

# Discriminating uninfected surgical bed cysts from bacterial brain abscesses after Carmustine wafer implantation in newly diagnosed IDH-wildtype glioblastomas

**Alexandre Roux**

GHU Paris: Groupe Hospitalier Universitaire Paris psychiatrie & neurosciences

**Hichem Ammar**

GHU Paris: Groupe Hospitalier Universitaire Paris psychiatrie & neurosciences

**Alessandro Moiraghi**

GHU Paris: Groupe Hospitalier Universitaire Paris psychiatrie & neurosciences

**Sophie Peeters**

UCLA: University of California Los Angeles

**Marwan Baroud**

GHU Paris: Groupe Hospitalier Universitaire Paris psychiatrie & neurosciences

**Gilles Zah-Bi**

GHU Paris: Groupe Hospitalier Universitaire Paris psychiatrie & neurosciences

**Joseph Benzakoun**

GHU Paris: Groupe Hospitalier Universitaire Paris psychiatrie & neurosciences

**Eduardo Parraga**

GHU Paris: Groupe Hospitalier Universitaire Paris psychiatrie & neurosciences

**Catherine Oppenheim**

GHU Paris: Groupe Hospitalier Universitaire Paris psychiatrie & neurosciences

**Chiara Benevello**

GHU Paris: Groupe Hospitalier Universitaire Paris psychiatrie & neurosciences

**Fabrice Chrétien**

GHU Paris: Groupe Hospitalier Universitaire Paris psychiatrie & neurosciences

**Pascale Varlet**

GHU Paris: Groupe Hospitalier Universitaire Paris psychiatrie & neurosciences

**Frédéric Dhermain**

IGR: Gustave Roussy

**Edouard Dezamis**

GHU Paris: Groupe Hospitalier Universitaire Paris psychiatrie & neurosciences

**Marc Zanello**

GHU Paris: Groupe Hospitalier Universitaire Paris psychiatrie & neurosciences

Johan Pallud (✉ [johanpallud@hotmail.com](mailto:johanpallud@hotmail.com))

Sainte-Anne Hospital Center <https://orcid.org/0000-0002-1652-9844>

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# Abstract

## Purpose

Carmustine wafers can be implanted in the surgical bed of high-grade gliomas, which can induce surgical bed cyst formation, leading to clinically relevant mass effect.

## Methods

An observational retrospective monocentric study was conducted including 122 consecutive adult patients with a newly diagnosed supratentorial glioblastoma who underwent a surgical resection with Carmustine wafer implantation as first line treatment (2005–2018).

## Findings

Twenty-two patients (18.0%) developed a postoperative contrast-enhancing cyst within the surgical bed: 16 uninfected cysts and six bacterial abscesses. All patients with an uninfected surgical bed cyst were managed conservatively, all resolved on imaging follow-up, and no patient stopped the radiochemotherapy. Independent risk factors of formation of a postoperative uninfected surgical bed cyst were age  $\geq 60$  years ( $p = 0.019$ ), number of Carmustine wafers implanted  $\geq 8$  ( $p = 0.040$ ), and partial resection ( $p = 0.025$ ). Compared to uninfected surgical bed cysts, the occurrence of a postoperative bacterial abscess requiring surgical management was associated more frequently with a shorter time to diagnosis from surgery ( $p = 0.009$ ), new neurological deficit ( $p < 0.001$ ), fever ( $p < 0.001$ ), residual air in the cyst ( $p = 0.018$ ), a cyst diameter greater than that of the initial tumor ( $p = 0.027$ ), and increased mass effect and brain edema compared to early postoperative MRI ( $p = 0.024$ ). Contrast enhancement ( $p = 0.473$ ) and diffusion signal abnormalities ( $p = 0.471$ ) did not differ between postoperative bacterial abscesses and uninfected surgical bed cysts.

## Conclusions

Clinical and imaging findings help discriminate between uninfected surgical bed cysts and bacterial abscesses following Carmustine wafer implantation. Surgical bed cysts can be managed conservatively. Individual risk factors will help tailor their steroid therapy and imaging follow-up.

# Introduction

*Isocitrate dehydrogenase (IDH)* wildtype glioblastoma (World Health Organization (WHO) grade IV astrocytoma) is the most common malignant primary brain tumor in adults<sup>1</sup>. Maximal safe resection, which is recommended as the first-line treatment, improves survival and increases the efficacy of adjuvant therapies<sup>1–3</sup>. Treatment guidelines for newly diagnosed *IDH*-wildtype glioblastomas recommend maximal safe surgical resection, with or without Carmustine (1,3-bis(2-chloroethyl)-1-nitrosourea, BCNU) biodegradable wafer implantation, followed by the standard radiochemotherapy protocol<sup>4–8</sup>. Carmustine wafer implantation in the surgical bed has been shown to improve survival of newly diagnosed and

recurrent high-grade gliomas<sup>7,9,10,10</sup>. Through its direct local application, high concentrations of Carmustine can be delivered to the surgical bed over a 3-week-long period while minimizing systemic adverse effects<sup>11,12</sup>. It provides a therapeutic bridge between surgery and adjuvant therapy onset<sup>11,12</sup>.

Carmustine wafer implantation can result in distinct adverse effects. In addition to an increased risk of brain abscess formation, increased local inflammatory changes may induce surgical bed cyst formation, leading to clinically relevant mass effect<sup>13</sup>. Patients presenting postoperatively with a symptomatic contrast enhancing surgical bed cyst pose diagnostic and management challenges. A revision surgery is regularly indicated if there is clinical suspicion of infection<sup>14,15</sup>. To our knowledge, no dedicated study has evaluated the risk factors for the development of a postoperative surgical bed cyst, and key elements to discriminate between an uninfected surgical bed cyst and a bacterial abscess are lacking.

We assessed: 1) the risk factors for surgical bed cyst formation following surgical resection with Carmustine wafer implantation of a newly diagnosed *IDH*-wildtype glioblastoma; 2) the clinical and imaging criteria allowing discrimination between an uninfected surgical bed cyst and a brain abscess.

## Materials And Methods

### Data source

We screened consecutive adult patients harboring a supratentorial newly diagnosed *IDH*-wildtype glioblastoma treated with surgical resection plus Carmustine wafer implantation as first treatment between December 2005 and December 2018 in a tertiary neurosurgical oncology center. Inclusion criteria were: 1) patients  $\geq 18$  years; 2) newly diagnosed supratentorial *IDH*-wildtype glioblastoma; 3) surgical resection with Carmustine wafer implantation as first-line treatment; 4) available postoperative MRI (including T1-weighted sequence with and without intravenous administration of contrast agents, fluid-attenuation inversion recovery (FLAIR) sequence, and diffusion weighted sequence) to quantify the extent of resection; and 5) available clinical and MR imaging follow-up during the first six postoperative months.

The decision to implant Carmustine wafers was not randomized but was decided by the treating neurosurgeon on clinical bases according to: 1) the guidelines from the French Neurosurgical Society<sup>8</sup>; 2) the presence of a contrast-enhanced and necrotic mass on preoperative MRI; 3) the preoperative neurosurgical expectation of a gross total removal of the contrast enhanced tumor mass; 4) the preoperative obtained informed consent of the patient; 5) the intraoperative extemporaneous histopathological diagnosis of a malignant glioma; and 6) the gross total resection suspected intraoperatively.

According to the inclusion criteria, 122 out of 160 screened patients were included in the final analysis. We excluded 27 patients without available follow-up postoperative MRIs, five patients without available early postoperative MRI, three patients who were lost to follow-up, and three patients without an *IDH*-wildtype glioblastoma (two *IDH*-mutant glioblastomas, one G43R diffuse glioma).

## Data collection

Data at surgery included: sex, age, Karnofsky performance status (KPS) score, revised Radiation Therapy Oncology Group - Recursive Partitioning Analysis (RTOG-RPA) classification system for glioblastoma<sup>16</sup>, tumor location, quantified volume of the contrast-enhanced tumor, quantified extent of surgical resection based on early postoperative MRI (within 48 h) on three-dimensional contrast-enhanced T1-weighted sequence (subtotal resection defined by the removal of  $\geq 90\%$  of enhancing tumor)<sup>2</sup>, search for restricted diffusion coefficient and gadolinium enhancement in parenchyma adjacent to Carmustine wafers, number of Carmustine wafers implanted, adverse postoperative events, histomolecular diagnosis, and *O6-methylguanine-DNA methyltransferase (MGMT)* promoter methylation status, if available. Follow-up data during the first six-postoperative months included: systematic clinical examination and MRI (six weeks, three months, and six months postoperatively), surgical bed cystic lesion occurrence, cystic lesion volume, contrast enhancement of the cystic lesion walls, signal on diffusion-weighted imaging (DWI), restricted diffusion on apparent diffusion coefficient (ADC) on the wall and inside the cystic lesion, residual air in the surgical bed, edema-related mass effect, related clinical symptoms, and practical management of the cyst (conservative, surgery, steroid therapy).

## Statistical analyses

To determine factors associated with the development of a postoperative surgical bed cyst or a brain abscess, univariate analyses were performed, computing unadjusted Odds Ratios (OR) and using the Chi square or Fisher's exact tests for comparing categorical variables, and the unpaired t-test or Mann-Whitney rank sum test for continuous variables, as appropriate. Variables associated with a  $p < 0.200$  level in unadjusted analysis were entered into logistic backward stepwise regression models. The final model retained only the variables significant at the  $p < 0.05$  level. Statistical analyses were performed using JMP software (version 14.1.0, SAS Institute Inc Cary, USA).

## Data availability

Data not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator for purposes of replicating procedures and results.

## Results

### Patient population

One hundred and twenty-two patients were included (63.9% men, mean age  $60.1 \pm 11.0$  years), 87 of them (71.3%) were previously reported in another study<sup>17</sup>. Patient and tumor characteristics are detailed in Table 1. The mean number of Carmustine wafers implanted was  $7.5 \pm 1.7$  per patient (median 8, range 4–16).

Table 1  
Patient and tumor characteristics.

Parameters	Value (n, %)
Age (years)	60.1 ± 11.0 (21–84)
Mean ± SD (range)	57 (46.7)
<60	65 (53.3)
≥60	
Sex	44 (36.1)
Female	78 (63.9)
Male	
Increased intracranial pressure	68 (55.7)
Absent	54 (44.3)
Present	
Focal neurological deficit	33 (27.0)
Absent	89 (73.0)
Present	
Epileptic seizure	81 (66.4)
Absent	41 (33.6)
Present	
Karnofsky Performance Status score	96 (78.7)
>70	26 (21.3)
≤70	
RTOG-RPA classes	9 (7.4)
III	87 (71.3)
IV	23 (18.9)
V	3 (2.4)
VI	

<b>Parameters</b>	<b>Value (n, %)</b>
Tumor location	34 (27.9)
Frontal	46 (37.7)
Temporal	35 (28.7)
Parietal	2 (1.6)
Insular	5 (4.1)
Occipital	
Tumor side	72 (59.0)
Right	50 (41.0)
Left	
Tumor volume (cc)	41.6 ± 38.2 (0.1-226.8)
Mean ± SD (range)	58 (47.5)
<30	64 (52.5)
≥30	
Number of Carmustine wafers	7.5 ± 1.7 (4–16)
Mean ± SD (range)	35 (28.7)
<8	87 (71.3)
≥8	
Extent of surgical resection	67 (54.9)
Total	29 (23.8)
Subtotal	26 (21.3)
Partial	
MGMT promoter methylation status	49 (40.2)
Methylated	34 (27.9)
Unmethylated	39 (31.9)
Missing data	

Parameters	Value (n, %)
Adverse postoperative events	22 (18.0)
New neurological deficit	4 (3.3)
Epileptic seizures	1 (0.08)
Hematoma requiring evacuation	4 (3.3)
Wound healing defect	6 (4.9)
Bacterial brain abscess	2 (1.6)
Thromboembolic complication	

MGMT: O6-methylguanine-DNA methyltransferase; RTOG: Radiation Therapy Oncology Group; RPA: Recursive Partitioning Analysis

During the first six postoperative months of imaging follow-up, 22 (18.0%) patients developed a contrast-enhanced cyst within the surgical bed. No additional cyst formation was observed on further imaging follow-up after these first six postoperative months. Sixteen presented uninfected surgical bed cysts and six presented bacterial abscesses according to postoperative follow-up. Three patients (2.5%) presented with recurrent disease confirmed by further imaging follow-up and requiring oncological treatments.

## Incidence of a postoperative bacterial abscess

Six patients (4.9%) had a surgical site bacterial abscess confirmed by the identification of an organism on cultures, which was diagnosed at a mean of  $26.2 \pm 10.6$  postoperative days (median 30, range 12–40) (Fig. 1). All cases benefited from a surgical procedure, which consisted in the evacuation of the bacterial abscess, an abundant washing of the operating site and bacteriological samples. The bone flap was systematically left in place. A bacterium was found in all patients (Supplementary Fig. 1). New postoperative related symptoms (focal neurological deficit, increased intracranial pressure) were present in the six patients (100%). An associated healing defect was present in 2 out of 6 patients (33.3%). Fever was present in 4 out of 6 cases (66.7%). The volume of the postoperative bacterial abscess (mean of  $44.9 \pm 23.0$  cc, median 35.5, range 23.0-80.8) was superior to the volume of the initial glioblastoma in 5 out of 6 cases (83.3%). All postoperative bacterial abscesses showed linear contrast enhancement of their walls, high signal and restricted diffusion on ADC inside the resection cavity on DWI, and residual air in the surgical bed. Increased mass effect compared to the early postoperative MRI was present in 5 out of 6 cases (83.3%).

## Incidence of a postoperative uninfected surgical bed cyst

The 16 non-infected surgical bed cysts were diagnosed at a mean of  $54.0 \pm 16.9$  postoperative days (median 60.0, range 20.0–90.0), three before radiotherapy onset and 13 at a mean  $20.2 \pm 13.8$  days after radiotherapy onset (median 18.0, range 2.0–55.0) (Fig. 1). The volume of these postoperative surgical

bed cysts (mean  $24.6 \pm 15.9$  cc, median 25.1, range 4.9–68.4) was inferior to the volume of the initial glioblastoma in 12 out of 16 cases (75.0%). All postoperative uninfected surgical bed cysts showed thin and linear membrane-like contrast enhancement of their walls. High signal on DWI was observed in 9 of the 11 available cases (81.8%). Restricted diffusion on ADC maps was observed in 9 of the 12 available cases (75.0%), which was limited to the rim of the resection cavity. Residual air was observed within the cyst in 9 out of 16 cases (56.2%). Concomitant brain edema and mass effect were present in 5 out of 16 cases (31.3%). Increased mass effect compared to the early postoperative MRI was present in 5 out of 16 cases (31.3%). New postoperative symptoms were present in 8 out of 16 patients (50.0%): increased intracranial pressure in 7 (43.7%), epileptic seizures in 4 (25.0%), and neurological deficits in 1 (6.3%) of the 16 patients. The remaining 8 patients (50.0%) were asymptomatic.

All above mentioned patients were managed conservatively. Symptomatic patients were treated with high dose steroid therapy and asymptomatic patients did not receive additional steroid therapy. No antibiotic therapy was administered. All surgical bed cysts resolved on imaging without surgical intervention at a mean of  $118.8 \pm 61.4$  days of follow-up (median 90, range 45–270) after diagnosis on imaging. No patient had to stop the ongoing adjuvant therapy.

## **Risk factors for the development of an aseptic surgical bed cyst**

Risk factors for the development of a postoperative surgical bed uninfected cyst are detailed in Table 2. In multivariable analysis, age  $\geq 60$  (adjusted OR, 4.04 [95% CI 1.24–13.09],  $p = 0.019$ ), number of Carmustine wafers implanted  $\geq 8$  (adjusted OR, 6.50 [95% CI 1.08–8.90],  $p = 0.040$ ), and partial surgical resection (adjusted OR, 5.03 [95% CI 1.22–20.64],  $p = 0.025$ ) were independent predictors of the development of a postoperative uninfected surgical bed cyst.

Table 2

Univariate and multivariate predictors of the development of an uninfected postoperative surgical bed cyst (n = 16).

Parameters at surgery	Univariate analyses			Multivariate analyses		
	uOR	95% CI	p-value	aOR	95% CI	p-value
Age (years)						
<60	1 (ref)			1 (ref)		
≥60	3.26	1.11–9.54	<b>0.031</b>	4.04	1.24–13.09	<b>0.019</b>
Sex						
Female	1 (ref)					
Male	1.82	0.55–6.02	0.328			
Increased intracranial pressure						
Absent	1 (ref)					
Present	0.73	0.25–2.14	0.560			
Focal neurological deficit						
Absent	1 (ref)					
Present	1.13	0.34–3.78	0.843			
Epileptic seizure						
Absent	1 (ref)					
Present	0.88	0.29–2.74	0.831			
Karnofsky Performance Status score						
>70	1 (ref)					
≤70	0.49	0.10–2.30	0.364			
RTOG-RPA classes						

MGMT: O6-methylguanine-DNA methyltransferase; OR: Odds ratio; RTOG: Radiation Therapy Oncology Group; RPA: Recursive Partitioning Analysis

Parameters at surgery	Univariate analyses			Multivariate analyses		
	uOR	95% CI	p-value	aOR	95% CI	p-value
III-IV	1 (ref)					
V-VI	0.49	0.10–2.30	0.364			
Tumor location						
Frontal	1 (ref)					
Temporal	0.59	0.16–2.05	0.388			
P						
Parietal	0.78	0.21–2.84	0.703			
Other	0.73	0.19–2.76	0.644			
Tumor side						
Right	1 (ref)					
Left	0.88	0.29–2.61	0.815			
Tumor volume (cc)						
<30	1 (ref)					
≥30	2.04	0.66–6.27	0.214			
Number of Carmustine wafers						
<8	1 (ref)			1 (ref)		
≥8	3.16	0.68–14.72	0.099	6.50	1.09–8.90	<b>0.040</b>
Extent of surgical resection						
Total	1 (ref)			1 (ref)		
Subtotal	0.99	0.24–4.13	0.988	1.01	0.22–4.74	0.987
Partial	2.57	0.77–8.56	0.124	5.03	1.22–20.64	<b>0.025</b>

MGMT: O6-methylguanine-DNA methyltransferase; OR: Odds ratio; RTOG: Radiation Therapy Oncology Group; RPA: Recursive Partitioning Analysis

Parameters at surgery	Univariate analyses			Multivariate analyses		
	uOR	95% CI	p-value	aOR	95% CI	p-value
MGMT promoter methylation status						
Methylated	1 (ref)					
Unmethylated	1.04	0.27–4.03	0.670			
Missing data	1.36	0.35–5.30	0.654			
MGMT: O6-methylguanine-DNA methyltransferase; OR: Odds ratio; RTOG: Radiation Therapy Oncology Group; RPA: Recursive Partitioning Analysis						

## Discriminating between a postoperative bacterial abscess and an uninfected surgical bed cyst

- When comparing postoperative bacterial abscesses to postoperative surgical bed cysts (Table 3), time from surgery to diagnosis was shorter (median 30 vs. 60 days,  $p = 0.004$ ), new symptoms were more frequent (100% vs. 50.0%,  $p = 0.009$ ) including new postoperative focal neurological deficits (83.3% vs. 6.3%,  $p < 0.001$ ) and fever (66.7% vs 0%,  $p < 0.001$ ), presence of air in the resection cavity was more frequent (100% vs. 56.3%,  $p = 0.018$ ), volume of the postoperative enhancing surgical bed cyst was more frequently superior to the volume of the initial glioblastoma (83.3% vs. 75.0%,  $p = 0.027$ ), and increased mass effect compared to the early postoperative MRI was more frequent (83.3% vs. 31.3%,  $p = 0.024$ ). Contrast enhancement pattern ( $p = 0.473$ ) and diffusion signal abnormalities ( $p = 0.471$ ) did not significantly differ between postoperative bacterial abscesses and non-infected surgical bed cysts.

Table 3

Clinical and imaging characteristics of postoperative bacterial abscesses (n = 6) and surgical bed cysts (n = 16).

Parameters at MRI diagnosis	Surgical bed cyst (n = 16) n (%)	Bacterial abscess (n = 6) n (%)	p-value
Time interval from surgery to diagnosis (days) (mean ± SD (range))	54.0 ± 16.9	26.2 ± 10.6	<b>0.004</b>
Symptomatic	8 (50.0)	0 (0)	<b>0.009</b>
No	8 (50.0)	6 (100)	
Yes			
Presence of increased intracranial pressure	9 (56.3)	1 (16.7)	0.084
No	7 (43.7)	5 (83.3)	
Yes			
Presence of new neurological deficit	15 (93.7)	1 (16.7)	<b>&lt; 0.001</b>
No	1 (6.3)	5 (83.3)	
Yes			
History of postoperative epileptic seizure	12 (75.0)	5 (83.3)	0.671
No	4 (25.0)	1 (16.7)	
Yes			
Postoperative fever	16 (100)	2 (33.3)	<b>&lt; 0.001</b>
No	0 (0)	4 (66.7)	
Yes			
Residual air in the resection cavity	7 (43.7)	0 (0)	<b>0.018</b>
No	9 (56.3)	6 (100)	
Yes			
Volume of the cyst superior to that of the initial tumor	4 (25.0)	1 (16.7)	<b>0.027</b>
No	12 (75.0)	5 (83.3)	
Yes			

Parameters at MRI diagnosis	Surgical bed cyst (n = 16) n (%)	Bacterial abscess (n = 6) n (%)	p-value
Surgical bed wall contrast enhancement	1 (6.3)	1 (16.7)	0.473
No	15 (93.7)	5 (83.3)	
Yes			
Restricted diffusion in the cyst walls	2 (7.1)	0 (0)	0.471
No	9 (92.9)	3 (100)	
Yes	5	3	
Data missing (no available diffusion-weighted imaging)			
Increased mass effect compared to early postoperative MRI	11 (68.7)	1 (16.7)	<b>0.025</b>
No	5 (31.3)	5 (83.3)	
Yes			

## Discussion

### Key results

In this retrospective monocentric cohort study of 122 adult patients harboring a supratentorial newly diagnosed *IDH*-wildtype glioblastoma treated with surgical resection plus Carmustine wafer implantation as first-line treatment, we show that: 1) 22 (18.0%) patients developed a contrast-enhancing cyst within the surgical bed during the first six postoperative months of imaging follow-up: 16 uninfected surgical bed cysts and 6 bacterial abscesses; 2) all patients with a non-infected surgical bed cyst were managed conservatively (no surgery, no antibiotic therapy); 3) all those surgical bed cysts resolved on imaging follow-up, no patient had to stop their ongoing adjuvant therapy; 4) independent risk factors for developing an uninfected postoperative surgical bed cyst were age  $\geq 60$  years, number of Carmustine wafers implanted  $\geq 8$ , and partial surgical resection; 5) shorter time from surgery to diagnosis, new postoperative symptoms (focal neurological deficit, fever), residual air in the resection cavity, volume of the postoperative contrast-enhancing cyst superior to the volume of the initial glioblastoma, and increased mass effect compared to the early postoperative MRI were more frequently observed in postoperative bacterial abscesses than in aseptic surgical bed cysts.

### Interpretation

To the best of our knowledge, no previous report has evaluated the risk factors for surgical bed cyst formation following Carmustine wafers implantation during the first resection of a newly diagnosed *IDH*-

wildtype glioblastoma. We report contrast-enhancing cysts within the surgical bed during the first six postoperative months of imaging follow-up in 18.0% of patients under study, corresponding to either uninfected surgical bed cysts or bacterial abscesses. The prevalence of surgical bed cysts after Carmustine wafer implantation varies in the literature from 3–58%<sup>15,18–20</sup>. This may be explained by a lack of systematic imaging follow-up data, since 50% of surgical bed cysts are asymptomatic according to our cohort, and by the varying level of inclusion of postoperative bacterial abscesses between reports. Interestingly, surgical bed cysts occur around the 8th postoperative week<sup>15</sup> while postoperative bacterial abscesses usually occur earlier in the first postoperative month<sup>21</sup>. This could be linked to the bacterial proliferation which would grow faster than the cystic formation which, also explaining the faster clinical deterioration. Interestingly, Hasegawa et al. reported a retrospective study involving 19 patients who benefited from a surgical resection plus Carmustine wafer implantation for newly-diagnosed and recurrent high-grade gliomas<sup>22</sup>. They found one case of surgical bed cyst, which required a new surgical procedure without bacteria identified on intraoperative samples. In the present study, the 16 uninfected surgical bed cysts showed a benign course, with presenting symptoms in 50% of cases and clinical and radiographic resolution in all cases after conservative management without surgery. High dose steroids were administered for symptomatic patients, as recommended<sup>19</sup>. These observations contrast with previous studies, which emphasize and justify the need for surgical treatment to treat elevated intracranial pressure despite corticosteroid treatment<sup>14,15,20</sup>. Of note, most of the previously published surgical bed cysts requiring surgical management occurred after resection and Carmustine wafer implantation for a recurrent glioblastoma. This may be related to inflammatory changes we did not encounter in the present series, focused on newly diagnosed glioblastomas.

We identified independent risk factors of developing an uninfected surgical bed cyst following surgical resection plus Carmustine wafer implantation as first treatment of *IDH*-wildtype glioblastomas: age  $\geq 60$  years, number of Carmustine wafers implanted  $\geq 8$ , and partial surgical resection. This will help in clinical practice to better identify patients at risk of developing a surgical bed cyst and at tailoring the postoperative management (clinical and imaging follow-up, duration and dose of steroid therapy). One study, including 36 cases of newly and recurrent glioblastomas, analyzed the relationship between cyst occurrence and some clinical and surgical data<sup>19</sup>, and identified partial resection as a risk factor, in accordance with our results.

The analysis of MRI findings in the setting of *IDH*-wildtype glioblastomas treated by surgical resection plus Carmustine wafer implantation followed by standard radiochemotherapy protocol is challenging, particularly in the initial postoperative months<sup>23</sup>. Discriminating between early recurrent disease and surgical bed cyst is a concern. Here, all surgical bed cysts showed a thin circular rim of contrast enhancement caused by the Carmustine wafers, which contrasts with the nodular appearance of recurrent disease. MR perfusion and MR spectroscopy might be helpful in identifying early recurrences<sup>15,20,24,25</sup>. Discriminating between postoperative surgical site bacterial abscess and an uninfected surgical bed cyst is another major concern. In our series, contrast enhancement pattern and diffusion signal abnormalities were not discriminating imaging parameters because, in the context of

Carmustine wafer implantation and of post-radiation inflammatory changes, the resection cavity and adjacent parenchyma showed a peak of restricted diffusion signal, from three weeks up to 6 months postoperatively, in addition to contrast enhancement<sup>12,24,26</sup>. We identified clinical and imaging parameters that may help discriminate between a bacterial abscess and an uninfected surgical bed cyst: cyst-related new postoperative focal neurological deficits, fever, residual air in the surgical cavity, volume of the cyst superior to that of the initial tumor, and increased mass effect compared to early postoperative MR imaging related to brain edema. In the six cases with a postoperative bacterial abscess, patients had worsening of their general (fever and asthenia) and/or neurological (focal neurological deficit and signs of increased intracranial pressure) condition, and their MRI showed signs consistent with a brain abscess (contrast enhancement, restricted diffusion, and residual air in the surgical bed). When both clinical and MRI findings were highly suspicious for a bacterial abscess, surgical intervention was performed, confirming the diagnosis. If the clinical and radiological criteria are not present, then clinic-radiological monitoring should be started. These observations, together with the timing of cyst occurrence, will orient the treatment strategy - conservative management versus surgical intervention - in each individual patient harboring a contrast-enhancing cyst within the surgical bed following surgical resection plus Carmustine wafer implantation.

## **Generalizability**

Strengths of this study include the data collection of a large case series in a tertiary neurosurgical oncology center and the homogeneous postoperative imaging follow-up. We controlled for patient-related and methodological biases by selecting a homogeneous and consecutive population of newly diagnosed supratentorial *IDH*-wildtype glioblastomas in adults who all underwent the same surgical procedure with the histopathological re-assessment of all cases according to the 2016 update WHO classification. The present study could help: 1) identify patients at risk of developing a postoperative surgical bed cyst after resection of a newly diagnosed *IDH*-wildtype glioblastoma with Carmustine wafer implantation; 2) discriminate between postoperative uninfected surgical bed cysts and bacterial abscesses; 3) manage these patients accordingly with early surgical intervention for postoperative bacterial abscesses and conservative management for postoperative uninfected surgical bed cysts. We cannot extend the results to patients harboring another subtype of high-grade glioma or a recurrent glioblastoma with previous oncological treatments.

## **Limitations**

These findings should be interpreted with caution, given the retrospective and monocentric design of the study, the exploratory design of the statistical analyses, the lack of a control group, and the lack of an external validation set, all limiting the generalizability of the results. Given the number of observed events, the application of multivariable models was limited, particularly regarding isolation of parameters discriminating between postoperative bacterial abscesses and uninfected surgical bed cysts. In addition, we lack bacteriological evidence excluding the possibility of a bacterial abscess in surgical bed cysts that

were all managed conservatively with positive outcomes. Further confirmatory analyses are required to reproduce the present results.

## Conclusion

Postoperative surgical bed cysts occurred in about 20% of cases following Carmustine wafer implantation during the initial resection of newly diagnosed *IDH*-wildtype glioblastomas. The identification of risk factors for formation of a postoperative surgical bed cyst in this particular patient population may help tailor postoperative steroid therapy and imaging follow-up schedule. In addition, we identified clinical and imaging characteristics that may help discriminate between an uninfected surgical bed cyst and a bacterial abscess, the latter requiring early surgical management.

## Abbreviations

ADC

Apparent Diffusion Coefficient

DWI

Diffusion-Weighted Imaging

FLAIR

Fluid Attenuated Inversion Recovery

IDH

Isocitrate Dehydrogenase

KPS

Karnofsky Performance Status

MGMT

O6-methylguanine-DNA methyltransferase

OR

Odds Ratio

RTOG

Radiation Therapy Oncology Group

RPA

Recursive Partitioning Analysis

WHO

World Health Organization

## Declarations

### Funding

None.

## Conflict of interest

The authors declare that they have no conflict of interest.

## Authorship

AR, HA, AM, MB, and ED did the data collection.

HA, and JP did the data analysis.

AR, HA and JP did the data interpretation.

AR, HA, AM, MB, GZB, JB, CO, CB, FC, PV, FD, ED, MZ, and JP wrote the report.

AR, HA, AM, MB, GZB, JB, CO, CB, FC, PV, FD, ED, MZ, and JP reviewed and approved the paper.

## Ethical approval for retrospective studies

The human research institutional review board approved the protocol (no. AC036). The requirement to obtain informed consent was waived for this observational retrospective study according to French legislation.

## Data availability statement

Data not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator for purposes of replicating procedures and results.

## Disclosure

None of the authors have any conflict of interest or financial disclosure in relation to this study. The manuscript has not been previously published in whole or in part or submitted elsewhere for review.

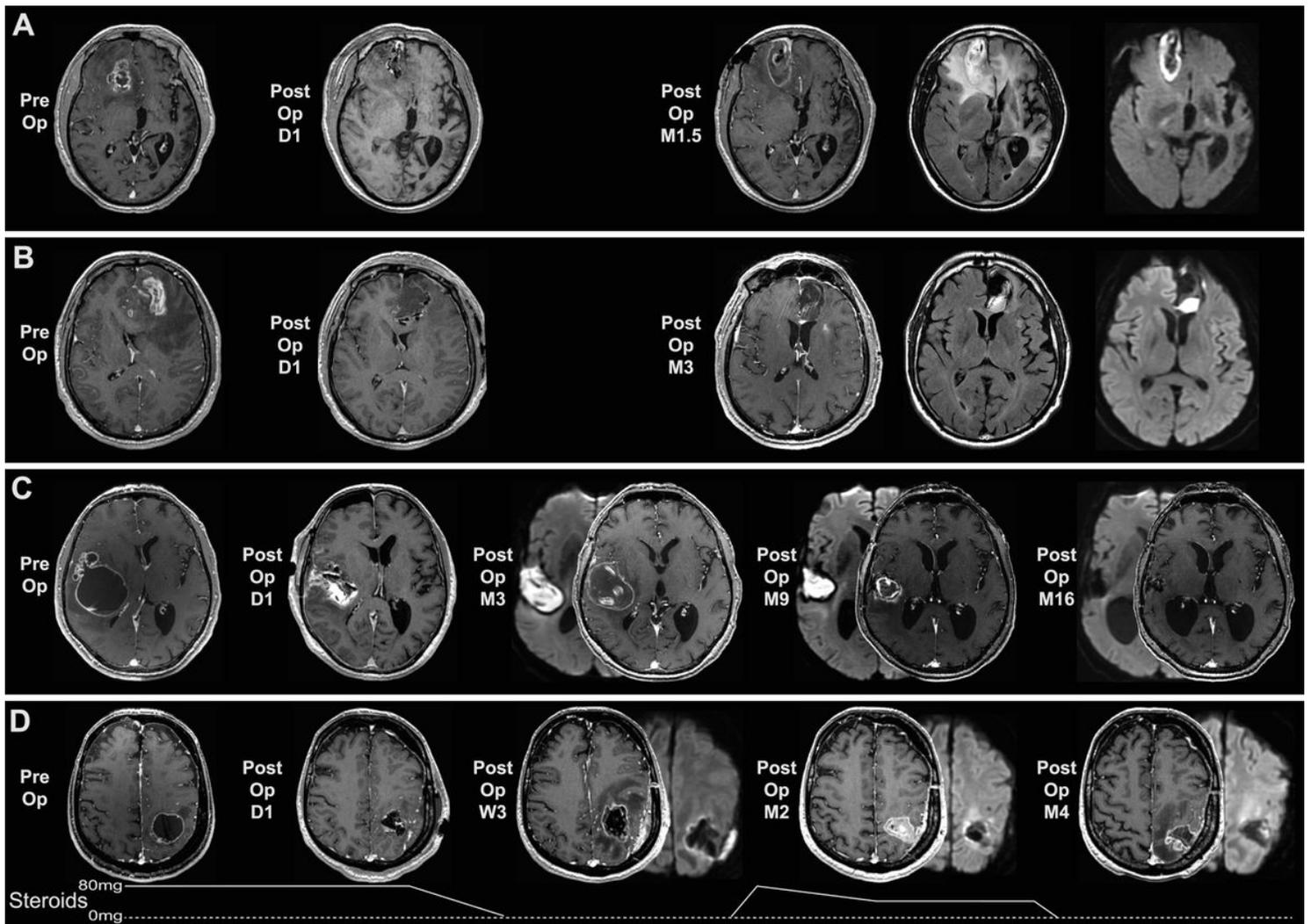
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## Figures



**Figure 1**

Case illustrations. A. Brain abscess in a 53-year-old man following total resection of a right frontal IDH-wildtype glioblastoma plus implantation of 6 Carmustine wafers. Preoperative (PreOp) and postoperative day one (PostOp D1) MRIs of three-dimensional contrast-enhanced T1-weighted sequences are presented on the left. At six weeks postoperatively, the patient presented with headaches, left hemiparesis, fever, and inflammatory serum markers. The six-week postoperative MRI (PostOp M1.5; three-dimensional contrast-enhanced T1-weighted sequence, fluid-attenuation inversion recovery sequence, and diffusion weighted sequence) demonstrated a surgical site bacterial abscess requiring surgical evacuation. B. Brain abscess in a 59-year-old man following subtotal resection of a left fronto-callosal IDH-wildtype glioblastoma plus implantation of 8 Carmustine wafers. Preoperative (PreOp) and postoperative day one (PostOp D1) MRIs of three-dimensional contrast-enhanced T1-weighted sequence are presented on the left. At three months postoperatively, the patient presented with headaches, fever, a subcutaneous collection, and inflammatory serum markers. The three-month postoperative MRI (PostOp M1.5; three-dimensional contrast-enhanced T1-weighted sequence, fluid-attenuation inversion recovery sequence, and diffusion weighted sequence) demonstrated a surgical site bacterial abscess requiring surgical evacuation. C. Surgical bed cyst in a 70-year-old man following total resection of a right fronto-insular IDH-wildtype

glioblastoma plus implantation of 8 Carmustine wafers. Preoperative (PreOp) and postoperative day one (PostOp D1) MRIs in three-dimensional contrast-enhanced T1-weighted sequences are presented on the left. The three-month postoperative MRI (PostOp M3; three-dimensional contrast-enhanced T1-weighted sequence and diffusion weighted sequence) demonstrated a postoperative surgical bed cyst without clinical signs. Due to the lack of signs of infection, the surgical bed cyst was managed conservatively with maintenance of systemic corticosteroid therapy at 40mg per day for 3 months with a subsequent gradual decrease until the sixth month. Imaging follow-up demonstrated progressive regression of the surgical bed cyst (PostOp M9, PostOp M16). D. Surgical bed cyst in a 49-year-old man following subtotal resection of a left parietal IDH-wildtype glioblastoma plus implantation of 8 Carmustine wafers. Preoperative (PreOp) and postoperative day one (PostOp D1) MRIs in three-dimensional contrast-enhanced T1-weighted sequences are presented on the left. At three weeks postoperatively, the patient presented with a right hemiparesis and speech disorder following discontinuation of corticosteroid therapy. The three-week postoperative MRI (PostOp W3; three-dimensional contrast-enhanced T1-weighted sequence and diffusion weighted sequence) demonstrated a postoperative surgical bed cyst. Due to the lack of signs of infection, the surgical bed cyst was managed conservatively with the reintroduction of systemic corticosteroid therapy at 80mg per day for 2 months followed by a gradual decrease until the third month. Imaging follow-up demonstrated progressive regression of the surgical bed cyst (PostOp M2, PostOp M4).

## Supplementary Files

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