Portable Intraoperative Computed Tomography Scan in Image-Guided Surgery for Brain High-grade Gliomas: Analysis of Technical Feasibility and Impact on Extent of Tumor Resection

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BACKGROUND: Intraoperative magnetic resonance imaging is the gold standard among image-guided techniques for glioma surgery. Scant data are available on the role of intraoperative computed tomography (i-CT) in high-grade glioma (HGG) surgery.
OBJECTIVE: To verify the technical feasibility and usefulness of portable i-CT in image-guided surgical resection of HGGs.
METHODS: This is a retrospective series control analysis of prospectively collected data. Twenty-five patients (Group A) with HGGs underwent surgery using i-CT and 5-aminolevulinic acid (5-ALA) fluorescence. A second cohort of 25 patients (Group B) underwent 5-ALA fluorescence–guided surgery but without i-CT. We used a portable 8-slice CT scanner and, in both groups, neuronavigation. Extent of tumor resection (ETOR) and pre- and postoperative Karnofsky performance status (KPS) scores were measured; the impact of i-CT on overall survival (OS) and progression-free survival (PFS) was also analyzed.
RESULTS: In 8 patients (32%) in Group A, i-CT revealed residual tumor, and in 4 of them it helped to also resect pathological tissue detached from the main tumor. EOTR in these 8 patients was 97.3% (96%-98.6%). In Group B, residual tumor was found in 6 patients, whose tumor's mean resection was 98% (93.5-99.7). The Student *t* test did not show statistically significant differences in EOTR in the 2 groups. The KPS score decreased from 67 to 69 after surgery in Group A and from 74 to 77 in Group B ($P = .07$ according to the Student *t* test). Groups A and B did not show statistically significant differences in OS and PFS ($P = .61$ and .46, respectively, by the log-rank test).
CONCLUSION: No statistically significant differences in EOTR, KPS, PFS, and OS were observed in the 2 groups. However, i-CT helped to verify EOTR and to update the neuronavigator with real-time images, as well as to identify and resect pathological tissue in multifocal tumors. i-CT is a feasible and effective alternative to intraoperative magnetic resonance imaging. Portable i-CT can provide useful real-time information during brain surgery and can be easily introduced in neurosurgical theaters in daily practice.

KEY WORDS: Extent of tumor resection, Glioblastoma, High-grade glioma, Image-guided surgery, Low-grade glioma, Neuronavigation, Intraoperative-CT, 5-ALA

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ABBREVIATIONS: EOTR, extent of tumor resection; **GTR,** gross total resection; **HGG,** high-grade glioma; **i-CT,** intraoperative computed tomography; **i-MRI,** intraoperative magnetic resonance imaging; **KPS,** Karnofsky Performance Status; **OS,** overall survival; **PFS,** progression-free survival

Image-guided surgery is an accepted and widespread tool in modern neurosurgery, with the goal to improve the safety and resection radicality in neuro-oncology,[1-3] particularly during resection of infiltrating and noncleavable tumors such as high-grade gliomas (HGGs).[2] Neuronavigation has well-known limitations due to brain shift, which occurs after dural

opening and tumor debulking. This limitation implies that images used by the navigation systems are usually not updated in real time.[4,5] Moreover, errors secondary to brain shift increase in cases of large brain tumors. Ultrasonography has been extensively used in the past, particularly for localization of deep-seated lesions.[5] Currently, its role in brain glioma surgery is limited because of low-resolution in identifying pathological tissue in peritumoral areas and small separate nodules.[5] Conversely, intraoperative magnetic resonance imaging (i-MRI) has been validated as a useful tool in resection of gliomas.[1,2,6-12] However, as dedicated equipment and specific competence are required and high costs are involved, i-MRI use in neurosurgical institutions and application in routine neurosurgical practice have been limited. Interestingly, a look at future research included in a systematic review on i-MRI–guided resection of glioblastomas highlighted that it would be important to investigate the use of other intraoperative tools to increase the safety and extent of tumor resection (EOTR), such as 5-aminolevulinic acid (5-ALA) fluorescence–guided surgery and intraoperative computed tomography (i-CT).[7] The use of i-CT in brain tumor surgery was first described in 1979 by Shalit et al.[13] Portable i-CT is a further technology introduced in neurosurgery.[3,4,14-22] Previously reported experience documented the effectiveness and feasibility of i-CT in the surgical treatment of vascular malformations, meningiomas, metastases, and low-grade brain tumors.[3,18] Conversely, its role in image-guided resection of HGGs has not been investigated yet.

The aim of this study was to report the clinical and radiological results in a series of patients with HGGs treated with i-CT–assisted image-guided surgery and to compare them with results obtained in a second cohort of patients treated with conventional image-guided surgery without i-CT.

In all cases, fluorescence-guided surgery with 5-ALA was also used to achieve a wider resection.

METHODS

A total of 25 consecutive patients (Group A), including 15 men, with a mean age of 58 years (range, 30-80 years), were operated on between July 2010 and July 2014 at the Department of Neurosurgery, Policlinico University Hospital, Catania, Italy, because of a suspected diagnosis of HGG. In all cases, image-guided surgery was also performed using portable i-CT. Preoperatively, MRI was performed according to institutional preoperative imaging protocol, including volumetric gadolinium-enhanced T1, T2, fluid-attenuated inversion recovery sequences, spectroscopic analysis, diffusion-weighted images, and perfusion-weighted images; in all but 6 cases, a contrast-enhanced CT scan was also obtained. Two patients presented with recurrent neoplasms, and 4 patients had multifocal neoplasms (Table 1).

Group A patients were compared with a historical consecutive series of 25 patients (Group B) (13 males), with a mean age of 61 years (range, 8-82 years), with glioblastomas; the latter group underwent surgery before the introduction of portable CT at our institution assisted with 5-ALA and neuronavigation only. The same preoperative imaging studies as in Group A were performed in Group B. All patients in both groups were operated on by the same 3 surgeons. We included in the current study 2 consecutive series of patients treated at the same institution. The absence of bias related to differences of demographic data in both groups was statistically verified.

5-ALA fluorescence guidance and neuronavigation were used in all patients in both groups. We performed an intended biopsy only in 1 patient in Group A. Afterward, in Group A patients, a postcontrast i-CT scan was obtained to assess intraoperatively the EOTR; in the only case of a biopsy, intraoperative CT control was useful to verify the exact site of sampling and to rule out early hemorrhagic complications. However, this patient was excluded from the current analysis. Pre- and postoperative Karnofsky performance status (KPS) score was assessed in both patient groups as well as overall survival (OS) and progression-free survival (PFS) data. Pre- and postoperative KPS score was measured 1 day before surgery and on the day of discharge (usually postoperative day 5). In Group A patients, we used an 8-slice small-bore portable CT scanner (CereTom; NeuroLogica, Danvers, Massachusetts) (Figure 1); a StealthStation S7 (Medtronic, Minneapolis, Minnesota) neuronavigation system was used for surgery in both groups.

Patient Positioning for i-CT

Group A patients, while under general anesthesia, were positioned using a dedicated Doro CereTom radiolucent skull clamp (NeuroLogica). In 3 patients, we experienced some difficulties in positioning the patient because of a reduced range of motion of the Doro CereTom skull clamp compared with standard neurosurgical clamps used when i-CT is not performed. In such cases, which were due either to the patient's anatomy (ie, short neck) or to tumor location requiring specific positioning (ie, tumors sited in the parietal lobe), we tried to obtain the best position by adjusting the flexion-extension head angles or by using either short or long dedicated Doro CereTom skull clamp arms, respectively (Figure 2A). A variable operating table inclination (ie, Trendelenburg vs reverse Trendelenburg) was used to facilitate the head position in the i-CT scanner. In other cases, patients were positioned in a lateral or prone decubitus position (Figure 2B). Another important tip during patient positioning is the proper angulation of the articulated arm fixing the skull clamp. It should be fixed in an anterior position (ie, well underneath the operating table) (Figure 2), which would avoiding any unexpected contact with the i-CT unit during its automated motion from the stand-by mode to the operating mode. Indeed, the i-CT scanner unit's base with its rail tracks is wider than the gantry. Proper angulation of the articulated arm and use of skull clamp–specific adaptors are essential to avoid any undue contact between the base of the scanner unit and the articulated arm. In our experience, before draping the patient, we always check that the i-CT unit could automatically get into the scanning position without any mechanical obstruction.

i-CT Scan Protocol

According to the manufacturer's settings, a standard volumetric acquisition protocol for i-CT was used: axial slices 1.25 mm in thickness with 512×512 image resolution. The portable CT scanner used allows us to cover the entire skull with a 25-cm field-of view and a 32-cm aperture of the gantry. Therefore, the head, face, and upper cervical spine are usually covered by the scan during its daily use on the ward. The skull clamp used in the operating theater is an obvious limitation to achieve the optimal field of view described. We used to adapt the head positioning within the gantry, including during the scan, at least 2 cm of skull caudally to the surgical field (Figure 2). The rotating laser light installed in the scanner helped to verify the correct positioning of the head in relation to the gantry.

TABLE 1. Characteristics of Patients Undergoing Intraoperative Computed Tomography During Surgery for High-grade Gliomas[a]

Patient No.	Sex	Age, y	No. of i-CT Scans	Further Resection	Final Resection[b]	Hystopathology	Tumor Location	Preoperative KPS Score	Postoperative KPS Score
1	F	47	2	No	GTR	GBM	Left frontal	80	90
2	M	73	3	Yes	GTR	GBM	Right frontal	50	40
3	F	43	3	No	GTR	GBM	Cerebellum	50	20
4	M	70	2	No	GTR	GBM	Left rolandic	60	60
5	F	59	2	Yes	GTR	GBM	Right frontal	70	90
6	M	32	2	No	GTR	GBM	Right rolandic	90	90
7	F	75	2	No	GTR	GBM	Right parietal	60	60
8	M	30	2	Yes	GTR	GBM	Right insular	90	100
9	M	71	2	No	Biopsy	AA	Left frontal	70	80
10	M	57	2	Yes	GTR	GBM	Left frontal	80	80
11	F	55	2	No	GTR[c]	GBM	Right multicentric	60	80
12	F	60	2	Yes	GTR[c]	GBM	Left multicentric	40	40
13	M	56	3	No	GTR	GBM	Left temporal	90	80
14	M	58	2	No	GTR	GBM	Right insular	80	100
15	M	62	2	No	GTR	GBM	Left parietal	80	80
16	F	80	2	No	GTR	GBM	Left frontoinsular	50	50
17	M	38	2	No	GTR	GBM	Right frontal	50	50
18	M	66	3	Yes	GTR[c]	GBM	Left multicentric	60	40
19	M	55	2	No	GTR	GBM	Left frontal	60	70
20	F	54	2	No	GTR	GBM	Right parietal	60	80
21	F	77	2	Yes	GTR[c]	AA	Left multicentric	80	90
22	F	38	2	No	GTR	GBM	Left frontal	50	50
23	M	75	2	No	GTR	GBM	Right frontoinsular	80	80
24	M	55	2	No	GTR	AO	Right rolandic	70	70
25	M	63	2	Yes	GTR	AO	Right frontal	60	60
Mean		57.96						66.80	69.20

[a]i-CT, intraoperative computed tomography; KPS, Karnofsky Performance Status; F, female; GTR, gross total resection; GBM, glioblastoma multiforme; M, male; AA, anaplastic astrocytoma; AO, anaplastic oligodendroglioma.
[b]According to intraoperative findings, as reported in operating theater medical records.
[c]GTR for multicentric tumor is intended as complete resection of the larger tumor together with separate nodules.

The scanner produces DICOM images, which we then transfer to the StealthStation workstation using a USB flash drive. Image transferring may be also performed via a cable connection between the neuronavigation and scanner workstations. However, we preferred a USB flash drive to avoid further cable crowding around the operating table.

In our early experience, patients underwent a postcontrast CT scan while already positioned in the operating room but before starting the surgical procedure; this was intended to be a primary CT scan, useful for making a comparative analysis of resection after performing the intraoperative scan. A second postcontrast scan was then obtained at the end of surgical resection as a control scan. Eighty milliliters of iodinate contrast (Iomeron [Bracco, Milan, Italy] 300 mg/mL, containing 61.24 g Iomeprol in 100 mL) were administered. The maximum recommended dose of Iomeron for adult patients is 200 mL, according to the manufacturer's instructions. The iodinate contrast dose (80 mL) was chosen based on the range recommended by the manufacturer. Moreover, our experience at our institution with the routine use of a portable CT scan for brain tumors has shown that 80 to 150 mL of iodinate contrast allows suitable enhancement of pathological tissue, and we observed that even a dose of 80 mL is sufficient to achieve HGG enhancement. We preferred a lower dose because postcontrast scans were repeated at least twice (either before and after resection or, in some patients, during and after tumor resection) during the surgical procedure. We started the scanning session at least 60 seconds after the end of the contrast injection to allow adequate enhancement of pathological tissue.

The i-CT is moved on a motorized rail track. It is essential to make sure that the floor is clean, and no materials (cottonoids, gauzes, papers, drapes) are left along the scanner's route to the patient's head to allow a correct trajectory (Figure 3). Indeed, even small objects may damage the rail tracks and alter the correct trajectory during acquisition. Moreover, the precise position of the gantry with respect to the surgical table and patient's head can be checked and recorded by the scanner's software before starting the precraniotomy i-CT scan to facilitate the correct gantry positioning during intraoperative image acquisitions. Afterward, the motorized rail tracks allow us to move the scanner exactly to the previously recorded position for intraoperative image acquisition.

Intraoperative imaging required 10 minutes on average for each scan (range, 8-12 minutes): draping and positioning of scanner (range, 2-3 minutes), contrast administration (range, 3-4 minutes), and patient registration and scan acquisition (range, 3-5 minutes). Such time is the

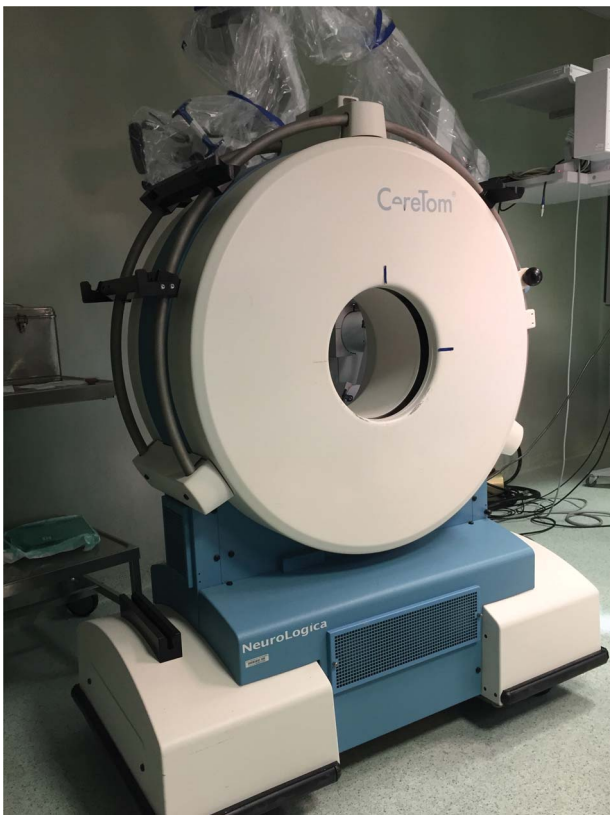

FIGURE 1. *The 8-slice, small-bore portable computed tomography scanner (CereTom Neurologica) used both intraoperatively and on the ward at our institution.*

real gap of interruption of surgery, including all stops necessary to perform the procedure.

In the last 15 patients, a postcontrast i-CT scan obtained in the theater was deemed unnecessary before starting surgery; in these cases, only a plain CT scan was performed before surgery and a postcontrast CT scan was obtained to verify the ETOR. However, the presurgical i-CT scan was used to verify the field of view included in the scan and the quality of volumetric images that would have been imported into the navigation system at a later stage in the event of unseen tumor remnants being revealed by i-CT. In the latter cases, the ETOR was assessed intraoperatively by comparing preoperative postcontrast MRI with the intraoperative postcontrast CT scan.

A postcontrast i-CT scan was performed after filling the surgical cavity with Ringer solution to minimize artifacts due to the presence of air. A dedicated plastic cover for the CereTom i-CT scanner was used to maintain the sterile surgical field (Figure 3).

The newly obtained i-CT scan was compared with the precraniotomy scan and/or with preoperative MRI (in the last 15 patients). Radical resection was considered as the absence of enhancing tissue on an i-CT scan. In cases of confirmed radicality, surgery was considered to be concluded. Conversely, if residual tumor was detected, the new images were uploaded into the navigation system and a further navigation-guided resection was performed. Such an occurrence is frequent in cases of small peripheral tumor remnants not always detected using 5-ALA (eg, in a hidden portion of the surgical field, under a blood clot, or still covered by a layer of nonfluorescent, ie, nontumoral, brain tissue) or in cases of multifocal neoplasm with a large mass and 1 or more satellite nodules. In these cases, when the larger mass is first approached, brain shift may hinder identification of detached nodules by neuronavigation. Therefore, the i-CT scan may provide an updated image, which is useful for navigation. In 1 case of an anaplastic oligodendroglioma, i-CT revealed the presence of calcified remnants. These were properly identified by navigation and resected (Figure 4). The final i-CT scan was also used to verify the absence of early hemorrhagic collections in the tumor cavity due to surgical maneuvers or unseen minor bleeding despite the hemostasis already secured by the surgeon to minimize the risk of postoperative overt hemorrhagic complications.

Neuronavigation

Gadolinium-enhanced volumetric T1 MRI sequences were used as reference examination for neuronavigation. Optic tools were used in all patients in Group B and in 16 of 25 patients in Group A. In the remaining 9 patients, electromagnetic navigation (AxiEm; Medtronic) was chosen

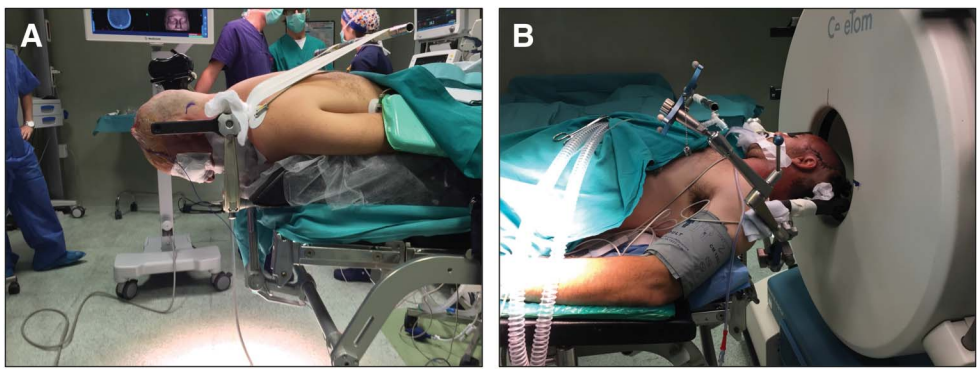

FIGURE 2. *Two examples of patient positioning are shown. The radiolucent skull clamp allows both prone position (A) and supine with rotated head (B). The size of the field of view can be checked using a rotating laser light installed within the scanner.*

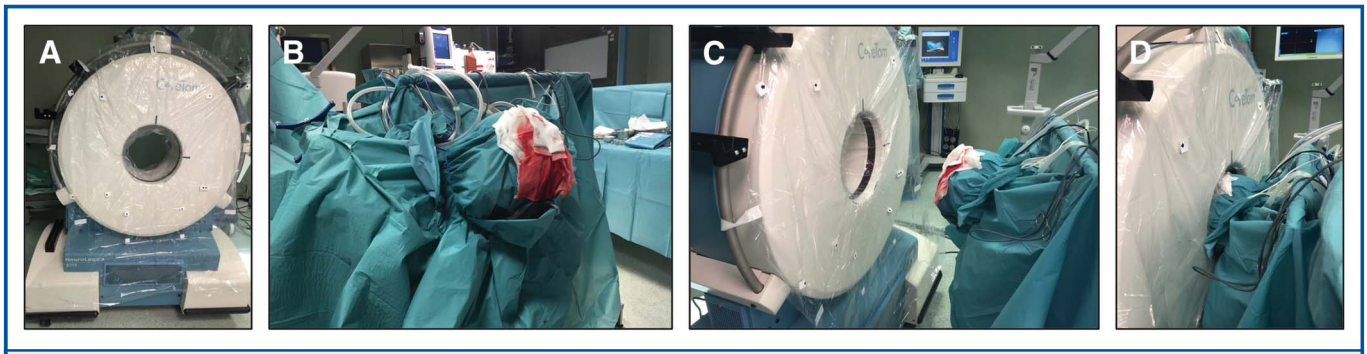

FIGURE 3. *Intraoperative photographs showing the intraoperative computed tomography scan protocol. The scanner is covered with a dedicated plastic cover to be kept sterile (A). Draping is adapted to the patient's head using rubber bands, and the surgical field is covered with gauze pads (B). The CereTom scanner moves toward the surgical table on motorized rail tracks (C) until the patient's head is positioned inside the gantry (D).*

(patients in the prone position or difficulties in setting up optic tools). Patient registration was performed using the superficial tracer modality without fiducials and periodically verifying the accuracy of navigation using known anatomic landmarks (eg, skull base, midline, vascular structures). In cases requiring uploading of intraoperative CT images, the new examination was merged with the preoperative reference MRI scan and used for navigation. Further patient registration was not required. Intraoperative, real-time updated CT images demonstrated the relevant usefulness for brain-shift correction in 4 patients of insular tumors (Table 1). We experienced the importance of also obtaining updated i-CT images for neuronavigation in cases of low-grade insular tumors, when 5-ALA fluorescence guidance is not applicable and pathological tissue is difficult to distinguish from normal white matter (Figure 5).

EOTR Analysis

As a general rule, we try to resect all 5-ALA fluorescence tumor seen during surgery, even the lighter fluorescence, whenever tissue eloquence, neuronavigation, and cortical-subcortical electric stimulation allowed.

Although i-CT was used to evaluate the presence of unrecognized enhancing residual tumor, the objective evaluation of the EOTR was performed on volumetric MRI. EOTR was evaluated by early postoperative (within 48 hours), gadolinium-enhanced MRI scan, and the absence of enhancing nodular tissue was considered compatible with gross total resection (GTR). Moreover, in all patients, GTR was verified using volumetric MRI evaluation according to the formula proposed by Sanai and Berger[23]:

$$\frac{\text{preoperative tumor volume} - \text{postoperative tumor volume}}{\text{postoperative tumor volume}} \times 100$$

One radiologist blinded to clinical outcome reviewed all patients' pre- and early postoperative MRI scans. Images were processed on a dedicated workstation (Advantage Workstation, VolumeShare 5, General Electrics, Fairfield, Connecticut). Volumetric measurements were performed on gadolinium-enhanced T1-weighted 3-dimensional fast spoiled gradient echo sequences, applying a volume-rendering segmentation technique. The radiologist, blinded to clinical outcome and operative details (i-CT–assisted surgery vs standard procedure), performed the imaging analysis by tracing the manual contour of the tumor lesion on axial images; in addition, 2-dimensional maximal length and short-axis were automatically generated for each lesion.

Statistical Analysis

Statistical analysis was performed using SPSS 16.0 software (IBM, Armonk, New York). Demographic data for both groups (sex and age at diagnosis) were compared using the Student *t* test. The Kaplan-Meier method was used to estimate OS and PFS and the log-rank test to assess the statistical significance of the compared data. OS was measured from the time of surgical resection to patient death or the last date when the patient was known to be alive. PFS time was defined as the time from surgical resection to the time of demonstrated tumor growth on follow-up imaging or evidence of neurological decline. Moreover, volumetric data obtained for the evaluation of EOTR were compared using the Student *t* test. The scores of both groups were compared using the log-rank test.

RESULTS

In Group A, histopathology revealed 21 cases (84%) of glioblastoma, 2 cases of anaplastic astrocytoma, and 2 of anaplastic oligodendroglioma, respectively. Conversely, all Group B tumors were diagnosed as glioblastomas.

In 8 of 25 Group A patients (32%), i-CT revealed intraoperatively unrecognized residual tumor; in 4 of these patients (16%) harboring a multifocal neoplasm, it helped to further resect the just seen neoplastic foci detached from the main tumor nodule (Figures 6, 7) and not detected by 5-ALA. In such cases, additional navigation-assisted resection was performed after importing the updated i-CT images into the navigation system (Table 1). Further exploration of those areas highlighted by the i-CT scan confirmed the presence of highly fluorescent tumor tissue. Correlation between residual tumor documented by i-CT and 5-ALA was evaluated using neuronavigation. Indeed, i-CT images were not affected by brain shift, and the enhancing tissue could be detected using the navigation probe. In all cases requiring further resection, we detected tumor fluorescent tissue covered by necrotic nonfluorescent tumor or normal nonfluorescent white matter. Moreover, neuronavigation documented in all cases a positive correlation between highly fluorescent tissue and i-CT contrast-enhancing areas. In 6 of 8 cases, we were able to see peripheral

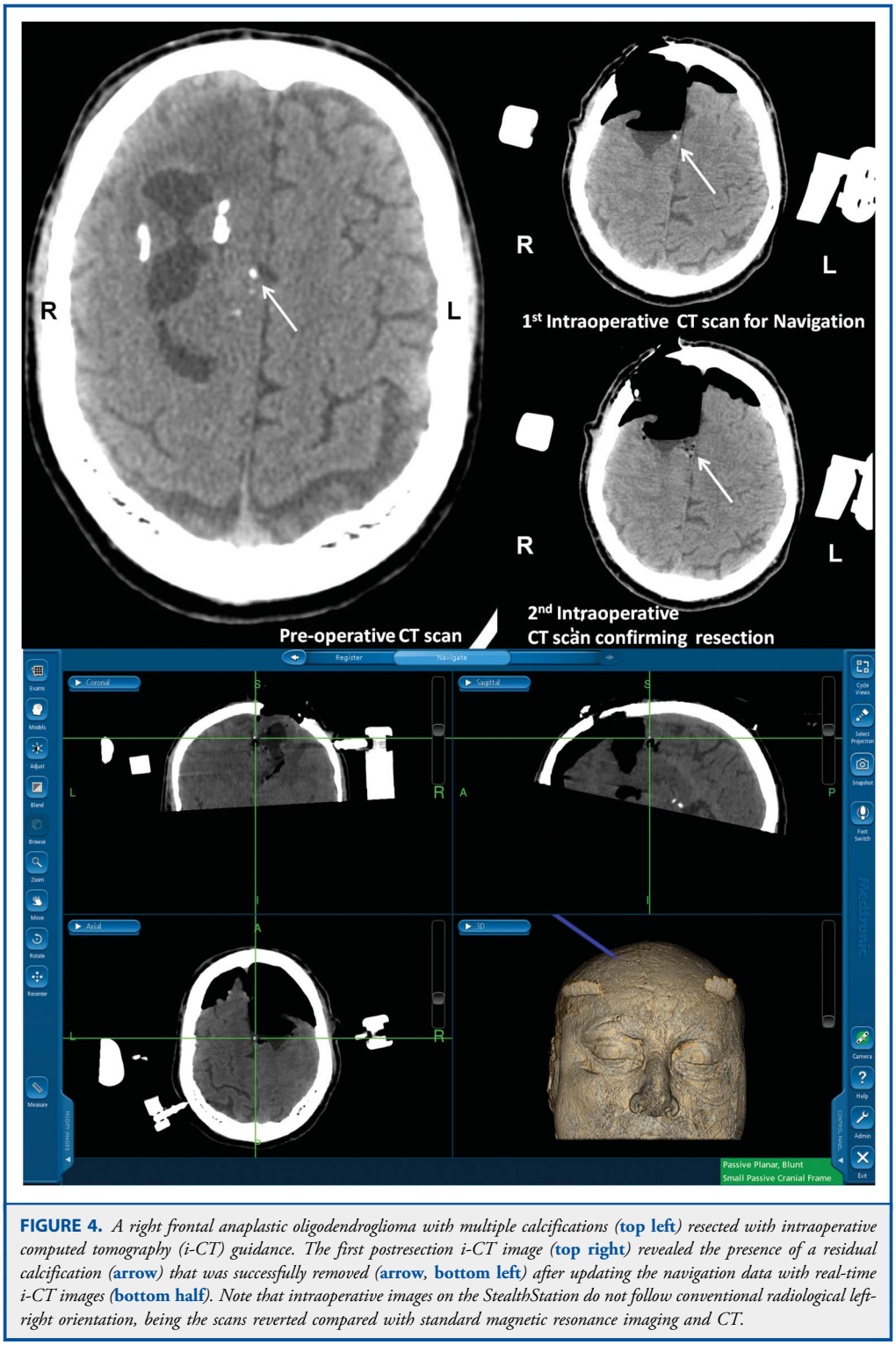

FIGURE 4. *A right frontal anaplastic oligodendroglioma with multiple calcifications (**top left**) resected with intraoperative computed tomography (i-CT) guidance. The first postresection i-CT image (**top right**) revealed the presence of a residual calcification (**arrow**) that was successfully removed (**arrow**, **bottom left**) after updating the navigation data with real-time i-CT images (**bottom half**). Note that intraoperative images on the StealthStation do not follow conventional radiological left-right orientation, being the scans reverted compared with standard magnetic resonance imaging and CT.*

vague fluorescence around the edges of residual tumor (confirmed by neuronavigation). In such cases, the resection was extended to include those infiltrating areas.

Revision surgery for residual tumor was never required. Only 1 patient in Group A experienced a postoperative hemorrhage that required a second surgery. Major complications were not observed

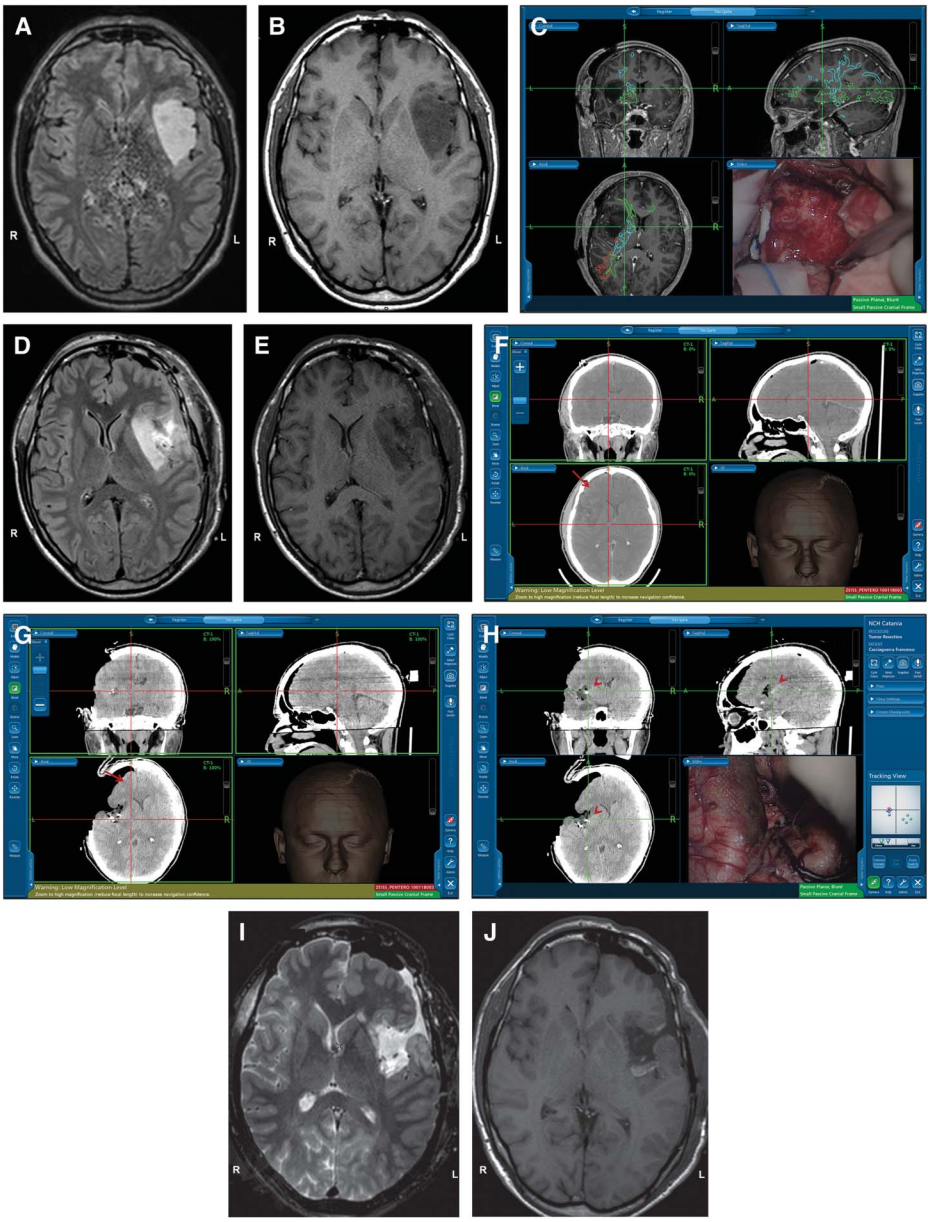

FIGURE 5. *Illustrative case: the usefulness of intraoperative computed tomography (i-CT) in correcting brain shift for neuronavigation is shown. A 39-year-old man with low-grade left insular glioma (**A**, **B**) could not tolerate an awake craniotomy; therefore, he underwent surgery while under general anesthesia. 5-Aminolevulinic acid was administered to the patient before surgery, but the tumor did not show any fluorescence. Thus, surgical resection was performed under neuronavigation and cortical/subcortical electrical stimulation guidance. Despite neuronavigation initially documenting a complete resection extending to the edge of basal ganglia (**C**), postoperative magnetic resonance imaging (MRI) showed residual neoplasm in the deepest part of the surgical field (**D**, **E**). The patient was then taken back to the operating room for a second surgical procedure to complete the tumor resection. An i-CT scan compared with preoperative images documented brain shift (**F**, **G**, **arrows**). We left 2 small cottonoids with radiopaque markers in the surgical cavity to mark the medial edges of resection. We tested the accuracy of new uploaded images touching the cottonoids with the navigation probe (**H**, **arrowheads**). Navigated CT images allowed a radical resection (**H**), confirmed by postoperative MRI (**I**, **J**). This case is not included in the current series but clearly demonstrates the role of i-CT in the correction of brain shift affecting the accuracy of neuronavigation. Note that intraoperative images on the StealthStation do not follow conventional radiological left-right orientation, being the scans reverted compared with standard MRI and CT.*

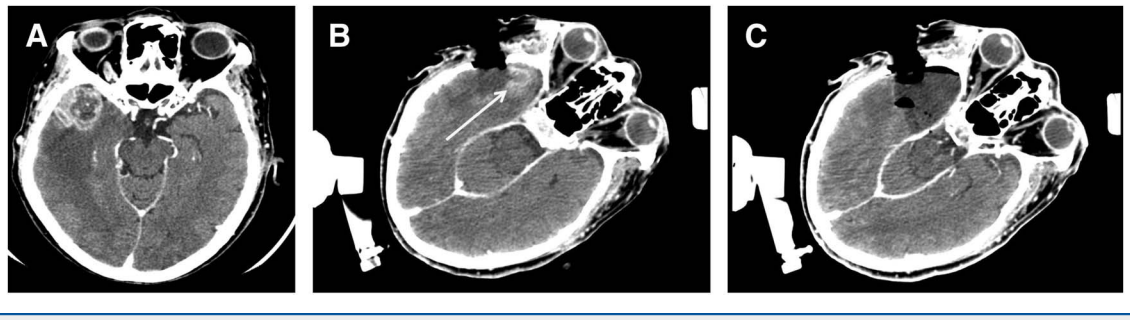

FIGURE 6. *The usefulness of intraoperative CT (i-CT) in resecting a right temporal pole glioblastoma (A) and detecting residual tumor is shown. i-CT revealed a remnant (B, arrow) after resection of a glioblastoma using 5-aminolevulinic acid guidance. The residual nodule was not detected because it was hidden under the border of craniotomy. Further dissection after i-CT allowed complete tumor resection (C).*

in either group. One patient in Group B experienced a transient worsening of preoperative neurological conditions; however, these completely recovered before discharge.

EOTR Analysis

In Group A patients (excluding the case of intended biopsy), the preoperative mean volume was 30.90 cm^3; residual disease was found on 7 early postoperative MRI examinations, with a mean volume of 1.16 cm^3.

In Group B, the preoperative mean volume was 36.90 cm^3; residual tumor was found in 6 patients, with mean volume of 0.628 cm^3.

With regard to Group A, patients with residual disease showed a mean 97.3% EOTR; in Group B, the mean resection rate was 98%.

The Student *t* test did not show any statistically significant difference in EOTR, measured by volumetric MRI, in the 2 groups (P = .5). Table 2 summarizes the results of the EOTR analysis (Table 2).

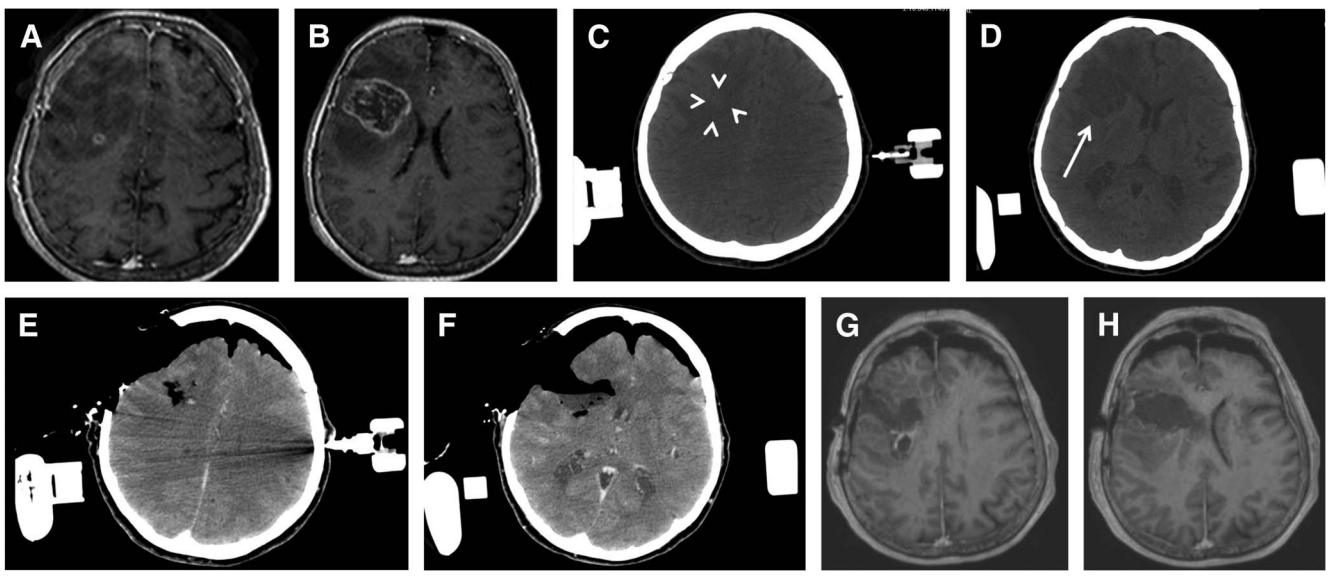

FIGURE 7. *Resection of a right frontal multicentric glioblastoma assisted by intraoperative computed tomography (i-CT) is shown. Preoperative, T1-weighted, gadolinium-enhanced, magnetic resonance imaging (MRI) showing a small posterior and superior tumor nodule (A) detached from the large right frontal tumor (B). The nodule was identified on the preoperative i-CT performed after patient positioning (C, arrowheads). The large frontal mass was also depicted (D, arrow). The small nodule was first approached and resected. A new postcontrast i-CT scan confirmed the resection and was used to update the data for navigation (E). The resection of the frontal mass was finally confirmed by the last postcontrast i-CT scan (F). Postoperative T1-weighted, gadolinium-enhanced, MRI demonstrated the complete resection of the multicentric neoplasm (G, H).*

TABLE 2. Extent of Tumor Resection Analysis in Both Groups

	Group A	Group B
Mean preoperative volume, cm^3	30.90	36.90
Range	0.8-84.3	8.0-85.4
SD	24.66	22.97
2-Dimensional maximal length, mm	45.65	51.0
Range	11.0-75.0	30.0-75.0
SD	17.40	13.43
Mean short axis, mm	31.76	32.0
Range	9.0-49.0	21.0-47.0
SD	11.76	7.27
Residual disease volume, cm^3	1.16 (7 cases)	0.628 (6 cases)
Range	0.12-2.20	0.16-1.67
Extent of tumor resection, %	97.3	98.0
Range	96-98.6	93.5-99.7

Demographic Data, KPS Score, OS, and PFS

The Student *t* test did not document statistically significant differences in age and sex distribution of both groups ($P = .06$ and .08, respectively). The KPS score changed from a preoperative mean of 67 to 69 after surgery in Group A and from a mean of 74 to 77 in Group B, respectively. Comparison of postoperative KPS score in both groups, verified by the application of the Student *t* test, did not show statistically significant differences ($P = .07$).

Groups A and B did not show differences in OS and PFS: $P = .61$ and .46, respectively, by the log-rank test (Figure 8).

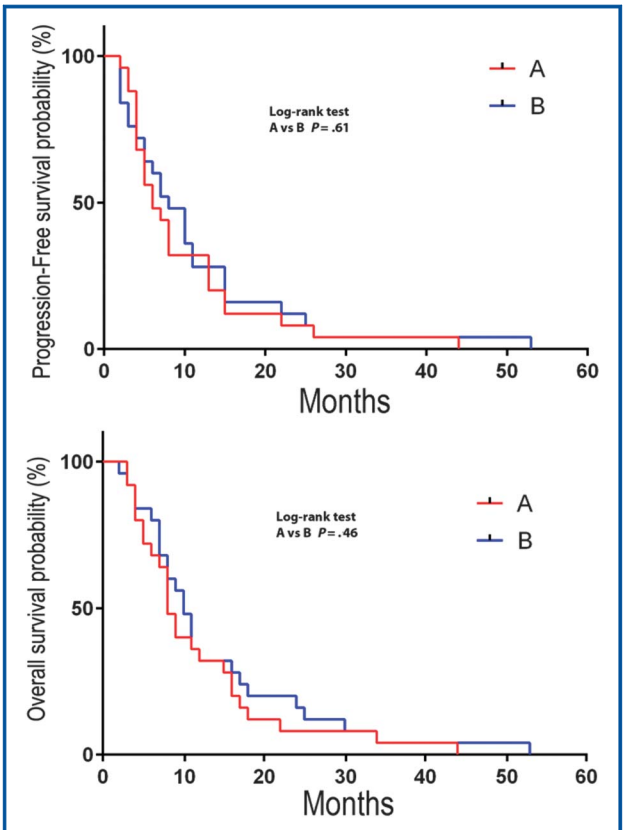

FIGURE 8. *Overall survival and progression-free survival according to the Kaplan-Meier method in group A and B patients showing no statistically significant difference.*

DISCUSSION

Over the past decade, several technical advancements (eg, neuronavigation, intraoperative ultrasound, i-MRI, and 5-ALA fluorescence-guided surgery) have been proposed to increase the surgical safety and EOTR in neuro-oncological patients, with the ultimate goal of improving patient survival and quality of life.[1-6,8,11-14,17,18]

The small-bore portable CT scanner has been shown to be a useful tool in several medical fields. It provides quick and high-quality scans that can be obtained without moving the patient outside the ward or the surgical theater. Such benefit is particularly important both for patients admitted to the emergency department or intensive care unit and for postoperative radiological monitoring of patients treated by neurosurgeons and maxillofacial and ear, nose, and throat surgeons.[14,24,25] Indications for the use of this new technology have increased during recent years, and its introduction in neurosurgical operating theaters is a further clinical application.[3,4,14-22,24-26] The utility of i-CT in neurosurgery has been reported in cases of functional (deep brain stimulators),[21,26] vascular,[3] endoscopic transsphenoidal, and oncological neurosurgery.[3,15]

In 2012, Carlson et al[14] analyzed the impact of i-CT in the surgical strategies of 49 neurosurgical procedures. They found that their surgical plan was changed after obtaining an i-CT scan in 33% of cases (16/49 patients). These data suggest a considerably high impact of i-CT on the surgical decision-making process. However, neurosurgical procedures included in their study were different, and such variance could have influenced figures. The preoperatively planned strategy for glioma surgery may be altered by i-CT, as reported by Hosoda et al.[18] They compared EOTR and outcome in 2 groups of patients treated for low-grade brain gliomas, 1 with i-CT and the other without it and found a more extensive resection and a better prognosis in the i-CT group. The same authors highlighted the concept that i-CT may improve surgeons' confidence during tumor resection, limiting their concerns about the EOTR. They also highlighted the role of i-CT in the early identification of complications. The paper by Hosoda et al[18] is the first report of a series of intra-axial tumors (ie, low-grade gliomas) treated with i-CT. Previous publications described the use of i-CT for brain tumor surgery, but they only reported sporadic experience.[16,19,20]

Gwinn et al[17] made an important contribution in the evolution of i-CT–based image guidance. They used i-CT during surgical resection of 4 supratentorial pediatric astrocytomas, introducing for the first time a portable CT scanner in the operating theater. The authors also observed that the air-brain interface may

alter image resolution. To overcome such problems, we suggest filling the surgical cavity with Ringer solution, covering the field with Spongostan (Soborg, Denmark), Gelfoam (Pharmacia and Upjohn Company, Kalamazoo, Michigan), or a large gauze and reflecting the dural and skin flaps over the cavity to reduce the air-brain interface (Figure 3).

A further application of i-CT in neurosurgery came from its integration with the neuronavigation systems. A similar advantage is achievable using i-MRI integrated with navigation systems, but the feasibility and accessibility of portable i-CT scanners are definitely superior. Indeed, this tool is easy to integrate in a standard operating theater and does not require dedicated instrumentation, as highlighted by Nakao et al.[4] At our institution, a radiologist was not routinely required in the theater to perform i-CT. A neurosurgeon, who was not part of the operating team but was already trained on how to use the portable i-CT scanner, was responsible for performing the i-CT scan and for uploading the real-time images into the neuronavigator.

Before introducing i-CT into daily neurosurgery, several authors demonstrated the feasibility and usefulness of i-MRI in neurosurgery.[1,2,6-12] Senft et al,[2] in 2011, analyzed a prospectively controlled series of 29 (of 58) patients assigned to the i-MRI group after randomization. The authors described a significant benefit for patients assigned to the i-MRI group in terms of PFS and EOTR.

Kubben et al[7] reviewed the literature on i-MRI, finding Level 2 evidence supporting the effectiveness of i-MRI–guided surgery compared with conventional neuronavigation-guided surgery for surgical resection of glioblastomas. The authors described a positive impact of i-MRI on increasing EOTR, quality of life, and survival. In particular, analyzing the i-MRI studies included in the review of Kubben et al,[7] we found reported rates of GTR in glioblastoma ranging from 16.6% to 88.8%.

Our postoperative volumetric MRI analysis suggests that in Group A, 17 patients had a GTR; in 7 of 8 patients with residual tumor (the patient treated with intended biopsy was excluded from the analysis), the mean resection rate was 97.3%. Similarly, in Group B, 19 patients had a GTR, and in the remaining 6 patients with visible tumor on early postoperative MRI a mean 98% tumor resection was performed. These values of tumor GTR compare favorably with those reported by authors using i-MRI. In Group A, there were 4 patients with multifocal neoplasm; in this subgroup, EOTR was evaluated also considering the detached enhancing nodules. Conversely, in Group B, only 1 patient presented with multifocal neoplasm. This finding may explain the slight difference in EOTR between the 2 groups, but the analysis of all single cases demonstrated that no large residual tumor was left in Group A. Although the mean rate of EOTR in Group B is slightly higher than in Group A, but not statistically significant, the smallest EOTR percentage in Group A is still a greater value of EOTR than the smallest one in Group B (ie, comparing the EOTR in both groups, the worst case with the largest residual tumor fragment in Group A has still a better EOTR than the worst case in Group B). This finding confirms the role of i-CT in also detecting small enhancing tumor remnants, which were then removed using real-time updated neuronavigation. Yet, in 7 patients with residual tumor documented by postoperative MRI, i-CT revealed residual tumor in 4 of 7 patients (in 3 patients, nodules in multifocal disease were unresectable). In the remaining 3 patients, i-CT did not document enhancing remnants. This mismatch with postoperative MRI could be explained by the small size of residual tumor, not always easily detectable on a CT scan.

Sanai et al[23,27] not only demonstrated that an EOTR rate of 78% or higher is the minimum value affecting patient survival, but also that 95% rate is the most significant predictor of survival in patients with HGGs. All Group A patients included in our study had an EOTR rate greater than 95% (ie, 97.3%); conversely, in Group B, an a EOTR rate of 93.5% was found on early postoperative MRI. In the 8 patients requiring further resection after i-CT, a significant improvement in EOTR was achieved. In such patients, i-CT allowed a resection rate higher than 95%, with an obvious advantage for patient survival, according to Sanai et al.[27]

Interestingly, our statistical analysis did not reveal significant differences in OS and PFS between the 2 groups because patients in both groups had extensive tumor removal, even in those patients in whom small residual tumor remnants were found. Although such a finding might apparently reduce the value of i-CT, promoting a possible use of 5-ALA only as an equally effective but less expensive tool to increase EOTR, it does not reduce the importance of i-CT as an aid in HGG surgery. Indeed, i-CT may be considered as a further adjunct to 5-ALA, allowing a safer and wider resection of deeply seated parts of tumors, even those that can be overlooked when using 5-ALA if covered by blood or nontumoral tissue, or when the role of neuronavigation becomes limited because of brain shift. Yet, i-CT helps the surgeon by allowing navigation with updated real-time images.

Despite the role of 5-ALA fluorescence in improving the extent of HGG resection as well as the importance of neuronavigation, i-CT could still represent an important tool for surgeons in selected cases.[28] In our experience, i-CT was helpful to detect detached tumor nodules in multifocal tumors and to confirm an apparent GTR. In 8 patients (32%), further resection after performing i-CT was needed. Such a rate is lower than that reported by Hosoda et al,[18] and this may be explained by a different histology in the series of Hosoda et al (LGGs vs HGGs).

5-ALA is highly sensitive in detecting tumoral tissue. Vague fluorescent tissue was found around the edges of contrast-enhancing areas documented by navigated i-CT in 6 patients. Although we think that the use of 5-ALA fluorescence guidance strongly contributed to improving the EOTR in our series, i-CT demonstrated its usefulness also in cases treated with 5-ALA fluorescence guidance; i-CT had a role in verifying resection of enhancing tumor and associated necrotic areas, in excluding intraoperative complications (ie, early intraparenchymal hemorrhage due to surgical manipulation or unseen minor bleedings in the tumor cavity) and allowing a reliable comparison with preoperative tumor imaging. Furthermore, we found residual tumor using i-CT in absence of

clear 5-ALA fluorescence in 4 Group A patients. This mismatch could be related to the presence of a "hidden" part of the tumor, not adequately lit under microscope or covered by a layer of necrotic/nonfluorescent tissue or by blood clots.

The real impact of i-CT as an adjunct to 5-ALA in improving tumor resection and OS and PFS should be evaluated in larger cohorts of patients to confirm our experience and improve the statistical significance of the data. Further comparative studies could be performed to clarify the importance of i-CT in HGGs compared with other intraoperative imaging tools such as i-MRI and ultrasound.

Another important finding in our experience is the impact of the time factor in the use of i-CT. The thorough intraoperative examination lasted 10 minutes on average, also including all preparatory steps (eg, draping, scan positioning). Despite the literature reports of a short scanning time for low-field i-MRI (7-13 minutes),[11] it is undeniable that the entire procedure, including scanner motion and positioning, contrast administration, and draping, commonly requires a longer interruption of surgical maneuvers. Therefore, a time factor appears to be a great advantage compared with i-MRI, not to mention the obvious advantages (linked with i-CT) of using standard equipment without the need to set up an MRI-compatible operating room. Conversely, the integration of a low-field i-MRI scanner in a standard operating room does require environmental adaptations or the integration of local radiofrequency shielding (ie, Polestar Medtronic i-MRI scanner, used in several clinical studies,[2,10,11] can be integrated in a standard operating room only if the surgical table is shielded by a dedicated device). It should be highlighted that anatomic resolution is definitely better with i-MRI, but in cases of enhancing HGGs, postcontrast i-CT images allow a satisfactory definition of the tumor and its edges.

CONCLUSION

Integration of i-CT with 5-ALA fluorescence-guided surgery and neuronavigation may result in further improvement in EOTR and clinical outcome. Our study is a retrospective evaluation of prospectively collected data from a single-institution experience, with the obvious limitations of a retrospective analysis. As previously discussed, prospective and more data are needed to carefully evaluate the impact of i-CT in surgery for HGGs. Nevertheless, our results confirm that i-CT could be a valid and useful adjunct in the neuro-oncological team's armamentarium, particularly in multifocal HGGs or in patients harboring small tumor remnants not always adequately detected by 5-ALA. Moreover, in deep infiltrating lesions, i-CT is an important tool to achieve a correction of brain shift for neuronavigation.

In conclusion, our experience suggests that i-CT, with the previously described advantages, is a tool that can provide real-time useful information during brain surgery.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

The authors describe their retrospective, nonrandomized experience with i-CT in a group of 25 patients with high-grade gliomas who underwent surgery with image guidance and 5-ALA. They compared this group with a second group that underwent surgery with image guidance and 5-ALA but no i-CT. They compared EOR, outcomes (both KPS and PFS) and found them to be the same. They noted that in 8 of the 24 patients in the i-CT group, i-CT discovered residual enhancing tumor, and the surgeons acted on that information. There are some obvious limitations to the conclusions that can be drawn due to the retrospective nature of the study, the nonrandomized comparison, and the small sample size. On the other hand, the value of this paper is that it is novel; the fact that 5-ALA did not show tumor in some cases where tumor showed up on i-CT and that comparable levels of resection were achieved compared with i-MRI series.

This paper is important as it provides some evidence that i-CT may be a useful intraoperative adjunct for glioma resection. The advantages of i-CT over i-MRI include lower costs, easier and faster use, less special equipment is necessary, and iCT can be easily repeated after a second resection is done. In centers that have i-CT or that cannot afford i-MRI, this gives some support to the use of i-CT in glioma surgery.

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