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Willems, Peter W.A.; Taphoorn, Martin J.B.; Burger, Huib; Van Der Sprenkel, Jan Willem Berkelbach; Tulleken, Cees A.F.

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Effectiveness of neuronavigation in resecting solitary intracerebral contrast-enhancing tumors: a randomized controlled trial

Peter W. A. Willems, M.D., Ph.D., Martin J. B. Taphoorn, M.D., Ph.D., Huib Burger, M.D., Ph.D., Jan Willem Berkelbach van der Sprenkel, M.D., Ph.D., and Cees A. F. Tulleken, M.D., Ph.D.

Department of Neurosurgery, University Medical Center Utrecht; Department of Neurology, Medisch Centrum Haaglanden, The Hague; and Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands

Object. The goal of this study was to assess the impact of neuronavigation on the cytoreductive treatment of solitary contrast-enhancing intracerebral tumors and outcomes of this treatment in cases in which neuronavigation was preoperatively judged to be redundant.

Methods. The authors conducted a prospective randomized study in which 45 patients, each harboring a solitary contrast-enhancing intracerebral tumor, were randomized for surgery with or without neuronavigation. Peri- and postoperative parameters under investigation included the following: duration of the procedure; surgeon's estimate of the usefulness of neuronavigation; quantification of the extent of resection, determined using magnetic resonance imaging; and the postoperative course, as evaluated by neurological examinations, the patient's quality-of-life self-assessment, application of the Barthel index and the Karnofsky Performance Scale score, and the patient's time of death.

The mean amount of residual tumor tissue was 28.9% for standard surgery (SS) and 13.8% for surgery involving neuronavigation (SN). The corresponding mean amounts of residual contrast-enhancing tumor tissue were 29.2 and 24.4%, respectively. These differences were not significant. Gross-total removal (GTR) was achieved in five patients who underwent SS and in three who underwent SN. Median survival was significantly shorter in the SN group (5.6 months compared with 9 months, unadjusted hazard ratio = 1.6); however, this difference may be attributable to the coincidental early death of three patients in the SN group. No discernible important effect on the patients' 3-month postoperative course was identified.

Conclusions. There is no rationale for the routine use of neuronavigation to improve the extent of tumor resection and prognosis in patients harboring a solitary enhancing intracerebral lesion when neuronavigation is not already deemed advantageous because of the size or location of the lesion.

Key Words • **frameless stereotaxy** • **image-guided neurosurgery** • **glioblastoma multiforme** • **cytoreduction** • **gross-total removal** • **prognosis**

Frameless stereotactic systems, or neuronavigation systems, offer a means to transpose imaging information to the surgical field. Since their introduction, their use has become increasingly popular in routine neurosurgical practice,[3,5,11–13,37,40] based on the assumption that neuronavigation increases the accuracy and, therefore, the effectiveness of surgical procedures.

This assumption should be tested for two reasons. First, whether additional intraoperative spatial information leads to increased surgical effectiveness depends on the way surgeons incorporate this information in their surgical techniques. Second, the spatial information offered by the navigation system can be significantly compromized by intraoperative tissue displacement (brain shift).[9,14,22,28,35]

Unfortunately, quantifying the clinical benefit of neuronavigation is not a simple endeavor. Many authors have made attempts at this, but their reports bear the disadvantages of subjective and qualitative outcome measures[4,5,12,13,16,34,36,38,40–42] or retrospective analyses.[31,43] Even in a prospective study the researcher needs to deal with problems introduced by different types of surgical procedures, different surgeons' intentions and abilities, and a lack of blindedness to study factors.

For these reasons we performed a study to quantify the effect of neuronavigation on one specific type of surgical procedure: the debulking of a solitary intracerebral contrast-enhancing tumor. Our primary aim was to determine whether the extent of resection would improve due to neuronavigation and whether this would result in extended patient

Abbreviations used in this paper: ACC = Anderson Cancer Center; BI = Barthel index; GBM = glioblastoma multiforme; GTR = gross-total removal; HR = hazards ratio; KPS = Karnofsky Performance Scale; MR = magnetic resonance; QOL = quality of life; SD = standard deviation; SN = surgery involving neuronavigation; SS = standard surgery.

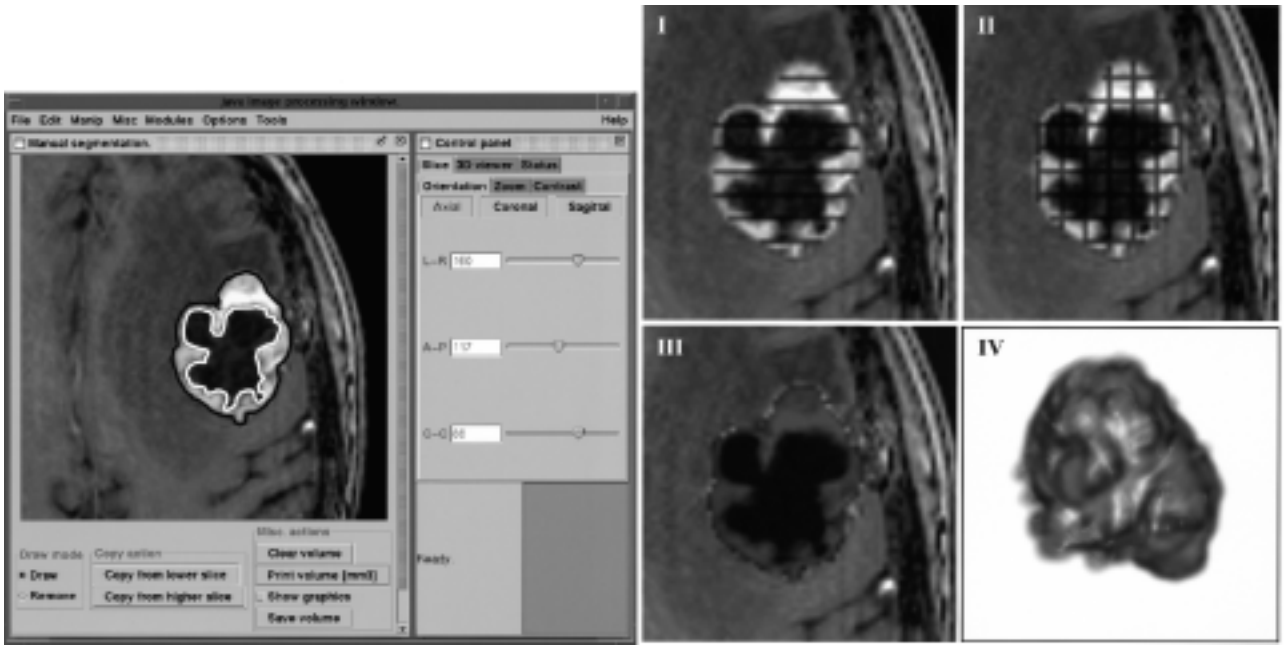

FIG. 1. Illustration of the segmentation process performed using in-house software. *Left:* Image of the user interface showing a representative case. Window width and level, image zoom, and slice orientation are adjustable, enabling accurate segmentation in all orthogonal planes. Two volumes are determined: the tumor volume and the contrast-enhancing volume. In many cases, the latter is derived by subtracting the nonenhancing volume from the total volume. No distinction is made between homogeneous or heterogeneous contrast enhancement. *Right:* Images illustrating the four steps used in each volumetric assessment: the axial slice located approximately through the tumor after delineating the total tumor volume in every fifth coronal slice (I); the same axial slice after delineating the total tumor volume in every fifth sagittal slice (II); the same axial slice after delineating the total tumor volume in every axial slice (III); and a three-dimensional reconstruction of the segmented volume (IV). The volume is automatically quantified based on the known voxel dimensions (1.1 mm^3).

survival without increasing the incidence of postoperative morbidity or decreasing the patient's postoperative QOL.

Clinical Material and Methods

Patient Selection and Randomization

Approval for this study was obtained from our institutional review board in August 1999, and patients were admitted to the study between November 1999 and December 2002. Because the histological diagnosis was unknown at the time of patient inclusion, we chose to include those patients harboring a solitary intracerebral space-occupying lesion with (partial) contrast enhancement that was eligible for surgical debulking with the intention of GTR. Patients were excluded from the study if they had received previous surgical treatment or if they harbored a known primary tumor elsewhere in the body. Finally, the study was not undertaken to determine whether neuronavigation can aid in the finding of a small deep-seated lesion; we believe that this is self-evident. Instead, we focused on the question of whether the extent of resection could be influenced by neuronavigation. Therefore, the surgeon needed to be more or less indifferent to the use of neuronavigation, considering the size and location of the lesion in each specific case, to allow inclusion of a particular patient.

After we had obtained their informed consent, the patients were divided into four strata according to their ages (<45 or ≥ 45 years) and KPS score (≤ 70 or >70).[44] The patients were evenly randomized to SS or SN by using a computer-generated list with allocation codes in random order, balanced for each stratum using blocks of four.

Preoperative Placement of Fiducial Markers and Image Acquisition

In patients in the SN group, four bone markers (OSTREG; Leibinger, Freiburg, Germany) were applied as registration fiducial markers prior to image acquisition. These were applied after local anesthesia had been induced by using a distribution strategy suggested by others.[21]

Preoperative MR images were obtained in patients in both the SS and SN groups by using a Philips ACS-NT 0.5-tesla system (Philips Medical Systems; Best, The Netherlands). The MR imaging studies involved contrast-enhanced axial three-dimensional T_1-weighted imaging of 140 axial slices with voxels measuring $1 \times 1 \times 1.1$ mm^3.

Depending on the localization of the lesion, the functional grade of the tumor was recorded according to a scheme developed at the M. D. Anderson Cancer Center (Houston, TX) (ACC Grade I, noneloquent brain; Grade II near eloquent brain; and Grade III, eloquent brain).[39] Volumetric measurements were performed to assess the total lesion volume as well as the contrast-enhancing volume by using in-house software (Fig. 1).

TABLE 1

*Characteristics of patients at the time of their inclusion in the study**

Factor	SS Group (22 patients)	SN Group (23 patients)
male sex (%)	36	26
age in yrs (mean ± SD)	60.8 ± 12.1	60.6 ± 12.1
total tumor volume in cm^3 (mean ± SD)	68.4 ± 48.9	54.2 ± 31.4†
contrast-enhancing volume in cm^3 (mean ± SD)	33.6 ± 26.6	37.0 ± 27.6†
ACC grade (no. of patients)		
I	7	8
II	7	11
III	8	4
histological diagnosis (no. of patients)		
anaplastic	5	3
GBM	16	15
metastasis	1	5
BI		
median	20	20
mean ± SD	18.1 ± 4.1	17.4 ± 5.0
KPS score		
median	80	80
mean ± SD	78.6 ± 15.5	77.4 ± 19.4

* anaplastic = anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic mixed glioma.

† Information available for 22 patients: in one patient preoperative images were lost from the archives.

Surgical Procedure

In cases scheduled for neuronavigation, the MR images were transferred to the planning station of the navigation system. Consecutive preoperative planning consisted of localization of the fiducial markers, determination of the surgical trajectory, and segmentation of the tumor boundary. This crude tumor segmentation only served to facilitate neuronavigation and was not used in any of the analyses.

When applicable, the neuronavigation tools used consisted of an infrared pointer device (STN; Carl Zeiss, Oberkochen, Germany), a mechanically tracked operating microscope with a heads-up display (MKM; Carl Zeiss), or both, depending on the surgeon's preference. All 13 neurosurgeons participating in this study were acquainted with the use of the neuronavigation equipment.

The duration of each procedure was recorded in two steps: from induction of anesthesia to skin incision and from skin incision to wound closure. The first step was used as an objective measure of time added to the preparation period for installation of the neuronavigation equipment. Immediately postoperatively, the surgeon was asked to indicate how useful neuronavigation had been, if used. Four categories, similar to those used by others,[43] were recognized: disadvantageous, neutral (neither a burden nor beneficial), advantageous, or essential for the procedure.

Postoperative Imaging

Magnetic resonance images were acquired within 72 hours postoperatively, as advocated by Forsting, et al.,[10] using the same imaging protocol as was followed preoperatively. Again, volumetric measurements were performed to assess both the total lesion volume and the contrast-enhancing volume.

Clinical Evaluation

In addition to an assessment of patient records, we also interviewed and examined the patients preoperatively, within 3 days postoperatively, and approximately 1 week, 6 weeks, and 3 months after surgery to gather information on adverse events and neurological status. The patients' KPS[15] and BI[20] scores were assessed preoperatively and again approximately 3 months postsurgically. A QOL questionnaire, the European Organization for Research and Treatment of Cancer QLQ-C30 extended with the Brain 20 module,[1] was filled out by each patient preoperatively and again approximately 3 months after surgery. Finally, the time of the patient's death was recorded.

Statistical Analysis

All analyses were performed with and without adjustment for potential prognostic variables. The histological diagnosis (anaplastic glioma, GBM, or metastasis) and the ACC grade were considered covariates with the potential to influence the surgical procedure and, therefore, were entered into the adjusted analyses regarding residual tumor volumes. All other adjusted analyses were performed with the histological diagnosis and the patient's KPS score and age as covariates, because these are generally accepted to have independent prognostic value in cases of high-grade gliomas.[8,18,24,25,45] Differences in proportions were tested for statistical significance by using the chi-square test. A statistical comparison of continuous outcome measures was performed using the Student t-test, and an adjustment was accomplished using multiple linear regression. To estimate survival curves, we used the Kaplan–Meier method. Adjusted analyses of survival were obtained using Cox proportional hazards models yielding HRs as measures of instant relative risk. Statistical significance was defined as a probability value less than 0.05.

Results

Study Population

Between November 1999 and December 2002, 46 patients entered the study; one was later excluded when surgery (and subsequent histological analysis) revealed a meningioma. From a database containing information on all patients surgically treated for an intracranial tumor, we learned that during the same period 280 patients underwent surgery for a high-grade glioma or metastasis. This category differs from our inclusion criteria in the sense that we did not include patients with nonenhancing tumors, multifocal tumors, or a known primary tumor elsewhere in the body. Nevertheless, these numbers suggest that only a small number of eligible patients were included in the study. This was largely due to logistical factors concerning the availability of imaging at the correct intervals. Twenty-two patients were randomized to the SS group and 23 to the SN group. In both treatment groups, patients were similarly distributed among the 13 neurosurgeons. Further descriptive statistics according to randomized intervention are presented in Table 1. A few differences of potential prognostic value were observed: the ACC grade distribution tended toward more

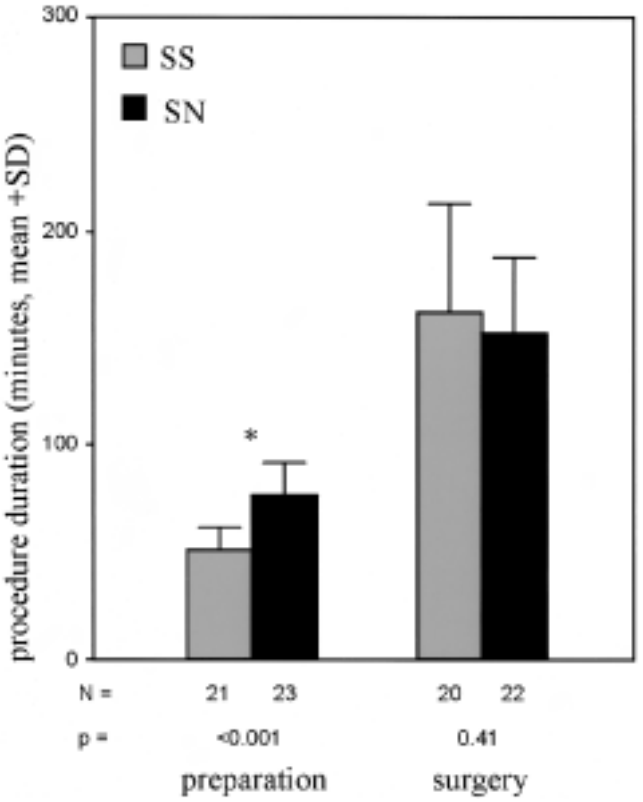

FIG. 2. Bar graph showing the duration (in minutes) of preparation and surgery. Preparation was measured from the time of anesthesia induction until skin incision and surgery from skin incision until skin closure. The numbers of cases (N) that were analyzed and the probability values (p) are provided below the bars.

Grade III lesions in the SS group, and the histopathological distribution tended toward more metastases in the SN group.

Procedure Duration

In all but one case involving SN, the MKM microscope system was used. On average, installation of neuronavigation equipment added 26 minutes to the preparation time ($p < 0.001$). The surgery took an average of 12 minutes less time when neuronavigation was used, but this was not significant (Fig. 2).

Usefulness of Neuronavigation

The surgeons' postoperative evaluations of the usefulness of neuronavigation are shown in Fig. 3. The use of neuronavigation was in no case deemed disadvantageous. It was believed to have been advantageous or essential for the procedure in 78% of the cases.

Extent of Resection

Pre- and postoperative MR imaging studies were available for segmentation in 42 patients. The reliable segmentation of tumor volume and contrast-enhancing volume was not feasible in eight and two cases, respectively. Moreover, the segmentation of contrast-enhancing tissue and, consequently its analysis, should be considered more robust than the segmentation of the total tumor volume.

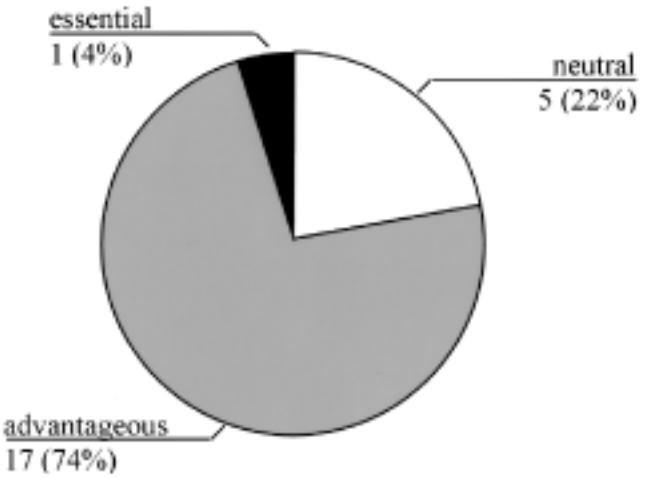

FIG. 3. Pie graph showing evaluations by surgeons of the usefulness of neuronavigation during the procedures, as indicated immediately postoperatively. The category "disadvantageous" was not used in any case. The category "neutral" is used to indicate that neuronavigation is neither experienced as a burden nor as beneficial.

A comparison of residual tumor volumes, relative to preoperative volumes, is found in Fig. 4. The mean difference between the SS and SN groups was 15.1% for tumor volume and 4.8% for contrast-enhancing volume. These differences were not significant in either the unadjusted or adjusted analysis, with probability values of 0.28 and 0.90, respectively. Gross-total removal was achieved in five patients in the SS group and three in the SN group, as evidenced by the lack of residual tumor tissue seen on postoperative MR images for both total tumor volume and contrast-enhancing volume.

Postoperative Course

When the findings of the first postoperative neurological evaluation (performed within 3 days posttreatment) were compared with those of the preoperative neurological evaluation, 31.8% of patients exhibited new or worsened neurological deficits (45.5% of patients in the SS group and 18.2% in the SN group; $p = 0.10$). In 64.3% of these patients, the new or worsened deficits subsequently subsided either completely or partially (80% of patients in the SS group and 25% in the SN group). The postoperative courses, as determined from all postoperative neurological evaluations during the first 3 months, showed no further remarkable differences between the two groups.

During the first 3 months after surgery, seven patients (31.8%) in the SS group and seven patients (30.4%) in the SN group experienced a new, nonneurological adverse event. In three patients in the SN group these events were fatal (pulmonary embolism, cardiac arrest with pulseless electrical activity, and postoperative pulmonary insufficiency). Other adverse events included pulmonary or urinary tract infection, surgical removal of an epidural hematoma, surgical cyst drainage, repeated tumor debulking, cerebrospinal fluid leakage, postoperative delirium, and insufficiently treated steroid-induced diabetes.

Postoperative BI and KPS scores were available in 23 patients 3 months after surgery (77.4% of patients still living

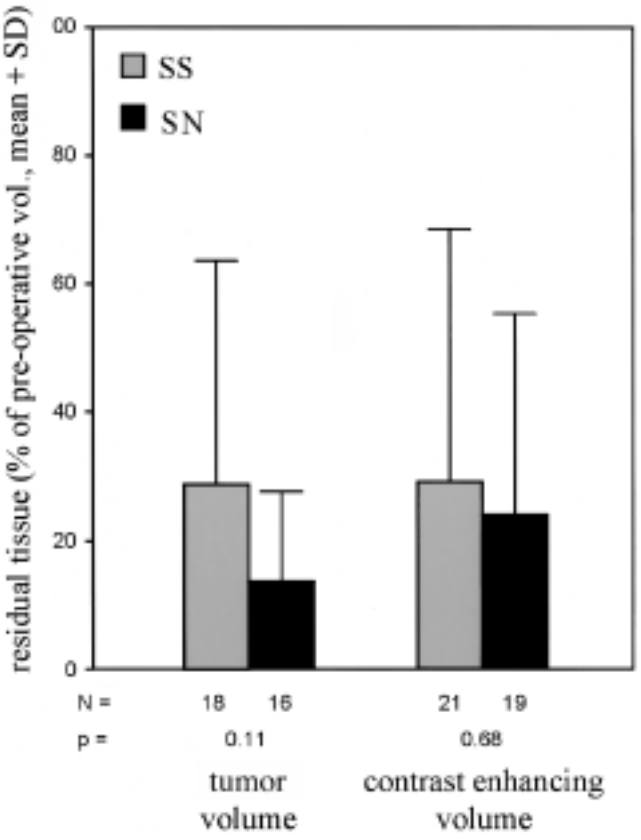

FIG. 4. Bar graph showing the difference between preoperative and early postoperative tumor volumes and contrast-enhancing volumes for each treatment group. Not all cases are represented by the bars because reliable measurements could not be performed in a number of cases. The numbers of cases that were analyzed and the probability values resulting from the unadjusted analysis are provided below the bars.

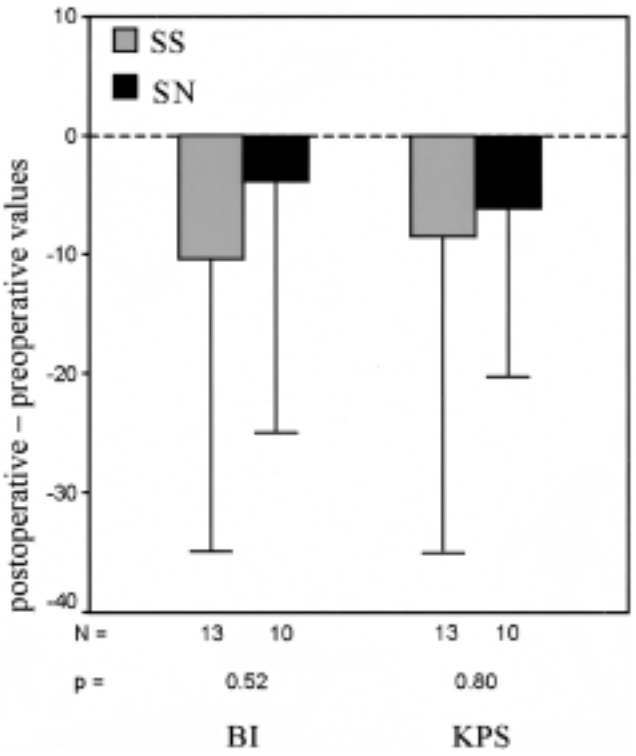

FIG. 5. Bar graph demonstrating the difference between the patients' preoperative and 3-month postoperative BI and KPS scores. Both scales range from 100 (for BI independent; for KPS no symptoms) to 0 (for BI extremely dependent; for KPS dead). Negative values for the difference indicate worsening of the patients' conditions. The numbers of cases analyzed and the probability values resulting from the unadjusted analysis are provided below the bars. Lines represent SDs.

at that interval). These are presented, relative to preoperative values, in Fig. 5. The differences were relatively small, but worsening in the patient's condition was more pronounced in the SS group than in the SN group, although this difference was not statistically significant. The possible advantageous influence of neuronavigation may be underestimated, because more patients in the SN group received radiotherapy (30% of patients in the SN group compared with 23% in the SS group) and fewer patients in the SN group continued to receive corticosteroid medications (20% of patients in the SN group compared with 46% in the SS group) at the 3-month follow up.

Postoperative QOL questionnaires were filled out by 19 patients at the 3-month follow up (64.5% of patients still living at that interval). All single-item measures and multi-item scales were calculated and compared with preoperative values (Fig. 6). The direction of change differed in seven of the 26 subscores (all from the Brain 20 questionnaire, four in favor of SN and three in favor of SS). Again, more patients in the SN group received radiotherapy (38% of patients in the SN group compared with 27% in the SS group) and fewer patients in that group continued to receive corticosteroid medications (13% in the SN group compared with 45% in the SS group) at the time the questionnaires were completed.

The average postoperative hospital stay ($\pm$ SD) was 14.6 $\pm$ 14.2 days in the SS group and 9.9 $\pm$ 6.1 days in the SN group. As noted earlier, three patients died during hospitalization. Twelve patients were transferred to another hospital (five patients in the SS group and seven in the SN group). The remaining 30 patients were discharged to their homes (17 patients in the SS group and 13 in the SN group).

Patient Survival

At the time of the study closeout, August 1, 2004, three patients were still alive and four had been lost to follow up. The median survival time was 9 months in the SS group and 5.6 months in the SN group. The results of the Kaplan–Meier analysis are shown in Fig. 7. The risk of mortality in patients in the SN group was on average approximately 60% higher than that in patients in the SS group, but this difference was not significant (HR = 1.6, p = 0.13). The adjusted analysis showed a significant doubling of the mortality risk in the SN group (HR = 2.2, p = 0.037). In a sensitivity analysis, the addition of the ACC grade as a covariate did not influence the results remarkably.

Discussion

In this report we describe a prospective randomized study

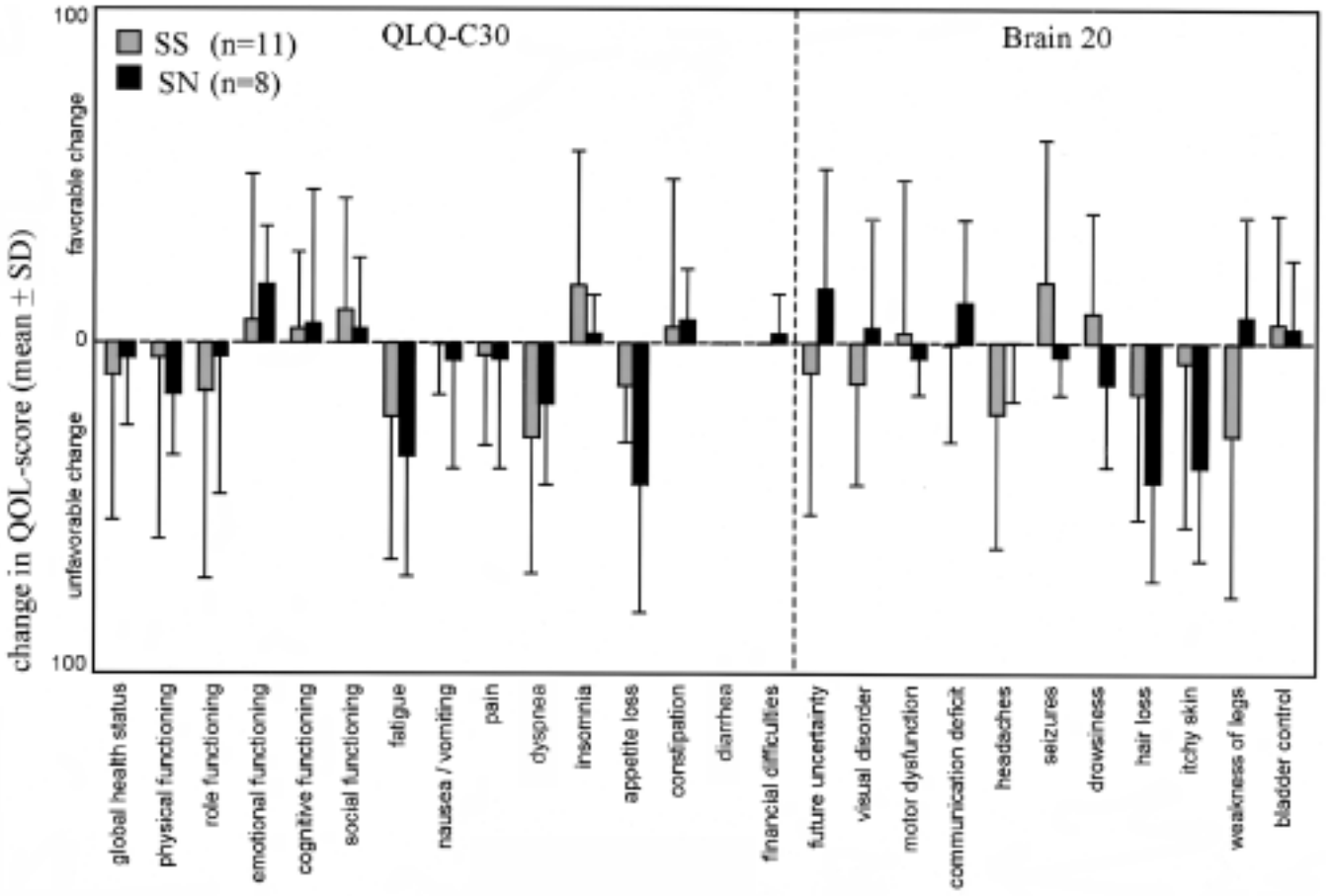

FIG. 6. Bar graphs showing the difference between preoperative and 3-month postoperative QOL results. Individual values can vary from 0 to 100 and can be subdivided into functional scales (100 being optimal) and symptom scales (0 being optimal). For a qualitative comparison, all results are displayed with favorable changes shown in the same direction.

designed to determine whether the routine use of neuronavigation in debulking solitary intracerebral (partially) contrast-enhancing tumors increases the extent of resection and prolongs patient survival. Secondary to these outcome measures, the duration of the surgical procedure and the 3-month postoperative clinical course, including the patients' BI and KPS scores and QOL self-assessments, were compared.

The histopathological characteristics of lesions in our study population reflect the fact that the mainstay of solitary intracerebral contrast-enhancing tumors eligible for debulking consist of high-grade gliomas (86.7% of the tumors were anaplastic gliomas or GBMs; the remaining lesions were metastases). Early reports did not demonstrate a beneficial effect of cytoreductive therapy on high-grade gliomas;[32] however, these studies relied on the surgeon's estimate of the extent of resection, which has been shown to be a very unreliable measure.[2,23] In the last decade researchers in many studies in which early postoperative computerized tomography and/or MR imaging have been performed have found that the extent of resection, and GTR in particular, is a strong and independent variable that affects survival.[2,7,10,18,19,23,30,45] Although the results of these studies support an argument for the radical resection of malignant gliomas, none of them may be considered conclusive because they are not derived from randomized prospective studies. One important reason such a randomized prospective study has not been performed has been the lack of an external control over the extent of resection.

Nevertheless, based on these results, techniques are being pursued that allow for safe and radical tumor resection. To date, the findings of only a few studies suggest a role for neuronavigation in this pursuit on the basis of objective evaluation.[33,43] In these studies, researchers compared the extent of resection in patients who underwent SN with those of historical controls. To our knowledge, there has been no previous report of a prospective randomized study in which the impact of neuronavigation on cytoreductive neurosurgical procedures was evaluated.

Our results failed to show a significant impact of neuronavigation on the extent of resection or on the ability to achieve GTR. Accordingly, patient survival was not prolonged by the use of neuronavigation; rather, survival appeared to be shortened by its use. It is important to note that based on these data it cannot be said whether aggressive resection of cerebral tumors has any prognostic implication for survival. We can merely conclude that neuronavigation did not improve the prognosis for tumor resection in this set of patients.

A number of study limitations should be recognized. First

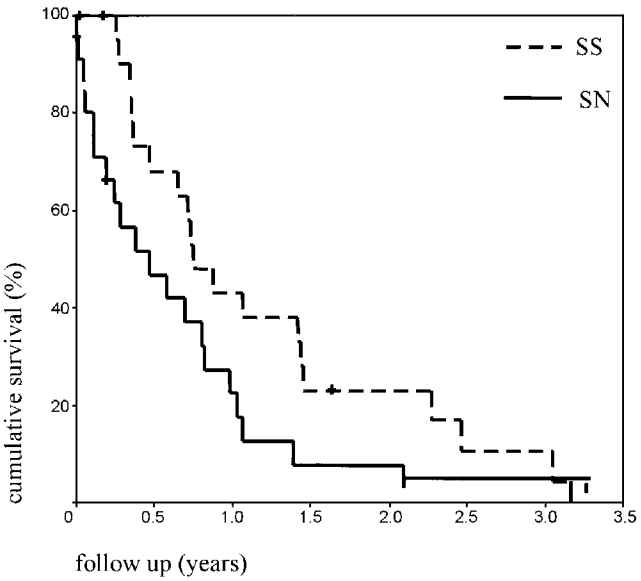

FIG. 7. Graph depicting the findings of the Kaplan–Meier survival analysis.

and most importantly, the analysis was underpowered. Based on the results of a power analysis, we originally planned to include 91 patients in each treatment group (182 patients total). We then decided to perform a pilot analysis involving the first 45 patients admitted to the trial; we believe that the results of that analysis, presented in this paper, discourage the continuation of the trial. Another limitation of this study is the fact that the surgeries were performed by many different surgeons, which introduced potential variations in surgical intentions and abilities. In addition, neither surgeon nor patient could be blinded to the type of treatment used in the procedure, and inclusion was only possible when the surgeon regarded neuronavigation as superfluous, resulting in a very specific patient population and hindering a comparison of our results with routine clinical practice.

Although the differences in survival rates may be explained by differences between the two treatment groups regarding the ACC grade and histopathological diagnosis (Table 1), another possible explanation is the coincidental early postoperative death of three patients in the SN treatment group. In our series, the number of patients who experienced (temporary) increased or new neurological deficits postoperatively was greater (although not significantly so) in the SS group than in the SN group. This may be due to differences in surgical procedures such as craniotomy size or brain retraction. In any case, these numbers suggest that neuronavigation did not result in careless or overly aggressive surgery, and it is therefore unlikely that the three fatalities were attributable to the use of neuronavigation.

In an attempt to evaluate the 3-month postoperative BI and KPS scores and QOL self-assessments, incomplete data were obtained. Because this was most probably caused by reduced patient compliance due to disease progression, this may have biased the results. Although this would be true for both treatment groups, it forces us to be cautious in our interpretation of the results, especially given that the influence of radiotherapy and corticosteroids may have led to an underestimation of the effect of neuronavigation. Nevertheless, important differences between the two treatment groups were not recognized.

In contrast to our disappointing results, neuronavigation was subjectively judged by the surgeon to be advantageous in the vast majority (78%) of cases. This is similar to surgeons' judgments in other studies (86.5%[43] and 81%[12]), and it is important to note that it does not bear any relevance to objective outcome measures.

An explanation for the fact that neuronavigation did not improve the extent of resection in our series may be found in two aspects of navigated open neurosurgery. First, the way in which surgeons' actions are influenced by the information offered by the neuronavigation system is uncontrollable. Based on skepticism regarding the impact of cytoreductive therapy on the prognosis of a glioma, having seen many recurrences throughout their careers, and a reluctance to risk the appearance of new postoperative neurological deficits, neurosurgeons may abort surgery prematurely. Second, the accuracy of the information offered by the neuronavigation system is known to degrade during the course of surgery, as a result of brain shift.[9,14,22,28,35] Neurosurgeons are aware of this fact, and thus it will also contribute to their caution.

In the pursuit of techniques that will allow radical resection, more promising results have been published regarding the use of neuronavigation together with intraoperative imaging.[6,17,26,27,29] These results are generally attributed to the fact that intraoperative imaging compensates for brain shift and demonstrates residual tissue at a time when surgery can still be continued. Therefore, future research may be better targeted at the improvement and evaluation of neuronavigation based on intraoperative imaging rather than on preoperative imaging.

Our results should by no means be extrapolated to other neurosurgical procedures. We chose to examine a very well-defined and frequently performed surgical procedure in which the efficacy of using neuronavigation has been thought to be debatable. We believe that the use of neuronavigation should be evaluated for each case individually, weighing known pros and cons. We confirmed earlier findings that neuronavigation adds to preparation time[43] and that a new preoperative MR imaging examination is usually required, adding to the cost of the surgery. These investments are only worthwhile when neuronavigation may be expected to improve surgical outcome. Unfortunately, to date little evidence exists with which to determine whether such an expectation is justifiable. Future studies are necessary to gather such evidence for each type of neurosurgical procedure.

Conclusions

Based on our results, we conclude that the extent of resection and consequent prolongation of patient survival is not enhanced by the use of neuronavigation in the debulking of solitary enhancing intracerebral tumors. Therefore, there is no rationale for its routine use in cytoreductive surgery when it is not a priori expected to be advantageous based on the size or location of the lesion.

Disclaimer

None of the authors has any personal or institutional financial interest in the devices described in this manuscript.

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Address reprint requests to: Peter W. A. Willems, M.D., Heidelberglaan 10, 3584 CX Utrecht, The Netherlands. email: p.willems@neuro.azu.nl.