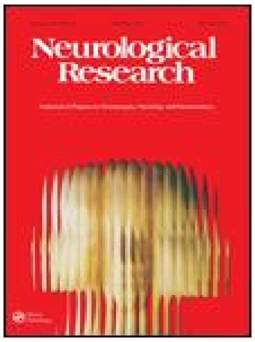

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The benefit of neuronavigation for neurosurgery analyzed by its impact on glioblastoma surgery

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The benefit of neuronavigation for neurosurgery analyzed by its impact on glioblastoma surgery

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Neuronavigation, today a routine method in neurosurgery, has not yet been systematically assessed in direct comparison with conventional microsurgical techniques. The aim of the present study was the direct comparison of the impact of neuronavigation on glioblastoma surgery regarding time consumption, extent of tumor removal and survival. For each of 52 patients operated for primary glioblastoma with neuronavigation, a patient operated on without navigation was matched. Completeness of tumor resection, including volumetric analysis, was examined by early post-operative MRI. Operating and survival times were obtained for all patients. At a rate of 86.5%, surgeons' opinions about neuronavigation were positive. Operating times were identical in the two groups, while preparation times were 30.4 min longer with navigation. Radiological radicality was achieved in 31% of navigation cases vs. 19% in conventional operations. The absolute and relative residual tumor volumes were significantly lower with neuronavigation. Radical tumor resection was associated with a highly significant prolongation in survival (median 18.3 vs. 10.3 months, $p < 0.0001$). Survival was longer in patients operated on using neuronavigation (median 13.4 vs. 11.1 months). Neuronavigation increases radicality in glioblastoma resection without prolonging operating time. Regarding the problem of brain shift, neuronavigation should be optimized by intra-operative real-time imaging. [Neurol Res 2000; **22**: 354–360]

Keywords: Neuronavigation; comparative study; microsurgery; glioblastoma surgery; outcome and process assessment (health care); Neurosurgery

INTRODUCTION

Neuronavigation, introduced into neurosurgical practice in the 1980s[1–4], has become a routine procedure in neurosurgery. The reports on the clinical application are unanimously positive. Neuronavigation is considered to have major advantages and to be superior to standard microsurgical techniques[5–10]. It has even been compared with the introduction of the operating microscope[11]. Nevertheless, critics say that there are insufficient data to substantiate this view[12] and, similar to the introduction of microsurgical techniques, hardly any systematic analysis has been conducted regarding the impact of neuronavigation on operative procedures and results as compared to standard microsurgical techniques[13,14]. To address this issue, the present study was performed to determine the usefulness of neuronavigation by investigating its effect on the surgical procedure and operative results in glioblastoma surgery as compared to conventional microsurgical techniques.

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MATERIALS AND METHODS

Patients and patient selection

Neuronavigation has been used in the surgical treatment of 68 patients with primary glioblastoma since the introduction of the technique in our department. They were followed up with early post-operative magnetic resonance imaging (EPMR) and further scans every 3–6 months. The protocol was planned according to a previous study on EPMR in high-grade glioma[15,16] in which 134 patients were included; these patients served as historical controls. Patients with prior intracranial operations or a histological diagnosis other than glioblastoma multiforme (WHO grade 4) were excluded from further analysis. In all, 52 patients could be matched to a patient in the historical group in whom microsurgical technique without neuronavigation had been used. Patients were matched according to age and side of the lesion prior to learning about surgical results. The lesions were matched as far as possible according to location and size, but due to the variability this was only partially successful. Data were collected either prospectively for EPMR and follow-up examinations or retrospectively for clinical data from patient records.

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Table 1: Characteristics of the two patient populations in comparison. *p*-values in the last row were derived from Fisher's Exact test[1] or Student's *t*-test[2]

	No navigation	Navigation	
Gender	27 m/25 f	34 m/18 f	$p=0.23^1$
Location side	26 left/26 right	26 left/26 right	
Age	56.07 ± 12.13 (22–76) yr	56.25 ± 11.3 (23–75) yr	$p=0.9^2$
Preparation time (min)	37.8 ± 10.8	68.2 ± 21.7	$p<0.001^2$
Operation time (min)	288.7 ± 95.4	288.6 ± 94.4	$p=0.99^2$
Total surgical time (min)	326.3 ± 95.5	356.9 ± 97.7	$p=0.11^2$

Operative procedures

All patients were operated on with the intention of achieving gross total removal of the tumor using standard microsurgical techniques. For neuronavigation different systems (a navigational microscope, arm-based and infrared camera systems) were used and installed after positioning of the patient as described before[6]. After patient-to-image registration, the navigational accuracy was recorded as the root mean square error (RMS) of the registration as displayed by the system's software. The surgeon's opinion regarding usefulness and purpose of neuronavigation was obtained.

Times for operative procedures from incision to wound closure and for pre-operative preparations (positioning to incision) were obtained from operative reports. The latter was chosen so as to obtain an objective measure of the time the installation of the systems might add to the preparation time. This was preferred to the navigational report forms for reasons of objectivity, completeness and comparability to the historical control group.

Post-operative ventilation time and stay in intensive care was derived from the patient records. Post-operative radiation therapy (hyperfractionated confirmation radiotherapy) or re-operation of recurrent tumors were recorded. Further treatment options (e.g. mistletoe therapy, etc.), common in glioblastoma patients, were observed but not recorded.

Evaluation of imaging data and follow-up

For the 52 patients of the historical control group, the pre-operative tumor volume was defined by measuring the area of the lesion in each of the axial MRI slices in mm^2. Multiplication with slice thickness (mm) yields the tumor volume per slice (mm^3) and by adding those volumes total tumor volume was calculated. The same method of assessing volumes of possible residual tumor in EPMR was applied for all patients. In patients in whom navigation had been used, the volume was calculated using the navigation system software after delineating the tumor contours. Where this was not possible, the first method of volumetry was used. EPMR was used to assess post-operative residual tumor as this method has been demonstrated to be superior for this purpose[15–18]. In this study the EPMR findings were evaluated independently by a neuroradiologist and one of the authors (CRW) for navigation cases; the data for the historical cases reported by another author (FKA) together with a neuroradiologist at the time of the previous study were taken for comparison. Follow-up scans were evaluated for recurrence of enhancing tumor in patients with radical resection or otherwise for progression of residual tumor. The date when recurrence or progression was observed was used to calculate the progression-free interval. If a very large recurrent tumor or marked progression was noted, a date halfway from the previous examination was assumed. Patients were followed until their death, which was used to calculate overall survival time.

Statistical methods

Statistical methods for unpaired data were applied since matching criteria were not sufficient. The following hypotheses were tested:

1. Neuronavigation significantly increases preparation time.
2. Neuronavigation significantly decreases operating time.
3. Neuronavigation significantly increases the percentage of radical operations.
4. Neuronavigation significantly decreases the volume of residual tumor.
5. Neuronavigation significantly prolongs survival time.

The level of significance was determined at $p=0.05$. To illustrate probable effects of operative radicality on the progression-free interval and survival time Kaplan Meier curves were plotted for both items. Statistical studies were performed using the SAS Software package, release 6, and the StatView Software package, release 5.0 (both SAS Institute, Inc., Cary, NC, USA) for different test procedures respectively, on a personal computer running under Windows98. The Student's *t*-test was used to compare continuous measures (tumor and relative residual volumes). For nominal variables Chi-square and Fisher's Exact tests were calculated and the log–rank (Mantel–Cox) test was applied to compare Kaplan Meier curves.

RESULTS

Comparison of patient groups

No significant demographic differences were found between patient groups (*Table 1*).

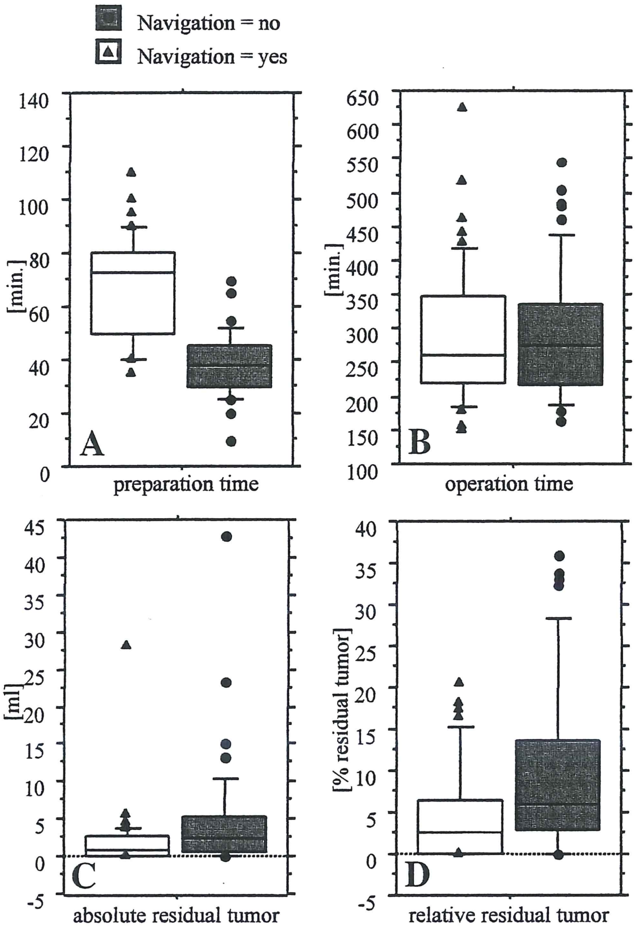


Figure 1: Comparison of the group operated with neuronavigation (unshaded with triangles) *vs.* the group operated conventionally (shaded with circles). For preparation time, absolute and relative residual tumor the difference between both groups was statistically significant (Student's *t*-test, *Tables 1* and *3*)

Assessment of neuronavigation

Surgeons' opinions

The intra-operative uses of neuronavigation, as stated by the surgeons, were planning of the approach (88.5%, 46 cases), locating critical areas/anatomical structures (73%, 38 cases), planning the cortical incision (67.3%, 35 cases), defining the tumor borders (84.6%, 44 cases), and checking the extent of tumor resection (71.1%, 37 cases). Overall, in 86.5% (45 cases) the surgeon judged neuronavigation to be helpful or advantageous for the procedure, and in 9.6% (5 cases) the surgeon was neutral; in 3.9% (2 cases) neuronavigation was considered a hindrance but never that it was harmful for the patient.

Navigation systems

In 38 of the cases a navigational microscope (MKM, Zeiss Corp., Oberkochen, Germany) and in 14 cases an infrared or arm-based pointer (Viewing Wand, ISG-Technologies, ON, Canada; OAS and OTS, Radionics Inc., Burlington, MA, USA) was used. Regarding preparation time, the microscope (68.7 ± 22.1 min) and pointer systems (66.8 ± 17.3 min) did not differ substantially. The navigation accuracy was higher with the microscope (2.6 ± 1.2 min) than with the pointer systems (3.3 ± 1.1 mm), but the difference did not reach significance ($p = 0.054$, *t*-test). There was no difference regarding residual tumor volume or percentage of radical operations between systems either.

Duration of the procedure (*Table 1* and *Figure 1*)

The mean preparation time was 37.8 min (median 37.5 min) without and 68.2 min (median 72.5 min) with neuronavigation ($p < 0.001$). On average neuronavigation added 30.4 min to the overall preparation time compared to standard microsurgical cases. Since no other difference in the preparation procedure could be identified, this increase was attributed to installing and referencing of the navigation systems, including sterile draping of the arm, pointers or reference frames. The mean operative times, on the other hand, were exactly the same for both groups: 288.7 min (median 275 min) without and 288.6 min (median 260 min) with neuronavigation ($p = 0.99$). The total surgical time taken as the sum of the preparation and operation times was accordingly longer in neuronavigation cases but the difference was not statistically significant ($p = 0.11$).

Radicality of resection

When assessing only the presence or absence of residual tumor in EPMR, the percentage of radical resection with neuronavigation was 30.7%, compared to 19.2% without it (*Table 2*). Comparing the two groups, the difference in frequency of radical tumor removal did not reach statistical significance (Chi-square: $p = 0.167$, 2-tailed Fisher's Exact Test $p = 0.249$). The mean initial tumor volume did not differ significantly in the two groups (*Table 3*). For those patients with uncertain findings on EPMR no tumor volume could be defined and they, therefore, could not be included in the analysis. This left patients either without (0 ml) or with definite residual tumor for consideration of residual tumor volume. For these, both the absolute and the relative volume of residual tumor was significantly higher in the conventionally operated group (*Table 3*). This was still true if only those patients with tumor remnants in EPMR were considered in order to exclude the influence of the higher percentage of radicality in the neuronavigation group.

Table 2: Radicality of tumor removal as assessed with early post-operative MR-imaging (EPMR) within 72 h after surgery

EPMR	No navigation	Navigation
Radical	10 (19.23%)	16 (30.77%)
Uncertain	5 (9.62%)	5 (9.62%)
Residual tumor	37 (35.58%)	31 (59.62%)

The difference in the percentage of radical resections was not statistically significant ($p = 0.167$ Chi-square).

Table 3: Volumetry of initial and residual tumor

	No navigation	Navigation	
Initial tumor volume (ml)	56.4 ± 33.4	50.2 ± 38.0	$p=0.4$
Residual tumor volume (ml)*	4.7 ± 7.5	1.8 ± 4.2	$p=0.026$
Relative residual tumor (%)*	9.7 ± 10.4	4.5 ± 5.6	$p=0.0046$
Residual tumor volume (ml)**	6.1 ± 8.0	2.8 ± 4.9	$p=0.05$
Relative residual tumor (%)**	12.4 ± 10.2	6.6 ± 5.7	$p=0.0094$

* Patients with uncertain findings in EPMR were excluded. ** Only patients with residual tumor in EPMR were included for this calculation. *p*-values in the last row were derived from Student's *t*-test[2].

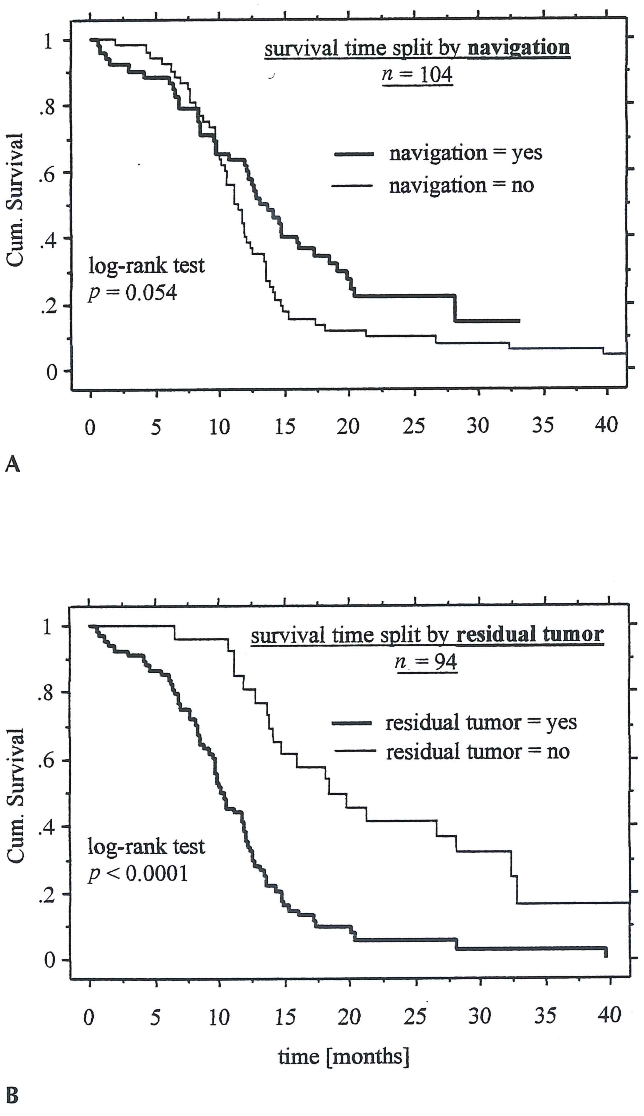


Figure 2: Kaplan Meier curves comparing the survival time for different subgroups. The difference of survival times between patients operated with *vs.* without neuronavigation was not statistically significant (**A**), but at the time of analysis, there were still 10 patients alive in the navigation group opposed to only one patient operated without neuronavigation. Grouping patients for radicality of tumor removal (**B**) yielded a highly significant prolongation in survival time for the group without radiologically detectable residual tumor (median 18.3 months) *vs.* those with residual tumor (median 10.3 months) in early post-operative MRI (10 patients with uncertain findings in EPMR were excluded from this analysis)

Survival time

Although median survival (13.4 months) was higher in the neuronavigation group than in the conventionally operated group (11.3 months), this difference was not statistically significant. Accordingly, Kaplan Meier analysis (*Figure 2A*) showed a longer survival for the group operated with neuronavigation, the difference just failing to reach statistical significance (log–krank test $p=0.054$) presumably because, at the time of the analysis, there were still 10 patients alive in the navigation group compared to one survivor in the conventionally operated group.

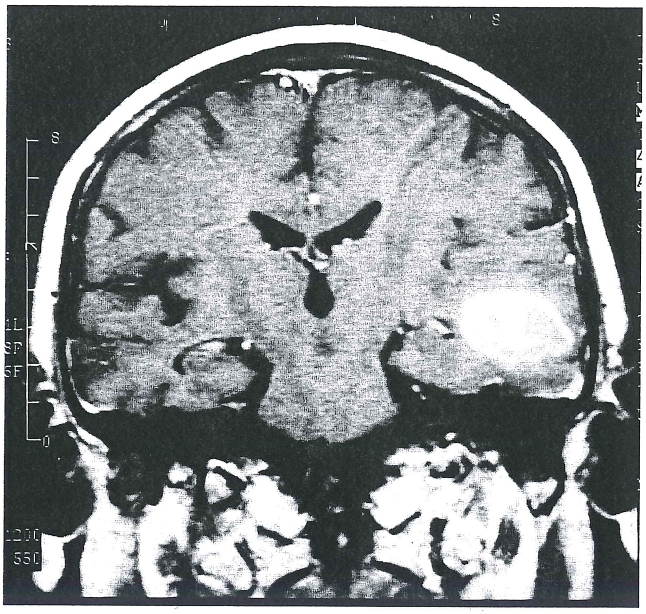
Grouping patients for absence or presence of residual tumor on EPMR revealed a highly significant difference for overall survival (*Figure 2B*) in favor of patients without radiologically detectable residual tumor. For patients with a radiologically radical tumor-resection according to EPMR mean survival time was 23.9 months (median 18.3 months) compared to a mean survival time of 11.1 months (median 10.3 months) for patients with residual tumor and 13.9 months (median 13.9 months) for patients with uncertain findings on EPMR.

DISCUSSION

Since its development, neuronavigation has rapidly been accepted by neurosurgeons and now is in routine use in many departments. Articles published on the topic mainly report on new technological developments[19–21], technology assessment, and on the clinical application or comparison of specific systems[6,10]. Most authors report major advantages of neuronavigation and according to the opinion of the surgeons using the systems it is superior to conventional microsurgical techniques[5,9,14], but these advantages have not been objectively demonstrated by systematic comparison.

Subjective impression

In the present study 86.5% of surgeons using neuronavigation judged its application positively and reported a variety of different intra-operative uses. Surgeons felt navigation to be particularly helpful in planning the surgical approach and defining tumor borders and for intra-operative orientation. This is well in accordance with the results of previous studies[6,22] and other reports have also stressed the positive judgment of the neurosurgeons operating with navigational assistance[7,9,13,23]. In a clinical series of 325 patients,



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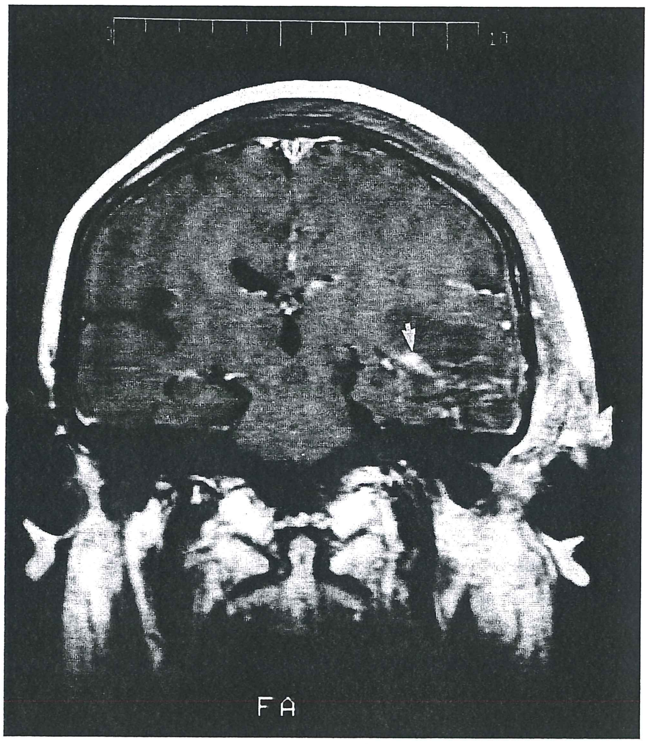

B

Figure 3: Example lesion operated on with neuronavigation. **A:** Pre-operative, contrast enhanced MRI scan of a patient with a left temporal glioblastoma. **B:** Early post-operative contrast enhanced MRI scan on the first post-operative day. Nodular enhancement on the medial border of the resection representing residual tumor (arrow) can be identified, despite the surgeon's impression of a radical resection of the lesion

Golfinos *et al.*[5] reported a subjective usefulness of up to 81.5% and a range of intra-operative uses similar to those reported here.

Objective assessment

Following these reports and our own positive experience, the present study was planned to substantiate the neurosurgeon's subjective impression and objectively demonstrate the benefits of neuronavigation in direct comparison with standard microsurgical techniques for a well-known pathological entity.

The installation of technical devices for intra-operative use obviously requires time. In the present study the use of a navigational device added 30.4 min to preparation time. The time required for setup, patient-to-image registration, additional draping maneuvers, and planning of the approach prior to skin incision correlates well with the findings of other groups, who have reported a time requirement of 10–43 min to set up their systems[13,14,24]. The assumption that the time required to set up the systems is equalized or surpassed by a shorter operating time has been made repeatedly[24], but it has hardly been analyzed objectively. Our findings do not support this view, since operation times are virtually identical for the two groups, thus prolonging total surgical time. This holds true, although no significant difference could be found for total surgical time (*Table 1*). Alberti *et al.*[13] report a slight reduction in total operating room time in 125 varying neuronavigation procedures compared to the same number of matched conventional cases, without statistical significance. Only for a subgroup of frame-based *vs.* frameless stereotactic biopsies could a significant reduction in operating room time be found, which is similar to the results reported by Sandeman *et al.*[14]. Installation of the neuronavigational systems may also be performed by a trained technician or nurse and does not necessarily increase the time-load of the neurosurgeon[5] but in the same time the surgeon is able to perform a more radical surgery.

Radicality of resection

The benefit of intra-operative integration of neuroradiological data has also been stressed in several reports in which the opinion is expressed that increased surgical radicality can be achieved with improved intra-operative orientation of the surgeon[25–28]. To our knowledge no comparative study has so far been published to prove this assumption in direct comparison to conventional microsurgical cases. For microsurgical operations of supratentorial high-grade gliomas with the intention of gross total removal, post-operative imaging showed residual tumor in up to 70%, in contrast to the surgeon's impression of radicality[15,16]. Accordingly, glioblastoma surgery in particular should benefit from intra-operative neuronavigation.

However, we could not show a statistically significant increase in the proportion of radiologically radical tumor resections through neuronavigation assessed with EPMR

(*Table 2*). Nevertheless, both the absolute and the relative volume of residual tumor detected in post-operative imaging could be reduced significantly in the group operated with neuronavigation (*Table 3, Figure 1*). The latter indicates that the improved intra-operative orientation with navigation leads to an increased amount of resected tumor tissue, as one would assume. Although this improvement was not sufficient to result in an increased percentage of radical tumor resection overall, the registration accuracy was not so low as to be responsible for this finding. A more likely reason is the intra-operative shift of anatomical structures as the resection of a lesion progresses. This so-called 'brain shift' leads to an increasing discrepancy betweeen the pre-operative dataset and the intra-operative anatomy, impairing the use of neuronavigation as a control for the radicality of resection. This problem and its implications have been described before[29–32] but the consequences for the extent of surgical tumor resection have not been demonstrated yet. These observations are not limited to glioblastoma surgery, as assessed here, but may be applied to intraparenchymal lesions with ill-defined margins in general, since these lesions are all subject to intra-operative brain shift[25,26]. The improvements that can be achieved with neuronavigation by surgeons who are aware of these problems might still be optimized by the integration of intra-operative imaging in order to compensate for brain shift. Particularly for those operations in which intra-operative shift is probable, several methods of intra-operative real-time imaging control have been repeatedly proposed. Recently, solutions have been implemented using different imaging methods such as intra-operative MRI[33–37], ultrasound[21,38,39], or CT[40–42], and first results indicate another increase in surgical radicality[43,44].

Impact on survival

The issue of radical surgery for high-grade gliomas is still a matter of controversy, but there is evidence that radicality of resection, when assessed by post-operative neuroimaging, increases progression-free and overall survival times[15,16,18,45]. Although this was not the main issue of the present study, we demonstrated that patients with no residual tumor on EPMR had a significantly prolonged survival (*Figure 2*). This finding adds more evidence to the opinion that radical surgery is beneficial for patients with glioblastoma, resulting in a prolonged survival time, which is one of the main justifications for those surgeons using neuronavigation in glioblastoma surgery.

Due to shorter follow-up in neuronavigation cases, of which 10 patients were still alive compared to one patient in the conventionally operated group, a final analysis of survival data cannot yet be made. Nevertheless, the difference nearly reached statistical significance and it is likely that the prolonged survival time in patients in whom neuronavigation is used (*Figure 2*) will reach statistical significance as the follow-up time increases.

CONCLUSION

Neuronavigation is a helpful instrument for neurosurgeons in glioblastoma surgery. The installation requires time, though not necessarily the neurosurgeon's, which is not gained by a shorter surgical procedure duration. However, this time investment pays off through the improved comfort and intra-operative orientation of the surgeon, resulting in a significant reduction of residual tumor volume. The problem of intra-operative brain shift, resulting in reduced accuracy and, hence, ultimately in sub-optimal surgical radicality, necessitates intra-operative update of the navigational data. This may be justified, because radical tumor removal in this study was associated with significantly longer survival times. Our findings demonstrate that neuronavigation, like other new technologies, has to be objectively and critically assessed in regard to the different indications, before its benefit can be ultimately judged. With an awareness of both the possibilities and limitations, neurosurgeons and patients can benefit substantially from the application of neuronavigational devices.

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