24.1 - 305.8)	
Location of Schwannoma			**<0.001**
Abdominal	52	20.9 (6.8 - 59.6)	
Pelvis	161	124.7 (37.5 - 335.1)	
Retroperitoneal	211	90.6 (31.8 - 261.0)	
Type			**0.002**
Ancient	36	66.7 (27.7 - 224.9)	
Cellular	50	264.9 (97.4 - 578.8)	
Other	8	147.7 (32.5 - 364.2)	
Major Nerve Involvement			0.249
No	200	53.9 (21.1 - 170.8)	
Yes	60	103.1 (19.1 - 231.0)	

*Data are reported as median (IQR), with p-values from Mann-Whitney tests or Kruskal-Wallis tests, as applicable. Bold p-values are significant at p<0.05. *The tumour volume at the first scan for which data were recorded.*

Table 3 – Predictors of tumour growth

	Total N	***Increase in Tumour Volume per Year***	***p-Value***
Age at Diagnosis (Years)			0.450
< 40	32	13.8% (2.8%, 21.4%)	
40 - 54	48	9.7% (2.4%, 16.9%)	
55 - 64	32	5.7% (0.4%, 15.1%)	
65+	34	8.8% (-0.9%, 20.2%)	
Gender			0.360
Female	74	11.4% (2.3%, 20.2%)	
Male	72	8.6% (0.4%, 17.2%)	
ASA (at Referral)			0.731
1	31	11.4% (1.7%, 21.2%)	
2	21	13.0% (5.0%, 20.2%)	
3-4	11	9.2% (-0.9%, 18.7%)	
Presentation			0.181
Incidental	85	8.9% (0.8%, 16.4%)	
Symptomatic	59	12.6% (3.1%, 21.0%)	
Location of Schwannoma			0.053
Abdominal	17	2.3% (-4.1%, 8.8%)	
Pelvis	60	11.0% (4.1%, 18.9%)	
Retroperitoneal	69	11.3% (0.0%, 20.2%)	
Type of Schwannoma			0.924
Ancient	5	6.4% (1.9%, 14.4%)	
Cellular	13	10.0% (1.7%, 21.0%)	
Major Nerve Involvement			0.654
No	41	9.2% (1.8%, 28.3%)	
Yes	18	11.9% (5.0%, 21.5%)	
Initial Tumour Volume (cm^3)*			0.306
< 25	37	8.7% (-0.1%, 14.6%)	
25 - 99	40	11.5% (1.6%, 28.2%)	
100 - 299	39	11.7% (2.6%, 19.0%)	
300+	30	8.7% (0.8%, 14.4%)	

*The average rate of change in tumour size was estimated for each patient by producing individual regression models, with the log_{10}-transformed tumour size set as the dependent variable. Only those patients with at least three scans (N=146) were included in the analysis. The gradients from the resulting models were then converted into percentage changes per year, which were summarised as median (IQR). Comparisons between groups were performed using Mann-Whitney tests and Kruskal-Wallis tests, and bold p-values are significant at p<0.05. *The tumour volume at the first scan for which data were recorded.*

Table 4 – Predictors of decision to operate

	Total N	Crude Surgery Rate (N, %)	Hazard Ratio (95% CI)	p-Value
Age at Diagnosis (Years)				0.154
< 40	108	78 (72.2%)	-	-
40 - 54	141	83 (58.9%)	0.73 (0.54 - 1.00)	0.051
55 - 64	117	67 (57.3%)	0.77 (0.56 - 1.07)	0.125
65+	119	67 (56.3%)	0.72 (0.52 - 1.00)	0.051
Gender				0.138
Female	272	175 (64.3%)	-	-
Male	213	120 (56.3%)	0.84 (0.66 - 1.06)	0.138
ASA (at Referral)				0.147
1	133	86 (64.7%)	-	-
2	114	86 (75.4%)	1.31 (0.97 - 1.77)	0.074
3-4	74	56 (75.7%)	1.30 (0.93 - 1.82)	0.129
Presentation				**<0.001**
Incidental	239	126 (52.7%)	-	-
Symptomatic	228	157 (68.9%)	1.53 (1.21 - 1.93)	**<0.001**
Location of Schwannoma				0.050
Abdominal	62	41 (66.1%)	-	-
Pelvis	175	95 (54.3%)	0.70 (0.48 - 1.00)	0.052
Retroperitoneal	242	155 (64.0%)	0.93 (0.66 - 1.31)	0.660
Type of Schwannoma				0.827
Ancient	47	36 (76.6%)	-	-
Cellular	55	45 (81.8%)	1.13 (0.73 - 1.76)	0.578
Other	8	5 (62.5%)	0.95 (0.37 - 2.41)	0.908
Major Nerve Involvement				**0.001**
No	239	182 (76.2%)	-	-
Yes	67	37 (55.2%)	0.56 (0.39 - 0.80)	**0.001**
Initial Tumour Volume (cm^3)*				0.577
< 25	102	57 (55.9%)	-	-
25 - 99	122	71 (58.2%)	1.08 (0.76 - 1.54)	0.652
100 - 299	108	59 (54.6%)	0.99 (0.69 - 1.43)	0.973
300+	92	56 (60.9%)	1.25 (0.87 - 1.81)	0.231
Tumour Growth (% per Year)**				**0.003**
<-2% (Reduction)	25	4 (16.0%)	4.04 (0.45 – 36.3)	0.212
-2% to 2% (Stable)	18	1 (5.6%)	-	-
3% to 20% (Increase)	69	9 (13.0%)	2.48 (0.31 – 19.6)	0.390
>20% (Increase)	34	14 (41.2%)	10.2 (1.33 – 77.7)	**0.025**

*Crude rates represent the total proportion of patients that underwent surgery during the follow up period. Hazard ratios and p-values are from univariable Cox regressions, which account for the period of follow up and timing of surgery, with HRs >1 representing a higher rate of surgery in the stated group. Bold p-values are significant at p<0.05. *The tumour volume at the first scan for which data were recorded. **Tumour growth was estimated using patient-level regression models for those with three or more available scans.*

Table 5a – Predictors of complications after surgery (part 1)

	Any Complication			High Grade Complication		
	Total N	***Rate***	***p-Value***	***Total N***	***Rate***	***p-Value***
Age at Diagnosis (Years)			0.356*			0.802*
< 40	61	13 (21.3%)		58	5 (8.6%)	
40 - 54	60	20 (33.3%)		57	4 (7.0%)	
55 - 64	51	12 (23.5%)		49	5 (10.2%)	
65+	49	16 (32.7%)		48	4 (8.3%)	
Gender			0.067			0.319
Female	128	29 (22.7%)		122	8 (6.6%)	
Male	93	32 (34.4%)		90	10 (11.1%)	
ASA (at Referral)			0.699*			0.855*
1	79	22 (27.8%)		75	7 (9.3%)	
2	69	18 (26.1%)		67	7 (10.4%)	
3-4	40	13 (32.5%)		39	3 (7.7%)	
Presentation			0.760			0.804
Incidental	105	27 (25.7%)		103	9 (8.7%)	
Symptomatic	111	31 (27.9%)		106	8 (7.5%)	
Location of Schwannoma			0.551			0.766
Abdominal	23	6 (26.1%)		23	2 (8.7%)	
Pelvis	78	25 (32.1%)		77	8 (10.4%)	
Retroperitoneal	116	29 (25.0%)		109	8 (7.3%)	
Type of Schwannoma			0.111			0.729
Ancient	32	13 (40.6%)		28	3 (10.7%)	
Cellular	42	8 (19.0%)		41	3 (7.3%)	
Other	5	2 (40.0%)		4	0 (0.0%)	
Major Nerve Involvement			0.511			0.305
No	125	34 (27.2%)		122	14 (11.5%)	
Yes	32	11 (34.4%)		29	1 (3.4%)	
Initial Tumour Volume (cm^3)**			0.093*			0.305*
< 25	36	5 (13.9%)		36	2 (5.6%)	
25 - 99	60	14 (23.3%)		58	4 (6.9%)	
100 - 299	49	16 (32.7%)		48	5 (10.4%)	
300+	43	12 (27.9%)		40	4 (10.0%)	
Tumour Growth (% per Year)***			**0.033***			-
<-2% (Reduction)	4	0 (0.0%)		4	0 (0.0%)	
-2% to 2% (Stable)	0	-		0	0 (0.0%)	
3% to 20% (Increase)	6	1 (16.7%)		6	0 (0.0%)	
>20% (Increase)	12	5 (41.7%)		12	0 (0.0%)	

*High grade complication is defined as a Clavien-Dindo grade of 3+. Clavien-Dindo grades were not available for N=9 patients, hence these were excluded from the analysis of high grade complications. p-Values are from Fisher's exact test/Chi-square test for comparisons of two/more than two groups, unless stated otherwise Bold p-values are significant at p<0.05. *p-Value from Mann-Whitney test, as the factor is ordinal. **The tumour volume at the first scan for which data were recorded. ***Tumour growth was estimated using patient-level regression models for those with three or more available scans.*

Table 5b – Predictors of complications after surgery (part 2)

	Any Complication			High Grade Complication		
	Total N	***Rate***	***p-Value***	***Total N***	***Rate***	***p-Value***
Reason for Operating			0.475			0.658
Symptomatic	81	19 (23.5%)		78	5 (6.4%)	
Uncertain diagnosis	72	20 (27.8%)		71	6 (8.5%)	
Enlarging lesion	31	7 (22.6%)		30	2 (6.7%)	
Anatomical obstruction / compression	13	6 (46.2%)		13	2 (15.4%)	
Other	12	4 (33.3%)		12	2 (16.7%)	
Originating from a Named Nerve			**0.003**			1.000
No	109	21 (19.3%)		107	8 (7.5%)	
Yes	54	23 (42.6%)		47	3 (6.4%)	
Major Nerve Division or Resection			**0.002**			0.403
No	131	30 (22.9%)		125	8 (6.4%)	
Yes	28	15 (53.6%)		26	3 (11.5%)	
Vascular Division or Resection			**<0.001**			**0.001**
No	79	15 (19.0%)		79	2 (2.5%)	
Yes	27	16 (59.3%)		27	7 (25.9%)	
Intention of Surgery			0.085			1.000
R0/R1	203	52 (25.6%)		197	16 (8.1%)	
R2	17	8 (47.1%)		14	1 (7.1%)	
Margin			0.121			1.000
R0/R1	194	50 (25.8%)		189	16 (8.5%)	
R2	21	9 (42.9%)		18	1 (5.6%)	

High grade complication is defined as a Clavien-Dindo grade of 3+. Clavien-Dindo grades were not available for N=9 patients, hence these were excluded from the analysis of high grade complications. p-Values are from Fisher's exact test/Chi-square test for comparisons of two/more than two groups, unless stated otherwise
Bold p-values are significant at p<0.05.

Supplementary Table 1 – Contributing centres

Name of Centre	**Number of Patients**
Brigham and Women's Hospital/Dana-Farber Cancer Institute. Boston, USA	26
Emory University Hospital. Atlanta, USA	83
Institute of Oncology Ljubljana. Ljubljana, Slovenia	21
Istituto Nazionale dei Tumori. Milan, Italy	37
Mayo Clinic. Jacksonville, USA	23
Moffitt Cancer Centre. Tampa, USA	13
Mount Sinai Hospital. Toronto, Canada	63
Netherlands Cancer Institute. Amsterdam, The Netherlands	10
Ottawa Hospital Research Institute. Ottawa, Canada	55
Peter MacCallum Cancer Centre. Melbourne, Australia	17
Queen Elizabeth Hospital. Birmingham, UK	52
Royal Marsden Hospital. London, UK	85

Supplementary Table 2 – Reasons given for operating/not operating

Factor	Total N	Statistic
Reason for Not Operating	180	
Stable and asymptomatic		77 (42.8%)
Risk of major nerve injury and asymptomatic		43 (23.9%)
Asymptomatic		22 (12.2%)
Complexity of resection		13 (7.2%)
Co-morbidity		8 (4.4%)
Other		17 (9.4%)
Reason for Operating	276	
Symptomatic		111 (40.2%)
Uncertain diagnosis		98 (35.5%)
Enlarging lesion		33 (12.0%)
Anatomical obstruction / compression		14 (5.1%)
Other		20 (7.2%)

Data are reported as N (%), and are based on the N=295 (60.8%) who underwent surgery, or the N=190 (39.2%) that did not. "Total N" represents the number of patients for whom data were recorded for the stated factor.

Supplementary Table 3 – Intra-operative factors and post-operative outcomes

Factor	**Total N**	**Statistic**
Schwannoma Originating from a Named Nerve	186	69 (37.1%)
Major Nerve Division or Resection	171	31 (18.1%)
Vascular Division or Resection	124	39 (31.5%)
Intention of Surgery	294	
R0/R1		273 (92.9%)
R2		21 (7.1%)
Surgical Margin	287	
R0/R1		263 (91.6%)
R2		24 (8.4%)
Any Complication	221	61 (27.6%)
Clavien-Dindo Grade	212	
No Complication		160 (75.5%)
1		19 (9.0%)
2		15 (7.1%)
3		11 (5.2%)
4		6 (2.8%)
5		1 (0.5%)
Post-operative Length of Stay (Days)	283	6 (4 – 9)

Data are reported as N (%) or median (IQR), and are based on the N=295 (60.8%) who underwent surgery, unless stated otherwise. "Total N" represents the number of patients for whom data were recorded for the stated factor.

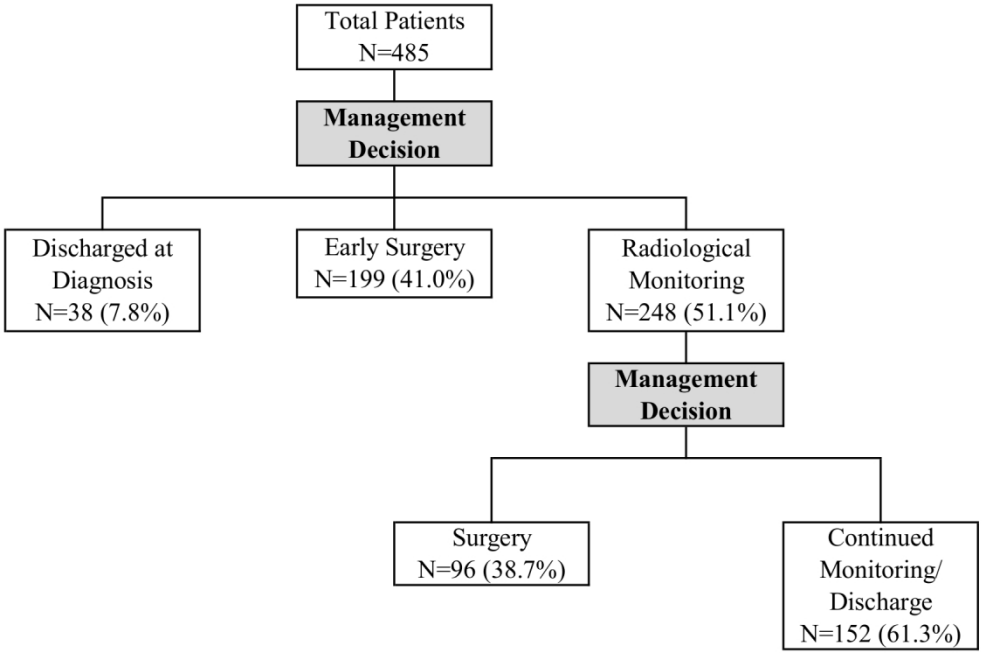

Figure 1 – Flow diagram of overall patient management

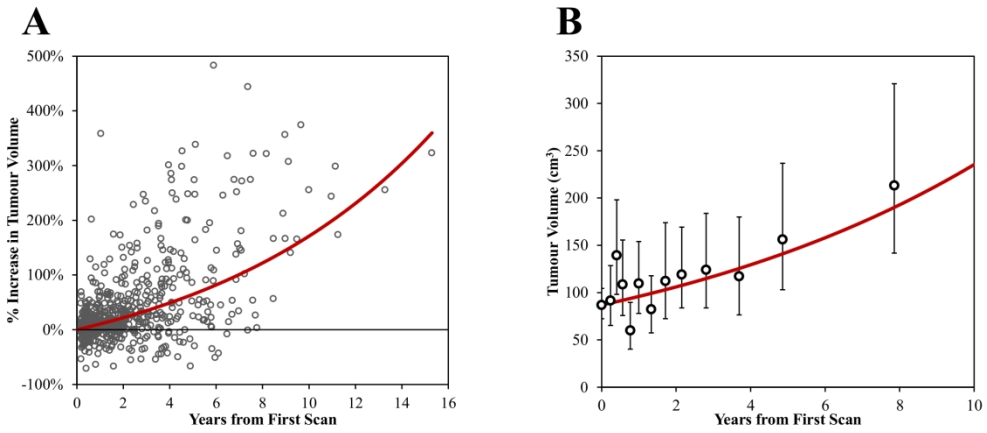

Figure 2 – Change over time in tumour volume. Figure 2A shows the percentage differences in tumour volume between the first scan for a patient to all subsequent scans. The y-axis was truncated at a 500% increase to improve scaling, resulting in N=7 scans being excluded from the plot. Figure 2B shows the geometric mean tumour volume within percentiles of the follow up time. Each point is based on between 53 and 66 scans, with the exception of the initial scans (at time=0, N=236), and whiskers represent 95% confidence intervals. For both plots, the trendline is from the general linear model described in text.

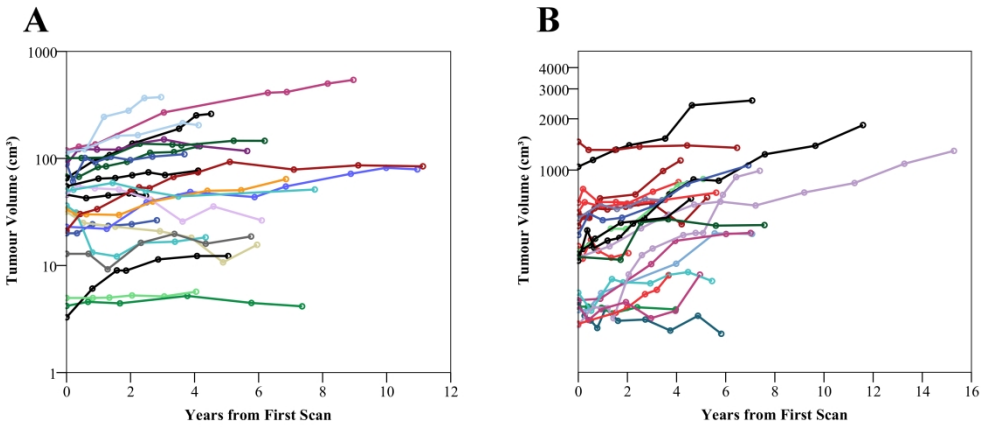

Figure 3 – Plots of tumour volume trajectories for patients with more than five scans. Patients with more than five scans were included in the plots. Due to the large variability in tumour volumes at referral, and the number of trajectories being plotted, patients were divided over two plots, based on the initial tumour volume. Figure 3A includes those with initial tumour volume <120cm3 (161 scans in 22 patients), with the remainder in Figure 3B (165 scans in 22 patients). Both plots use a logarithmic y-axis to improve scaling

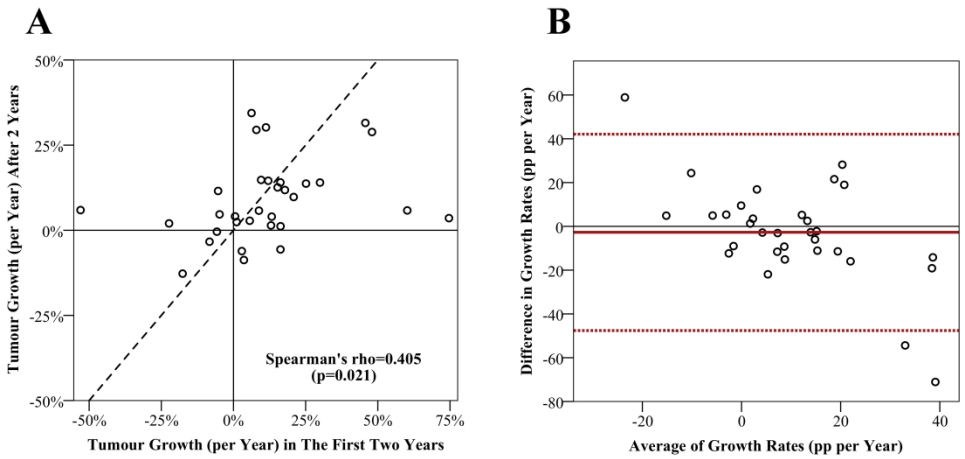

Figure 4 – Comparisons of short and long term growth rate. The plots show the data for the N=32 patients that had at least three scans in the first two years, and at least three subsequent scans. Figure 4A is a comparison of the gradients over these two periods, with the broken line plotted at y=x. Figure 4B is a Bland-Altman plot of growth rates in the first two years, and across subsequent scans. The solid red line represents the mean difference between these two growth rates, whilst broken lines are 95% prediction intervals. pp=percentage points.

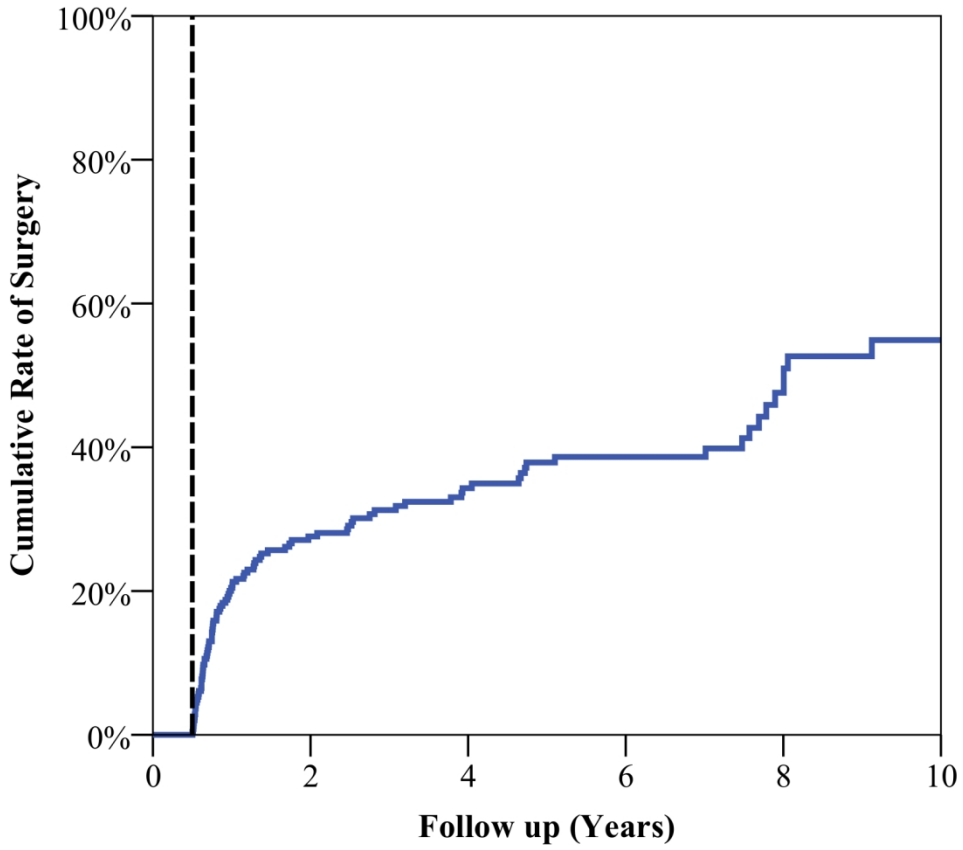

Figure 5 – Kaplan-Meier curve of the time to surgery in the radiologically monitored group. Only patients undergoing radiological monitoring (N=248) were included in the analysis, hence those treated surgically within six months of diagnosis (broken line) or discharged at diagnosis were excluded.