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CLINICAL STUDY

Meningeal haemangiopericytoma and solitary fibrous tumour: a retrospective bi centre study for outcome and prognostic factor assessment

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Abstract To describe the outcome of patients diagnosed with central nervous system haemangiopericytoma (HPC) or solitary fibrous tumour (SFT) and identify factors that may influence recurrence and survival. Between January 2000 and September 2016, a retrospective search identified 55 HPCs/SFTs. The patients underwent a total of 101 surgical resections and 56.9% received radiation therapy. Median follow-up was 7.8 years. 28 patients (50.9%) were re-operated for tumour recurrence. At the end of the study, 21 patients (42%) had no residual tumour on the last scan. Surgical recurrence-free survival at 5 years was 75.2%, 95% CI [63.3–89.3] and, the median surgical recurrence-free survival was 7.4 years. In the adjusted analysis, venous sinus invasion (present vs. absent) (HR 3.39, 95% CI [1.16, 9.93], $p = 0.026$), completeness of resection (HR 0.38, 95% CI [0.15–0.97], $p = 0.042$) and tumour subtype (SFT vs. HPC) (HR 3.02, 95% CI [1.02, 8.91], $p = 0.045$) were established as independent prognostic factors. At the end of the study, 25 patients were deceased (45.5%). and only 15 patients (27.3%) had no residual tumour on the last scan and were alive. Overall survival at 5 years was 80.2, 95% CI [69.3–92.8] and the median overall survival was 13.1 years. None of the investigated variables was associated with overall survival. Patients who received radiation therapy demonstrated neither a reduced risk of surgical recurrence ($p = 0.370$) nor a longer overall survival ($p = 1.000$). SFTs/HPCs are associated with a significant risk of recurrence that may reduce the survival of the patients. Total tumour resection upon initial surgery is associated with a lower risk of relapse but not with a prolonged survival. We did not observe a significant improvement in any of the clinical outcomes after radiation therapy.

Keywords Haemangiopericytoma · Solitary fibrous tumour · Radiotherapy · Recurrence · Prognostic factors

Abbreviations

CI	Confidence interval
HPF	High power field
HR	Hazard ratio
IQR	Inter quartile range
WHO	World Health Organization
RT	Radiation therapy
STR	Sub total resection
TR	Total resection

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Introduction

The 2007 World Health Organization (WHO) classification of tumours of the central nervous system (CNS) distinguished meningeal haemangiopericytomas HPCs from solitary fibrous tumours (SFT) given their distinct clinicopathologic behaviour. Nonetheless, it has recently been demonstrated that both SFTs and HPCs, including those occurring in the neuraxis, share inversions at 12q13, fusing the NAB2 and STAT6 genes. This leads to a nuclear expression of STAT6 that can be detected by immunohistochemistry [1].

Therefore, in the 4th edition of the WHO classification of tumours of soft tissue and bone (2013), these neoplasms are no longer separate entities [2]. It has become clear that meningeal SFTs and HPCs are overlapping, if not identical. For this reason, the 2016 WHO classification of CNS tumours has merged both neoplasms under the same category of [3].

SFTs and HPCs show high risks of recurrence rates and are known metastasize systemically. Complete surgical excision is the treatment of choice of HPCs and SFTs. Further optimal management is difficult to establish. Which patients might benefit from radiotherapy and what the optimal time to deliver it following surgery remains unclear. The rarity of these tumours which incidence is thought to be less than six cases for 1,000,000 habitants per year, make it difficult to study their behaviour [4]. Following the recommendations of the last WHO classification of CNS tumours, we wanted to investigate the outcome of patients affected by meningeal HPC/SFT and search for clinical and pathological prognostic factors associated with recurrence and survival.

Clinical material

A retrospective neuropathology database search was carried out between January 2000 and September 2016 at the National Hospital for Neurology and Neurosurgery, London and, at the Queen Elizabeth University Hospital, Glasgow. All patients with a diagnosis of intracranial or spinal intradural HPC or SFT were included in this study. We considered SFT and HPC as a unique neoplasm and conducted the analysis ad hoc. There was no specific inclusion criterion and no patient was excluded from the study. Histology slides were reviewed in 59.5%. All pathology reports were carefully examined. Tumour type, mitosis count per 10 high power fields (HPFs) (mitotic index), Ki-67 index (MIB-1), presence of necrosis, hypercellularity and, brain invasion were separately extracted. In cases of recurrence, histology reports were compared to those from previous resections. The tumour grade was evaluated according to the WHO 2000, 2007 or 2016 in use at the time of surgery and also according to the "Marseille grading system", a shared histopronostic system recently proposed, based on hypercellularity, mitotic count and necrosis [5].

Patient demographic and medical data were collected retrospectively. We used radiographic and surgical reports, and all available in- and out-patient records. Patients' pre and post-operative images were studied. Tumour location was divided into ten categories. However, some locations *e.g.* petroclival had only a few cases making them unsuitable for statistical analysis. These cases were placed in a new category named "others locations".

Age at diagnosis was defined according to the date of first surgery. Surgical resection was evaluated using the operative records. We defined two categories: complete or total resection (TR) and incomplete resection or subtotal resection (STR).

If radiation therapy (RT) was given, data on the technique, overall dose and time of completion were collected. For deaths, the cause was searched and recorded separately according to whether or not the death was related to surgery, tumour progression or other causes.

Patient outcome and clinical status were assessed through medical records, the patient database and information obtained from the general practitioners. A patient being unreachable for 2 years was considered as lost to follow-up and right-censored in the survival analysis.

Statistical analysis

Survival statistics were based on time to relapse, which was measured from the age at diagnosis to the date of last follow-up, the date of surgery for recurrence or on the date of death only if related to the surgery or the tumour progression (cause-specific or corrected survival; individuals who died of other causes were censored) [6, 7]. Survival function was assessed by the Kaplan–Meier method and the Mantel Cox log-rank test was used to compare different survival functions according to clinical and therapeutic factors. A univariate Cox regression analysis was subsequently run on clinical and pathological criteria. Independent prognostic factors with a p value < 0.20 were assessed with a multivariate stepwise Cox model. Tumour subtype was forced in the adjusted regression.

Because death was the most untoward event, mortality was the primary outcome of interest and surgical recurrence the secondary. We used the Wald test, analysis of deviance, Akaike and Bayesian information criteria in the search of the best-fit model. A *p* value < 0.05 was considered as statistically significant. For the analysis, we considered equally any form of radiation therapy (RT). Analysis was performed with the R programming language and software environment for statistical computing and graphics (R version 3.4.0 (2017-04-21)) and the survival package among others [8, 9]. The statistical program and workflow was written in R Markdown v2 with RStudio® for dynamic and reproducible research [10].

Results

Population description

Of the 55 cases collected, 30 were SFTs (54.5%). 32 patients were male (58.2%) and median age at diagnosis

was 51.3 years, IQR [41.3–58.9]. There were no paediatric cases. The most common tumour location was parafalcine in 36% (Table 1).

A total of 101 surgical resections were performed. Median follow-up since the diagnosis was 7.8 years, IQR [2.6–11.6]. Five patients were lost to follow-up.

Radiation therapy

28 patients (54.9%) received radiotherapy. Four patients (7.8%) received stereotactic radiotherapy or radiosurgery (Gamma knife®) (median dose = 18 Gy), of which three already had had conventional radiotherapy.

For the analysis, we considered equally any form of radiation therapy (RT): external beam and stereotactic radiotherapy together with radiosurgery (n = 29). The median delay between the surgery and the end of the radiotherapy was 0.9 years, IQR [0.3–3.4]. Eleven patients (44%) had early adjuvant radiotherapy within the first six post-operative months and 12 patients (40%) received radiotherapy after the first post-operative year.

Table 1 Patients' characteristics

Characteristics	n (%)
Gender male	32 (58.2%)
Median age at surgery	51.3 years, IQR [41.3–58.9]
Location	
Convexity	5 (10%)
Para sagittal/falx	18 (36%)
Skull base	12 (21.8%)
Spine	14 (6%)
Intra-ventricular	1 (2%)
Right side of the meningioma	19 (35.8%)
Pre-operative embolisation	14 (25.9%)
Resection status	
Total resection	32 (61.5%)
Subtotal resection	20 (38.5%)
Venous sinus invasion	18 (38.3%)
Histological sub-types	
Solitary fibrous tumour	30 (54.5%)
Haemangiopericytoma	25 (45.5%)
WHO grading	
Grade I	18 (32.7%)
Grade II	29 (32.73%)
Grade III	8 (32.73%)
Median mitoses count	2 per 10 HPFs, IQR [1–4.75]
Median Ki-67 (MIB-1)	5%, IQR [3–10]
Radiotherapy	28 (50.9%)
Stereotactic radiotherapy	4 (7.3%)
Chemotherapy	5 (10.2%)

71.4% of the patients (n = 20) who were re-operated for recurrence received also radiotherapy. Nine patients (17.6%) had radiotherapy following radiological recurrence but were not re-operated. 46.9% of the patients (n = 15) who had a TR also underwent radiotherapy, compared to 65% (n = 13) in the incomplete resection group. However, there is no statistical interaction between radiotherapy and completeness of resection (Wald test p value = 0.199). Therefore, RT is an independent predictor of the surgical recurrence-free risk.

Surgical recurrence-free outcome

28 patients (50.9%) were re-operated, at least once, for tumour relapse. The median time between the 1st and the 2nd surgery was 5.7 years, IQR [2.4–9]. At the end of the study, only 21 patients (42%) had no residual tumour on the last scan. The median surgical recurrence-free survival was 7.4 years. Surgical recurrence free survival at 1, 2, 5 and 10 years were respectively: 90%, 95 % CI [82–98.7]; 87.8%, 95 % CI [79.1–97.5], 75.2%, 95 % CI [63.3–89.3] and, 38.6%, 95 % CI [25.2–59.2] (Fig. 1a).

The univariate Cox regression analysis identified that venous sinus invasion (HR 2.36, 95 % CI [1–5.59], p = 0.05), completeness of resection (HR 0.25, 95 % CI [0.11–0.6], p = 0.002) and histological brain invasion (HR 0.14, 95 % CI [0.03–0.63], p = 0.01) were associated with the surgical recurrence risk (Table 2).

Univariate analysis suggested an association between the subtype of tumour (SFT vs. HPC), the KI-67 index and the surgical recurrence-free survival. This did not reach statistical significance but did satisfy the criteria for inclusion in the subsequent multivariate analysis.

In the adjusted analysis, venous sinus invasion (present vs. absent) (HR 3.39, 95 % CI [1.16–9.93], p = 0.026), completeness of resection (HR 0.38, 95 % CI [0.15–0.97], p = 0.042) and tumour subtype (SFT vs. HPC) (HR 3.02, 95 % CI [1.02–8.91], p = 0.045) were established as independent prognostic factors (Table 3).

The patients who received radiotherapy did not demonstrate a longer surgical recurrence-free survival (log-rank test p value = 0.366) (Table 2; Fig. 1e).

Overall survival outcome

Twenty-five patients were deceased (45.5%). However, only 21 died following the tumoral progression (38.2%).

At the end of the study, only 15 patients (27.3%) had no residual tumour on the last scan and were alive. Overall survival probability at 1, 2, 5 and 10 years were respectively: 94.3%, 95 % CI [88.2–100], 94.3%, 95 % CI [88.2–100], 80.2%, 95 % CI [69.3–92.8] and 65.7%, 95 % CI [52.2–82.6] (Fig. 2a).
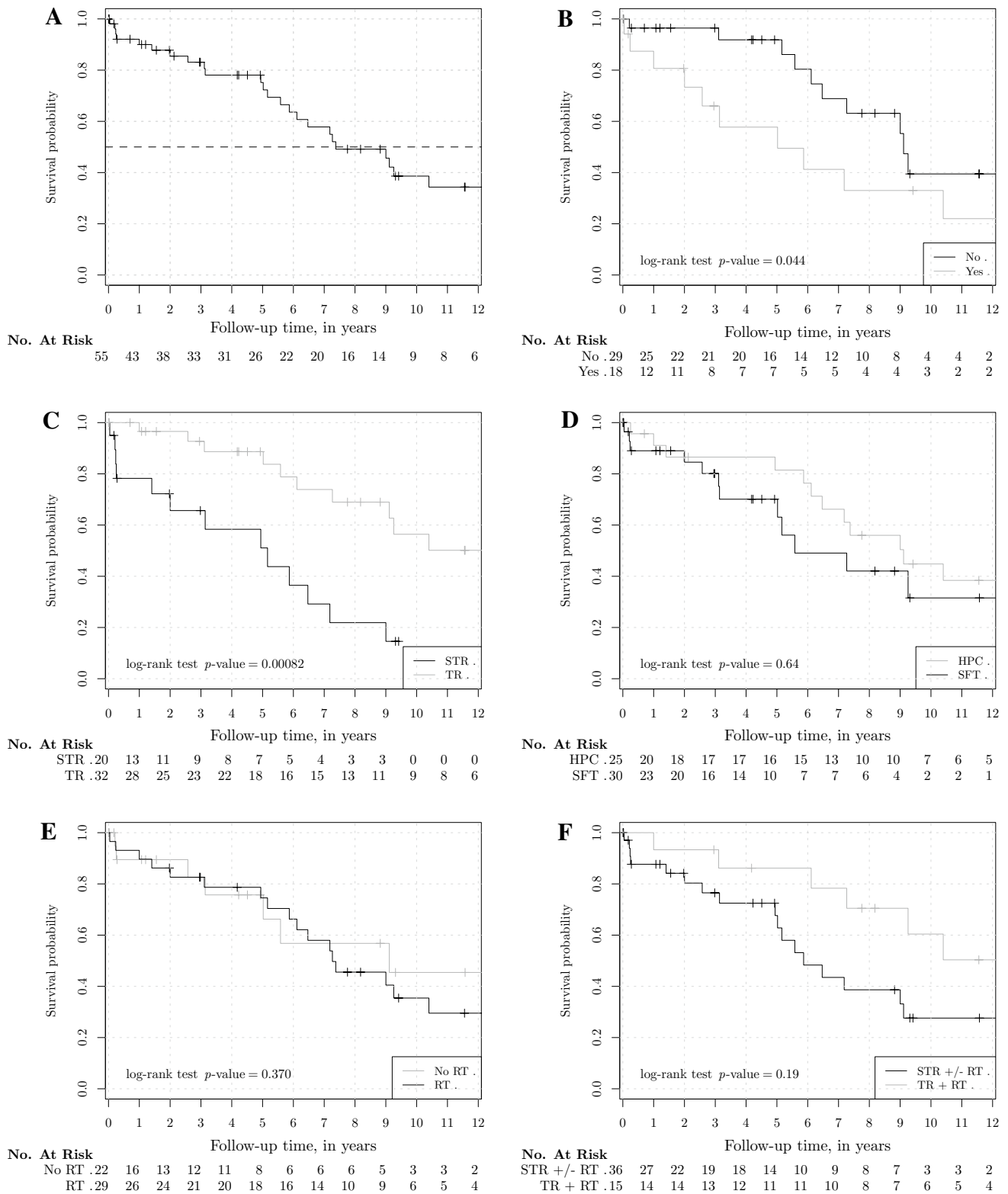
Fig. 1 Kaplan–Meier survival curves of the surgical recurrence-free survival. **a** Overall recurrence-free survival. **b** Surgical recurrence-free survival by venous sinus invasion. **c** Surgical recurrence-free survival by completeness of resection. **d** Surgical recurrence-free survival by tumour sub-type. **e** Surgical recurrence-free survival by radiotherapy. **f** Surgical recurrence-free survival by completeness of resection and RT

Table 2 Univariate Cox regression for haemangiopericytoma and solitary fibrous tumour surgical recurrence-free and overall survival

Variable	Recurrence			Overall survival		
	HR[a]	[95% CI][b]	p Value	HR[a]	[95% CI][b]	p Value
Gender male	0.85	0.4, 1.84	0.69	1.03	0.46, 2.33	0.94
Age at diagnosis ≤51.3 years	1.24	0.58, 2.68	0.58	0.71	0.3, 1.67	0.43
Convexity versus others location	1.44	0.41, 5.07	0.57	2.03	0.54, 7.6	0.29
Convexity and parafalcine versus all others location	0.99	0.39, 2.52	0.98	0.86	0.29, 2.56	0.79
Side (right vs. left)	1.55	0.66, 3.66	0.32	1.92	0.81, 4.54	0.14
Venous sinus invasion (present vs. absent)	2.36	1, 5.59	**0.05**	1.54	0.63, 3.73	0.34
Total vs. subtotal resection	0.25	0.11, 0.6	**<0.001**	0.88	0.36, 2.14	0.78
Solitary fibrous tumour vs. haemangiopericytoma	1.2	0.55, 2.61	0.64	1.56	0.68, 3.56	0.29
Histological grading at first surgery (I vs. II & III)	0.92	0.4, 2.1	0.83	0.67	0.26, 1.7	0.39
Histological marseille grading at first surgery (I & IIa vs. IIb & III)	0.45	0.03, 7.19	0.57	0.33	0.05, 2.46	0.28
Mitoses count ≤ 2 (median)	1.43	0.54, 3.84	0.47	0.75	0.29, 1.96	0.55
Mitoses count > 5	0.53	0.12, 2.32	0.4	1.3	0.36, 4.65	0.69
Ki-67 > 5 (median)	0.38	0.11, 1.29	0.12	0.89	0.24, 3.31	0.86
No histological brain invasion	0.14	0.03, 0.63	**0.01**	0.37	0.08, 1.77	0.21
Hypercellularity	0.5	0.08, 3.11	0.45	1.07	0.2, 5.72	0.94
Radiotherapy or radiosurgery	1.49	0.63, 3.53	0.37	1	0.38, 2.63	1
Radiotherapy or radiosurgery within the post-operative year	0.73	0.26, 2.06	0.55	0.82	0.26, 2.53	0.73
Total resection + radiotherapy or radiosurgery versus subtotal resection	0.58	0.25, 1.33	0.2	1.05	0.44, 2.51	0.92
Neurosurgical centre	0.79	0.35, 1.77	0.57	0.96	0.39, 2.34	0.93
Redo surgery for recurrence	NA[c]	NA	NA	0.73	0.28, 1.9	0.51

The bold in p value underlines the statistically significance of the probability

[a]Hazard ratio

[b]95% Confidence interval

[c]Not applicable

Table 3 Multivariate Cox regression for haemangiopericytoma and solitary fibrous tumour surgical recurrence-free survival

Variable	HR[a]	[95% CI][b]	p Value
Venous sinus invasion (present vs. absent)	3.39	1.16, 9.93	**0.03**
Total versus subtotal resection	0.38	0.15, 0.97	**0.04**
Solitary fibrous tumour versus haemangiopericytoma	3.02	1.02, 8.91	**0.05**

The bold in p value underlines the statistically significance of the probability

[a]Hazard ratio

[b]95% Confidence interval

It suggested an association between the side of the tumour, the subtype of tumour (SFT vs. HPC) and the overall survival that did not reach statistical significance but did warrant inclusion in the subsequent multivariate analysis. In the adjusted analysis, no factor was independently associated with the overall survival (Table 4). The patients who received radiotherapy did not demonstrate a longer overall survival (log-rank test p value = 0.995) (Table 2; Fig. 2d).

Discussion

Despite its methodological limitations, including its retrospective nature and the number of lost to follow-up patients; this study is one of the largest series in the literature on outcome and prognostic factors affecting the recurrence and survival of SFTs and HPCs. A full central neuropathology review was not possible due to limited study resources. Nonetheless, histology slides were reviewed by
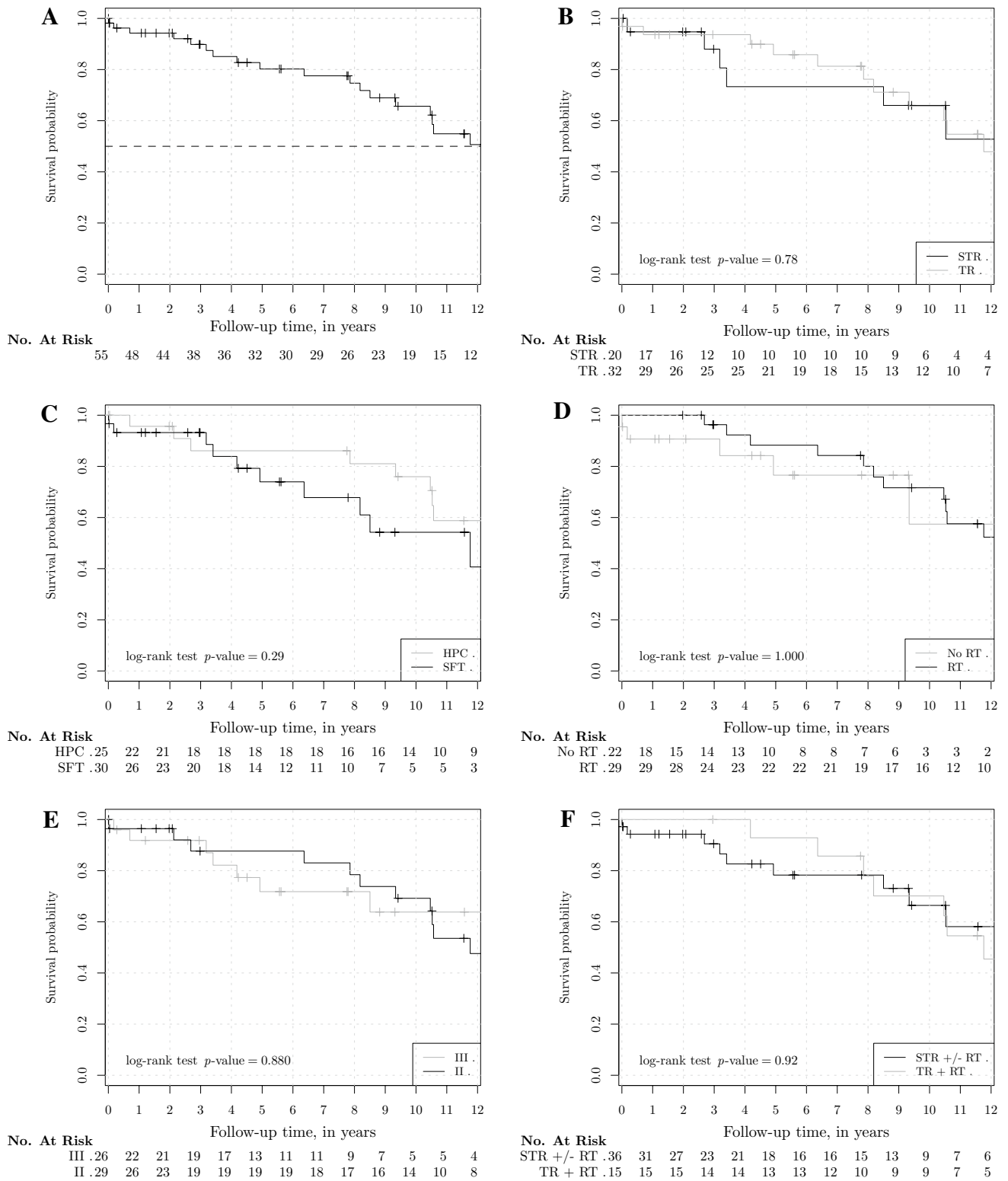
Fig. 2 Kaplan–Meier survival curves of the overall survival. **a** Overall survival. **b** Overall survival by completeness of resection. **c** Overall survival by tumour sub-type. **d**. Overall survival by radiotherapy **e**. Overall survival by WHO grade **f**. Overall survival by completeness of resection and RT

Table 4 Multivariate Cox regression for haemangiopericytoma and solitary fibrous tumour overall survival

Variable	HR[a]	[95% CI][b]	p Value
Total versus subtotal resection	0.85	0.35, 2.08	0.73
Solitary fibrous tumour versus haemangiopericytoma	1.82	0.76, 4.37	0.18

The bold in p value underlines the statistically significance of the probability

[a]Hazard Ratio

[b]95% Confidence interval

a second pathologist in 59.5% to confirm the diagnosis. In the literature, only a handful of reports have presented a joint analysis of these tumours and, mostly from a histologic point of view. Very few studies has been reported on the outcome of combined HPCs and SFTs, with discordant results [5, 11].

Pathology

HPC were initially classified as a sarcoma in the 1993 WHO classification of tumours of the CNS. The separation of meningeal HPCs from SFTs has been justified inter alia by higher propensity of HPCs for recurrence and metastasing, classified at least grade II, whilst no grade was allotted to SFTs, generally thought to be benign [12].

Numerous studies have confirmed the similarities between meningeal HPCs and its soft-tissue counterpart, as well as the distinction of HPC from the various forms of meningioma [13]. In 1997 Perry et al. noticed overlapping histological and immunohistochemical features between SFTs and HPCs, only distinguishable on the basis of the strong, diffuse CD34 positivity in SFTs. Bouvier et al. made similar observation and suggested a new classification merging both tumours which may be a better predictor of the outcome [5]. Soon after, a NAB2—STAT6 gene fusion was identified in SFTs and in HPCs, leading to the unification of these two entities in the last WHO 2016 classification of CNS under a combined term of solitary fibrous tumour/hemangiopericytoma [1, 3, 14].

One may think that combining two different microscopic-looking tumours only because they share a common genetic mutation is quite simplistic.

On the other hand, many suggest that artificial separation between SFT and HPC is merely a histopathological reflection. To date, this long-standing debate has been cut off, at least from the biological point of view. Nevertheless, from the outcome one, many questions remained. Does the prognosis depends upon both HPC versus SFT and/or upon pathological grading (I vs. II vs. III) solely?

Omitting for the limitations of our study using different grading systems at different times, there is no statistically significant difference in outcome with regard to either of these questions except with multivariate analysis for recurrence-free survival by tumour subtype. This finding may be the result of the effect of unbalanced sample size, influence of missing data and most likely the presence of complex statistical interactions. However, regarding the relative limited number of cases, this could not be worked out. Even more, we found that the surgical recurrence-risk is greater for SFT, on contrary to what is generally admitted, a finding not sufficiently robust to challenge the merging choice.

By reviewing all the pathological reports, it clearly appeared that denomination of the tumour was somewhat arbitrary and non-consensual between pathologists often leading to a conclusion like "solitary fibrous tumour of the haemangiopericytoma type". Designation of one or the other diagnosis is variable over the period of the study.

Our results does neither support nor challenge the merging or both tumour entities. In a sense, it will simplify the research on these rare tumours by slightly increasing the number of cases. However, it may introduce complex interactions between tumour subtype and WHO and Marseille grading systems which disagree on how to categorise the tumour and therefore on the prognosis.

Surgery

Since the seminal publication of Simpson in 1957, there is a general agreement about the importance of resection completeness of meningeal tumours [15]. Even if meningioma and HPCs/SFTs are different types of meningeal tumour, one may legitimately think that they should follow about the same rule. Nevertheless, it seems obvious that sub-totally removed HPCs/SFTs may recur or continue to grow. Surgical resection of SFTs/HPCs is not usually more difficult compared to meningioma. However, some tumours are highly vascularized what may increase the per-operative bleeding and make the surgical procedure more difficult. A total resection can still be achieved when the tumour is located on the convexity. This becomes more difficult with parasagittal lesions infiltrating a venous sinus wall. Tumours invading the cerebral venous sinuses recurred significantly earlier. This finding was previously reported by Melone et al. [16].

The extent of resection is the most powerful prognostic factor for recurrence of HPCs/SFTs [17–20]. Most cohort studies have confirmed the effect of the extent of resection on recurrence rate and overall survival [5, 16, 21–23]. Invasive skull base HPCs/SFTs (e.g. petroclival) or those infiltrating deeply into a venous sinus (tentorium cerebelli), cannot usually be removed entirely without high risks of post-operative complication. Therefore, most neurosurgeons prefer a safer but still useful brain decompression, achieving a maximal safe resection, leaving the patient in a

reasonable functional state and the tumour remnant for RT. Being re-operated on for a HPC/SFT recurrence did not increase the survival (HR 0.73, *p* value = 0.51) in our study.

Radiation therapy

RT after surgical resection of HPCs and SFTs continues to be controversial. 52.7% of our patients received RT. This percentage is within reported ranges of 24–100% [24]. For HPCs, most neurosurgeons and neuro-oncologists would advocate adjuvant RT especially if the tumour was not entirely excised. Results regarding the usefulness of RT have mainly been evaluated in HPCs and they are mixed.

For some authors RT reduces the recurrence rate [16, 20, 22, 25]. For others it increases the survival [23, 25, 26]. Stereotactic radiotherapy or radiosurgery might be an interesting option as multiple recurrences usually occur over time with the need of re-irradiation [27].

In our study, RT did not influence recurrence (HR 1.49, *p* 0.37), or survival (HR 1, *p* = 1).

About half of the patients received systematic adjuvant RT within the first post-operative year and the other half RT when the relapse occurs. Cox regression according these two categories was either associated with the recurrence (HR 0.73, *p* 0.55), nor the survival (HR 0.82, *p* = 0.73). There is a trend in the reduction of the surgical recurrence-free risk for the patients who underwent total resection and adjuvant radiation therapy (Fig. 1f). Even if we could not observe its benefit, we believe that adjuvant RT may be useful for tumours displaying grade II or III even in case of complete removal. Once the tumour has relapsed, the prognosis is usually unfavourable.

Outcome

In the dozen publications on SFTs and HPCs mainly, involving ten cases or more, there are important variety in reported outcomes that raise multiple questions about optimal tumour management. In the CNS, the clinical behaviour of HPC is particularly aggressive, with recurrence rates of 61–76% and metastasis rates of 23–64%. Reported 5-year overall survival probabilities vary between 67 and 96% with median overall survival between 7 and 16.2 years [16, 19, 21, 22]. Concerning SFTs, median recurrence times range from 6 to months and median recurrence rates from 12.5 to 50% [23]. In the absence of available prospective or randomized data, retrospective studies are used to guide therapeutic recommendations. This population has been heterogeneously treated. This fact represents the "real-world clinical scenario", the clinical situation we face in our everyday practice. The lack of clarity regarding treatment rationales make difficult to determine the real survival benefit of any particular therapy. The recent creation of a new entity combining the terms of solitary fibrous tumour/haemangiopericytoma may promote further studies.

Inclusion of more patients and reduction of missing data will be needed to increase the statistical power sufficiently to reveal and confirm such predictive factors.

Conclusion

SFTs/HPCs are associated with a significant risk of recurrence that may reduce the survival. Total tumour resection upon initial surgery is associated with a lower risk of relapse but not with a prolonged survival. We did not observe a significant improvement in any of the clinical outcomes after radiotherapy.

Compliance with ethical standards

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