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WHO Grade II Meningioma: epidemiology, survival and interest of post-operative radiotherapy in a multicenter cohort of 88 patients

Méningiomes de grade II : épidémiologie, survie et intérêt de la radiothérapie post-opératoire sur une cohorte multicentrique de 88 patients

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Disclosure of interest

The authors declare that they have no competing interest

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Abstract

Background. Meningioma is the most common primary intracranial tumor, representing 13-36.6% of all primary central nervous system tumors. Meningiomas are benign in about 90% of cases. World Health Organization (WHO) grade II meningioma is associated with a high rate of recurrence and poorer survival than in grade I. The reference treatment is surgery, which should be as complete as possible. Currently, in grade II, there are no recommendations for systematic adjuvant treatment such as radiotherapy. We studied a homogeneous series of grade II meningiomas treated by surgery in two university hospital centers to analyze use of radiotherapy and its efficacy.

Methods. We retrospectively analyzed patients in our database with WHO grade II meningioma, operated on between 2007 and 2010 in the university hospitals of Montpellier and Bordeaux, France. Clinical and radiological data, treatments and survival were analyzed.

Results. Eighty-eight patients were included. Five-year overall survival was 89.7%. Nineteen patients received radiotherapy during follow-up, without significant impact on survival ($p=0.27$).

Conclusion. In WHO grade II meningioma, it is currently difficult to establish clear recommendations for radiotherapy. The present study is in accordance with the literature that early postoperative radiotherapy is not mandatory in grade II meningioma with macroscopically total resection.

Meningioma, radiotherapy, neuro-oncology, WHO classification

Résumé

Introduction. Les méningiomes sont les tumeurs primitives intracrâniennes les plus fréquentes représentant entre 13 et 36.6% de l'ensemble des tumeurs primitives du système nerveux central. Les méningiomes sont bénins dans environ 90% des cas. Les méningiomes de grade II de la classification OMS sont associés à un haut risque de récurrence et à une survie plus faible que les méningiomes de grade I. Le traitement de référence est la chirurgie, aussi complète que possible. Actuellement, pour les méningiomes de grade II, il n'y a pas de recommandation pour un traitement adjuvant systématique comme la radiothérapie. Nous avons étudié une série homogène de méningiomes de grade II traités par chirurgie dans deux hôpitaux universitaires pour analyser l'utilisation de la radiothérapie et en évaluer son efficacité.

Méthodes. Nous avons analysé rétrospectivement les patients de notre base de données, opérés entre 2007 et 2010 d'un méningiome de grade II dans les hôpitaux universitaires de Montpellier et Bordeaux. Les données cliniques, les caractéristiques radiologiques, les traitements reçus ainsi que la survie ont été analysés.

Résultats. Quatre-vingt-huit patients ont été inclus. La survie globale à 5 ans pour les méningiomes de grade II était de 89.7%. Dix-neuf patients ont reçus un traitement par radiothérapie au cours du suivi. L'analyse de survie n'a pas montré de différence significative entre les patients irradiés et non-irradiés ($p=0.27$)

Conclusion. A propos des méningiomes de grade II, il est actuellement difficile d'établir des recommandations claires concernant la radiothérapie. Notre étude est en accord avec la littérature en ce qui concerne l'absence de nécessité d'une radiothérapie post-opératoire précoce dans les cas d'exérèse macroscopiquement complète de méningiomes de grade II.

Méningiome, radiothérapie, neurooncologie, classification OMS

Introduction

Meningioma is the most common primary intracranial tumor, representing 13-36.6% of all primary central nervous system tumors. Meningiomas are benign in about 90% of cases (1–5). World Health Organization (WHO) grade II meningioma is associated with a high rate of recurrence and poorer survival than in grade I (6,7). In comparison to the WHO classification of 2000 (8), the rate of grade II increased in the 2007 classification (9) from 5% to 20-35%, conversely to the rate of grade I, since meningioma with cortical invasion came to be considered as grade II (9). The rate of WHO grade III remained stable at 1-2% (10–12). The more recent 2016 WHO classification of central nervous system tumors (11) showed no significant difference in comparison to the 2007 classification (9).

An American study reported epidemiology of WHO grade II and III meningiomas between 2004 and 2010 using the CBTRUS (Central Brain Tumor Registry of United States) (13). Incidence of grade II was approximately 0.30 per 100,000 person-years and incidence of grade III was about 0.06 (13). A French study of all primary central nervous system tumors by Darlix et al. (14), using the French Brain Tumor Database (FBTDB), reported incidence of grade II meningioma, adjusted on the French population, of 0.43 per 100,000 person-years (0.37 per 100,000 person-years if adjusted on the American population) and 0.06 for grade III. Treatment of meningioma is based on surgery, which should be as complete as possible (12). Several studies advocated systematic adjuvant radiotherapy (15–17) while others favored classical surveillance (18). The optimal approach in grade II meningioma is not well-defined. A review of literature by Sun et al. (19) defined recommendations for WHO grade II and III meningiomas depending on the quality of the surgical resection. They recommended radiotherapy in both incomplete resection in grade II and complete resection with disturbing neuropathologic characteristics such as mitosis index >8.

The recommendations by Goldbrunner et al. (12) for grade II meningioma with macroscopically total resection favor classical surveillance or adjuvant radiotherapy. For incomplete resection, they advised adjuvant radiotherapy (54-60 Gy in 1.8-2.0 Gy fractions; level of evidence III, recommendation level C).

The aim of the present study was to analyze patients with grade II meningioma, operated on between 2007 and 2010, in two university medical centers, studying several characteristics:

overall survival (OS), progression-free survival (PFS), the percentage of patients treated by radiotherapy and reasons for adjuvant radiotherapy and, finally, the efficacy of radiotherapy.

Methods

Selection of patients

A retrospective study included patients from our database (French Brain Tumor DataBase-FBTDB (4), or "RnhTPSNC: *Recensement national histologique des Tumeurs Primitives du Système Nerveux Central* " in French) with newly diagnosed and histologically confirmed grade II meningioma according to the 2007 WHO classification (9), operated on between January 1st, 2007 and December 31st, 2010. Patients without histological confirmation and patients who with prior history of meningioma surgery were excluded. Data were crossed between the RnhTPSNC and PMSI medical information system program ("*Programme de Médicalisation des Systèmes d'Information*") and the specialized Gironde regional registry, to increase the accuracy of inclusion. The study was approved according to French legislation (CCTIRS n°10.548; CNIL n°911013).

Clinical characteristics

Data concerning clinical characteristics (age, gender, medical history, neurological examination, Karnofsky performance status (KPS), WHO performance status), radiological characteristics (topography, tumor volume), treatments (resection quality on Simpson grade (20), adjuvant therapy or not) and survival were collected and analyzed. Radiotherapy was considered "early" when immediately postoperative, and "late" when performed after progression or recurrence.

Radiological analysis

Tumor topography was accurately analyzed on preoperative T1-weighted spoiled gradient echo MR images obtained with and without gadolinium. Preoperative tumor volume was calculated from the 3 largest diameters (D1, D2, and D3) on the 3 orthogonal planes (axial, sagittal, and coronal). Volume was estimated by ellipsoid approximation ($[D1 \times D2 \times D3]/2$), as previously reported for gliomas (21).

Radiological characteristics were analyzed on preoperative CT scan (presence or not of calcifications, cysts, bone erosion, enhancement after injection).

Follow-up screened for recurrence or progression of any residue on regular MRI.

Surgery

Quality of surgical resection was evaluated on Simpson grade, assessed on the postoperative CT scan or MRI. In cases without postoperative imaging, Simpson grade was evaluated only from the operative report. Dates of any revision surgeries for progression were noted.

Adjuvant therapy

Characteristics of the adjuvant therapy (radiotherapy or chemotherapy) were collected. For radiotherapy, type of radiation was specified: stereotaxic or conformational radiotherapy or tomotherapy. Radiation dose and duration were collected.

Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) software version 22 (IBM Corp.). The analysis included a descriptive part of initial data and the oncological treatments. Duration of follow-up, OS and PFS were analyzed. PFS, comparing early radiated and non-radiated meningiomas, concerned only WHO grade II meningiomas. Survival was estimated by the Kaplan-Meier method and defined as the time from first surgery (corresponding to histological diagnosis) to death or else censored at the date of last MRI follow-up. The log-rank test was used to compare survival curves between strata. The proportional hazards assumption was checked before comparing survival curve. A Cox proportional hazard regression model was performed to assess prognostic factors, including age, Simpson grade and use of postoperative radiotherapy.

RESULTS

Clinical characteristics

Eighty-eight patients (59 women and 29 men: sex ratio, 2.03) operated on for grade II meningioma between 2007 and 2010 in the 2 centers were included. Clinical characteristics of the population are summarized in Table I. Median age at diagnosis was 60.5 years. Presenting

symptoms were most frequently headache (31.8%), seizure (29.5%), cognitive and/or behavioral disorder (27.3%) and sensory and/or motor deficit (28.4%) (Table I). Meningiomas were surgically resected based on the size of the tumor and/or the volumetric progression evaluated on successive MRI scans.

One patient had received brain irradiation during childhood after surgery for medulloblastoma.

Clinical examination before surgery

The majority of patients (n=55, 62.5%) had KPS of 80% or 90% and WHO performance status of 1 (n=40, 45.5%) (Table I). There was no statistical difference between the populations of the two centers for preoperative status (p=0.18 for KPS).

Radiographic characteristics

Tumor volume

Median tumor volume was 41.6 cm³, with no significant difference between the 2 centers (p=0.71).

Tumor location

The majority of meningiomas was located on the convexity (n=57, 67.8%) (Table I).

Surgical resection

In 59 cases, resection was assessed intraoperatively and on postoperative imaging, and in 30 cases only based on information from the operative reports.

For the majority of patients (n=47, 56.6%), resection of the meningioma and its base of implantation was complete, with Simpson grade 1. Only 7 patients (8.4%) had subtotal or partial resection with Simpson grade 4 (Table I). There was no significant difference in Simpson grade between centers (p=0.15).

Neuropathology

Eighty-eight patients had WHO grade II meningioma (93.6%), mostly atypical (n=76, 80.9%). Nine were chordoid (9.6%) and 3 were clear-cell meningioma (3.2%).

The majority of atypical meningiomas (57.3%) were so classified because of infiltration in the adjacent cerebral cortex despite low mitosis index. Thirty-two patients (42.7%) were classified as having atypical meningioma because of a high mitosis index (≥ 4 mitoses for 10 fields).

Postoperative clinical examination

The first clinical examination after discharge was between the second and the fourth month after surgery.

The majority of patients had KPS index 80 or 90 (n=54, 66.7%). There was global improvement at this stage of follow-up over preoperative evaluation. Results were similar for the WHO performance status, with a majority of patients PS=0 (n=38, 46.9%) (Table I). There was no significant difference between centers (p=0.82 for KPS).

Follow-up, global survival and progression-free survival

Median follow-up was 69.2 months.

Nine patients died during follow-up. Five-year survival was 89.7%.

PFS was 55.8 months. Analysis of the subgroups of irradiated and non-irradiated patients showed PFS of 39.1 months for the former (n=19), versus 60.4 months for the latter (p=0.02)

PFS in the group with early adjuvant radiotherapy (n=7) was 69.3 months, versus 60.4 months without (n=81) (p=0.52).

Median PFS in the subgroup considered as atypical meningioma due to the number of mitoses (n=32) was 60 months, and 65.4 months (p=0.15) in the subgroup of atypical meningioma according to pathological characteristics such as infiltration of the adjacent cortex or low mitosis index (< 4) (n=44).

Radiotherapy

Nineteen patients (21.6%) had adjuvant radiotherapy (Figure 1).

The majority had conformational radiotherapy, with a median dose of 56 Gray spread over approximately 20 sessions over 6 to 8 weeks. Four patients had tomotherapy, with a median dose of 52.8 Gray.

One patient had stereotactic radiosurgery in the postoperative period, then a second surgery followed by conformational radiotherapy for recurrence.

Survival according to treatment

Survival curves of irradiated and non-irradiated patients showed no significant difference (log-rank test, $p=0.27$; Figure 2). Survival curves for patients with early adjuvant radiotherapy versus all others showed no significant difference (log-rank test $p=0.93$; Figure 3).

Multivariate analysis for overall survival identified age as an independent prognostic factor for survival (HR, 1.09; 95% CI, 0.12-0.87; $p=0.02$). Simpson grade and postoperative radiotherapy were not independent factors for survival in the cohort as a whole (HR, 0.498; 95% CI, 0.06-4.02; $p=0.168$; and HR, 1.96; 95% CI, 0.47-8.2; $p=0.234$, respectively) (Table II)

DISCUSSION

Five-year survival in WHO grade II meningioma was 89.7%. This is consistent with the literature. Durand et al. (22) reported 78.4% 5-year survival for grade II meningioma patients operated on between 1990 and 2004. In a more recent study including 194 patients with grade II meningioma (23), 5-year survival was 83.2%. Hammouche et al. analyzed 79 patients with atypical meningioma and showed 5-year survival of 81% (24).

Consequences of the WHO 2007 and 2016 classifications of tumors of the central nervous system

In the WHO 2007 classification, meningiomas with otherwise grade I histological features but with microscopic brain invasion were moved to grade II (9). The WHO 2016 classification confirmed the addition of brain invasion as a criterion for atypical meningioma (11). These classifications resulted in an increase in the number of meningioma classified as grade II, but did not answer the controversial question of postoperative radiotherapy for grade II meningioma.

Survival and contribution of radiotherapy

Grade II meningioma

To treat WHO grade II meningioma after maximal surgical resection, two main options are described in literature: classical surveillance, and adjuvant radiation (radiotherapy or radiosurgery). The role of radiotherapy in grade II meningioma is controversial. There is no recommendation for systematic early adjuvant radiotherapy.

In the present cohort, the majority of patients had classical clinical and MRI monitoring after surgery to identify potential recurrence or progression of residue. Only 7 had early adjuvant radiotherapy; no clinical or neuropathological criteria underlay this choice. The 5-year survival rate was 89.7%, with no difference according to early radiotherapy or according to radiotherapy, whatever the timing versus non-irradiated meningioma.

Surveillance

Our findings are in agreement with the current literature. Graffeo et al. (18) analyzed 69 patients and showed that classical surveillance after complete surgical resection of atypical meningioma was not associated with higher risk of recurrence or increased mortality.

Jenkinson et al. (28) reported that early adjuvant radiotherapy had no influence on the progression of atypical meningioma after total surgical resection.

Champeaux et al. (29), in 206 WHO grade II meningiomas, reported that radiotherapy did not increase overall survival even when resection was not complete. Macroscopically total resection, age <62 years, and absence of invasion of the adjacent cortex were independent factors associated with better outcome.

Champeaux et al. (23) analyzed 224 patients and showed that, in case of recurrence of grade II meningioma, revision surgery was more effective than radiotherapy alone. This strategy was applied in our 2 centers in case of recurrence.

In a series of 90 patients, Lee et al. (30) reported that adjuvant radiotherapy was effective in lowering recurrence rates in patients after subtotal resection but did not provide significant benefit for patients after gross-total resection.

Adjuvant radiotherapy or radiosurgery

Conversely, Amsbaugh et al. (15) in 92 patients with WHO grade II or III meningioma, showed that stereotactic radiosurgery decreased mortality in comparison with surgery alone; adjuvant therapy increased PFS in high-grade meningioma.

Bagshaw et al. (16), in 59 patients, reported that adjuvant radiotherapy increased the rate of local control for atypical meningioma, whatever the Simpson grade. They concluded that initial aggressive treatment was important due to the difficulty of control of recurrence. However, the present findings did not support this conclusion.

Lagman et al. (17), in 619 patients with subtotal resection of atypical meningioma, reported that potential benefit with adjuvant radiosurgery in comparison to classical surveillance.

A study retrospectively analyzing a cohort of 2,515 patients (31) reported that adjuvant radiotherapy for patients who underwent sub-total resection was associated with better overall survival than with no adjuvant radiotherapy. However, they confirmed that gross-total resection was associated with better OS than with subtotal resection.

In the present cohort, the significant difference in PFS between irradiated and non-irradiated patients was most likely due to the fact that radiotherapy was not radiated early in the postoperative period but implemented only when recurrence appeared on successive MRI scans.

To sum up, in WHO grade II meningioma, we did not find benefit with systematic adjuvant radiotherapy after surgery, even in case of residue. Radiotherapy and stereotactic radiosurgery seem to be adapted for progressive tumors after other surgical resections (Figure 4).

In some cases of grade II meningioma, when resection cannot be complete, early adjuvant radiotherapy on the residue can be indicated according to tumor growth-rate (32). Adjuvant radiotherapy could be also justified in case of multiple successive surgeries.

Perspectives

The present study is limited by the size of the population, concerning only 2 centers. Future study on a larger population is needed to evaluate more precisely the benefit of early adjuvant radiotherapy for WHO grade II meningioma. A future population study, at nation-wide level, will assess the impact of postoperative radiotherapy, or the absence of postoperative radiotherapy, on overall survival and on quality of life at 10-years' follow-up. The patients concerned are those with grade II or III meningioma operated on in France during the period 2007-2010.

Clinical trials could help to answer this question but, given the median survival, it is difficult to carry out.

A multicenter phase-3 clinical trial is ongoing, to evaluate Radiation versus Surveillance following surgical resection of Atypical Meningioma (a randomized controlled trial: ROAM trial, EORTC 1308). It will compare radiotherapy versus active monitoring in patients who have undergone gross total surgical resection (Simpson grade 1-3) of atypical (grade II) meningioma (33,34). Forty of the 190 patients needed have already been included.

Another solution would be to retrospectively identify clinical, radiological and biological parameters in irradiated and non-irradiated patients, to shed light on prognosis.

Molecular profiles of WHO grade II meningiomas are one of the potential breakthrough points in future studies (35). Furthermore, it would be interesting to accurately describe the rate of progression of WHO grade I meningioma.

CONCLUSION

The classification of WHO grade II meningioma includes tumors with different progression profiles. However, therapeutic strategy is still under discussion. The present findings are consistent with current literature attesting that systematic early adjuvant radiotherapy after macroscopically complete surgical resection is not justified. Radiotherapy can follow multiple surgeries in case of recurrence. A further larger-scale multicenter prospective randomized controlled study and/or a study in a larger population may help to answer this question.

The issue is not whether we should be prescribing radiotherapy for every grade II meningioma, but rather to identify which meningiomas would benefit from adjuvant therapy following first or second surgery

FIGURE LEGENDS

Figure 1. Treatment of WHO (World Health Organization) grade II meningioma.

Nineteen patients with WHO grade II meningioma received radiotherapy.

Figure 2. Survival curve: irradiated (blue) versus non-irradiated WHO grade II meningioma (red); $p=0.27$

There was no significant difference between irradiated and non-irradiated WHO grade II meningiomas (log-rank test, $p=0.27$)

Figure 3. Survival curve: early (blue) versus late irradiated WHO grade II meningioma (red); $p=0.93$

There was no significant difference between early irradiated WHO grade II meningioma (radiotherapy in the immediate postoperative period) and WHO grade II meningioma with later radiotherapy (log-rank test, $p=0.93$)

Figure 4. Proposed novel decision-tree for grade II meningioma.

Table I. Clinical characteristics of the population ($n=88$), pre- and post-operative evaluation of Karnofsky Performance Status and WHO Performance Status and extent of resection on Simpson grade ($n=83$).

The majority of meningiomas were located on the convexity. There were no significant differences in population characteristics between the 2 centers.

The majority of patients ($n=55$, 62.5%) had a KPS 80% or 90% and WHO Performance Status 1 ($n=40$, 45.5%) without significant difference between the 2 centers.

Postoperative evaluation between 2 and 4 months after surgery highlighted global improvement in KPS and WHO Performance Status.

Surgical resection was complete, with Simpson grade 1 for the majority of patients (n=47, 56.6%). Only 7 patients (8.4%) had subtotal or partial resection with Simpson grade 4.

* 4 missing data

** 5 missing data

*** 7 missing data

Table II. Multivariate analysis of overall survival.

HR: Hazard Ratio; CI: Confidence Interval

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Figure 1. Treatment of WHO grade II meningioma.

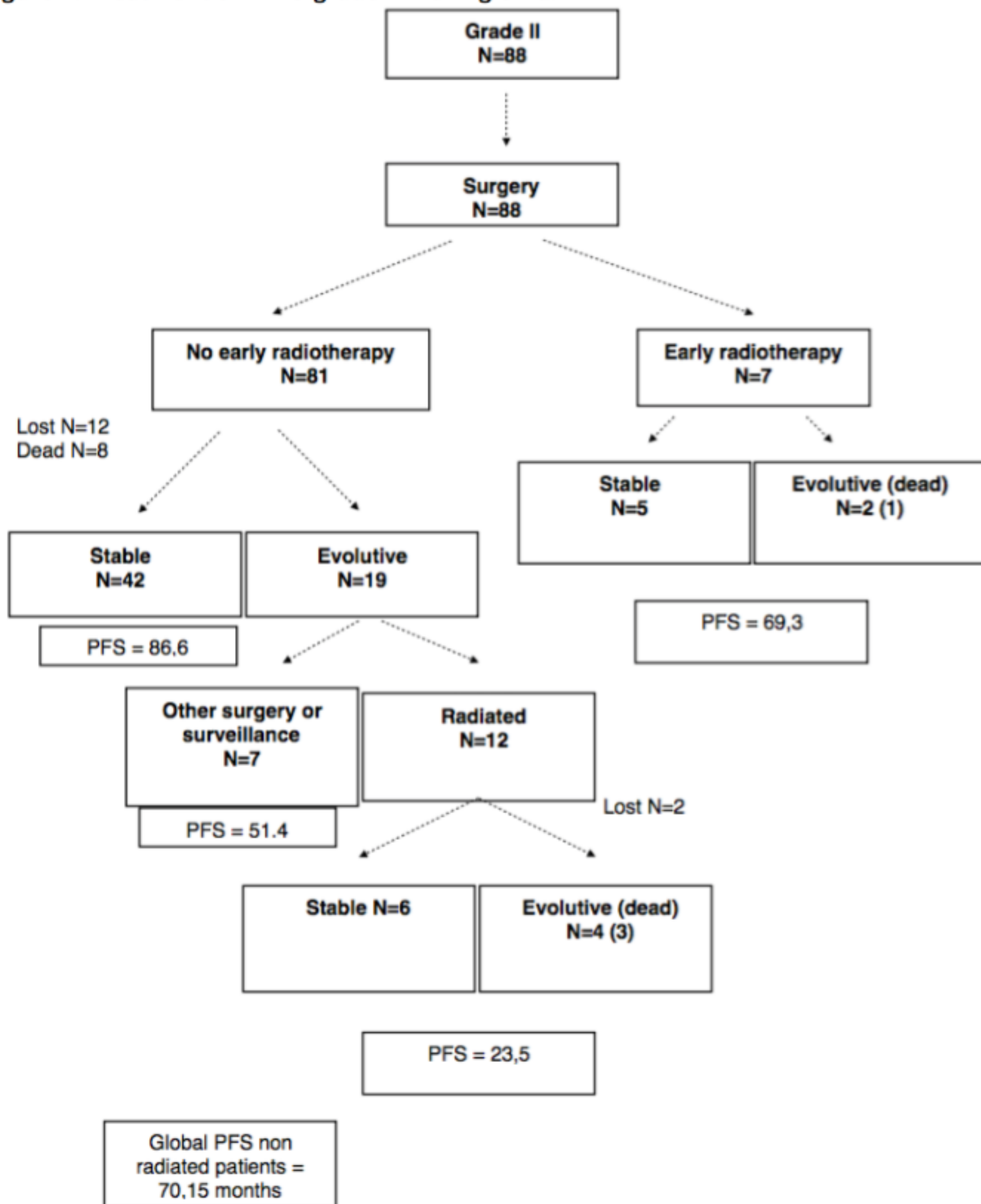


Figure 2. Survival curve: radiated WHO Grade II meningioma (blue) versus non radiated WHO Grade II meningioma (red); $p=0.27$

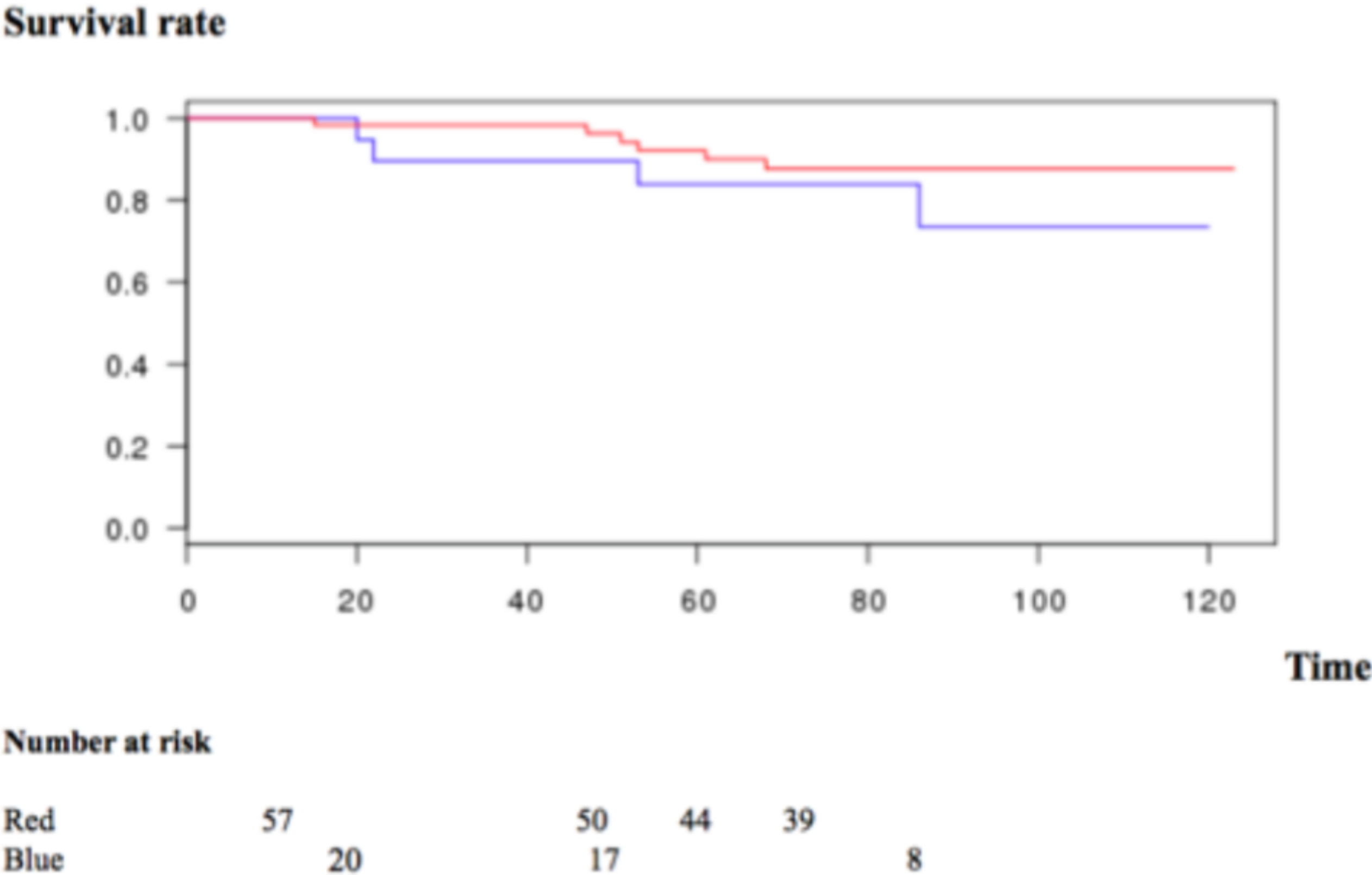
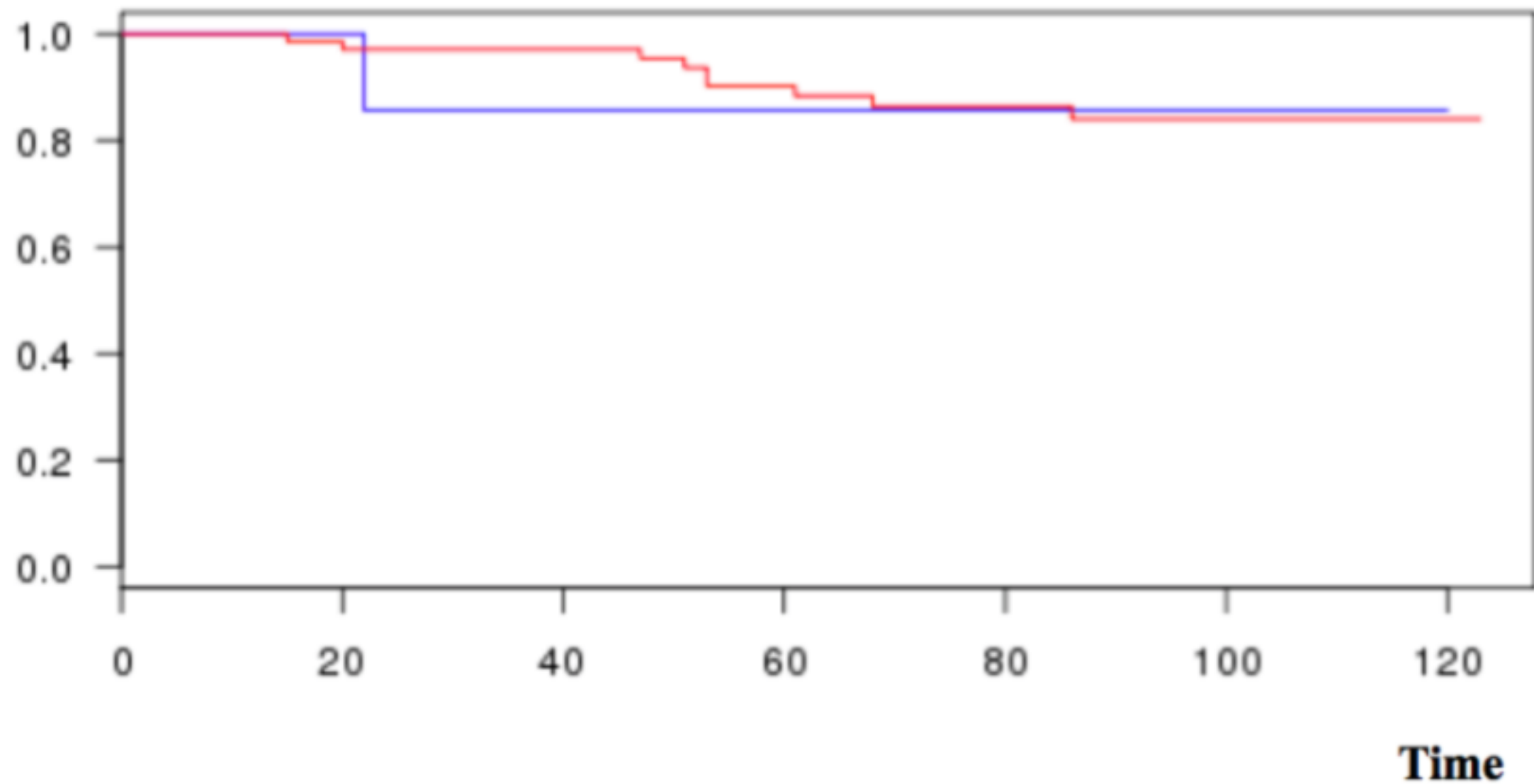


Figure 3. Survival curve: early radiated WHO Grade II meningioma (blue) versus non-early radiated WHO Grade II meningioma (red); $p=0.93$

Survival rate



Number at risk

Red	61		54	45	34
Blue		7			

Figure 4. Proposition of a novel decision tree algorithm for grade II meningiomas

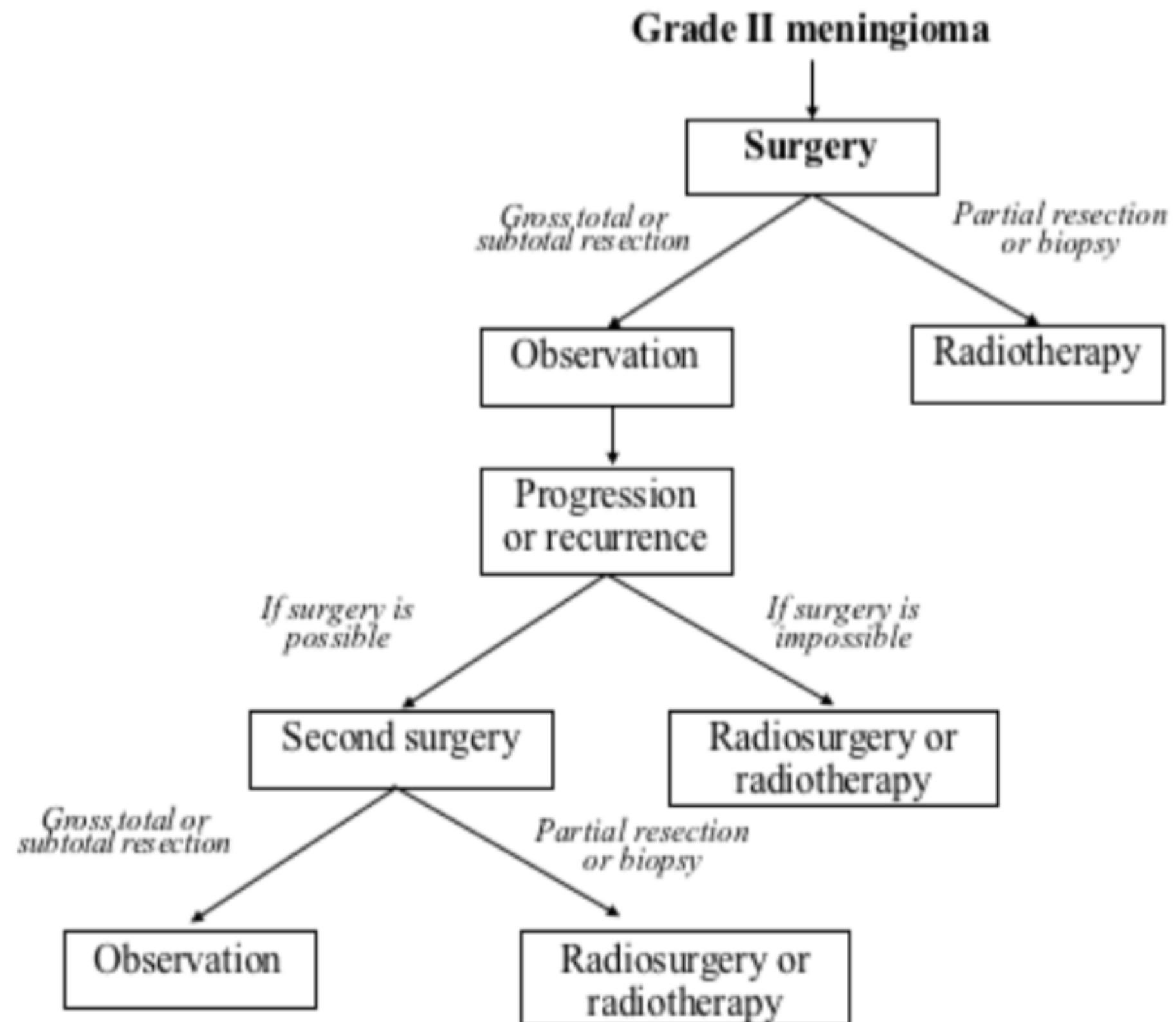


Table I. Clinical characteristics of the population (n=88), pre- and post-operative evaluation of Karnofsky Performance Status and WHO Performance Status and extent of resection on Simpson grade.

CLINICAL CHARACTERISTICS		
Sex ratio (F/M)	2.03	
Median age at diagnosis	60.5	
FIRST SYMPTOMS		
Headache	28 (31.8%)	
Seizure	26 (29.5%)	
Cognitive and/or behavioral disorder	24 (27.3%)	
Sensory and/or motor deficit	25 (28.4%)	
Language disorder	15 (17%)	
Visual disorder	15 (17%)	
Intracranial hypertension	5 (5.7%)	
Asymptomatic	5 (5.7%)	
LOCATION*		
Convexity	57 (67.8%)	
Parasagittal	9 (10.7%)	
Ethmoid	4 (4.8%)	
Sphenoid / Spheno-orbital	7 (8.3%)	
Pterional	1 (1.2%)	
Cerebellum	4 (4.8%)	
Spinal	2 (2.4%)	
SIMPSON GRADE (N=83)**		
1	47 (56.6%)	
2	19 (22.9%)	
3	10 (12.1%)	
4	7 (8.4%)	
KARNOFSKY PERFORMANCE STATUS	PREOPERATIVE N=88	POSTOPERATIVE N=81***
100	6 (6.8%)	16 (19.7%)
80-90	55 (62.5%)	54 (66.7%)
60-70	25 (28.4%)	11 (13.6%)
<60	2 (2.3%)	0
WHO PERFORMANCE STATUS		
0	31 (35.2%)	38 (46.9%)
1	40 (45.5%)	36 (44.4%)
2	16 (18.2%)	7 (8.6%)
3	0	0
4	1 (1.1%)	0

Table II. Multivariate analysis of overall survival

	HR (95% CI)	p
Age (≤ 65 vs > 65)	1.09 (0.12-0.87)	0.02
Postoperative radiotherapy	1.96 (0.47-8.2)	0.234
Simpson Grade (1-2 vs 3-4)	0.498 (0.06-4.02)	0.168