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Patterns of pain-free response in 497 cases of classic trigeminal neuralgia treated with Gamma Knife surgery and followed up for least 1 year

Clinical article

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Object. The goal of this study was to establish whether clear patterns of initial pain freedom could be identified when treating patients with classic trigeminal neuralgia (TN) by using Gamma Knife surgery (GKS). The authors compared hypesthesia and pain recurrence rates to see if statistically significant differences could be found.

Methods. Between July 1992 and November 2010, 737 patients presenting with TN underwent GKS and prospective evaluation at Timone University Hospital in Marseille, France. In this study the authors analyzed the cases of 497 of these patients, who participated in follow-up longer than 1 year, did not have megadolichobasilar artery- or multiple sclerosis-related TN, and underwent GKS only once; in other words, the focus was on cases of classic TN with a single radiosurgical treatment. Radiosurgery was performed with a Leksell Gamma Knife (model B, C, or Perfexion) using both MR and CT imaging targeting. A single 4-mm isocenter was positioned in the cisternal portion of the trigeminal nerve at a median distance of 7.8 mm (range 4.5–14 mm) anterior to the emergence of the nerve. A median maximum dose of 85 Gy (range 70–90 Gy) was delivered. Using empirical methods and assisted by a chart with clear cut-off periods of pain free distribution, the authors were able to divide patients who experienced freedom from pain into 3 separate groups: patients who became pain free within the first 48 hours post-GKS; those who became pain free between 48 hours and 30 days post-GKS; and those who became pain free more than 30 days after GKS.

Results. The median age in the 497 patients was 68.3 years (range 28.1–93.2 years). The median follow-up period was 43.75 months (range 12–174.41 months). Four hundred fifty-four patients (91.34%) were initially pain free within a median time of 10 days (range 1–459 days) after GKS. One hundred sixty-nine patients (37.2%) became pain free within the first 48 hours (Group PF_{≤ 48 hours}), 194 patients (42.8%) between posttreatment Day 3 and Day 30 (Group PF_{> 48 hours, ≤ 30 days}), and 91 patients (20%) after 30 days post-GKS (Group PF_{> 30 days}). Differences in postoperative hypesthesia were found: in Group PF_{≤ 48 hours} 18 patients (13.7%) developed postoperative hypesthesia, compared with 30 patients (19%) in Group PF_{> 48 hours, ≤ 30 days} and 22 patients (30.6%) in Group PF_{> 30 days} (p = 0.014). One hundred fifty-seven patients (34.4%) who initially became free from pain experienced a recurrence of pain with a median delay of 24 months (range 0.62–150.06 months). There were no statistically significant differences between the patient groups with respect to pain recurrence: 66 patients (39%) in Group PF_{≤ 48 hours} experienced pain recurrence, compared with 71 patients (36.6%) in Group PF_{> 48 hours, ≤ 30 days} and 27 patients (29.7%) in Group PF_{> 30 days} (p = 0.515).

Conclusions. A substantial number of patients (169 cases, 37.2%) became pain free within the first 48 hours. The rate of hypesthesia was higher in patients who became pain free more than 30 days after GKS, with a statistically significant difference between patient groups (p = 0.014).
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KEY WORDS • freedom from pain • trigeminal neuralgia • pattern • Gamma Knife surgery • stereotactic radiosurgery • treatment response

Abbreviations used in this paper: BNI = Barrow Neurological Institute; GKS = Gamma Knife surgery; Group PF = pain-free group; MS = multiple sclerosis; TN = trigeminal neuralgia.

LARS Leksell first introduced the concept of stereotactic radiosurgery in 1951, when he treated a patient suffering from classic TN using a prototype-guiding device linked to a dental x-ray machine.¹⁴

The use of GKS in the treatment of TN became more and more frequent starting in the 1990s, and an increasing number of articles confirming its safety and efficacy have appeared since 1996,^{1–4,6,10,13,16–21,24} in what we called a “revolution” in functional neurosurgery in our recent editorial.²²

The mechanisms of action that could explain the effectiveness of GKS for TN remain unclear, even though we now have persuasive evidence that demyelination of trigeminal sensory fibers plays an important role.¹⁵ Several animal studies have also been performed in attempts to clarify the pathophysiological aspects of postoperative GKS effects.^{12,27}

As we pointed out in our editorial,²² the number of articles about the role of GKS in the armamentarium for treating TN is continually growing. Thus far, few of them discuss the mechanism of action and neuromodulator effect of this radiosurgical technique because in many aspects the radiobiology remains unclear.

Methods

Patient Population and Selection for Treatment

Between July 1992 and November 2010, 737 patients presenting with intractable TN were treated with GKS and followed up prospectively at the Timone University Hospital in Marseille, France. We accepted for treatment patients fulfilling the criteria of the International Headache Society,⁷ which included long-standing pain refractory to pharmacological treatment with agents such as carbamazepine, phenytoin, baclofen, gabapentin, and so forth.

Four hundred ninety-seven patients with more than 1 year of follow-up comprised the study group that we finally analyzed. We deliberately excluded from our study patients whose TN was related to a megalolichobasilar artery or MS, as well as those who underwent a second GKS treatment. We focused only on cases of classic TN in which there was only 1 radiosurgical procedure.

Radiosurgical Technique

During this 18-year study, various models of the Gamma Knife (Elekta AB) were used: models B, C, 4C, and Perfexion. After a local anesthetic agent had been applied, the Leksell model G stereotactic frame (Elekta) was affixed to the patient head. All 497 patients (100%) underwent stereotactic MR imaging and CT scanning so that we could identify the position of the trigeminal nerve. The MR imaging sequences that we used included T2-weighted constructive interference in steady state without contrast and contrast-enhanced T1-weighted images. The CT routinely supplemented this imaging to correct any distortion errors on the MR images.

A single 4-mm isocenter was used for all 497 patients and was positioned in the cisternal portion of the trigeminal nerve, at a median distance of 7.8 mm (range 4.5–14 mm) from the nerve's emergence from the brainstem.

Patients continued their medication unchanged for 1 month after GKS and then were able to diminish their drug doses depending on the treatment's efficacy. We

normally saw these patients for a neurological examination, including an assessment of facial sensibility and motility and corneal reflex, at 3 months, 6 months, and 1 year post-GKS, and then yearly thereafter.

A team consisting of a neurosurgeon, radiation oncologist, and a medical physicist performed dose selection and planning.

Follow-Up and Assessment of Outcome

The director of Marseille-Mediterranean University and the ethical committee of Timone University Hospital approved our study. Follow-up information was obtained by direct clinical evaluation or telephone interview by the first author (C.T.), who was not involved in the selection of cases for treatment.

We evaluated the probability of onset of sensory disturbance and pain recurrence in patients who became pain free after GKS. We recorded and analyzed the pre- and post-GKS latency intervals, paying attention to date every event, the use of medication, the need for further surgical procedures, and so forth, as well as the time needed for every patient who became pain free to develop new or recurrent disorders, so that we could assess all available information accurately.

Pain was scored using the BNI pain scale,²⁴ which uses the following grades: I, no trigeminal pain with no medication; II, occasional pain that does not require medication; IIIa, no pain with continued medication; IIIb, persistent pain controlled by medication; IV, some pain not adequately controlled by medication; and V, severe pain with no relief.

For hypesthesia we used the BNI facial hypesthesia scale,²⁴ which uses the following grades: I, no facial numbness; II, mild facial numbness but not bothersome; III, facial numbness that is somewhat bothersome; and IV, facial numbness that is very bothersome. For patients presenting with facial nerve sensory dysfunction, we inquired about their quality of life as it related to TN and whether this sensory problem bothered them. We also asked these patients whether they had mastication difficulties.

Statistical Analysis

Data were recorded using Microsoft Excel 2000. All statistical analyses were performed using R software (version 2.12.0, R Foundation for Statistical Computing). The survival R package was used for survival analysis.

We first conducted a descriptive analysis of recorded data for all 497 patients. We then compared the characteristics of all 3 groups. Analysis of variance was performed when conditions were verified; otherwise we performed the Kruskal-Wallis test. For qualitative variables, we performed the chi-square test when valid or the Fisher test otherwise.

To evaluate outcomes such as hypesthesia and pain recurrence, the time-to-event was estimated using the Kaplan-Meier method. A bivariate analysis was then performed to identify predictive factors among the collected variables. For qualitative variables, Kaplan-Meier curves were used to represent time-to-event graphically among

the different groups and were compared using the univariate log-rank test. Proportionality of hazards was assessed graphically by using log cumulative hazard plots.

All tests were 2-sided and p values < 0.05 were judged to be significant.

Evaluating and Deciding Patterns of Pain Free

We tried to establish different patterns of pain-free responses. We used empirical tests to divide patients into different groups depending on the time that passed after GKS before they became pain free. We also made a chart showing the distribution of patients and clear cut-offs of freedom from pain (Fig. 1), with 2 major peaks, one at 2 days (48 hours) and the other at 30 days. Other small or medium peaks could be seen, but the number of patients achieving them was half or less compared with the other 2 peaks. That is why we finally chose 3 patient groups: patients who became pain free within the first 48 hours after GKS (Group PF_{≤ 48 hours}); those who became pain free more than 48 hours after GKS but before or at 30 days after the procedure (Group PF_{> 48 hours, ≤ 30 days}); and those who became pain free more than 30 days after GKS (Group PF_{> 30 days}). We tested the patients' clinical parameters and tried to establish whether the rates of hypesthesia and pain recurrence were higher in one group or another, and if these results were statistically significant.

Results

General Data

The median age of the 497 patients was 68.3 years (range 28.1–93.2 years). The median age in Group PF_{≤ 48 hours} was 68.3 years (range 33.1–90.8 years), compared with 68.5 years (range 28.8–93.2 years) in Group PF_{> 48 hours, ≤ 30 days} and 68.3 years (range 43.3–87.8 years) in Group PF_{> 30 days} ($p = 0.991$).

The median time between the first appearance of TN and treatment in Group PF_{≤ 48 hours} was 76.5 months (range 0.8–531 months), compared with 67.5 months (range 1–387.5 months) in Group PF_{> 48 hours, ≤ 30 days} and 71 months (range 5–529 months) in Group PF_{> 30 days} ($p = 0.554$).

The median follow-up period was 43.75 months (range 12–174.4 months).

Four hundred fifty-four patients (91.34%) initially became pain free at a median time of 10 days (range 1–459 days) after GKS. Of these, 169 (37.2%) became pain free within the first 48 hours (Group PF_{≤ 48 hours}), compared with 194 (42.8%) who became pain free between Day 3 and Day 30 (Group PF_{> 48 hours, ≤ 30 days}) and 91 patients (20%) who became pain free after 30 days (Group PF_{> 30 days}). Table 1 shows initial freedom from pain as well as the development of hypesthesia and pain recurrence within the 3 groups.

We studied the clinical parameters in all 3 subpopulations. The pre-GKS assessment showed no statistically significant differences (see Table 2) between the 3 groups regarding the side of the pain ($p = 0.73$), presence of bilateral pain ($p = 0.85$), number of dermatomes involved in the pain ($p = 0.41$), presence of atypical ($p = 0.805$) or

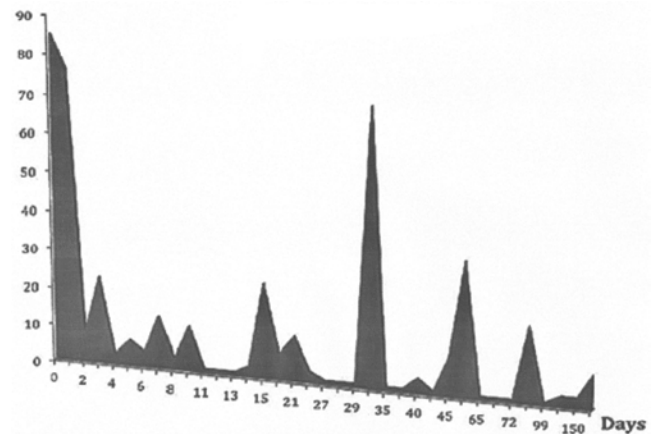


Fig. 1. Graph depicting the distribution of pain-free intervals after radiosurgery in a population of 497 patients with classic TN and only 1 GKS treatment. (Patients with megadolichobasilar artery- or MS-related TN were not included in the study group.)

continuous ($p = 0.201$) pain, neurovascular conflict evident on preoperative MR images ($p = 0.743$), or the sex of the patients ($p = 0.612$).

The number and types of previous surgical interventions were also assessed. A summary is shown in Table 3. Whether the patient had undergone previous surgical treatment ($p = 0.576$), the number of preoperative GKS interventions ($p = 0.611$), and most types of previous intervention—thermocautery on the same side ($p = 0.565$), balloon microcompression ($p = 0.982$), microvascular decompression ($p = 0.999$) and glycerol injection ($p = 1$)—were not statistically significant. Only previous contralateral thermocautery ($p = 0.04$) was statistically significant for patterns of pain freedom.

Regarding preoperative hypesthesia, we found no statistically significant difference between the 3 pain-free groups ($p = 0.874$), as seen in Table 4. Only 1 person had preoperative anesthesia dolorosa; that patient was in Group PF_{≤ 48 hours} ($p = 0.572$).

TABLE 1: Initial freedom from pain in and development of hypesthesia and pain recurrence in the 3 patient groups*

Variable	No. of Patients (%) (total no. of patients = 454)			p Value
	Group 1	Group 2	Group 3	
initially pain free	169 (37.2)	194 (42.8)	91 (20)	
hypesthesia				0.014
yes	18 (13.7)	30 (19)	22 (30.6)	
no	113 (86.3)	128 (81)	50 (69.4)	
pain recurrence				0.515
yes	59 (34.9)	71 (36.6)	27 (29.7)	
no	110 (65.1)	123 (63.4)	64 (70.3)	

* Group 1 = Group PF_{≤ 48 hours}; Group 2 = Group PF_{> 48 hours, ≤ 30 days}; Group 3 = Group PF_{> 30 days}.

TABLE 2: Preoperative assessment of the 3 patient groups regarding some clinical aspects and the neurovascular conflict seen on preoperative MR images

Variable	No. of Patients (%)			p Value
	Group 1 (169 patients)	Group 2 (194 patients)	Group 3 (91 patients)	
side of pain				0.73
rt	94 (55.6)	102 (52.6)	52 (57.1)	
lt	75 (44.4)	92 (47.4)	39 (42.9)	
bilat pain				0.85
yes	7 (4.1)	6 (3.1)	4 (4.4)	
no	162 (95.9)	188 (96.9)	87 (95.6)	
no. of territories of pain				0.41
1	87 (51.5)	116 (59.8)	48 (52.7)	
2	71 (42)	63 (32.5)	37 (40.7)	
3	11 (6.5)	15 (7.7)	6 (6.6)	
atypical pain				0.805
yes	36 (21.3)	37 (19.1)	20 (22)	
no	133 (78.7)	157 (80.9)	71 (78)	
continuous pain				0.201
yes	42 (24.9)	34 (17.5)	17 (18.7)	
no	127 (75.1)	160 (82.5)	74 (81.3)	
previous neurovascular conflict seen on MRI				0.743
yes	92 (54.4)	110 (56.7)	54 (59.3)	
no	77 (45.6)	84 (43.3)	37 (40.7)	
sex of patient				0.612
male	79 (46.7)	82 (42.3)	43 (47.3)	
female	90 (53.3)	112 (57.7)	48 (52.7)	

Post-GKS Hypesthesia

Among all 497 patients, the hypesthesia rate at 5 years was 20.4%; at 7 years the rate reached 21.1% and remained stable until 14 years post-GKS, with a median delay of onset of 12 months (range 1–65 months).

Statistically significant differences ($p = 0.014$) between the 3 pain-free groups were identified for post-GKS hypesthesia: postoperative sensory disturbances developed in 18 patients (13.7%) in Group PF_{≤ 48 hours}, compared with 30 patients (19%) in Group PF_(> 48 hours, ≤ 30 days) and 22 patients (30.6%) in Group PF_{> 30 days}. Table 5 shows these findings. When hypesthesia was classified as mild or severe (discreet or important, respectively), the p value was 0.823, and when it was assessed using the BNI scale, the p value was 0.598.

Until 1 year after GKS, the risk of hypesthesia was similar in the 3 groups, but afterward there was a strong risk of hypesthesia in Group PF_{> 30 days}.

We conclude that the lowest hypesthesia rate was found in patients who became pain free earliest (Group PF_{≤ 48 hours}, 13.7% of patients) and the highest hypesthesia rate was found in patients who became pain free last (Group PF_{> 30 days}, 30.6% of patients).

Figure 2 shows the probability of hypesthesia onset within the 3 subgroups.

Probability of Maintaining Pain Relief and Management of Pain Recurrence

One hundred fifty-seven patients (34.4%) who became pain free after GKS experienced a recurrence of TN pain with a median delay of 24 months (range 0.62–150.06 months).

There were no statistically significant differences in the pain recurrence rates between patient groups: 66 patients (39%) in Group PF_{≤ 48 hours}, 71 patients (36.6%) in Group PF_(> 48 hours, ≤ 30 days), and 27 (29.7%) patients in Group PF_{> 30 days} experienced at least 1 recurrence of pain ($p = 0.515$).

Whether patients underwent additional surgical intervention ($p = 0.619$); if performed, the number of additional surgical procedures ($p = 0.477$); and the type of additional surgical intervention ($p = 0.849$ for thermocoagulation; $p = 0.873$ for balloon microcompression; $p = 0.602$ for microvascular decompression; and $p = 1$ for cortical stimulation) were not found to be statistically significant. A summary of these findings is shown in Table 6.

Figure 3 shows the probability of maintaining pain relief in the 3 subgroups.

Evaluation of Outcome at the Last Follow-Up

At the last follow-up, our results showed no statisti-

TABLE 3: Previous surgical intervention

Variable	No. of Patients (%)			p Value
	Group 1 (169 patients)	Group 2 (194 patients)	Group 3 (91 patients)	
surgical treatment before GKS				0.576
yes	61 (36.1)	60 (30.9)	31 (34.1)	
no	108 (63.9)	134 (69.1)	60 (65.9)	
no. of surgeries before GKS				0.611
0	108 (63.9)	134 (69.1)	60 (65.9)	
1	38 (22.5)	36 (18.6)	16 (17.6)	
2	15 (8.9)	12 (6.2)	11 (12.1)	
≥3	8 (4.7)	12 (6.2)	4 (4.4)	
previous thermocoagulation on same side				0.565
yes	132 (78.1)	160 (82.5)	74 (81.3)	
no	37 (21.9)	34 (17.5)	17 (18.7)	
previous contralateral thermocoagulation				0.045
yes	4 (2.4)	194 (100)	0 (0)	
no	165 (97.6)	194 (100)	91 (100)	
previous balloon microcompression				0.982
yes	21 (12.4)	25 (12.9)	12 (13.2)	
no	148 (87.6)	169 (87.1)	79 (86.8)	
previous microvascular decompression				0.999
yes	13 (7.7)	15 (7.7)	7 (7.7)	
no	156 (92.3)	179 (92.3)	84 (92.3)	
previous glycerol injection				1
yes	1 (0.6)	2 (1)	0 (0)	
no	168 (99.4)	192 (99)	91 (100)	
previous contralateral GKS				0.08
yes	0 (0)	5 (2.6)	1 (1.1)	
no	169 (100)	189 (97.4)	90 (98.9)	

cally significant differences between the 3 subgroups ($p = 0.874$ for the BNI classification). Table 7 shows these results.

Discussion

Even if the role of GKS in the armamentarium for treating TN is now well established, the radiobiological mechanisms of action associated with the procedure remain poorly understood.

When we discuss clinical and histopathological chains of events we cannot separate the causes of TN, which can differ greatly from one case to another: compression by an overlying artery or vein (thought to account for 80%–90% of cases⁹) with focal demyelination, close apposition of demyelinated axons, few residual oligodendrocytes, and no inflammatory cells;⁸ primary demyelinating disorders (MS) with demyelination extending along the proximal part of the trigeminal nerve root and, in some cases, to the junction with the peripheral nerve system, juxtaposed axons, and the presence of variable thinly myelinated fibers; masses in the posterior

fossa, small infarcts or angiomas in the pons or medulla oblongata, prosthetic materials inserted during microvascular decompression;⁵ bone compression of the nerve;^{23,25} and idiopathic cases or, less frequently, familial TN.¹¹ In the majority of cases, the cause of TN seems to be demyelination, especially present at the level of the trigeminal root entry zone.¹⁵

Few studies have been conducted to understand the mechanism of action that occurs when GKS is used as a tool for treatment.

TABLE 4: Preoperative hypesthesia in the 3 patient groups

	No. of Patients (%)			p Value
	Group 1 (169 patients)	Group 2 (194 patients)	Group 3 (91 patients)	
Preop Hypesthesia				
no hypesthesia	131 (77.5)	158 (81.4)	72 (79.1)	0.874
slight hypesthesia	34 (20.1)	33 (17)	18 (19.8)	
severe hypesthesia	4 (2.4)	3 (1.5)	1 (1.1)	

TABLE 5: Hypesthesia after GKS

Variable	No. of Patients (%)			p Value
	Group 1 (169 patients)	Group 2 (194 patients)	Group 3 (91 patients)	
hypesthesia after GKS				0.014
yes	18 (13.7)	30 (19)	22 (30.5)	
no	113 (86.3)	128 (81)	50 (69)	
type of hypesthesia				0.823
discrete	13 (72.2)	21 (70)	14 (63.6)	
important	5 (27.8)	9 (30)	8 (36.4)	
BNI type of hypesthesia				0.598
mild facial numbness	15 (83.3)	27 (90)	18 (81.8)	
facial numbness, somewhat bothersome	2 (11.1)	3 (10)	3 (13.6)	
facial numbness, very bothersome	1 (5.6)	0 (0)	1 (4.6)	

Kondziolka et al.¹² irradiated 2 male baboons (*Papio cynocephalus anubis*) using doses of 80 and 100 Gy. Light and electron microscopic examinations were performed to analyze specimens of the trigeminal nerve 6 months after the procedure. The authors discovered acute degenerating axons with some identifiable myelinated axons, small foci of necrosis (including Schwann cell nuclei necrosis), and normal trigeminal ganglion when they used 80 Gy. At 100-Gy doses they found axon degeneration with myelin vacuolation and expansion of the endoneurial intracellular matrix, which was consistent with edema. In one specimen, almost the entire width of the nerve was necrotic. Axon degeneration was noted outside the necrotic zone, but the histological features normalized toward the ganglion. The authors concluded that the histological effects were dose related and consisted of

primary axon injuries. They also observed no evidence of inflammation 6 months after GKS, and the extent of nerve edema was mild. Kondziolka et al. presumed that acute inflammation likely occurs after nerve irradiation (perhaps within the first few days) and may have effects on pathophysiological nerve processes, relieving pain quickly.

Szeifert et al.²⁶ studied the histopathological findings in a patient who suffered from TN and was treated 2 times by GKS (in the first procedure, the maximum dose was 90 Gy; in the second procedure, performed 10 months later, the maximum dose was 70 Gy). The patient died of a hemorrhagic stroke 26 days following the second intervention, and an autopsy was performed. Histopathological studies demonstrated changes in the trigeminal nerve that differed according to the sites of each treatment dose. Chronic radiation-induced changes were identified 11 months after the first treatment, at the site treated with 90 Gy: there was a well-circumscribed, hypocellular fibrotic lesion with hyaline-degenerated collagen bundles and scattered fibrocytes. Acute radiation-induced changes, indicative of the early consequences of radiosurgery, were identified 26 days after the second treatment, at the site treated with 70 Gy: there was a sharply demarcated necrotic center containing fibrinoid material and tissue debris, which was encircled by surviving nerve bundles.

Conclusions

Our study was rather empirical (but also based on a statistical chart of distribution) in classifying the distribution of pain-free patients into the 3 subtypes. Our data indicate that pathophysiological mechanisms similar to those described in the other cited studies could be involved, but also some new ones—unknown for the moment—that could help explain the different patterns of freedom-from-pain responses after GKS. A substantial number of patients, 169 (37.2%), became pain free within the first 48 hours (Group PF_{≤48 hours}) after GKS; this is quite a large population. These patients had the lowest rate of hypesthesia in our series (13.7%), particu-

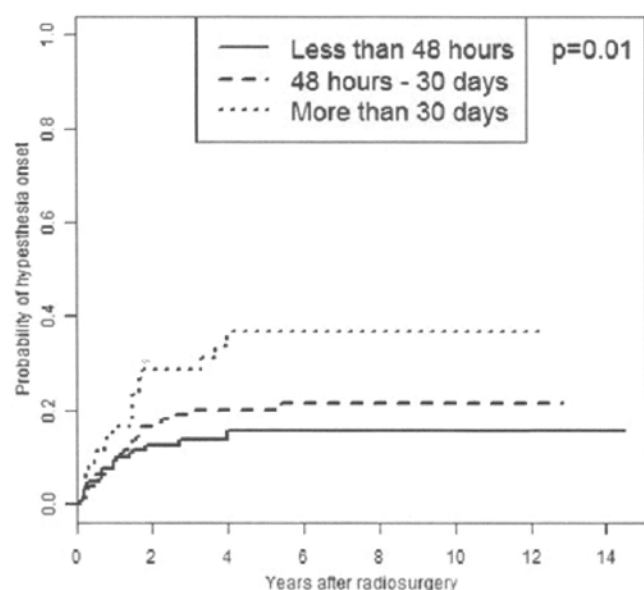


Fig. 2. Post-GKS hypesthesia in the 3 pain-free patient subgroups: Group PF_{≤48 hours}, Group PF_(>48 hours, ≤30 days), and Group PF_{>30 days}.

TABLE 6: Management of pain recurrence with number and type of further surgical interventions

Variable	No. of Patients (%)			p Value
	Group 1 (169 patients)	Group 2 (194 patients)	Group 3 (91 patients)	
surgical treatment after GKS				0.619
yes	33 (19.5)	39 (20.1)	14 (15.4)	
no	136 (80.5)	155 (79.9)	77 (84.6)	
no. of surgeries after GKS				0.477
1	26 (78.8)	28 (71.8)	8 (57.1)	
2	6 (18.2)	9 (23.1)	4 (28.6)	
≥3	1 (3)	2 (5.1)	2 (14.3)	
further thermocoagulation				0.849
yes	10 (30.3)	10 (25.6)	3 (21.4)	
no	23 (69.7)	29 (74.4)	11 (78.6)	
further balloon microcompression				0.873
yes	19 (57.6)	22 (56.4)	9 (64.3)	
no	14 (42.4)	17 (43.6)	5 (35.7)	
further microvascular decompression				0.602
yes	4 (12.1)	8 (20.5)	3 (21.4)	
no	29 (87.9)	31 (79.5)	11 (78.6)	
further cortical stimulation				1
yes	0 (0)	1 (2.6)	0 (0)	
no	33 (100)	38 (97.4)	14 (100)	

larly compared with patients in the Group PF_{> 30 days}, in which hypesthesia developed in 22 patients (30.6%) (data statistically significant, $p = 0.014$). The pain recurrence rate was 39% in Group PF_{≤ 48 hours}, compared with 26.6% in Group PF_(> 48 hours, ≤ 30 days) and 29.7% in Group PF_{> 30 days}, but these data were not statistically significant ($p = 0.515$).

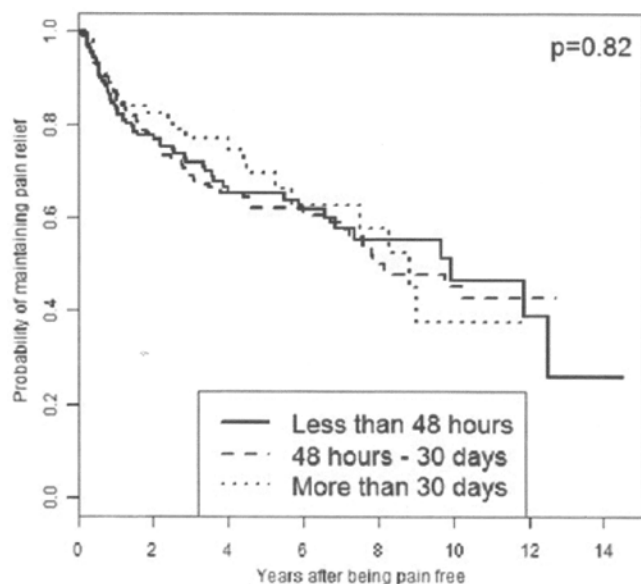


FIG. 3. Probability of maintaining pain relief in the 3 pain-free patient subgroups: Group PF_{≤ 48 hours}, Group PF_(> 48 hours, ≤ 30 days), and Group PF_{> 30 days}.

Given that targeting a small volume of normal tissue with a high radiation dose probably does not produce a destructive effect, the neuromodulatory mechanisms of GKS still need to be further analyzed and understood.

Disclosure

Professor Régis declares receiving support for non-study related clinical or research effort from Elekta AB. No other potential conflicts have been reported.

Author contributions to the study and manuscript preparation include the following. Conception and design: Tuleasca, Carron, Levivier, Régis. Acquisition of data: Tuleasca. Analysis and interpretation of data: Tuleasca, Resseguier, Gaudart. Drafting the article: Tuleasca. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Tuleasca. Statistical analysis: Resseguier, Gaudart. Administrative/technical/material

TABLE 7: Outcome at the last follow-up based on BNI classification

Variable	No. of Patients (%)			p Value
	Group 1 (169 patients)	Group 2 (194 patients)	Group 3 (91 patients)	
BNI classification				0.874
good outcome	165 (97.6)	188 (96.9)	88 (96.7)	
poor outcome	4 (2.4)	6 (3.1)	3 (3.3)	

support: Tuleasca, Donnet, Roussel, Levivier, Régis. Study supervision: Donnet, Roussel, Gaudart, Levivier, Régis.

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