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2 Factors Affecting Operative and Excess Long-term Mortality in 935 Patients with Intracranial Meningioma
Clinical Study

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ABSTRACT: BETWEEN 1953 AND 1980, a total of 935 patients underwent surgery for intracranial meningioma in the Department of Neurosurgery of the Helsinki University Hospital. The patients were followed up until death or the end of the year 1987. The cumulative observed survival rate was 91% at 3 months, 89% at 1 year, and 63% at 15 years. The relative survival rate, that is, the ratio of the the observed and the expected rates, was 91% at 3 months, 89% at 1 year, and 78% at 15 years. Significant risk factors for operative mortality (7%) for the 652 patients operated on from 1966 to 1980 were poor preoperative clinical condition, absence of epilepsy, old age, incomplete tumor removal, pulmonary embolism, and an intracranial hematoma requiring evacuation. For those 828 patients who survived the first postoperative year, the factors predicting an excess risk of death for up to 15 years were incomplete tumor removal, poor pre- and postoperative clinical condition, anaplasia of the tumor, and hyperostosis. Patients whose tumors were not completely removed had a 4.2-fold relative excess risk of death as compared with patients whose tumors were completely removed, and patients who had malignant tumors had a 4.6-fold risk as compared with those who had benign tumors.

KEY WORDS: Brain neoplasm; Meningioma; Prognosis; Surgery; Survival analysis; Survival rate

Intracranial meningiomas are amenable to surgical treatment because more than 90% are histologically benign [33,40] and the majority can be completely removed [1,25,30,39]. From 20 to 32% of seemingly completely removed meningiomas recur [21,26], but the recurrences, as well as the remnants of subtotal removals, usually grow slowly [12,18]. The prospect of permanent cure has encouraged neurosurgeons to design demanding approaches to remove even meningiomas that invade the skull base [35,37]. An attempt to remove the entire tumor can, however, be risky because of invasion of the bone, cerebral arteries, venous sinuses, or cranial nerves, and may cause unnecessary damage in a patient who would have been better off after a subtotal removal.

Computed tomographic (CT) scanning and magnetic resonance imaging have made incidental diagnoses more frequent; less than 10% of all meningiomas will ever cause symptoms [32], and it is difficult to predict which ones will benefit from surgery. Consequently, whether it is better to remove or not to remove a meningioma depends on the location, size, and attachment of the tumor, and on the patient's age, neurological deficits, and coexisting diseases, and the decision is not always easy.

We do not know how much excess mortality intracranial meningiomas cause, since the few survival studies report only the observed survival rates [4,6,7,26,39]. These do not tell us how much meningiomas shorten life, for meningioma patients, owing to their advanced age, have considerable mortality from other causes. Detailed data on how operative mortality and long-term survival are affected by characteristics of the patients (e.g., age, clinical condition), of the tumors (e.g., location, size, attachment, anaplasia), and of the operations (e.g., extent of removal, complications) are needed to reduce the mortality caused by meningiomas. Our study was designed to analyze the impact of these very characteristics on operative mortality and long-term excess mortality of patients operated on for intracranial meningioma. Mortality due to causes other than meningioma was taken into account by calculating relative survival rates, which compare the observed survival of patients to their expected survival. Expected survival was derived from life tables of the general population matched for age, sex, and the year of diagnosis.

PATIENTS AND METHODS

Patients

From 1953 through 1980, a total of 1,023 primary operations for an intracranial tumor termed "meningioma" were performed in the Department of Neurosurgery of Helsinki University Hospital, Helsinki, Finland. Primary orbital meningiomas are not included in this tally.

Histological reexamination

Histological specimens from 975 of the 1,023 tumors were available for review (Table 1) [20]. Paraffin sections were stained with either hematoxylin and eosin or by van Gieson's method, or both. In unequivocal cases, the slides were stained for glial fibrillary acidic protein to differentiate meningiomas from gliomas, or for reticulin to differentiate from meningeal hemangiopericytomas [19]. Nine hundred thirty-six tumors that fulfilled the criteria of a meningioma were further classified according to histological anaplasia as benign (Grade I), atypical with incipient signs of anaplasia (Grade II), or overtly anaplastic (Grade III) (Table 1) [22]. The grading corresponds essentially to the recent proposal by the World Health Organization Working Group (Histological Typing of Tumours of the Central Nervous System, 2nd meeting, Zurich, Switzerland, March 28-

April 1, 1990) and to the previous World Health Organization classification [41].

Clinical features

All hospital records, operative notes, office notes, pathology reports, and neuroradiological reports of the 936 patients were reviewed. To determine the best postoperative clinical condition reached by the patient, additional data were gathered from the Central Statistical Office of Finland, the hospitals where the patients were seen after operation, and from inquiries mailed to those patients alive between 1982 and 1984. All clinical data were originally collected for a study on recurrence of meningiomas [20-22]. The factors analyzed for impact on survival were extracted from the case reports (Table 2).

The pre- and postoperative clinical condition of the patients was coded according to a modified five-point Glasgow Outcome Scale [23]. Postoperative condition was defined as the best condition the patient reached within 2 years after the operation. Patients with no neurological symptoms, or symptoms but no neurological deficits, were coded as Class 1; patients with slight neurological deficits (e.g., paresis of cranial nerves) were coded as Class 2; patients with major neurological deficits requiring daily assistance (e.g., hemiparesis) were coded as Class 3; and the patients who had needed acute hospital care preoperatively because of impaired consciousness and/or permanent hospital care in the postoperative stage were coded as Class 4. In essence, the modified scale closely resembles that of Awad et al. [4].

The tumors were classified by 10 different locations based on neuroradiological findings and the operative notes: convexity, parasagittal region, falx, olfactory region, sellar region, sphenoid ridge, middle fossa, ventricle, tentorium, or posterior fossa (Table 3). For regression analyses, five locations were created by joining the parasagittal region and falx, the olfactory and sellar regions, and the sphenoid ridge and middle fossa. The few intraventricular tumors and the tentorial tumors located above the tentorium were added to those of the middle fossa (Table 2).

Attachment and infiltration of the tumor into adjacent structures were coded as positive if mentioned in the neuroradiological or surgical notes, and otherwise as negative. Tumor tissue left at removal because of endangered adjacent structure was coded as positive if mentioned in the operative notes, and otherwise as negative. The extent of removal was graded according to Simpson [37]: complete with excision (Grade I) or coagulation (Grade II) of the dural insertion, or incomplete, leaving behind tumor tissue slightly (Grade III), grossly (Grade IV), or totally (Grade V) (Table 2) [38]. The Simpson classification was based solely on the original operative notes; no postoperative radiological data were used. The extent of removal with regard to location and attachment or infiltration is shown in Table 3.

Preoperatively, 927 (99%) patients underwent a plain skull x-ray; 830 underwent carotid angiography, 19 vertebral angiography, and 49 both. Air studies were performed in 294 patients (31%), and CT scans were performed in 109 (12%). The CT scan has been available in Finland since the summer of 1978. Only 35 patients underwent neither angiography nor a CT scan; of these, 32 had an air study and 3 only a plain skull x-ray.

Follow-up data could be found in the files of the Finnish Cancer Registry for 935 of the original 936 patients. All 935 patients were followed up until death or for a minimum of 7 years, until the common closing date of the study, December 31, 1987; 618 of the patients were followed up for more than 7 years, and 314 for more than 15 years (Fig. 1). No patient became unavailable for follow-up.

Statistical methods

Survival rates. The observed survival rates were calculated using the actuarial method, starting from the date of operation. The standard errors were derived by Greenwood's formula, and the 95% confidence intervals were calculated by adding or subtracting 2 standard errors from the respective rate [8]. Correction for competing causes of death was made by calculating the relative survival rate (RSR). The RSR is the ratio of the observed to the expected survival rate [5,15]. The expected survival rates were derived from the life tables of the general Finnish population by sex, 5-year calendar periods, and 5-year age groups; that is, the RSR is adjusted for sex, age, and calendar period [10,16,27]. The average loss of life was calculated by comparing the observed length of life after diagnosis with that expected [14]. The number of excess deaths was calculated from the observed and expected number of deaths by taking the individual potential follow-up times into account by calculating an expected life table for the patients [16]. Thus, due to predictable withdrawals, the expected number of deaths was smaller than deduced from the number of patients alive at the beginning of the follow-up period and from the expected survival rate of a comparable general population.

Regression modeling. For the regression analyses, the follow-up time was divided into three consecutive periods: 0 to 3 months from operation, 4 to 12 months from operation, and 1 to 15 years from operation.

Death within the first 3 months from operation was defined as operative mortality. The factors influencing the operative mortality were analyzed with logistic regression using the GLIM statistical software [2,29]. Since this follow-up interval was short, there was no need to take competing causes of death into account. The factors influencing operative mortality were studied only for the 652 patients operated on between 1966 and 1980, as there was a marked decline in operative mortality during the mid-1960s, mainly as a result of improved technical facilities. Prior to this, the factors are merely of historical interest. All variables were entered into the model in a step-up fashion, and those remaining significant were kept in the model. To determine the significance of the addition of each variable into the model, the differences in deviance between hierarchical models were compared with the corresponding differences in the degrees of freedom using the chi-square distribution. Three models were constructed for operative mortality. For the first, the

preoperative model, only data available preoperatively were used. For the second, the operative model, preoperative data and data from the operation were used. For the third, the postoperative model, postoperative data were also used.

As the mortality between 3 months and 1 year postoperatively was much higher than expected, the factors affecting survival during this interval were studied separately. Death was caused mostly by the tumor or by sequelae of the operation. The analysis was performed using logistic regression. A single model for this period was fitted, similar to the fitting of the models for operative mortality. The relative risks (RRs) were used to quantify the effect of each prognostic factor on the operative mortality and the mortality during the 4th to 12th postoperative months (number of deaths/number of persons at risk).

The long-term survival was analyzed with a modified Cox regression analysis that uses annual relative instead of observed survival rates [17]. These analyses were also performed with the GLIM statistical software [29]. The model with the best fit was built in a step-up fashion, adding the individually significant ($P < 0.05$) variables to the model one at a time, and keeping in the model those variables that remained significant.

The excess risk of death attributable to the meningioma was derived for every patient from a comparison (number of deaths/number of person-years) with the mortality in a corresponding general population comparable in terms of sex, age, and calendar period. The relative excess risk of death (RER) was derived from the model with the best fit as ratios between the estimated excess mortality rates of the respective patient groups [17]. In other words, the RER was determined by comparing the excess risks of death with each other in defined patient groups. One patient group was regarded as the reference category, and their excess risk was defined as unity. The excess risks of the other groups were then compared with that of the reference group. For example, the RER among patients aged 65 years or more was 1.5 as compared with an RER of 1.0 among patients aged 45 to 64 years, the reference group in this comparison; however, there was an excess risk of death in the latter group as well. The RER of patients aged 45 to 64 years was set to unity just for this internal comparison. The category with the largest number of patients was chosen as the reference category for each variable, in order to obtain narrow confidence intervals for the relative risks.

RESULTS

Survival rates

The cumulative observed survival rate for the 935 patients was 90.6% at 3 months, 88.6% at 1 year, 82.5% at 5 years, 71.7% at 10 years, and 62.6% at 15 years, according to the life table analysis (Fig. 2). Observed deaths were distributed as follows: 90 during the period of 0 to 3 months from surgery (operative mortality), 17 during the 4th to 12th months, and 210 during the 2nd to 15th follow-up years (Fig. 1). The cumulative expected survival rate for the 935 patients was 99.8% at 3 months, 99.1% at 1 year, and 80.3% at 15 years (Fig. 2). There were 2 expected deaths at 3 months, 9 at 1 year, and altogether, 157 cumulative expected deaths at 15 years. Consequently, there were 88 cumulative excess deaths in the patient population at 3 months, 98 at 1 year, and 160 at 15 years. The cumulative RSR was 90.8% at 3 months, 89.4% at 1 year, 86.9% at 5 years [95% confidence interval (CI), 84-89%], 81.2% at 10 years (95% CI, 78-85%), and 77.9% at 15 years (95% CI, 74-82%) (Fig. 2). The excess deaths occurred mainly during the first year after operation, but there also was some excess mortality later: altogether, 62 excess deaths during the 2nd to 15th follow-up years (Fig. 2). The RSR decreased only 2.5% from the 2nd to the 5th follow-up year, but 5.0% from the 5th to the 9th follow-up year. In the mean, the patients' expected length of life after the operation was 23.6 years (22.6-24.6 years), and that of the matched general population 26.4 years. Thus, the patients' estimated loss of life was 11% in the 15-year follow-up period. A total of 781 patients with a benign (Grade I) meningioma survived the first postoperative year with 15-year RSRs, according to location and condition, as shown in Table 4.

Prognostic factors of operative mortality

The operative mortality (death within 3 months of operation) was 16% from 1953 to 1965, 6% from 1966 to 1974, and 8% from 1975 to 1980. The risk factors were analyzed for the 652 patients who were operated on from 1966 to 1980, with an operative mortality of 7% (46/652). Regression modelling was performed in three phases, first analyzing the preoperative data, then adding the operative data, and finally, adding the postoperative data (Table 5). Of the preoperative factors, poor clinical condition (neurological deficits classified as Class 3 or 4), absence of epilepsy, and old age were significantly associated with operative mortality (Table 5). Of factors that became known during the operation, incomplete removal of the tumor (Simpson's Grades III-V) was the only significant additional factor in the model (Table 5). When postoperative complications were added, pulmonary embolism and removal of an intracranial hematoma significantly increased the risk of operative mortality, and the preoperative clinical condition lost its significance; there were, therefore, five factors in the final model (Table 5).

The relative risks of death show how the significant factors affected the risk of operative mortality (Table 5). For example, age and preoperative clinical condition predicted operative mortality, so that the operative mortality of patients less than 45 years of age and in a good (n = 151), or poor (n = 18) clinical condition was 3% and 0%, respectively. The corresponding percentages for those more than 64 years of age and in a good (n = 68) or poor (n = 32) clinical condition were 6% and 25%, respectively.

Prognostic factors of excess mortality in the 4th to 12th follow-up months

During the 4th to the 12th postoperative months, 17 patients died. Postoperative condition,

postoperative pneumonia, and the histological type of the tumor were significant prognostic factors for death during this period, and no other factor tested was significant. The patients in poor postoperative condition (Class 3 or 4) had a 14-fold RR as compared with those in good condition (Class 1 or 2). The patients with postoperative pneumonia had a sevenfold RR as compared with those who did not have pneumonia. The RR was increased sevenfold by histologically malignant tumors (Grade II or III) as compared with benign ones (Grade I).

Prognostic factors of excess mortality in the 2nd to 15th follow-up years

Among the 828 patients who survived the first postoperative year, there were 62 excess deaths during the 2nd to 15th follow-up years. There were five significant prognostic factors for the excess mortality: extent of removal, preoperative clinical condition, postoperative clinical condition, histological type of the tumor, and hyperostosis (Table 6). All other factors relating to the patients, tumors, or operations remained nonsignificant, according to the regression analysis.

The patients who had complete removal of the tumor with excision (Simpson's Grade I) or coagulation (Simpson's Grade II) of the dural insertion fared better than the patients with incompletely removed tumors (Simpson's Grades III-V) (Fig. 3). The difference between Grade I and II removals was inconspicuous. For the complete removals, the RSR was 92% at 1 year, 91% at 5 years (95% CI, 88-93%), and 84% at 15 years (95% CI, 80-89%) (Fig. 3). For the incomplete removals the RSR was 77% at 1 year, 69% at 5 years (95% CI, 62-77%), and 50% at 15 years (95% CI, 39-60%) (Fig. 3). Most of the long-term excess mortality after incomplete removal seemed to occur between the 5th and 9th follow-up years (Fig. 3). The patients with incompletely removed tumors lost 36% of their expected length of life, while those with complete removal only lost 5%, and their RER was 4.2-fold (Table 7).

The RSR for patients with a benign tumor (Grade I) was 90% at 1 year, 87% at 5 years (95% CI, 85-90%), and 80% at 15 years (95% CI, 75-84%) (Fig. 4). The RSR for patients with a malignant tumor (Grade II or III) was 88% at 1 year, 81% at 5 years (95% CI, 68-93%), 57% at 10 years (95% CI, 41-73%), and 51% at 15 years (95% CI, 33-70%) (Fig. 4). The patients with a malignant tumor lost 35% of their expected length of life, while those with a benign tumor lost only 9%, and their RER was 4.6-fold (Table 7).

The patients in poor preoperative condition (Class 3 or 4) had a 2.3-fold RER as compared with patients in good preoperative condition (Class 1 or 2) (Table 7, Fig. 5). The RSR for patients with good preoperative condition was 94% at 1 year and 85% at 15 years (95% CI, 80-90%), and that for patients with poor preoperative condition was 77% at 1 year and 59% at 15 years (95% CI, 50-67%) (Fig. 5). Patients in poor postoperative condition had a 3.6-fold RER as compared with those in good postoperative condition (Table 7).

The RSR of patients who did not have hyperostosis was 89% at 1 year and 81% at 15 years (95% CI, 76-86%), and that of those who did have hyperostosis was 92% at 1 year and 67% at 15 years (95% CI, 57-76%) (Fig. 6). The impact of hyperostosis became apparent only after the 7th follow-up year (Fig. 6). The patients with hyperostotic tumors lost 16% of their expected length of life, while those with no hyperostosis lost only 9%, and had a 2.1-fold RER (Table 7).

There were no significant differences in the long-term RSR for patients operated on during the different study periods, nor between the sexes, although both the observed and relative survival of men was less than that of women. Except for hyperostosis, no attachment into adjacent structures proved significant for the long-term survival; neither was the location significant (Table 4). The 15-year RSR of the 189 patients whose tumors were in the parasagittal region or falx and whose preoperative condition was good was 91%, and that of the 66 patients with tumors in this area and whose preoperative condition was poor was 72%. In comparison, the 15-year RSR for the 73 patients with a posterior fossa tumor and whose preoperative condition was good (Class 1 or 2) was 71%, and that of the 19 patients with tumors in this area and whose preoperative condition was poor (Class 3 or 4) was 37%.

DISCUSSION

The diagnosis of a slowly growing, curable, but potentially lethal tumor in an elderly patient prone to operative complications, especially when the tumor is incidental or technically difficult to access, poses a serious challenge in balancing benefits against risks. We know neither the overall treatment mortality of intracranial meningiomas, as patients not undergoing surgery have been excluded from the reported series, nor the long-term excess mortality, since only observed survival rates are given [4,6,7,25,26,39]. The observed rates do not tell us how much intracranial meningiomas shorten life, for these mostly elderly patients have considerable mortality from other causes.

Two alternatives exist for assessing mortality from meningioma. If the exact causes of death are known, the mortality can be calculated directly, but such data are seldom available. Even if careful reports of the terminal events are available, the causative role of the meningioma may be impossible to define. The other alternative is to determine the mortality from meningioma indirectly, by comparing the observed and the expected survival rates, and to express the excess mortality by the RSR, the ratio of the two. The ideal expected survival rate is the survival rate of a population identical to that of the the patients, except for the intracranial meningioma and its sequelae. In practice, the expected survival rates are derived from the life tables of the general population by matching for age, sex, and calendar period, yielding a sufficiently accurate estimate [15,16]. In our study, the difference between the observed and relative survival was 15% at 15 years: 63% versus 78%.

We recently reported a population-based study on 1,986 patients with intracranial meningioma diagnosed during life from 1953 to 1984 in Finland [36]. After diagnosis, the patients' short-term excess mortality was considerable--17% at 1 year--and their excess mortality in the long term was continuous--12% between the 2nd and the 15th follow-up years. The mortality at 1 year was strongly related to surgery: 8% for the 663 patients operated on, as against 61% for the 126 patients not operated on in the years 1979 to 1984, inclusive. As there were no data in the Finnish Cancer Registry on the clinical condition of patients, topography of tumors, course of surgery, and operative complications, we conducted the present study to see how these factors predicted operative and excess long-term mortality.

Operative mortality

The operative mortality of 7% for the 652 patients from the years 1966 to 1980 is high: the cumulative mortality of a matched general population would reach 7% only after 7 years. The percentages themselves are not important, since the series spans 15 years, mostly from the era before the advent of computed tomography. On the other hand, we believe that the factors associated strongly and independently with operative mortality are still valid today.

Of the data available on admission, old age, severe neurological deficits, and absence of epilepsy were associated with operative mortality. Previous reports also show an increased risk of operative mortality among the aged, and among patients who did not receive anticonvulsive medication [3,4,7,28]. The risk of operative mortality was less among patients with epileptic seizures, presumably because they had smaller tumors and more supratentorial tumors, and because their preoperative condition was somewhat better. Operative complications occurred more often in patients in poor clinical condition.

Analysis of the data available at 3 months after operation showed incomplete removal of tumor, pulmonary embolism, and removal of a postoperative hematoma to be additional poor prognostic factors. The general aim at operation was to achieve complete removal, but factors suggesting a poor prognosis may have influenced the surgeon to content himself with less than complete removal. It seems that incomplete removal predicted operative mortality, in part because, of the factors tested, it best described the difficulties of tumor removal--for example, of cranial base tumors involving adjacent structures. Table 3 shows the extent of removal according to the location and attachment of the tumors, but, evidently, a much larger series is needed to define how the involvement of adjacent structures, such as the cerebral arteries, affects operative mortality.

Deep venous thrombosis is estimated to develop in 29 to 43% of neurosurgical patients in the acute postoperative stage [31]. The overall incidence of pulmonary embolism is not known, but fatal pulmonary embolism occurred in 1.2% of our patients; this tallies with 1% reported for general neurosurgical patients [31]. In our series, pulmonary embolism, diagnosed in 18% of operative mortality, was not associated with poor preoperative clinical condition. Although pulmonary embolism in neurosurgical patients is so prevalent, there is no generally accepted protocol for the prevention of it [24]. The other significant prognostic factor among the postoperative complications, removal of a postoperative hematoma, occurred more often in patients whose preoperative condition was poor.

The operative mortality could be reduced by excluding patients with known risk factors, by reducing the impact of preventable factors, or, possibly, by modifying the operative strategy. In our series, the operative mortality would have been 3.6% instead of 7.1%, if only patients younger than 65 years with preoperative epilepsy and in good condition had been operated on, but then the number of patients operated on would have been 223 instead of 652. If pulmonary embolism and postoperative hematoma could have been prevented, the operative mortality would have dropped to 4.3%. Some of the 168 patients with an incompletely removed tumor survived for a long time, 35 were observed to survive for at least 15 years (Fig. 3). Consequently, some patients might have fared better if only partial removal had been attempted. Few of the 652 patients operated on in the years 1966 to 1980 had incidental meningiomas, and, for instance, only 71 had epileptic seizures but no neurological deficits (Class 1 condition). Still, some of them would have lived for years without operation, albeit with increasing neurological deficits. Yet more comprehensive data on the preoperative condition of the patients, monitoring during and after surgery, and attempts to prevent complications must be analyzed to minimize operative mortality.

Long-term excess mortality

The World Health Organization classifies meningiomas according to histological anaplasia from benign (Grade I) to sarcomatous (Grade IV) [41]. In our series, meningiomas with incipient (Grade II) or overt (Grade III) signs of anaplasia occurred in 4.7% and 1.0% of the patients; Zülch and Mennel [40] present corresponding figures of 5.1% and 3.2%. Old patients did not have more malignant meningiomas (II-III) than young ones, but malignant meningiomas were more frequent in men (12%) than in women (4%). In a previous analysis of this series, the recurrence rate after seemingly complete removal was 3%, 38%, and 78% at 5 years for Grade I, II, and III meningiomas, respectively [22]. We now find that malignant meningiomas (Grades II-III) caused a high long-term excess mortality, which tallies with their known increased growth rate and poor response to surgery [34]. However, there were also long-term survivors, indicating that the histological assessment at the time of surgery is only a crude indicator of the future behavior of the tumor. As malignant meningiomas are potentially lethal, particular attention should be paid to their follow-up.

The extent of tumor removal was the most significant factor associated with long-term excess mortality. When the clinical condition was good and removal seemingly complete, excess mortality among

those patients having a histologically benign tumor was low after the first follow-up year. Coagulation instead of excision of the dural insertion was not associated with increased mortality, although it is known to increase the recurrence rate [21,26,37]. It seems that incomplete removal indicated a potentially lethal topography more sensitively than did the location of the tumor. Patients with residual tumors had high excess mortality for about 10 years after operation, but then the annual RSR was close to 100%, suggesting that some meningiomas progress very slowly. To make rational decisions about additional operations, more data on the long-term course of residual tumors invading adjacent neural, vascular, and bony structures are required.

Hyperostosis adjacent to the tumor was encountered in 20% of all patients, and in 28% of the convexity tumors and 33% of the sphenoid ridge tumors. Hyperostotic bone is invaded by meningioma cells [9,11]. In our series, hyperostosis was associated with a higher recurrence rate after seemingly complete removals of benign meningiomas [21], and such recurrences explain, at least partly, the excess mortality appearing about 7 years after operation (Fig. 6). Hyperostotic tumors may also be biologically different from other meningiomas in other ways [13].

Many of the factors tested by the regression analysis were not significantly associated with the operative or the excess long-term mortality, some of them because the series included few patients with tumors with these rare characteristics. The strict criteria of significance should keep the risk of false positive results small. Of course, a number of factors possibly explaining the excess mortality were never tested, either because we were not aware of them or they were not available in our data.

In summary, intracranial meningiomas, traditionally regarded as benign and curable tumors, caused both considerable operative mortality and a long-term excess mortality when the patients were old, in poor clinical condition, or had tumors that could not be completely removed. Some of these high-risk patients will not benefit from surgery unless the operative strategy and technique can be improved and prevention of operative complications is vigorous. Particular attention should be paid to the follow-up of patients with incompletely removed, hyperostotic, or malignant tumors.

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REFERENCES: [1-41]

1. Adegbite AB, Khan MI, Paine KWE, Tan LK: The recurrence of intracranial meningiomas after surgical treatment. J Neurosurg 58:51-56, 1983.
2. Armitage P, Berry G: Statistical methods in *medical research.* Oxford, Blackwell Scientific Publications, 1987, ed 2, pp 388-389.
3. Assietti R, Pinna G, Introzzi G, Gaetani P, Tangenti A, Rodriguez y Baena R, Sangiovanni G, Magrassi L, Rainoldi F, Butti G: Statistical analysis of operative mortality and recurrence in intracranial meningiomas, in Paoletti P, Takakura K, Walker MD, Butti G, Pezzotta S (eds): *Neuro-Oncology.* Dordrecht, Netherlands, Kluwer Academic Publishers, 1991, pp 329-332.
4. Awad IA, Kalfas I, Hahn JF, Little JR: Intracranial meningiomas in the aged: Surgical outcome in the era of computed tomography. Neurosurgery 24:557-560, 1989.
5. Berkson J, Gage RP: Calculation of survival rates for cancer. Proc Staff Meet Mayo Clin 25:270-286, 1950.
6. Chan RC, Thompson GB: Morbidity, mortality, and quality of life following surgery for intracranial meningiomas. J Neurosurg 60:52-60, 1984.
7. Cornu P, Chatellier G, Dagreou F, Clemenceau S, Foncin J-F, Rivierez M, Philippon J: Intracranial meningiomas in elderly patients: Postoperative morbidity and mortality, factors predictive of outcome. Acta Neurochir Wien 102:98-102, 1990.
8. Cutler SJ, Ederer F: Maximum utilization of the life table method in analyzing survival. J Chronic Dis 8:699-712, 1958.
9. Derome PJ, Visot A: Bony reaction and invasion in meningiomas, in Al-Mefty O (ed): *Meningiomas*. New York, Raven Press, 1991, pp 169-180.
10. Ederer F, Axtell LM, Cutler SJ: The relative survival rate: A statistical methodology. NCI Monogr 6:101-121, 1961.
11. Essbach H: Die Meningiome. Vom standpunkt der organoiden Geschwulstbetrachtung, in Hueck W, Frei W (eds): *Ergebnisse der allgemeinen Pathologie und pathologischen Anatomie des Menschen und der Tiere.* München, Verlag von JF Bergmann, 1943, pp 185-490.
12. Firsching RP, Fischer A, Peters R, Thun F, Klug N: Growth rate of incidental meningiomas. J Neurosurg 73:545-547, 1990.
13. Freedman H, Forster FM: Bone formation and destruction in hyperostoses associated with meningiomas. J Neuropathol Exp Neurol 7:69-80, 1948.
14. Hakama M, Hakulinen T: Estimating the expectation of life in cancer survival studies with incomplete follow-up information. J Chronic Dis 30:585-597, 1977.
15. Hakulinen T: On long-term relative survival rates. J Chronic Dis 30:431-443, 1977.

16. Hakulinen T: Cancer survival corrected for heterogeneity in patient withdrawal. Biometrics 38:933-942, 1982.
17. Hakulinen T, Tenkanen L: Regression analysis of relative survival rates. Appl Stat 36:309-317, 1987.
18. Hoshino T, Nagashima T, Murovic JA, Wilson CB, Davis RL: Proliferative potential of human meningiomas of the brain: A cell kinetics study with bromodeoxyuridine. Cancer 58:1466-1472, 1986.
19. Jäskeläinen J, Servo A, Haltia M, Wahlström T, Valtonen S: Intracranial hemangiopericytoma: Radiology, surgery, radiotherapy, and outcome in 21 patients. Surg Neurol 23:227-236, 1985.
20. Jäskeläinen J: Intracranial meningioma. *Factors affecting recurrence.* Doctoral dissertation, University of Helsinki, Helsinki, Finland, 1986.
21. Jäskeläinen J: Seemingly complete removal of histologically benign intracranial meningioma: Late recurrence rate and factors predicting recurrence in 657 patients. Surg Neurol 25:461-469, 1986.
22. Jäskeläinen J, Haltia M, Servo A: Atypical and anaplastic meningiomas: Radiology, surgery, radiotherapy and outcome. Surg Neurol 25:233-242, 1986.
23. Jennett B, Bond MR: Assessment of outcome after severe brain damage. Lancet 1:480-481, 1975.
24. Kakkar VV, Stringer MD: Prophylaxis of venous thromboembolism. World J Surg 14:670-678, 1990.
25. Lecuire J, Dechaume JP, Buffard P: Les méningiomes de la fosse cérébrale postérieure. Neurochirurgie 17(Suppl 2):1-146, 1971.
26. Mirimanoff RO, Dosoretz DE, Linggood RM, Ojemann RG, Martuza RL: Meningioma: Analysis of recurrence and progression following neurosurgical resection. J Neurosurg 62:18-24, 1985.
27. Official Statistics of Finland VI A: 121, 126, 134, 142, 147, 152: *Mortality: Life Tables* 1956-60, 1961-65, 1966-70, 1971-75, 1976-80, and 1981-85. Helsinki, Finland, Central Statistical Office of Finland, 1963, 1968, 1974, 1980, 1984, 1987.
28. Papo I: Intracranial meningiomas in the elderly in the CT scan era. Acta Neurochir Wien 67:195-204, 1983.
29. Payne CD (ed): The GLIM System. Release *3.77. Generalized Linear Interactive Modelling Manual.* Oxford, Numerical Algorithms Group, 1986, pp 1-183.
30. Pertuiset B, Farah S, Clayes L, Goutorbe J, Metzger J, Kujas M: Operability of intracranial meningiomas. Personal series of 353 cases. Acta Neurochir Wien 76:2-11, 1985.
31. Powers SK, Edwards MSB: Prevention and treatment of thromboembolic complications in a neurosurgical patient, in Wilkins RH, Rengachary SS (eds): *Neurosurgery*. New York, McGraw-Hill Book Company, 1985, pp 406-410.
32. Rausing A, Ybo W, Stenflo J: Intracranial meningioma: A population study of ten years. Acta Neurol Scand 46:102-110, 1970.
33. Rohringer M, Sutherland GR, Louw DF, Sima AAF: Incidence and clinicopathological features of meningioma. J Neurosurg 71:665-672, 1989.
34. Salcman M: Malignant meningiomas, in Al-Mefty O (ed): *Meningiomas*. New York, Raven Press, 1991, pp 75-85.
35. Samii M, Ammirati M, Mahran A, Bini W, Sepehrnia A: Surgery of petroclival meningiomas: Report of 24 cases. Neurosurgery 24:12-17, 1989.
36. Sankila R, Kallio M, Jäskeläinen J. Hakulinene T: Long-term survival of 1986 patients with intracranial meningioma diagnosed from 1953 to 1984 in Finland: Comparison of the observed and expected survival rates in a population-based series. Cancer 1992, in press.
37. Sekhar LN, Jannetta PJ: Cerebellopontine angle meningiomas. Microsurgical excision and follow-up results. J Neurosurg 60:500-505, 1984.
38. Simpson D: The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry 20:22-39, 1957.
39. Skullerud K, Löken AC: The prognosis in meningiomas. Acta Neuropathol (Berl) 29:337-344, 1974.
40. Zülch KJ, Mennel HD: Malignant meningiomas in Klug W, Brock M, Klinger M, Spoerri O (eds): *Advances in Neurosurgery*. New York, Springer-Verlag, 1975, vol 2, pp 3-11.
41. Zülch KJ: Histological typing of tumours of *the central nervous system. International histological classification of tumours. No. 21*. Geneva, World Health Organization, 1979.

COMMENTS

In 1938, Cushing and Eisenhardt [(1)] published their classic monograph on meningiomas, which contained invaluable information on 281 patients with meningiomas that were operated upon. The monograph summarizes important information as well on 172 patients that had survived more than 5 years. In 1957, Simpson [(4)] described the probability of recurrence of meningiomas, but was unable to draw specific conclusions on the frequency, cause, or individual biological characteristics of the tumor responsible for recurrence. In 1986, Jääskeläinen [(3)] described late recurrence and was fortunate enough to follow up some patients for more than 20 years. He reported that the time in which the tumor volume doubled varied from 50 to more than 500 days. In this paper, Dr. Kallio and associates have accomplished the monumental task of compiling the data on 935

patients with intracerebral meningiomas and assessing the factors affecting operative mortality and "excess long-term survival." Although the authors skillfully analyzed the preoperative, operative, and postoperative data in their group of patients, they did not refer to two techniques that can be utilized to determine the biological tumor kinetics of meningiomas: flow cytometry and bromodeoxyuridine (BUDR) labeling. In the study by Ironside et al. [2], tumor aneuploidy was correlated with poor clinical outcome. Other studies utilizing a labeling index were able to predict faster tumor growth, and therefore, the possibility of more frequent recurrence. The relation of estrogen and progesterone binding sites to tumor growth and clinical behavior in meningiomas was not discussed in this paper. Drs. Kallio et al. succinctly emphasize the major risk factors associated with operative morbidity and mortality. Their statistical data will be invaluable to the surgeon as he formulates his operative plans and can be shared with patients and their families, so that they can better understand the prognosis. They stress that in high-risk patients with tumors in difficult locations, such as the skull base, the operatiave strategy, technique, and expectations must be continually modified to decrease operative morbidity and mortality.

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REFERENCES: [1-4]

1. Cushing H, Eisenhardt L: Meningiomas: Their *Classification, Regional Behavior, Life History, and Surgical End Results*. Springfield, IL, Charles C Thomas, 1938.
2. Ironside JW, Battersby RDE, Lawry J, Loomes RS, Day CA, Timperly WR: DNA in meningioma tissues and explant cell cultures: A flow cytometric study with clinical pathological correlates. J Neurosurg 66:588-594, 1987.
3. Jäskeläinen J: Seemingly complete removal of histologically benign intracranial meningiomas: Late recurrence rate and factor predicting recurrence in 657 patients. Surg Neurol 26:461-469, 1986.
4. Simpson D: The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry 20:22-39, 1957.

In this paper, Kallio et al. present survival data on a large series of patients who were treated for an intracranial meningioma. Factors associated with operative mortality are identified as well as those factors associated with long-term mortality. As our population ages and our imaging studies improve, more patients with incidental meningiomas are being encountered. The information presented in this paper will be very helpful for making rational decisions

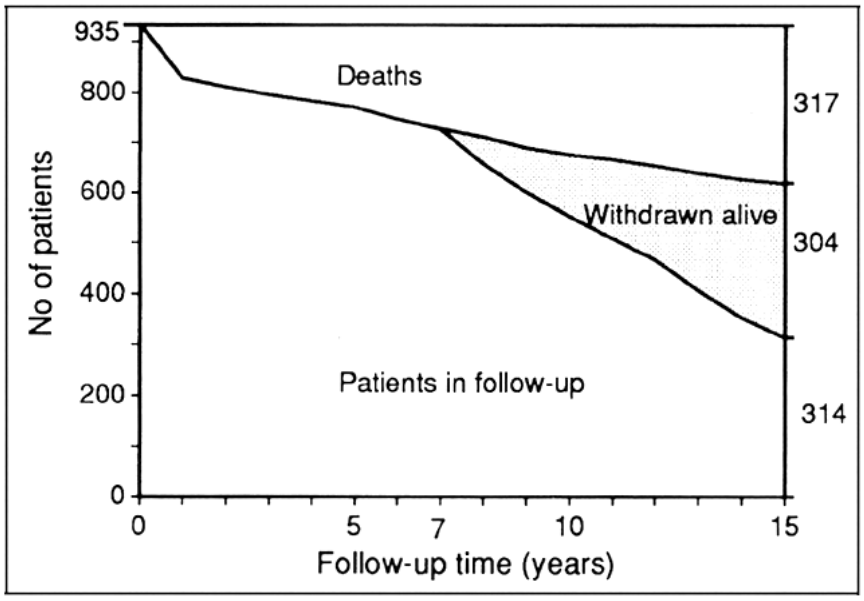

Figure 1. Follow-up data on 935 patients who underwent removal of an intracranial meningioma. The cumulative total number of deaths (317), withdrawals (304), and patients in follow-up (314) at 15 years are depicted on the right of the graph.

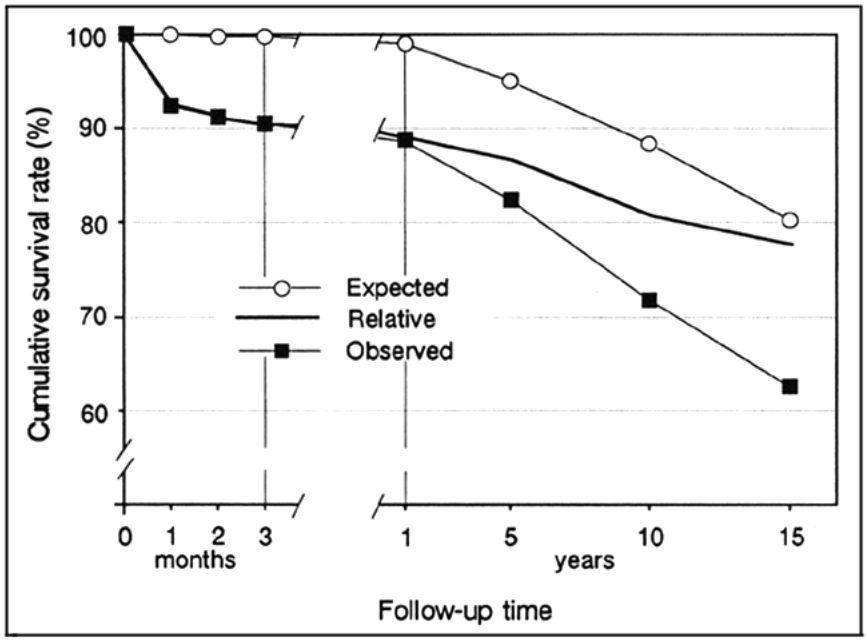

Figure 2. Cumulative expected, observed, and relative survival rates of 935 meningioma patients. Follow-up time is divided into three periods: 0 to the 3rd month, the 4th to 12th months, and the 2nd to 15th years.

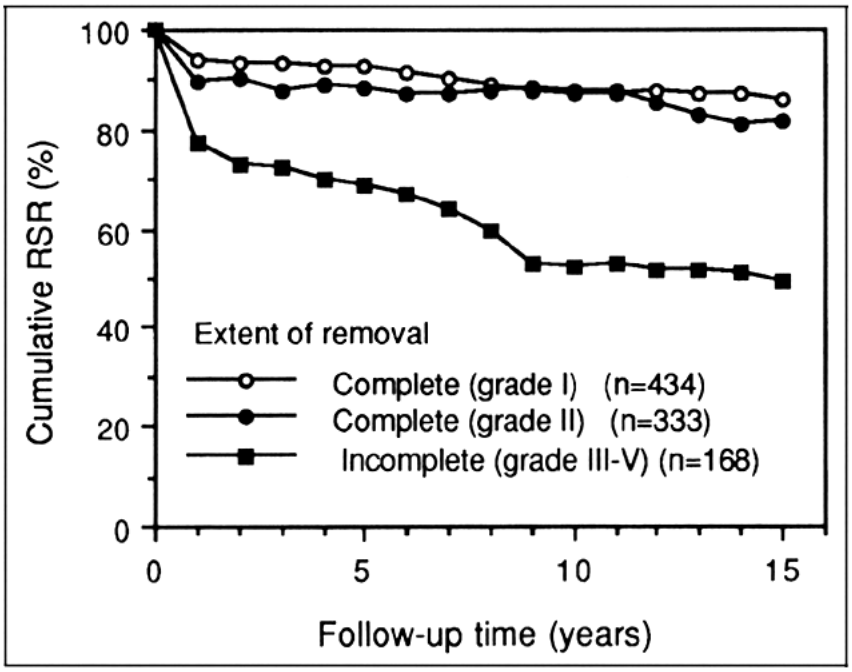

Figure 3. Relative survival rates (*RSR*) after complete (Simpson's Grades I-II) or incomplete (Simpson's Grades III-V) removal of a meningioma.

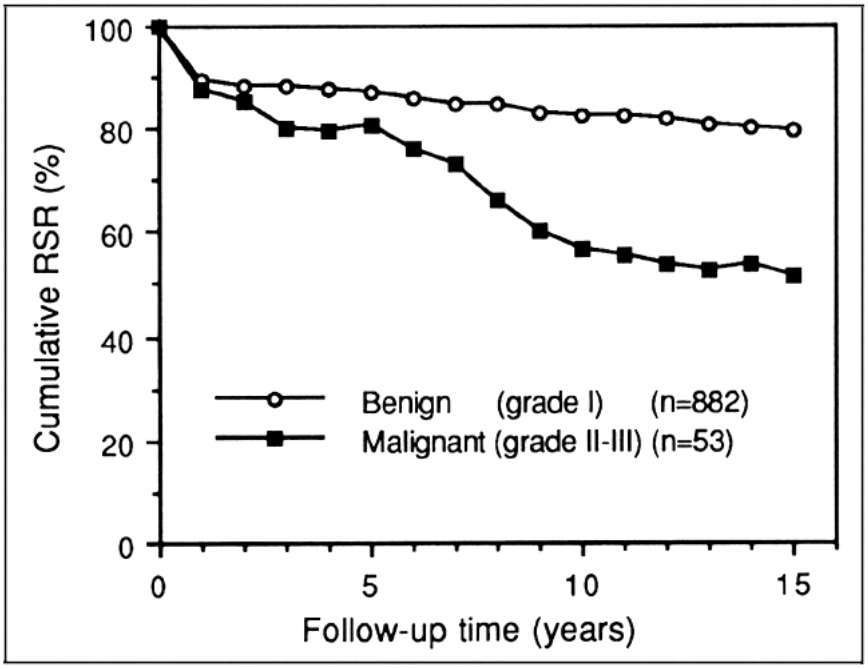

Figure 4. Relative survival rates (*RSR*) after removal of a histologically benign (Grade I) or malignant (atypical Grade II or anaplastic Grade III) meningioma.

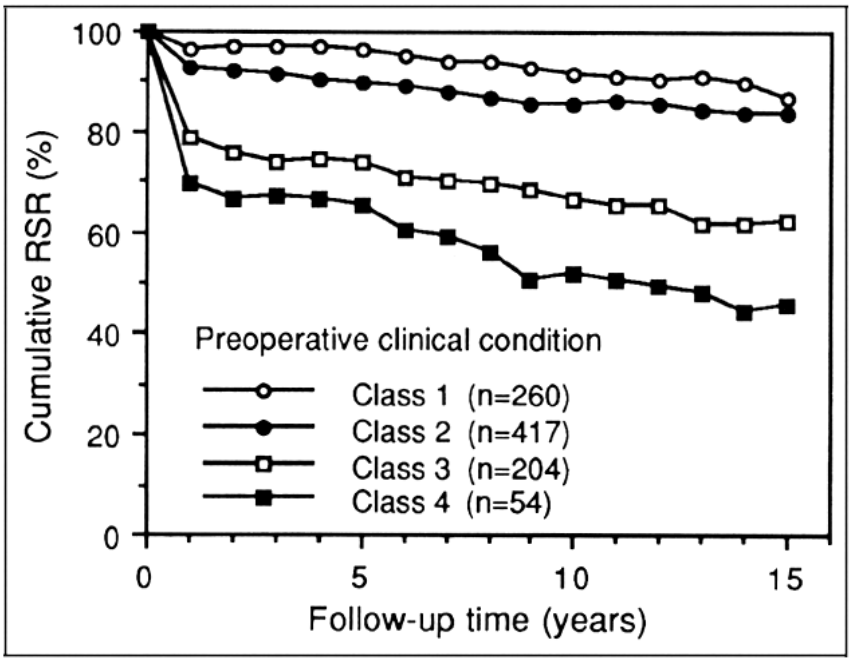

Figure 5. Relative survival rates (*RSR*) of meningioma patients in good preoperative condition with no (Class 1) or slight (Class 2) neurological deficits and of patients in poor preoperative condition with severe neurological deficits (Class 3) or who were in need of hospital care (Class 4).

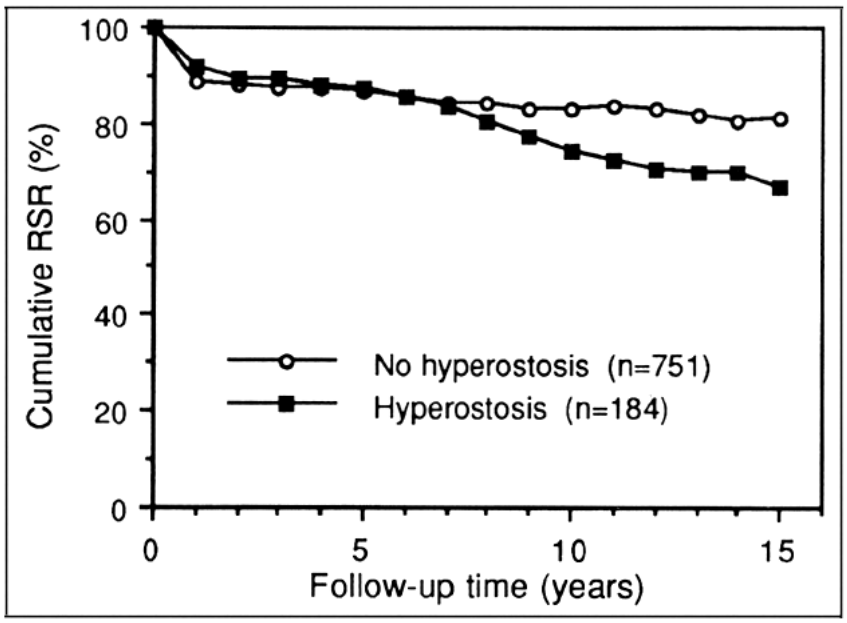

Figure 6. Relative survival rates (*RSR*) of patients with or without hyperostosis adjacent to the meningioma.

Diagnosis after Reexamination	Number (%)
Meningioma	936
Benign (Grade I)	883 (94.3)
Atypical (Grade II)	44 (4.7)
Anaplastic (Grade III)	9 (1.0)
Sarcomatous (Grade IV)	
Hemangiopericytoma	18
Glioma, Grade III–IV	7
Oligodendroglioma	1
Carcinoma metastasis	2
Melanoma metastasis	1
Fibrosarcoma	1
Sample not diagnostic	9
Total	975

Table 1. Results of Reexamination of Tissue Samples of 975 Intracranial Tumors Originally Termed Meningiomas

Factor	Number (%)	Factor	Number (%)
Sex		Histological type[a]	
Male	276 (30)	Benign (Grade I)	882 (94)
Female	659 (70)	Malignant (Grade II–III)	53 (6)
Age (yr; mean, 50 yr)		Infiltration of tumor into:	
3–44	97 (10)	Venous sinus	264 (28)
45–64	548 (59)	Cerebral artery	86 (9)
65–74	290 (31)	Optic nerve	193 (21)
Period of operation		Other cranial nerves	83 (9)
1953–1965	283 (30)	Bone (hyperostosis)	184 (20)
1966–1974	341 (37)	Tumor remaining adjacent to:	
1975–1980	311 (33)	Venous sinus	101 (11)
Headache	385 (41)	Cerebral artery	53 (6)
Preoperative epilepsy	421 (45)	Optic nerve	52 (5)
Papilledema	290 (31)	Other cranial nerve	30 (3)
Preoperative clinical condition[a]		Bone (hyperostosis)	38 (4)
Good (Class 1–2)	677 (72)	Extent of removal[c]	
Poor (Class 3–4)	258 (28)	Complete (Grade I–II)	767 (82)
Location of tumor		Incomplete (Grade III–V)	168 (8)
Convexity	209 (22)	Units of blood transfused at operation (1 unit = 450 ml)	
Parasagittal and falx	255 (27)	0	93 (10)
Olfactory and suprasellar	169 (18)	1–4	497 (53)
Sphenoid ridge and middle fossa	211 (23)	>4	345 (37)
Posterior fossa	92 (10)	Removal of postoperative hematoma	56 (6)
Bilateral tumor	186 (20)	Meningitis	33 (4)
Consistency of tumor		Pneumonia	27 (3)
Hard or soft	153 (16)	Pulmonary embolism	23 (2)
Normal	753 (84)	Removal of bone flap	31 (3)
Weight of tumor (g)		Postoperative clinical condition[a] (n = 828)[d]	
1–27	218 (23)	Good (Class 1–2)	690 (83)
28–59	226 (24)	Poor (Class 3–4)	138 (17)
60–320	234 (25)		
Not known[b]	257 (28)		

[a] See Patients and Methods for grading of clinical condition and histological anaplasia.

[b] Not measured or tumor removed incompletely.

[c] Simpson's Grade I, complete removal with excision of dura; Grade II, complete removal with coagulation of dura; Grade III–V, incomplete removal.

[d] Number of patients who survived the first postoperative year.

Table 2. Clinical Features of the 935 Meningioma Patients

Location of Tumor	Area of Attachment[a]	Extent of Removal (Simpson's Grade)[b]			
		I	II	III–V	I–V
Convexity		192	12	5	209
	Hyperostosis	54	3	2	59
Parasagittal region		116	35	23	174
	Hyperostosis	34	4	9	47
	Venous sinus	116	35	23	174
Falx		66	11	4	81
	Venous sinus	25	6	3	34
Olfactory region		3	62	9	74
	Optic nerve	0	33	4	37
	Cerebral artery	0	8	5	13
Sellar region		0	71	24	95
	Optic nerve	0	67	24	91
	Cerebral artery	0	31	10	41
Sphenoid region		24	69	59	152
	Hyperostosis	9	10	31	50
	Optic nerve	1	13	45	59
	Other cranial nerves	0	6	15	21
	Cerebral artery	2	37	45	84
Middle fossa		6	19	12	37
	Cranial nerves	1	2	7	10
Intraventricular		8	0	3	11
Tentorial		9	12	7	28
	Venous sinus	4	7	3	14
Posterior fossa		10	42	22	74
	Cranial nerves	2	23	18	43
	Venous sinus	3	9	3	15

[a] One tumor may attach to or infiltrate into more than one adjacent structure.
[b] The number of patients is given for each category.

Table 3. Extent of Removal of Tumor, According to Location and Attachment

Location of Tumor and Preoperative Condition[a]	Extent of Removal[b]			
	Complete		Incomplete	
	Number of Patients	RSR at 15 years (%)[c] % (95% Ci)	Number of Patients	RSR at 15 years (%)[c] % (95% Ci)
Convexity				
Good	132	91 (81–102)	4	126
Poor	36	86 (64–109)	0	
Parasagittal region and falx				
Good	157	102 (94–111)	14	26 (0–68)
Poor	46	88 (69–107)	5	78 (21–135)
Olfactory and suprasellar region				
Good	76	98 (86–110)	13	65 (27–102)
Poor	41	69 (48–91)	10	38 (1–74)
Sphenoid ridge and middle fossa				
Good	91	95 (82–108)	49	84 (67–101)
Poor	25	90 (68–113)	8	66 (19–113)
Posterior fossa				
Good	48	89 (73–106)	15	49 (5–94)
Poor	8		3	

[a] Good, Class 1 or 2 neurological deficits; poor, Class 3 or 4 neurological deficits.
[b] Complete, Simpson's Grade I with excision or Grade II with coagulation of dura; incomplete, Simpson's Grades III–V.
[c] The 95% confidence interval is given in parentheses. The RSR was not calculated for small patient groups.

Table 4. Cumulative Relative Survival Rate (RSR) at 15 Years after Operation, According to Location of Tumor, Extent of Removal, and Preoperative Clinical Condition of the Patient, for the 781 Patients with Benign (Grade I) Meningioma Surviving the First Follow-Up Year

Factor	Preoperative Model[a]			Operative Model[b]			Postoperative Model[c]		
	RR	95% CI[d]	*P* Value	RR	95% CI	*P* Value	RR	95% CI	*P* Value
Preoperative clinical condition			<0.0005			<0.0005			NS
Good (Class 1–2)	1.0	Reference		1.0	Reference		1.0	Reference	
Poor (Class 3–4)	2.2	1.2–3.9		2.3	1.2–4.1		1.9	1.0–3.5	
Preoperative epilepsy			<0.005			<0.005			<0.001
No	1.0	Reference		1.0	Reference		1.0	Reference	
Yes	0.4	0.2–0.7		0.4	0.2–0.8		0.4	0.2–0.8	
Age (yr)			<0.01			<0.01			<0.005
3–44	0.3	0.1–0.9		0.3	0.1–0.8		0.4	0.1–1.0	
45–64	1.0	Reference		1.0	Reference		1.0	Reference	
65–74	1.6	0.8–3.3		1.8	0.9–3.7		1.5	0.7–3.1	
Extent of removal						<0.005			<0.005
Complete				1.0	Reference		1.0	Reference	
Incomplete				3.0	1.6–5.5		2.9	1.6–5.5	
Pulmonary embolism									<0.0005
No							1.0	Reference	
Yes							7.5	3.3–17.0	
Removal of intracranial hematoma									<0.0005
No							1.0	Reference	
Yes							3.9	1.9–8.0	

[a] Nonsignificant preoperative factors: sex; headache; papilledema; period of operation.

[b] Nonsignificant operative factors: location of tumor; histological type of tumor; bilateral tumor; weight; infiltration of tumor into venous sinus, cerebral artery, optic nerve, other cranial nerve, or bone; tumor left in venous sinus, cerebral artery, optic nerve, other cranial nerves, or bone.

[c] Nonsignificant (NS) postoperative factors: preoperative clinical condition; meningitis; removal of bone flap; amount of blood transfused at operation.

[d] CI, confidence interval.

Table 5. Results of Fitting Logistic Regression Models to the Operative Mortality of the 652 Patients Operated on in the Years 1966-1980 and Point Estimates of the Mean Relative Risk (RR) of Operative Mortality Derived from the Regression Models

Model	Deviance	df[a]	Difference in Deviance[b]	Difference in df
Constant (plus)	841.8	1207		
Extent of removal	809.5	1206	32.3**	1
Postoperative clinical condition	784.9	1205	24.6**	1
Histological type of tumor	770.7	1204	14.2**	1
Preoperative clinical condition	763.3	1203	7.4*	1
Hyperostosis	756.0	1202	7.3*	1

[a] df, degrees of freedom.
[b] Significance of term inclusion: * $P < 0.01$; ** $P < 0.0005$.

Table 6. Results of Fitting Generalized Linear Models to the Annual Relative Survival Rates in the 2nd to 15th Follow-up Years of the 828 Patients Surviving the First Postoperative Year

Factor	RER	95% Confidence Interval
Extent of removal		
Complete	1.0	Reference
Incomplete	4.2	2.8–6.3
Postoperative clinical condition		
Good	1.0	Reference
Poor	3.6	2.4–5.5
Histological type of tumor		
Benign	1.0	Reference
Malignant	4.6	2.9–7.4
Preoperative clinical condition		
Good	1.0	Reference
Poor	2.3	1.5–3.5
Hyperostosis		
No	1.0	Reference
Yes	2.1	1.4–3.2

Table 7. Point Estimates of the Mean Relative Excess Risk of Death (RER) during the 2nd to 15th Postoperative Years, Derived from the Regression Model with the Best Fit for the 828 Patients Surviving the First Postoperative Year