Title: Granular clinical history and outcome in 51 patients with primary and secondary malignant meningioma

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Abstract

Objective: WHO grade 3 meningiomas, also known as malignant meningiomas (MM), are rare, and the heterogenous clinical course in patients with MM is not well described. To characterize the clinical courses of patients with MM, granular clinical data was gathered from 51 patients treated at the Department of Neurosurgery and Radiation Oncology, Rigshospitalet in Copenhagen, Denmark between 2000-2020.

Methods: We investigated outcome and timing in terms of 1) tumor progression and grade transformation in patients previously diagnosed with grade 1 or grade 2 meningiomas (patients with a secondary malignant meningioma, sMM) 2) performance status and complications following surgery and 3) transition to non-curative treatment and ultimately death. We analyzed complications, time between recurrences and outcome (Modified Rankin Score) for every surgery, both malignant and premalignant.

Results: Of the 51 patients, 24 (47%) had a sMM. Time to grade 3 transformation in the sMM group varied widely (0.5-22 years, median 5.5 years), but after transformation to a WHO grade 3 tumor, sMM and patients with a primary malignant meningioma (pMM) did not differ significantly in overall survival and cumulative risks of progression. Median OS for all 51 patients was 4.2 years (CI95% 2.6-7.2 years). Time from the decision to shift from curative- to non-curative treatment until death was 3.8 months and the 30-day mortality rate following surgery was 9.8%. From a cumulative number of 151 surgeries, 10 surgeries were followed by improvement on the Modified Rankin Scale (mRS), mRS was unchanged in 70 and worsened in 71. The MM was the underlying cause of death in 30 out 31 patients who had deceased at the end of follow-up.

Conclusions: Taken together, our findings emphatically described a significant morbidity and mortality from the disease itself and from the treatment. Our findings warrant studies of prognostic factors for earlier support and adjuvant measures and identify a need for better palliative strategies in this patient group.

Introduction:

Meningioma is the most common primary intracranial tumor and accounts for 37% of all intracranial tumors[1]. Malignant meningioma (MM), also known as WHO grade 3 meningioma, represent 1-3% of all meningiomas and constitute three histological subtypes according to the 2016 WHO classification[2]. The MM are rare and subsequently we lack knowledge of natural history and phenotypes. The literature reports dismal outcomes despite radiation or experimental therapies[3-6], and the main treatments for the initial tumor and recurrences remain surgery.

Despite the malignant character with inevitable need of palliative care[3], timing and implementation of palliation has been neglected. The overall survival (OS) and progression-free survival (PFS) appear to be highly variable between individual patients[4–8]. Some live years after initial treatment with repeated surgery and ensuing morbidity while others deteriorate and succumb rapidly. A patient with MM can either present de novo as a grade 3 meningioma (primary malignant meningioma, pMM) or develop secondarily as a malignant recurrence of a previously operated WHO grade 1/2 meningioma (secondary malignant meningioma, sMM). Living with a chronic disease that is initially envisioned as potentially curable can complicate the transition to non-curative strategies or end of life care. We hypothesize that detailed individual patient histories reflect the heterogeneity of different needs of the patients and that synthesizing data of typical clinical courses could assist clinicians and palliative team members to provide better treatment and support to minimize suffering for the rare patients who have MM. We collected clinical data from 51 consecutive patients with sMM and pMM treated at Rigshospitalet during a 20-year period. We obtained detailed data for every surgery and constructed timelines for all individual patients. Specifically, we investigated outcome and timing in terms of 1) time from diagnosis to malignant transformation and tumor progression 2), time from non-curative treatment decision to death, and 3) performance status and complications following surgery.

Methods:

Patient Cohort

We retrospectively reviewed a population-based cohort of consecutive patients with MM treated at Copenhagen University Hospital, Rigshospitalet in Denmark during the period 2000-2020. During inclusion, no patient with MM of the catchment area of approximately 2.2 million inhabitants had surgery for MM at other hospitals. End of follow-up was May 2021. The patients with MM were identified through searching the Snomed code M95303: WHO grade 3 meningioma in the pathology database. The Danish Civil Registration system enabled coupling of meningioma samples to individual patients. A clinical database was constructed based on retrospective information from patients' medical records. Premorbid data included i) performance status quantified by the Karnofsky performance score, ii) level of self-care ability (whether the patient needed assistance at home or not) and iii) comorbidity quantification with the Charlson Comorbidity Index (CCI). Tumor specimens were retrieved for all patients and a senior neuropathologist re-evaluated full section tissue-slides and confirmed the WHO grade of representative tumor specimens on H&E stained slides according to the 2016 WHO classification. The 2016 classification states that a meningioma with >20 mitotic figures per 10 high

power fields (x40 magnification visual field) or frank anaplasia or rhabdoid or papillary morphology are grade 3.[2]

Individual patient timelines were constructed for all 51 patients. The timelines comprised i) time to recurrence of every tumor, ii) radiotherapy and dosage relative to surgery, iii) epilepsy or anti-epileptic drugs (AED) before- or after surgery and iv) the patient's performance status quantified using the modified Ranking Score (mRS). For every surgery, i) type of complications, ii) severity of complications according to Ibañez[9], iii) Simpson grade and iv) outcome at first follow-up was noted. Simpson grade was established by review of surgical descriptions by an experienced neurosurgeon. Radiological data included i) tumor location, ii) the presence of multifocal disease and iii) recurrence. Recurrence was defined as the radiologists' descriptions of growth of tumor components, new tumor lesions in a different location or regrowth in earlier surgery cavity on standard MRI protocol (T1, T2 and T2-FLAIR). The underlying cause of death was determined by reviewing the patients' medical records.

This study was approved by the Regional Scientific Ethical Committees, Capital Region of Denmark (approval H-6-2014-010) and the need for patient consent was waived. The data handling was approved by the Danish Data Protection Agency(approval VD-2018-365).

Statistics

Median time between treatment and subsequent recurrences was estimated as time from surgery to growth verified on MRI scan. Median time to malignant transformation was estimated as time from grade 1 or 2 surgery to the MM surgery. We defined a time point of the decision to overgo to a non-curative treatment in this patient group: time of non-curative treatment decision (TNC). TNC was defined as the documented time of (1) the decision not to operate with curative intent or (2) referral to a palliative unit, whichever came first. We calculated time from the TNC to death and depicted events with a Kaplan-Meier curve. This analysis was performed on patients where a decision to overgo to a non-curative treatment strategy had been made after the WHO grade 3 diagnosis (n=31). For an overview over the mRS across serial tumor recurrences, baseline mRS (prior to any surgery) was used in combination with the best mRS after every surgery.

Overall survival (OS) was defined as time from first MM surgery (WHO 3 MM diagnosis) to death. We applied a Cox proportional hazard regression when investigating clinical factors' association with OS (age, sex, primary/secondary, skull base/non-skull base, anaplastic/non-anaplastic). Proportionality was tested and found valid using the Schoenfeld residuals. Age at diagnosis of MM was included as a continuous covariate and linearity was tested with restricted cubic splines and found adequate ($\chi 2$ $p > 0.1$). Differences in OS between sMM and pMM was tested with the log rank test and survival curves were obtained using the Kaplan-Meier method. For differences in recurrence, we applied the Aalen-Johansen estimator and considered death without recurrence as a competing risk. Gray's test was applied to test if a significant difference existed between the two groups and survival curves were obtained using the Aalen-Johansen method. We considered $p < 0.05$ statistically significant. We used R version 4.0.2[10] for computing.

Results:

Demographic data, premorbid function, and distribution of surgeries

Fifty percent of the patients were female. Prior to the meningioma diagnosis, 48 patients needed no assistance, 3 had assistance at home and none were in a nursing home. The preoperative median Karnofsky Perfomance Score before any meningioma surgery was 80 (range 50-100). Most patients had no comorbidities (n=31) whereas 18 had a weighted CCI of 1-2 and two patients had a weighted CCI of >2. Of the 51 patients, two had genomic factors that could explain the malignant meningioma and two had previous childhood CNS tumors that were irradiated. The median number of surgeries per patient was 2 (range 2-10) and the mean 3. Six patients had more than 5 surgeries. Three patients had 7 or 8 surgeries, and one patient had 10 surgeries (fig. 1). Complications were quantified as the highest surgical Ibañez score for any intracranial meningioma surgery (table 1). Assessing only the first WHO grade 3 surgery, we found 23 patients in the pMM group (85%) with no complications and 12 (50%) in the sMM group without complications. For an overview of data on patient level, see table 1.

Secondary and primary malignant meningioma

Twenty-four (47%) of the patients had sMM (malignant transformation of a previous grade 1 or 2 meningioma). In the sMM group, 11 (46%) had a WHO grade 1 tumor at debut and 13 (54%) had a WHO grade II. Time to WHO grade 3 transformation showed a median of 65.7 months (5.47 years, range 0.54-22.1 years). A history of a previous premalignant tumor could be as long 22 years and, in this case, the patient presented with a meningoepithelial grade 1 tumor. In 12 patients (50%) premalignant tumors were evident 5 years before the grade 3 diagnosis and two patients had had more than 3 premalignant surgeries 5 years before the grade 3 diagnosis.

Recurrences and survival

The median follow-up time from the first MM to death or end of follow-up was 8.2 years (range 0.4-24.6 years) in all patients. Twenty patients were alive at the end of follow-up and none were lost to follow-up. The median time between surgery and a following recurrence was 367 days (range 7 to 4467) based on 118 recurrences in all patients. Median time between a WHO grade 3 surgery and the following recurrence was 274 days (range 7 to 3201 days, 75 recurrences) in patients with a grade 3 recurrence. In the sMM group, median time between a grade 1/2 and a following recurrence was 800 days (range 36 to 4467 days, 43 recurrences). Reviewing the patients' files, cause of death (n=31) was deemed to be the MM disease in all but one case (documented tumor growth and no other potentially fatal competing diseases). None of the clinical variables investigated had any statistically significant association to OS (Supplementary table 1).

The median cumulative incidence of recurrence (CIR) for all patients was 15.1 months (CI95% 9.9-30.7 months) and CIR after one year was 42% (CI95%

30-57%) (Fig 2a). In the sMM group, CIR at one year was 56% (CI95% 38-76%) and in the pMM group CIR was 32% (CI95% 18-52%) at one year (Fig 2b). Gray's test did not show a significant difference in CIR between the two groups ($p = 0.08$). The median OS for all 51 patients was 50 months (CI95% 31-86 months) and we found no significant difference in OS between pMM and sMM patients (Fig. 2c, Wald test $p = 0.9$).

Surgical treatment and complications

The 51 MM patients had a total of 151 surgeries for their meningiomas. Of the 151 surgeries, 43 (28.5%) surgeries were in the pMM group, whereas 108 surgeries (71.5%) were in the sMM group and 53 (35.1 %) of these resulted in a meningioma grade 1 or 2 diagnosis. Of the 98 MM surgeries, 75 (76.5%) showed anaplastic histology. Premalignant histological subtypes consisted of meningoepithelial, fibrous, transitional, and angiomatous WHO grade 1 tumors and atypical WHO grade 2 tumors. For four of the WHO grade 1 tumors, we did not have pathology records of the histological subtype or tissue. Most tumors were convexity meningiomas (47.7%) or parasagittal meningiomas (29.8%). The precise localization was difficult to establish as 58.9% of the tumors were multifocal (defined by the radiologist's assessment in which more than two individual components were described). Thus, all locations for all tumors were noted (Table 2). A Simpson grade was established in 80.8% (n=122) of all surgeries and of these, a Simpson grade I+II was present in 52.4% surgeries (n=64).

Complications were evident in 50.3% (n=76) of all surgeries with postsurgical bleeding the most frequent (Table 2). Six patients (11.8%) died within 30 days of their MM surgery. It was unclear whether the disease burden or technicalities of the surgery were the cause of death in one of the six patients. The six cases were distributed across the entire study period. We detected no change in surgical management of MM across the years. Supplementary table 2 shows an overview of the patients who died within 30 days. Despite various chemotherapeutic strategies attempted in five patients, we did not see a long-term response. Supplementary table 3 shows an overview of adjuvant radiotherapy and chemotherapy.

Epilepsy, pain, and performance status across serial surgeries

Ten patients in the pMM group (37%) presented with seizures. Four additional patients developed epilepsy after their MM surgery. In the sMM group, 16 patients (66.7%) had epilepsy before their MM surgery and one additional patient developed epilepsy after their first MM surgery. At the end of follow-up, anti-epileptic medication (AED) and seizure control was checked for all patients; in the pMM group, 13 (48%) patients were on AED´s while the corresponding number was 16 (67%) in the sMM group. We saw no evidence of any surgery having relieving effects in relation to AED treatment or seizures.

In eight patients (16%), pain was a dominating and incapacitating symptom in their disease course. In three cases, tumor growth and subsequent pressure created neuralgiform facial pain. In the remaining five, it was either a strong headache or intense cranial pain when eating.

For every surgery, the best mRS was noted between surgeries. In all 151 surgeries, mRS improved in 10 cases, was unchanged in 70 and worsened in 71

cases. In patients with >5 surgeries (n = 6), the last surgeries seldomly maintained a following status quo in mRS. These patients needed assistance at home, had headaches and significant neurological morbidity. Figure 3 shows mRS development in relation to the patients' surgery order and WHO grade.

Time from non-curative decision to death

A documented decision to change to a non-curative strategy (referral to palliative team and/or no surgery with curative intent) was evident in 33 patients. For two patients, a non-curative strategy was chosen before their MM diagnosis. The reasons for switch to a non-curative phase were a concurrent systemic cancer in one patient and another patient had multiple recurrences of an aggressive atypical meningioma that was considered incurable before transformation to a WHO grade 3 meningioma. These two were excluded from the following Kaplan-Meier curve (Fig. 4). Of the patients who had a non-curative strategy chosen after and because of their MM diagnosis (n = 31) median time from non-curative decision (TNC) to death was 3.79 months (CI95% 2.27-8.96 months). The long-term survivors after TNC (>12 months) had no common denominators in either treatment, sex, age, or sMM/pMM status.

Discussion:

Our granular analysis of 51 MM patients has shown that the patients with sMM had highly varying times to malignant transformation. Half of the patients with sMM had a premalignant grade 1/2 tumor 5 years before the MM diagnosis; the median time to transformation was 65.7 months. Overall survival of sMM and pMM patients did not differ significantly once transformation had occurred. The meningioma was the underlying cause of death in all but one patient; the mean time from change to non-curative treatment to death was 3.8 months. Moreover, we saw that only ten out of 151 cumulative surgeries were followed by improvement in mRS. We found a relatively high 30-day mortality rate and complication rate. We noticed an opportunity to improve palliative strategies for patients with MM.

Repeated surgeries and complications

Thirty-four patients (66.7%) in our cohort underwent more than one surgery with a median of 2 surgeries per patient (range 1-10). The numbers are similar to the previous studies in literature: a median of 2 (range 1-5[11] or range 1-9[12]) and a mean of 3 surgeries per patient[13]. The similarities indicate that the treatment is comparable to other centers, which makes our results applicable to others.

The purpose of repeated surgeries could be to improve survival or neurological function. Sughrue et al. (2010) described a significant survival benefit from a second surgery[13]. The possible benefit of the 3rd, 4th or even 5th surgery is, however, unknown. Additional surgeries may have prolonged life but after the 5th surgery, daily life invariably included assistance at home, pain, and neurological deficits. Thus, most repeated surgeries could not improve the clinical condition. Our 51 patients underwent a total of 151 surgeries, and clinical outcome in terms of mRS improved only after 10 of these, 7 of which were first-time surgeries. In contrast, the mRS worsened after 71 surgeries and remained unaltered after 70. It

is not feasible to uncritically equalize mRS with the outcome after surgery as mRS may either continue to improve with rehabilitation or worsen due to progressive disease or radiotherapy despite initially good results.

Of all patients with MM, 47% had sMM (malignant transformation of a previous grade 1 or 2 meningioma). The median time from first meningioma diagnosis to first MM surgery ("time to transformation") was 65.7 months and similar to 70 months in a recently published cohort [12]. We found no differences in OS or the cumulative incidence of recurrence between sMM and pMM patients. It has been suggested that pMM and sMM may differ in prognoses, but previous studies are inconclusive[6,7,11,14–18].

We did not interpret the low proportion of surgeries that led to an improved condition to necessarily reflect complications but rather to reflect a disease that was dangerous to manage surgically, especially when surgeries were mandated for deep, invasive or recurrent tumors. Six patients (11.8%) died within 30 days of MM surgery which was unexpected, since 30-day mortality following surgery of benign or MM seldomly exceeds 1.5%[24,29]. In one patient undergoing palliative surgery, death could have been imminent regardless surgery and ensuing complications, but mortality in the remaining five (9.8%) was a direct cause of the MM surgery. Interestingly, all but one of the intraventricular meningiomas belonged to this group. Surgical mortality may reflect patient factors since meta-analyses of data from elderly meningioma patients, with expected higher risk, reported a mean overall incidence of complications of 20% per patient (range 3-61%) and a 30-day mortality rate up to 12% which is more in line with our findings[19].

Despite numerous surgeries, 19 patients (37.3%) did not have surgical complications in any of their intracranial surgeries and only eight (15.7%) had life-threatening adverse events requiring treatment in ICU. A database study on admission records in intracranial meningioma surgery showed an adverse discharge disposition of 35% between 2001 and 2010 in the US which again underlines that morbidity could be unexpectedly high also in mostly benign meningioma surgery[20]. After the first MM surgery in our cohort, 16 patients (31.4%) experienced surgical complications which is again similar to a recent MM cohort reporting of Sá-Marta et al. (2021)[12] where the perioperative complications for the first MM surgery were 42,3% and Sughrue et al. (2010)[13] with an overall neurosurgical complication rate of 21% including CSF leaks, wound complications and hydrocephalus. Assessment of complications for the individual surgeries in our cohort showed that 50,3 % of the 151 surgeries had a complication, primarily comprising a tumor site, epi- or subdural hemorrhage and CSF leaks.

Taken together, our data indicates an elevated risk of surgical complications in MM. Our reported 30-day mortality rate still warrants further measures to improve decision-making, patient selection and presurgical work-up.

Mortality, morbidity, and non-curative decisions

Our data suggested a very high likelihood of death from the meningioma once a diagnosis of MM has been established. The median overall survival was 50 months (CI95% 31-86 months) which is in agreement with previous MM cohorts[11,12,14–16,21–23]. In contrast to several previous studies, our data were from a consecutive population-based cohort, which is associated with high external validity. Importantly, death in our cohort was a direct or indirect cause of the MM in all patients who died which is different from benign meningiomas. We have

previously followed parasagittal meningiomas which have particularly high risks of recurrence and found a median survival of more than 25 years[24] with a meningioma-specific mortality of not more than 50%. Considering that MM had a median time to recurrence of as short as 15.1 months, that mRS rarely improved after surgery and the inevitable failure to cure a MM, we need to re-evaluate how to best manage these patients.

The high mortality and morbidity in the patients in our MM cohort suggest that some patients may have undergone overly aggressive therapies while earlier palliation might have improved quality of life and survival, as has been described in analyses of other groups of patient with malignant disease[25–27]. We extended our analyses beyond survival and recurrence to understand the decision making when transitioning to non-curative treatment. Thirty-one patients had a documented decision of a non-curative strategy made after their first MM. The median survival from TNC to death was 3.8 months (CI95% 2.3-9.0 months). After this decision, one would expect a focus-shift to palliative strategies. In concordance to the WHO definition of palliation[28], 3.8 months seems a relatively short time to shift perspective and "improve the quality of life of patients and that of their families who are facing challenges associated with life-threatening illness, whether physical, psychological, social or spiritual." By nature of medical documentation and focus on surgeries, we had no systematic documentation of spiritual and psychological needs. Our aggregated, detailed data suggest that management should not only focus on surgery to prolong life, but also to explicitly analyze expectations, realistic natural course with or without curative measures and closely investigate individual patients' need of psychological, spiritual, and medical support.

Timing and management of palliation in meningioma have not been studied although patients with intractable meningiomas[3] comprise a well-known entity. We suggest that patients with MM will benefit from palliative care (PC)[3]. Randomized controlled trials (RCT) of early palliative care have shown positive effects in various advanced cancers[25,29–31] and an RCT investigating early PC in patients with glioblastoma is ongoing[32]. However, one must be aware of possible discordant prognostic awareness[33] and in the case of MM, the prognosis can be heterogenous and presenting the worst case scenario for the patient might not be beneficial. Histology is insufficient to identify benign meningiomas at risk of malignant transformation. New molecular markers, such as TERT promoter mutations and CDKN2A/B homozygous deletions[34] will hopefully aid clinicians to plan treatment, convey the possibility of a non-curative treatment phase and give timely information to this subgroup of patients where tumor aggressiveness is reflected in a detectable biomarker.

Our data also suggest that the comorbidities following a MM diagnosis can significantly mark the clinical course and we infer that these conditions would impact the quality of life and could hinder an effective rehabilitation and return to everyday life: Eight patients in our material had severe complex pain syndromes with a potential need for interdisciplinary pain management already early in the disease course. Moreover, the epilepsy burden: 57% of the patients had epilepsy and/or AED treatment, which was higher than in patients with benign meningiomas[35]. General antiepileptic medication is not indicated for brain-tumor patients[36] because the number needed to treat is too high to balance complications of medication. In contrast, medical treatment even prophylactically may be

indicated in patients with malignant meningioma both to prevent seizures and to decrease anxiety based on fear for seizures.

Limitations and strengths

Though data on individual timelines exist and could be beneficial in understanding multiple disease courses in this patient group, we are operating on the balance between showing detailed data and ensuring patient anonymity. Thus, individual timelines for every patient cannot be shown. Fifty-one patients with MM constitute a relatively large cohort considering the rarity of this disease, but the number might have been too low to convey sufficient statistical power when investigating clinical risk-factors in relation to recurrence and survival. Our study is retrospective and based on careful revision of patient files, and though thoroughness is key, files do not always convey the reality. Moreover, the diagnosis of epilepsy warrants a thorough clinical work-up, and we based the diagnosis on patients' files and medication lists with clear indications for treatment. We present data from a single institution and cooperative endeavors in investigating parameters described in this study could aid future decision making. The main strength of our study is that we have worked meticulously with data from every patient and every surgery in this population-based, consecutive cohort.

Conclusions:

Our results highlight that a patient with a malignant meningioma has a substantial risk of undergoing multiple surgeries and the elevated risk of surgical complications which must be factored into the decision making. This emphasizes the need to gather information on patients' experiences including quality of life and what is most important for shared decision-making. Taken together, our analysis has identified some therapeutic implications: 1) AED treatment should be considered in all patients with MM as 57% of patients in our material had epilepsy during their disease course 2) complex pain syndromes caused suffering in a subgroup of patients; they should be vigorously addressed and preferably treated in interdisciplinary teams 3) potential benefits of early palliative care must be considered in patients with a malignant meningioma while uncertainty and heterogeneity of the clinical courses must be factored in in the communication to the patient and relatives.

Disclosures:

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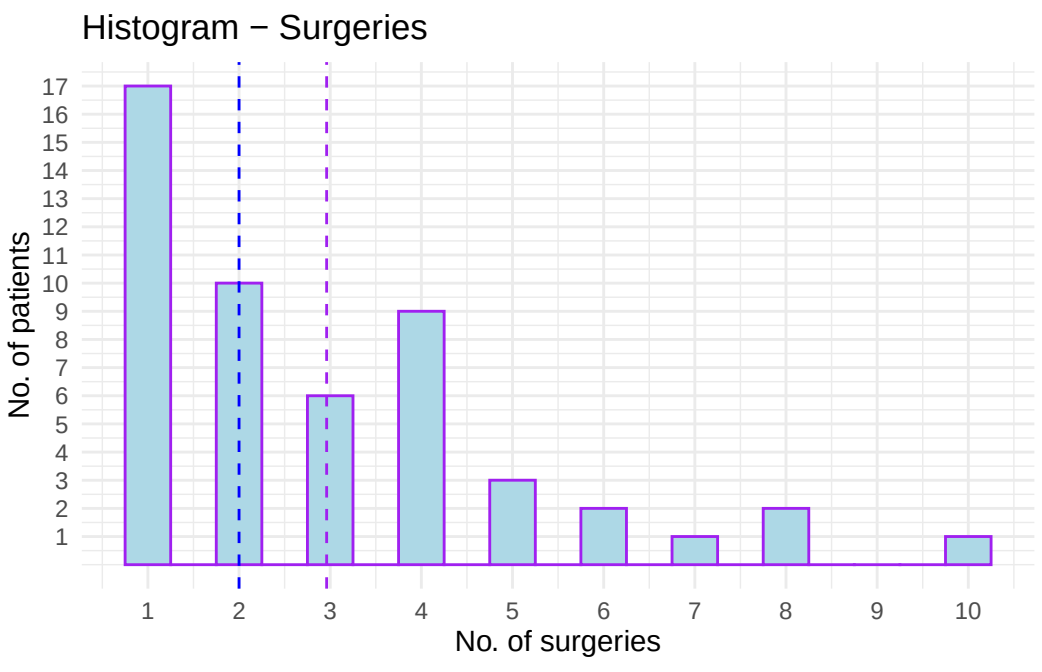
Figure Legends

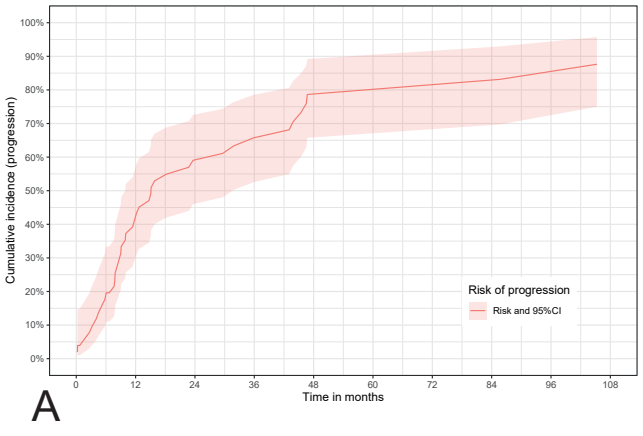
Figure 1. Histogram of surgeries per patient. The median and mean are marked with dotted lines (blue and purple respectively).

Figure 2. (a) Cumulative incidence of recurrence after MM diagnosis in 51 patients. **(b)** Cumulative incidence of recurrence in patients with pMM (n=27) and sMM (n=24). **(c)** Overall survival in patients with pMM and sMM.

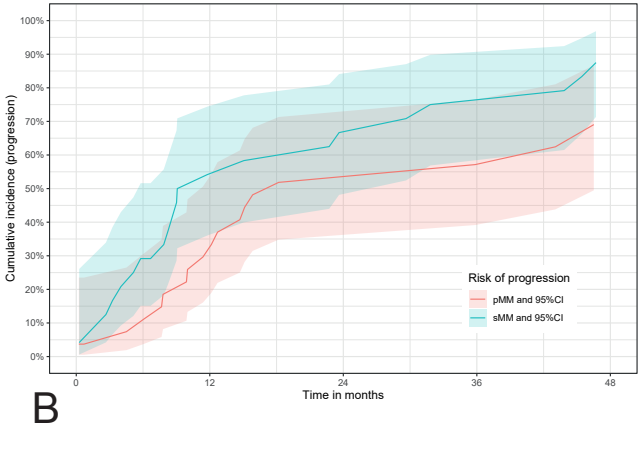
Figure 3. The x-axis depicts the chronological order of surgeries. "0" is the first surgery with a WHO grade 3 diagnosis. Patients are sorted and listed on the y-axis ordered by total number of surgeries. Shapes denote WHO grade. Color denotes improvement, worsening or status quo regarding the modified Rankin Score (mRS) pre and post-surgery.

Figure 4. Kaplan-Meier curve from the non-curative decision (decision to do no further surgery or referral to palliative care, TNC) until death.

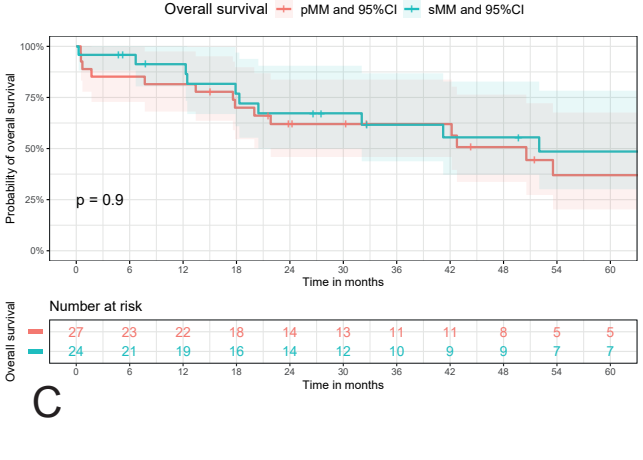

Histogram − Surgeries
No. of patients
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
1
2
3
4
5
6
7
8
9
10
No. of surgeries


Cumulative incidence (progression)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Risk of progression
Risk and 95%CI
0
12
24
36
48
60
72
84
96
108
Time in months

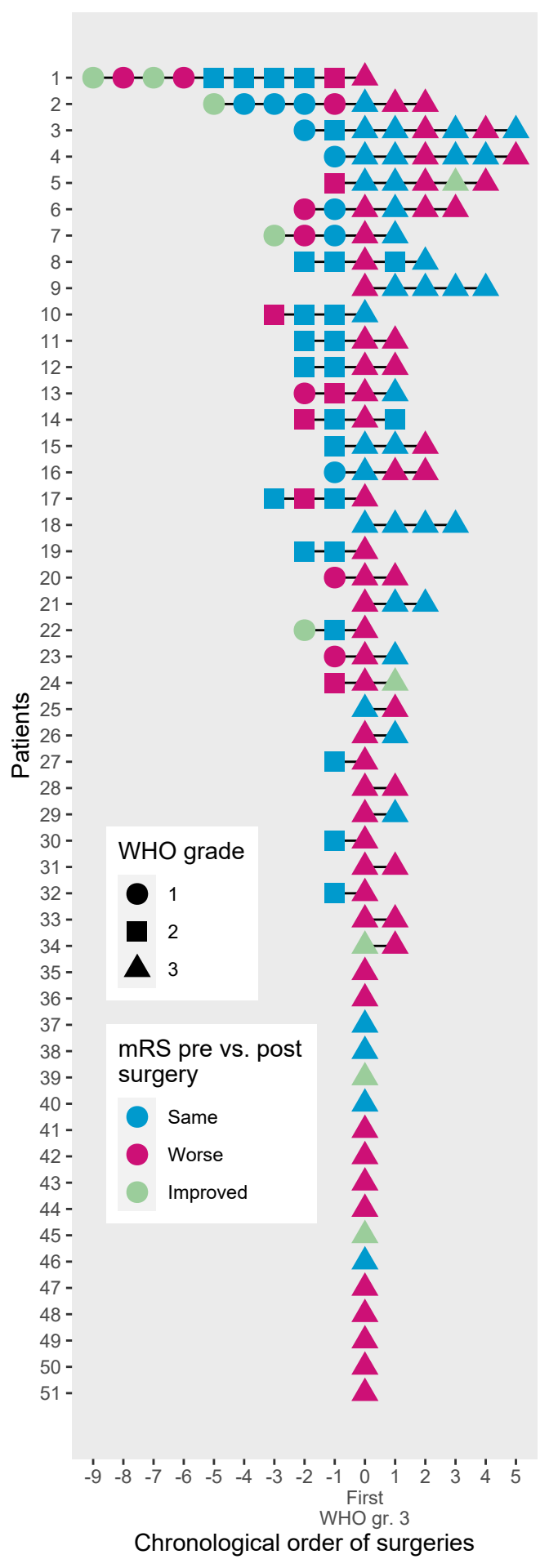
A


Cumulative incidence (progression)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Risk of progression
pMM and 95%CI
sMM and 95%CI
0
12
24
36
48
Time in months

B


Overall survival
pMM and 95%CI
sMM and 95%CI
Probability of overall survival
100%
75%
50%
25%
0%
p = 0.9
0
6
12
18
24
30
36
42
48
54
60
Time in months
Number at risk
Overall survival
27 23 22 18 14 13 11 11 8 5 5
24 21 19 16 14 12 10 9 9 7 7
0
6
12
18
24
30
36
42
48
54
60
Time in months

C


Patients
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
WHO grade
1
2
3
mRS pre vs. post surgery
Same
Worse
Improved
-9
-8
-7
-6
-5
-4
-3
-2
-1
0
1
2
3
4
5
First WHO gr. 3
Chronological order of surgeries

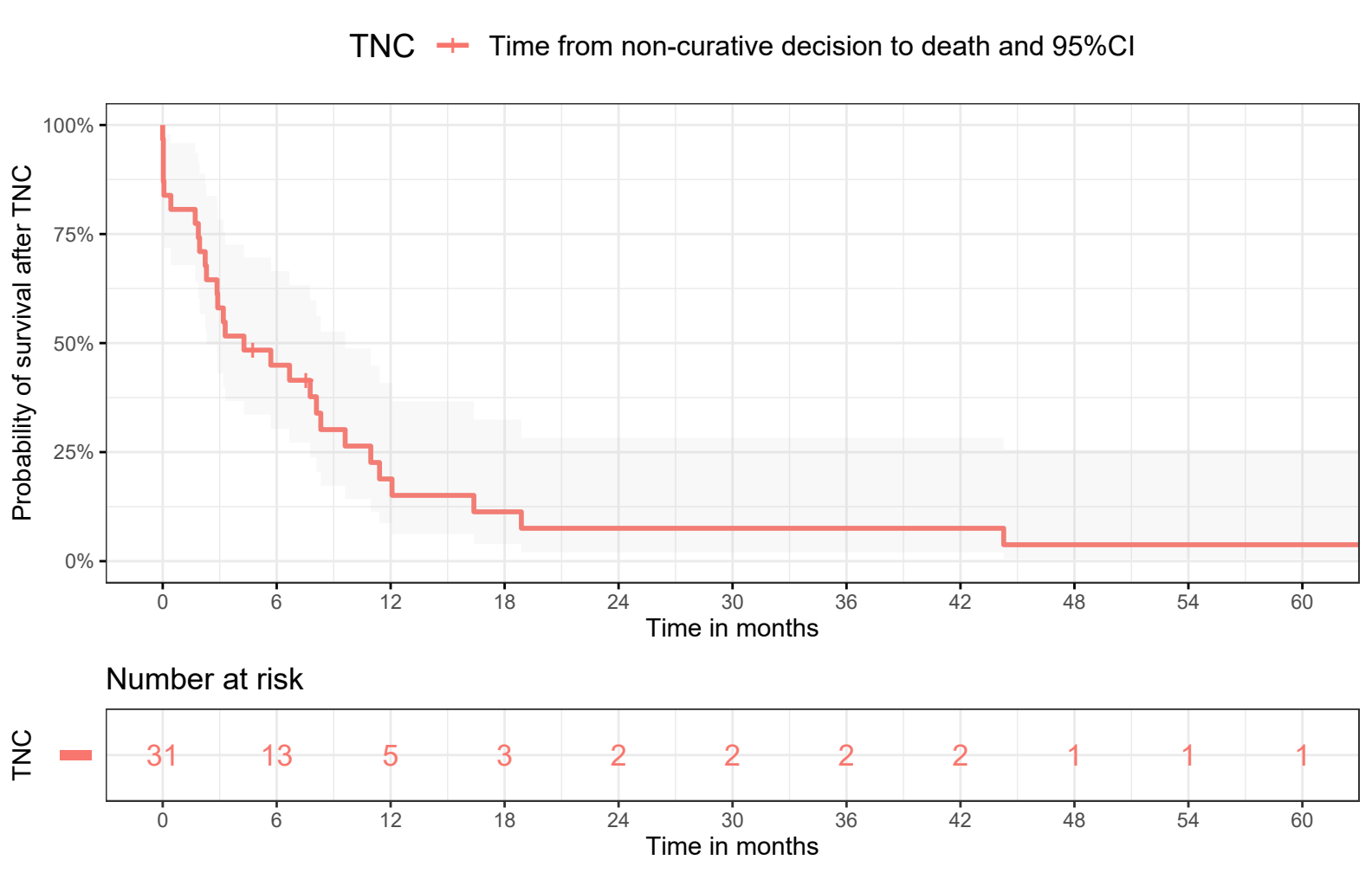

TNC
Time from non-curative decision to death and 95%CI
Probability of survival after TNC
100%
75%
50%
25%
0%
0
6
12
18
24
30
36
42
48
54
60
Time in months
Number at risk
TNC
31
13
5
3
2
2
2
2
1
1
1
0
6
12
18
24
30
36
42
48
54
60
Time in months

Table 1. Cohorts characteristics

	Total (n=51)	**Primary (n = 27)**	**Secondary (n = 24)**
Sex, male n (%)	25 (49)	12 (44)	13 (54)
Age, median (range)	61 (10-87)	67 (10-87)	59 (32-77)
Germline mutations, n (%)	2 (4)	1 (2)	1 (2)
Earlier CNS tumours, n (%)	2 (4)	1 (2)	1 (2)
Anaplastic, n (%)	42 (82)	19 (70)	23 (96)
Papillary, n (%)	4 (8)	3 (11)	1 (4)
Rhabdoid, n (%)	5 (10)	5 (18)	0 (0)
Total surgeries, n	151	43	108
Gr. 3 surgeries, n	98	43	55
No. of gr. I/II surgeries, n	53	0	53
Surgeries / patient, median (range)	2 (1-10)	1 (1-5)	4 (2-10)
Surgeries / patient, mean	3	1,6	4,5
Skullbase location, n (%)	9 (18)	2 (7)	7 (29)
Death within 30 days of surgery, n (%)	6 (12)	5 (19)	1 (4)
Maximum Ibañez surgical complication score per patient, n			
Ibañez Grade I	6	3	2
Ibañez Grade II	13	5	6
Ibañez Grade III	8	4	4
Ibañez Grade IV	5	4	1
Maximum Ibañez surgical complication score for first WHO grade 3 per patient, n			
Ibañez Grade I	4	1	3
Ibañez Grade II	5	0	5
Ibañez Grade III	4	0	4
Ibañez Grade IV	3	3	0
Received radiotherapy, n (%)	39 (77)	16 (59)	23 (96)
Distant metastasis*	2	1	1
Performance status and morbidity			
Karnofsky Perfomance Score Premorbid, median (range)	80 (50-100)	80 (50-100)	80 (60-100)
No assistance at home, n	48	24	24
Assistance at home, n	3	3	0
Weighted Charlson Comorbidity Index, n			
0	31	16	15
1-2	18	10	8
3-4	1	0	1

>=5	1	1	0

*Liver and spinal metastasis.

Table 2. Cohort characteristics on surgery level

	All tumors	pMM[1]	sMM[1]	sMM WHO gr. I/II
No. of tumors, n (%)	151 (100)	43 (100)	55 (100)	53 (100)
WHO grade 3	98 (64.9)	43 (100)	55 (100)	-
WHO grade 2	32 (21.2)	-	-	32 (60.4)
WHO grade 1	21 (13.9)	-	-	21 (39.6)
Histology, n (%)				
Anaplastic	75 (49.7)	26 (60.5)	49 (89.1)	-
Rhabdoid	15 (9.9)	14 (32.5)	1 (1.8)	-
Papillary	8 (5.3)	3 (7.0)	5 (9.1)	-
Atypical	32 (20.5)	-	-	31 (58.5)
Meningoepithelial	4 (2.6)	-	-	4 (7.5)
Fibrosum	1 (0.7)	-	-	1 (1.9)
Transitional	11 (7.3)	-	-	11 (20.8)
Angiomatosum	1 (0.7)	-	-	1 (1.9)
NA	4 (2.6)	0 (0)	0 (0)	4 (7.5)
Location, n (%)				
Convexity	72 (47.7)	17 (39.5)	28 (50.9)	27 (50.9)
Parasagittal	45 (29.8)	7 (16.3)	23 (41.8)	15 (28.3)
Parafalcine	35 (23.2)	9 (20.9)	13 (23.6)	13 (24.5)
Sphenoid	40 (26.5)	5 (11.6)	16 (29.1)	19 (35.8)
Anterior midline	28 (18.5)	6 (14.0)	7 (12.7)	15 (28.3)
Orbital[2]	31 (20.5)	5 (11.6)	10 (18.2)	16 (30.2)
Posterior fossa	26 (17.2)	12 (27.9)	10 (18.2)	4 (7.5)
Tentorial	13 (8.6)	7 (16.3)	4 (7.3)	2 (3.8)
Intraventricular	9 (6.0)	9 (20.9)	0 (0)	0 (0)
Multifocal tumor, including locations above	89 (58.9)	23 (53.5)	32 (58.2)	34 (64.2)
Simpson grade, n (%)				
I	20 (13.2)	9 (20.9)	4 (7.3)	7 (13.2)
II	44 (29.1)	15 (34.8)	16 (29.1)	13 (24.5)
III	20 (13.2)	6 (14.0)	8 (14.5)	6 (11.3)
IV	33 (21.9)	6 (14.0)	18 (32.7)	9 (17.0)
V	5 (3.3)	3 (7.0)	2 (3.6)	0 (0)
NA	29 (19.2)	4 (9.3)	7 (12.7)	18 (34.0)
Surgical complications, n (%)				
Tumor site bleed	15 (9.9)	8 (18.6)	4 (7.3)	3 (5.7)
Epi/subdural bleed	7 (4.6)	4 (9.3)	1 (1.8)	2 (3.8)
Superficial bleed	3 (2.0)	2 (4.7)	1 (1.8)	0 (0)

Wound infection	6 (4.0)	2 (4.7)	2 (3.6)	2 (3.8)
Meningitis	3 (2.0)	1 (2.3)	2 (3.6)	0 (0)
Intracranial abscess	3 (2.0)	0 (0)	2 (3.6)	1 (1.9)
Ostit	1 (0.7)	1 (2.3)	0 (0)	0 (0)
Death within 30 days (see Supplementary table 2)	6 (4.0)	5 (11.6)	1 (1.8)	-
CSF leak	7 (4.6)	2 (4.7)	3 (5.5)	2 (3.8)
Seizures	7 (4.6)	2 (4.7)	2 (3.6)	3 (5.7)
New neurological deficit extending +30 days	5 (3.3)	0 (0)	3 (5.5)	2 (3.8)
No postoperative complications	75 (49.7)	19 (44.2)	30 (54.5)	26 (49.1)
Other post op complications[3]	13 (8.6)	2 (4.7)	7 (12.7)	4 (7.5)

[1]sMM: patient with secondary malignant meningioma. pMM: patient with primary malignant meningioma.
[2] A patient with 10 surgeries had an orbital meningioma and thus accounted for a third of all the orbital surgeries.
[3]Pneumocephalus, brain swelling.

Supplementary Table 1. Cox proportional hazard regression of clinical factors' association to overall survival (OS)

		n	Hazard ratio for OS (95% CI)	p-value
Age	Years (cont.)	51	1.016 (0.99-1.05)	0.28
Sex	Male	25	1.00	
	Female	26	0.62 (0.29-1.31)	0.21
Primary/secondary	Primary	27	1.00	
	Secondary	24	1.033 (0.50-2.12)	0.93
Location	Non-skull base	42	1.00	
	Skull base	9	1.30 (0.44-3.82)	0.63
Histology	Non-anaplastic	9	1.00	
	Anaplastic	42	1.80 (0.66-4.93)	0.25
Simpson grade[1]	III-IV	20	1.00	
	I-II	29	0.62 (0.28-1.36)	0.23

All factors are age-adjusted (excl. age).

[1]Two WHO grade 3 surgeries (first surgery) had missing Simpson grade and were excluded from this analysis.

Supplementary Table 2. Mortality within 30-days of WHO grade 3 surgery

sMM / pMM[1]	Surgery no.	Postoperative complication	Intracranial location
pMM	1	Hematoma and infarction	Intraventricular
pMM	1	Arterial infarction, perforators to brainstem and basal ganglia.	Falcotentorial
pMM	1	Bone plate infection, sepsis	Convexity
pMM	2	Surgical trauma and intracranial abscess	Intraventricular
pMM	5	Venous infarction, postoperative prolonged seizures, pulmonary embolism	Intraventricular
sMM	10	Intracranial abscess	Orbital, extending to sphenoid

[1]sMM: patient with secondary malignant meningioma. pMM: patient with primary malignant meningioma.

Because of the apparent immortality bias, premalignant surgeries had no fatal outcome within 30 days. Three of six patients died within 30 days of their first surgery, one after the 2nd, one after the 5th surgery and one after the 10th surgery. Five patients died because of complications directly related to the surgery: venous or arterial infarction in three, sepsis following a bone plate infection in one and infarction and abscess formation in one patient. Finally, it was unclear whether the disease burden or technicalities of the surgery were the cause of death in one of the six patients; the last surgery (MM) was with palliative intent and the patient already had an intracranial infection (abscess in relation to the tumor). Of the six patients, three had an interventricular MM.

Supplementary Table 3. Overview of adjuvant regimes administered

	All patients	After grade 3 tumor	After grade 1/2 tumor
Fractionated radiosurgery (2 x 30 Gy or 1.8 x 33 Gy)	39	33	8
Stereotactical radiosurgery (18 Gy)	8	8	0
Other regimes (eg. 3 Gy x 10)	4	4	0
Proton radiation or ion carbon treatment	4	3	1
Chemotherapy (experimental protocols)	5	5	0
Lutetium-DOTATATE	1	1	0

A total of 39 patients (76.5%) received adjuvant radiotherapy. Of these 39, 21 received further adjuvant treatment including stereotactic radiosurgery, other fractionated radiotherapy regimes (e.g. 3 x 10 Gy), proton or ion treatment or chemotherapy (experimental protocols). Twelve patients did not receive radiotherapy: three died within 30 days of first MM surgery, three did not want additional treatment, and five had a performance status that, at the time of decision making, did not allow for radiotherapy, and one had severe claustrophobia. Therefore, any investigation of survival and progression between the radiated and non-radiated group would be biased as patients in the non-radiated group had a worse clinical status. Experimental chemotherapy was tried after all other treatment options were exhausted. Experimental chemotherapeutical and biological agents for MM included Irinotecan, Temozolomide, Doxorubicin, Etoposide and Bevacizumab.