

## Sexuality after surgery for diffuse low-grade glioma

Werner Surbeck, Guillaume Herbet, and Hugues Duffau

Department of Neurosurgery, Cantonal Hospital of St. Gallen, St. Gallen, Switzerland (W.S.); Department of Neurosurgery, Gui de Chauliac Hospital, Montpellier University Medical Center, Montpellier, France (G.H., H.D.); Institute of Neuroscience of Montpellier, INSERM U1051, Team “Plasticity of Central Nervous System, Human Stem Cells and Glial Tumors,” Saint Eloi Hospital, Montpellier University Medical Center, Montpellier, France (G.H., H.D.)

**Corresponding Author:** Hugues Duffau, MD, PhD, Department of Neurosurgery, Gui de Chauliac Hospital, Montpellier University Medical Center, 80 Avenue Augustin Fliche, 34295 Montpellier, France (h-duffau@chu-montpellier.fr).

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**Background.** Although neurological and neurocognitive outcomes have previously been studied after resection of diffuse low-grade glioma (DLGG), the impact of surgery on sexual life has not been investigated. Our aim was to assess whether DLGG surgery could have consequences on sexual experience.

**Methods.** Anonymous standardized questionnaires concerning sexual functioning, including the Arizona Sexual Experiences Scale (ASEX) and a subjective statement, were completed by 32 patients who underwent surgery for DLGG. All patients returned to a normal social and professional life following resection, with neither neurological deficits nor depression. No radiotherapy was administered, and patients who received chemotherapy were without treatment for at least 1 year.

**Results.** Seventeen patients (53%) reported a postoperative sexual change, with subjective deterioration in 15 (88%) and improvement in 2 (12%). Sexual dysfunction according to ASEX affected 9 of 15 women (60%) and 5 of 17 men (29%). Right-sided resections were associated with more difficulties in reaching orgasm than left-sided resections ( $P < .02$ ). Men with temporal lobe resection displayed more reduction in sexual drive ( $P < .003$ ) and sexual arousal ( $P < .004$ ) than women, resulting in significant higher overall ASEX scores for temporal lobe resections in men ( $P = .01$ ). Men remaining on antiepileptic drugs who underwent right-sided resection displayed higher overall ASEX scores than women ( $P = .031$ ).

**Conclusions.** This first evaluation of sexual life after surgery for DLGG suggests that sexual dysfunction is common in this population. Therefore, we suggest that sexual health should consistently be addressed during routine pre- and postoperative examination of patients with DLGG.

**Keywords:** diffuse low-grade glioma, quality of life, sexual dysfunction, surgery.

Sexual health is a fundamental element of human well-being. Sexual dysfunction (SD) significantly affects interpersonal relationships and overall quality of life for both men and women.<sup>1</sup> Sexual functioning in patients suffering from tumors that involve sexual or pelvic organs, as well as in those whose treatment affects the hormonal systems responsible for mediating sexual function, is a topic of great concern and intensive research.<sup>2</sup> In contrast, sexuality in patients with brain tumors has remained largely neglected, despite the fact that even critically ill patients suffering from glioblastoma may still desire sexual intimacy.<sup>3</sup>

Diffuse low-grade glioma (DLGG) usually affects young adults who enjoy a normal social and professional life.<sup>4</sup> Accumulating evidence over the past 2 decades has highlighted the crucial role of surgical cytoreduction (by delaying anaplastic transformation)

on overall survival of these patients.<sup>5–7</sup> Thanks to methodological advances in brain-mapping techniques and the resulting substantial risk reduction of such interventions, surgery is considered the first therapeutic option for DLGG patients today.<sup>8</sup> However, postoperative quality of life should be preserved in these patients with normal activity.<sup>9</sup> Although postoperative neurological and neurocognitive outcomes (including language, working memory, attention, and even mentalizing) have been previously studied,<sup>10–15</sup> the impact of surgery on sexual life has not been investigated in DLGG patients. To our knowledge, the present study is the first evaluation of SD in a neuro-oncological patient population that has been performed on a homogeneous series of patients operated on for DLGG who enjoy a normal social and professional life.

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## Materials and Methods

### Patient Selection

The study participants were selected by chart review among patients who underwent surgery for WHO grade II glioma (ie, diffuse low-grade glioma as confirmed by postoperative neuropathological analysis) at the Gui de Chauliac Hospital in Montpellier, France, between 2006 and 2013. All patients were operated on by the senior author (H.D.) under local anesthesia with intraoperative electrical mapping using a methodology extensively described in previous reports.<sup>6,9,10</sup> The inclusion criteria were defined as follows: age between 18 and 60 years; return to a normal social and professional life after the intervention; absence of any permanent postoperative neurological deficit; no prior radiotherapy; and no prior chemotherapy for at least 1 year. Patients with a history of neurological disorders other than symptomatic epilepsy were excluded from the study, as were those diagnosed or treated for depression. Sixty patients were included in the study using these criteria. Sex and age, as well as all information regarding seizures and antiepileptic medication were extracted from chart review. The site of tumor resection was based on postoperative magnetic resonance image. All participants gave informed consent to participating in the study.

### Questionnaire

An anonymous standardized questionnaire was sent to the selected patients containing the following inventories:

#### Subjective Impact of the Intervention on Sexual Pleasure

The participants were asked to state whether their current sexual experience has improved, deteriorated, or remained unchanged compared with the status before surgery.

#### Arizona Sexual Experiences Scale

The Arizona Sexual Experiences Scale (ASEX) is a brief, 5-item rating scale designed to assess the core elements of sexual function: sex drive, arousal, penile erection/vaginal lubrication, ability to reach orgasm, and orgasmic satisfaction. Each item is rated with a 6-point scale, with higher scores reflecting greater impairment. A total ASEX score  $\geq 19$ , any one item with a score of  $\geq 5$ , or any 3 items with a score of  $\geq 4$  have all been found to be correlated with SD.<sup>16</sup> We used the French version of the inventory, which has been proven valid and reliable by a recent study.<sup>17</sup>

## Results

Of the 60 participants contacted, 32 (53%) completed and returned the questionnaire. They did not differ from those who did not reply in terms of age ( $t_{(58)} = 0.19$ ,  $P = .84$ ), sex ( $\chi^2 = 0.003$ ,  $P = .98$ ), time elapsed since surgery ( $t_{(58)} = 0.60$ ,  $P = .5$ ), tumor laterality ( $\chi^2 = 0.137$ ,  $P = .712$ ), epileptic seizures ( $\chi^2 = 0.004$ ,  $P = .95$ ), and antiepileptic drugs (AEDs) ( $\chi^2 = 0.68$ ,  $P = .41$ ). Seventeen participants were male, and 15 were female. The mean age of the participants was  $38.6 \pm 9.3$  years (range, 19–58 years). Mean time since surgery was  $38.3 \pm 17.9$  months (range, 8–93 months). Fourteen participants (44%) underwent DLGG resection within the left hemisphere and 18 (56%) within

the right hemisphere. Thirteen resections (41%) involved temporal lobe structures, while the remaining 19 (59%) did not. Individual participant data are displayed in Tables 1 and 2.

Seventeen of the 32 participants (53%) reported a postoperative sexual change, with subjective deterioration of sexual well-being in 15 (88%) and improvement in 2 (12%). No significant difference between temporal and extratemporal resections was reported in relation to subjective postoperative sexual change ( $\chi^2 = 1.32$ ,  $P > .05$ ).

Fourteen participants (44%) met the definition for SD according to the ASEX criteria. Nine of 15 women (60%) and 5 of 17 men (29%) were affected. Despite this notable gender difference when applying the ASEX criteria for SD, there was no significant difference between men and women when considering individual ASEX item scores or the overall ASEX score in the statistical analyses ( $P \geq .1$  for all comparisons using  $t$  statistic). Right-sided resection was associated with SD in 10 out of 18 participants (56%) and left-sided resection in 4 out of 14 (29%) participants. Group analysis revealed that right-sided resections had significantly higher scores than left-sided resections with regards to ASEX item 4 (ability to reach orgasm) ( $t_{(30)} = -2.48$ ,  $P < .02$ ). Other comparisons did not reach significance ( $P > .11$ ). SD was more frequent in temporal than extratemporal surgeries with 7 out of 13 (54%) and 7 out of 19 (37%) participants respectively. However, group analyses did not support this qualitative observation ( $P > .10$  for all comparisons).

At the last follow-up, 26 (81%) participants were seizure free. The remaining 6 participants (19%) presented with nondisabling, simple partial seizures only. Remaining seizures were associated with SD in 2 participants (33%). Of the 14 participants with SD, 5 were off AEDs (36%), 7 (50%) were on a single AED, and the remaining 2 participants (14%) were on 2 and 3 AEDs, respectively. Six out of 18 participants (33%) without SD were off AEDs, while 7 (39%) were on a single AED, and 5 (28%) were on 2 AEDs. Group analyses did not yield any statistically significant differences in specific and global ASEX measures between participants taking AEDs versus others who did not (all  $P > .64$  using simple 2-tailed  $t$  test).

A 3-way factorial ANOVA with *gender*, *temporal versus extratemporal resections* and *AED intake* as between-subject factors revealed only a significant interaction effect between *gender* and *temporal versus extratemporal resections* ( $F_{(1, 24)} = 7.51$ ,  $P = .011$ ), demonstrating that male patients with a resection including the temporal lobe displayed significant higher overall ASEX scores than female patients. With regard to individual ASEX items, the same result was reiterated for ASEX item 1 (sexual drive) ( $F_{(1,24)} = 11.14$ ,  $P < .003$ ) and ASEX item 2 (sexual arousal) ( $F_{(1,24)} = 11.64$ ,  $P < .004$ ). We found the same interaction effect for ASEX item 5 (satisfaction with orgasm) but in the opposed direction (ie, *gender\*temporal versus extratemporal resections*) ( $F_{(1,24)} = 5.69$ ,  $P = .025$ ), suggesting that women who underwent resections excluding temporal lobe structures had significantly higher scores than men.

A further 3-way factorial ANOVA including *gender*, *resection side* and *AED intake* as between-subject factor did not reveal main effects of factors but, importantly, highlighted a second-order interaction effect (ie, *gender\*resection side\*AED intake*) ( $F_{(1,24)} = 5.23$ ,  $P = .031$ ). The precise analysis of this complex effect indicated that male patients remaining on AED treatment who underwent right-sided resection displayed significantly

**Table 1.** Demographic and clinical characteristics of the patients

Patient	Sex	Age, y	Handedness	Tumor Side	Months After Surgery	Epileptic Seizures	Number of AEDs	Localization					
								Frontal	Insular	Temporal	Parietal	Occipital	
1	F	50	Right	Left	45	–	–						+
2	F	43	Right	Right	29	–	–						+
3	M	54	Ambidextrous	Left	45	–	–						
4	F	37	Right	Right	39	–	–	+					
5	M	42	Left	Right	47	SPS	3						
6	M	35	Left	Left	51	–	1		+				
7	F	40	Right	Right	32	–	1		+				
8	F	38	Right	Right	93	–	2		+				
9	F	27	Right	Right	29	–	1	+	+				
10	F	25	Right	Right	24	SPS	2	+	+				
11	F	29	Right	Right	52	–	1	+	+				
12	F	35	Right	Right	49	SPS	1	+	+				
13	M	31	Right	Right	28	–	1	+	+				
14	F	44	Right	Right	52	–	1	+	+				
15	M	52	Left	Left	57	–	–	+	+				
16	M	30	Right	Left	40	SPS	1	+					
17	M	28	Left	Left	52	SPS	2	+					
18	M	31	Right	Left	55	–	1	+					
19	M	55	Right	Left	21	–	1	+					
20	M	34	Right	Right	29	–	–	+					
21	F	43	Right	Left	18	–	1	+					
22	M	39	Right	Left	65	–	1	+					
23	M	38	Right	Left	8	–	2	+					
24	F	38	Right	Left	24	–	1	+					
25	F	33	Right	Right	22	–	–	+					
26	F	43	Right	Right	43	–	–	+					
27	M	49	Right	Right	11	–	1						+
28	M	40	Left	Right	26	SPS	2						+
29	M	58	Left	Left	55	–	–						+
30	M	31	Right	Right	15	–	2						+
31	F	19	Right	Right	26	–	–						+
32	M	45	Right	Left	45	–	–						+

Abbreviations: AED, antiepileptic drug; F, female; M, male; SPS, simple partial seizures.

higher overall ASEX scores than female patients. We reached the same conclusion when considering ASEX item 3 (erection/lubrication) ( $F_{(1,24)} = 6.40, P = .018$ ). Conversely, an opposed second-order interaction effect was found when processing ASEX item 5 (satisfaction with orgasm) ( $F_{(1,24)} = 6.59, P = .016$ ). The analysis of this interaction suggested that women remaining on AEDs who underwent left-sided resection had significantly higher scores on ASEX item 5 than men under the same condition.

## Discussion

With the introduction and progress of new therapeutic modalities, many types of cancer now take the form of chronic diseases. Against this background, quality of life becomes a major issue in the medical care of affected patients. This is equally applicable for cancers of the central nervous system. Early and more aggressive resection has led to significantly prolonged overall survival in

DLGG patients over the past 2 decades.<sup>5–7</sup> This trend has been accompanied by increasing knowledge of the functional anatomy of the brain and advances in awake mapping that allow identification and preservation of an increasing number of functions, including sensorimotor, language, and cognitive functions (eg, judgment) as well as complex psychological phenomena such as social interactions and empathy.<sup>18–20</sup> Therefore, awake surgery enables preservation or even improvement of quality of life for DLGG patients, who generally continue to live a normal social and professional life.<sup>4,6</sup> However, although postoperative neurological and neurocognitive outcomes have previously been studied,<sup>10–15</sup> the impact of surgery on sexual life has not been investigated in DLGG patients.

Here, we demonstrate for the first time to our knowledge that sexual dysfunction is common among patients operated on for DLGG. Thus, it is very likely that the rate of SD has been underestimated in the previous literature. This is also true in our own experience because the patients did not complain spontaneously of

**Table 2.** Impact of surgery on sexual experience

Patient	Subjective Changes	ASEX					Sexual Dysfunction*
		Q1	Q2	Q3	Q4	Q5	
1	-	3	3	2	3	2	No
2	-	3	2	2	3	2	No
3	Negative	5	5	4	4	4	Yes
4	-	3	3	4	4	4	Yes
5	Negative	6	6	6	6	6	Yes
6	Negative	4	3	2	3	4	No
7	Negative	5	5	4	5	5	Yes
8	Positive	3	2	2	3	3	No
9	Negative	4	3	3	5	4	Yes
10	Negative	4	2	1	3	3	No
11	-	3	3	2	4	3	No
12	-	4	4	5	4	3	Yes
13	Negative	6	6	3	3	3	Yes
14	Positive	3	3	2	2	2	No
15	-	3	3	3	3	3	No
16	Negative	3	2	2	2	2	No
17	-	3	2	2	2	2	No
18	-	3	2	3	3	2	No
19	Negative	4	5	3	4	4	Yes
20	-	3	3	2	3	2	No
21	Negative	4	3	3	4	5	Yes
22	-	4	3	3	3	3	No
23	-	3	3	2	2	2	No
24	-	3	4	4	3	4	Yes
25	Negative	4	4	3	5	3	Yes
26	Negative	6	6	4	4	6	Yes
27	-	4	4	3	3	3	No
28	-	3	3	3	3	4	No
29	-	4	3	3	3	3	No
30	Negative	3	4	5	4	3	Yes
31	Negative	4	4	3	4	3	Yes
32	Negative	4	3	3	3	3	No

\*according to the ASEX criteria.

SD. Yet, sexual health is a fundamental element of human well-being. While current commonly used health-related quality of life questionnaires such as the EORTC Quality of Life Questionnaires (QLQ-C30 and QLQ-BN20) and the Functional Assessment of Cancer Therapy Questionnaires (FACT-G and FACT-Br) are highly valuable instruments for monitoring quality of life in patients with DLGG during treatment,<sup>21</sup> they are rather unsuitable for evaluating sexual well-being. While QLQ-C30 and QLQ-BN20 do not address the topic at all, the FACT questionnaires handle sexual functioning with a single item (“I am satisfied with my sex life”). Additional questions are mandatory for investigating sexuality more thoroughly and should be incorporated into such questionnaires in the future. In the interim, the brief 5-item ASEX rating scale assessing the core elements of sexual function seems perfectly suitable to cover this fundamental issue. Indeed, subjective changes in sexual functioning affected 53% of our patients. Deterioration of sexual experience constitutes by far the most common reported change (88% of cases, while

improvement was noted only in 12% of patients). While the percentage of men and women complaining of postoperative worsening are comparable, the prevalence of SD according to the ASEX criteria is considerably higher among women (60%) than among men (29%). However, because cutoff scores are set on a continuum of increasing symptom burden, this gender difference may be quite artificial and may explain why there was no statistically significant gender difference when isolated ASEX item scores or overall ASEX scores were compared by group analysis. This finding indicates a high rate of sexual concerns even among male patients.

Interestingly, previous series on the effect of brain surgery on sexual function were performed in the context of epilepsy surgery.<sup>22-29</sup> These studies focused almost exclusively on patients with temporal lobe epilepsy and reported no postoperative change in sexuality for the majority of patients. If a change was noted, it was typically an improvement or increase in sexual behavior<sup>30</sup> In our study, the high proportion of subjective postoperative deterioration of sexual well-being following oncological surgery contrasts with the abovementioned findings in epilepsy surgery. We are aware of the relative low response rate, which is probably due to the intimate nature of the survey. However, as patients tend to express satisfaction more than dissatisfaction with their treatment,<sup>31</sup> we do not feel that the response represents an overrepresentation of patients with complaints but rather that sexual dysfunction among DLGG patients is at least as frequent as suggested by this study’s results. Therefore, this high rate may be partly related to the psychosocial burden of a being afflicted with an incurable tumoral disease, which could interfere with sexual experience,<sup>32</sup> even though we might have reduced this factor by excluding co-morbid depression. Indeed, the latter is frequent in chronic illness and cancer and is associated with a prevalence of SD that is almost twice as high compared as the controls.<sup>33</sup> On the other hand, one could argue that that sexual problems among DLGG patients are in fact relatively rare in comparison with other cancers. For example, treatment-related sexual problems affect most patients suffering from malignancies involving the sexual and pelvic organs, leading to a very high prevalence of sexual dysfunction: up to 100% in breast cancer, up to 80% in ovarian and cervical malignancies, and up to 90% in prostate cancer.<sup>34</sup> The treatment of DLGG, however, does not interfere with sexual organs or body appearance. Therefore, one would expect sexual problems to occur at very low frequencies in DLGG patients, which does not seem to be the case in our series.

We should acknowledge that we did not control for cancer-related fatigue, which constitutes a limitation of the present study. Fatigue may be observed in patients with DLGG<sup>35</sup> and could have a detrimental effect on sexual activity by attenuating their level of physical activity.<sup>36</sup> It is also conceivable that sexual functioning might have improved somewhat since surgery. However, studies on the impact of stroke on sexuality show a revival of sexual activity 3 to 6 month post stroke.<sup>37</sup> In the absence of any data on the recovery of sexual life after brain damage, we used this as a reference and included only patients operated on more than six months before enrollment in the study. Further longitudinal studies would be necessary to address this point more rigorously.

Although the study was not designed to investigate the impact of resection sites on sexual well-being, it is worth noting that right-sided resections were associated with significantly

greater difficulty reaching orgasm than left-sided resections. This finding concurs with functional imaging studies revealing balanced bilateral activation during sexual arousal<sup>38</sup> but lateralization during orgasm and widespread right hemisphere hyperperfusion<sup>39</sup> or left hemisphere hypoperfusion<sup>40</sup> suggesting a right hemispheric dominance of release from sexual tension (orgasm).<sup>41</sup> In the same vein, there is a significant lateralization predominance of the epileptogenic region to the right hemisphere in patients with temporal lobe epilepsy who experience sexual auras.<sup>42,43</sup> In terms of gender differences, we found that male patients with a resection including the temporal lobe displayed significantly higher overall ASEX scores than female patients under the same circumstances. With regard to the ASEX subgroups, men demonstrate more reduction in sexual drive and greater difficulty in becoming sexually aroused than women who were operated on in the temporal region. In contrast, women who underwent resections that excluded temporal lobe structures had a significantly greater decrease in orgasm satisfaction than men. This result is intriguing because it contradicts previous assumptions of gender-specific neural organization of psychosexual behavior with a temporal dominance in women.<sup>43</sup> In previous reports of epilepsy patients with sexual auras, the majority were female, which suggests that the neural organization of psychosexual behavior may differ in human male and female brains.<sup>41,43</sup> Regarding the role of the temporal lobes in the mediation of human sexual behavior, this was underlined by case reports on Klüver-Bucy syndrome after bilateral temporal lobectomies that had been performed for epileptic or psychiatric reasons.<sup>30</sup> In accordance with these findings, the only series examining the effect of epilepsy surgery on sexual function, including both temporal and extratemporal surgeries allowing group comparison, found that postoperative sexual change was significantly more likely in patients who underwent temporal resection than those who underwent extratemporal resection.<sup>28</sup>

Finally, we found an interactive effect between sex, resection side, and AED intake, which suggested that to remain under AEDs may increase the risk of developing SD in male patients operated on the right hemisphere. These findings concur with insights provided by epilepsy surgery: postoperative freedom from seizures and discontinuation of AEDs have consistently been identified as predictive factors for improvement of sexual functioning.<sup>29</sup>

Given its intimacy and complexity, sexual functioning remains largely inaccessible to intraoperative stimulation mapping. Using direct electrical stimulation, it was possible to evoke sexual arousal and/or orgasmic ecstasy by stimulation of mesiotemporal<sup>43-45</sup> and basal forebrain structures<sup>46</sup> in only a handful of patients. Our current knowledge on the central representation of human sexual sensations is mainly based on neurological patients presenting with epileptic seizures and sexual auras.<sup>30</sup> Despite the introduction and advances in functional neuroimaging techniques, which open a new window for the study of sexual sensations both in healthy participants and those with sexual disorders,<sup>38</sup> much work remains to be done to better understand the brain basis of human sexuality. For this purpose, future studies designed to detect possible different effects of resection sites on sexual functioning are mandatory to better inform patients about possible sexual side effects before a planned surgery, as we have recently done with regard to emotional processes such as mentalizing.<sup>14,20</sup>

## Conclusion

The results of this study suggest that SD is common among patients operated on for DLGG. Given the subjective and intimate nature of these concerns, addressing sexual dysfunction may be uncomfortable for physicians who are unfamiliar with management of sexual health. This is all the more important because most affected patients do not seek help due to feelings of embarrassment or because they do not view it as a medical problem.<sup>47</sup> In light of increasing overall survival in DLGG patients due to multimodal and multistage long-term therapeutic approaches,<sup>6</sup> a better understanding of the consequences of specific treatment arms on sexual well-being is crucial for preserving patients' quality of life. The present findings serve as motivation to integrate the assessment of SD into the routine examination of DLGG patients, both before and after surgery, in order to involve comprehensive sexual health programs for specific therapy if necessary. Prospective data are needed to quantify the extent of resection of tumor-infiltrated brain tissue that may cause SD or aggravate a pre-existing SD.

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