Double Anterior Stereotactic Cingulotomy for Intractable Oncological Pain

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Keywords

Cingulotomy · Cognitive function · Intractable pain · Metastatic disease · Oncology · Pain relief · Palliative care

Abstract

Background: Stereotactic anterior cingulotomy has been used in the treatment of patients suffering from refractory oncological pain due to its effects on pain perception. However, the optimal targets as well as suitable candidates and outcome measures have not been well defined. We report our initial experience in the ablation of 2 cingulotomy targets on each side and the use of the Brief Pain Inventory (BPI) as a perioperative assessment tool. **Methods:** A retrospective review of all patients who underwent stereotactic anterior cingulotomy in our Department between November 2015 and February 2017 was performed. All patients had advanced metastatic cancer with limited prognosis and suffered from intractable oncological pain. **Results:** Thirteen patients (10 women and 3 men) underwent 14 cingulotomy procedures. Their mean age was 54 ± 14 years. All patients reported substantial pain relief immediately after the operation. Out of the 6 preoperatively bedridden patients, 3 started ambulating shortly after. At the 1-month follow-up, the mean preoperative Visual Analogue Scale score decreased

from 9 ± 0.9 to 4 ± 2.7 ($p = 0.003$). Mean BPI pain severity and interference scores decreased from levels of 29 ± 4 and 55 ± 12 to 16 ± 12 ($p = 0.028$) and 37 ± 15 ($p = 0.043$), respectively. During the 1- and 3-month follow-up visits, 9/11 patients (82%) and 5/7 patients (71%) available for follow-up reported substantial pain relief. No patient reported worsening of pain during the study period. Neuropsychological analyses of 6 patients showed stable cognitive functions with a mild nonsignificant decline in focused attention and executive functions. Adverse events included transient confusion or mild apathy in 5 patients (38%) lasting 1–4 weeks. **Conclusions:** Our initial experience indicates that double stereotactic cingulotomy is safe and effective in alleviating refractory oncological pain.

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Introduction

Pain is one of the most common symptoms among cancer patients, particularly in those who suffer from advanced metastatic disease. Despite advances in palliative

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oncological care, standard therapies fail to achieve the desired pain relief or result in intolerable side effects in nearly 10% of cases [1–4]. Patients who suffer from refractory oncological pain may benefit from targeted neurosurgical procedures that selectively intervene in the pain pathways. Patients who suffer from localized pain below the C4 dermatome are candidates for selective cordotomy to disconnect the nociceptive pathways traveling in the spinothalamic tract [5–7]. However, many patients suffer from diffuse pain due to widespread metastases or head-and-neck malignancies not amenable to cordotomy. In this carefully selected subset of patients, small but increasing evidence indicates that stereotactic anterior cingulotomy could be an effective treatment option [8, 9]. The dorsal anterior cingulate cortex is considered part of the limbic circuit and is thought to have a major role in cognitive and emotional processing, as well as the perception of pain [10]. Functional neuroimaging studies have contributed to the idea that the dorsal anterior cingulate cortex takes part in modulation of nociceptive information received by somatosensory areas [11–14].

In November 2015, following an initially promising outcome of a stereotactic cingulotomy case, a collaboration of the palliative care service, the pain unit, and the neurosurgical department of our hospital was established in order to evaluate the role of neurosurgical interventions for medically intractable pain in advanced cancer patients.

In this study, we report our initial experience with stereotactic cingulotomy for refractory oncological pain in terms of indications, outcomes, and complications while discussing previous literature. In addition, we present our experience with the use of 2 pain assessment tools in analyzing the response to this procedure: the Brief Pain Inventory (BPI) and the Palliative Care Outcome Scale (POS).

Patients and Methods

This is a retrospective review of all patients who underwent stereotactic cingulotomy in our department between November 2015 and February 2017. Their medical charts were reviewed for demographic data (age, sex), oncological diagnoses, functional status, and pain characteristics (distribution, intensity) before and after surgery.

All aspects of this retrospective chart review were approved by the Institutional Ethics Committee.

Patient Selection

All patients referred for neurosurgical intervention for medically refractory oncological pain were evaluated by an interdis-

plinary team consisting of a palliative care physician and nurse, a pain specialist, and a neurosurgeon.

Patients were considered appropriate candidates for neurosurgical interventions when they fulfilled the following selection criteria: (1) advanced oncological disease with limited prognosis per treating oncologist; (2) diffuse pain syndromes not amenable to targeted interventions (e.g., nerve blocks); (3) radiotherapy was no longer an option; and (4) failure to achieve a sustained pain relief by best medical treatment or due to the development of intolerable side effects. In all cases, a full and open discussion was performed in front of the patients and families regarding the benefits and risks of the procedures as well as their alternatives.

Outcome Assessment

Pain outcome was assessed using the 10-point Visual Analogue Scale (VAS) prior to the procedure, on day 1 postoperatively, and at the 1- and 3-month follow-up appointments. Patients who could not come for follow-up visits were interviewed by telephone. Doses of analgesics were measured as the equivalent oral morphine dose to allow unified measurement of opioid dose reduction.

In addition, patients also completed the BPI and the POS questionnaires. BPI is a self-administered questionnaire that assesses the severity of pain and its impact on functioning. Accordingly, its 2 main components are the BPI pain intensity scale and the BPI pain interference scale (scoring from 0 to 40 and from 0 to 70, respectively). It was originally developed for the assessment of cancer-associated pain but is now also used for other chronic pain conditions.

The POS questionnaire is based on 10 items (scoring 0–40) and was found to be a valid tool in assessing fundamental issues in palliative care, including physical, psychological, and mental aspects, as well as the provision of information and support.

Eventually, patients were asked whether it was worthwhile to undergo the procedure. Adverse events were noted immediately during hospitalization and at follow-up.

Neurocognitive Assessment

Patients were assessed by neuropsychologists and completed a computerized battery of cognitive tests before the surgery and at the 1-month follow-up appointment. The NeuroTrax comprehensive testing program was used for the assessment of various cognitive functions, including visual and verbal memory, attention, executive functions, information processing speed, verbal function, visuospatial perception, and motor skills (Table 1) [8]. Previous validation studies have shown that NeuroTrax tests are comparable to traditional neuropsychological tests in their ability to differentiate cognitively healthy individuals from those with mild cognitive impairment [15]. Test scores were calculated using software and, normalized for age and education level, compared to a large NeuroTrax normative database of healthy individuals (NeuroTrax Corporation, 2014).

Based on tests scores, the software generates index scores that summarize performance in particular cognitive domains and are fit to an IQ style scale, with a higher score reflecting better performance (mean: 100, SD: 15). A global cognitive score computed as the average of these index scores represents overall cognitive performance (global cognitive score). Alternate test forms, provided by the software, were used before and after surgery to minimize any learning effect. Index scores and the global cognitive score were compared before and after surgery for each pa-

Fig. 1. Axial T2 (a), coronal T2 (b), and sagittal T1 (c) MRI images 1 day postoperatively showing double bilateral anterior cingulotomy.

Table 1. Cognitive domain and tests of the NeuroTrax comprehensive testing program

NeuroTrax index score	Cognitive tests and function
Memory	Verbal memory: immediate and delayed recognition Nonverbal memory: immediate and delayed recognition
Executive function	Composite scores of “Go-NoGo” paradigm, Stroop interference, and task of motor planning (“catch” game)
Problem solving	Matrix
Visual spatial perception	Visual spatial imagery
Verbal function	Verbal rhyming
Attention	Reaction time
Information processing speed	Staged information processing speed: accuracy and RT Staged information processing speed: 1-, 2-, and 3-digit arithmetic composite scores
Motor skills	Staged information processing speed: intertap interval Catch game: RT for first move Finger tapping

RT = Reaction time.

tient to examine the impact of surgery on their cognitive functioning (Table 1 provides lists of tests and the cognitive domains assessed).

Statistical Analysis

Survival curves and median survival times were analyzed based on the Kaplan-Meier product limit method. Characteristics of pain (VAS and BPI severity and interference scores) were compared before and after surgical treatment. Comparison between the pre- and the postoperative status was performed for each patient using the Wilcoxon nonparametric paired test. Average values were presented as means $\pm$ SD or medians and ranges; a value of $p < 0.05$ (two sided) was considered statistically significant. Characteristics between 2 groups of categorical data were compared using the Pearson χ^2 test and the Fisher exact test. All statistical procedures

were performed using Statistica 6 (StatSoft Inc.) and SPSS 21.0 software (SPSS Inc., Chicago, IL, USA).

Surgical Techniques

Preoperative high-resolution (3-T) magnetic resonance imaging (MRI) was obtained before the operation. We used enhanced axial T1-weighted MPRAGE (magnetization-prepared rapid gradient echo) images (with gadolinium) for target localization and trajectory planning to avoid blood vessels. In the first 3 cases, we used a single target on each side, 24 mm behind the tip of the frontal horn, 7–8 mm from the midline. At that time point, patient 2 had recurrence of pain; follow-up MRI showed shrinkage of the lesions, and the patient underwent a second cingulotomy procedure to enlarge the cingulotomy lesion more anteriorly, again with good pain relief that lasted for 2 months. In the following cases, we de-

Table 2. Individual patient data

No.	Age, years	Sex	Cancer diagnosis	Pain distribution	KPS preop.	Preop. VAS BPI-S BPI-I	KPS 1 month postop.	1-month VAS BPI-S BPI-I	Discharge destination	Survival	Duration of pain relief	Achieved goal of treatment
1	44	F	Soft tissue sarcoma	Abdomen, bone	50	9 – –	70	3 – –	Home	1 mo (deceased)	1 mo	Yes
2	55	F	Parotid Ca.	Pelvis; lower limb	70	9 – –	70	8 – –	Home	11 mo	1 mo	No
3	78	F	Colo-rectal cancer	Pelvis	40	10 23 59	40	– – –	Hospice	1 mo (deceased)	1 mo	Yes
2	55	F	Parotid Ca.	Pelvis; lower limb	70	9 – –	70	3 – –	Home	10 mo	2 mo	Temporary
4	50	F	Cervical Ca.	Abdomen; pelvis, retroperitoneum; skeleton	60	7 30 58	70	2.5 16 45	Home	5 mo	5 mo	Yes
5	66	M	Colo-rectal cancer	Spine; hip	30	8 29 65	50	0 0 20	Rehab.	3 mo (deceased)	3 mo	Yes
6	73	M	Sacral chordoma	Pelvis; lower limbs	50	10 40 60	60	4.5 16 42	Home	9 mo (deceased)	5 mo	Temporary
7	32	M	Lymphoma	Spine	30	10 – –	70	1 – –	Rehab.	9 mo	9 mo	Yes
8	55	F	Sarcoma	Left arm/leg; skeleton	50	9.5 29 52	50	6 22 22	Home	2 mo	1 mo	No
9	53	F	Thyroid Ca.	Low back pain; left leg	40	8.5 28 58	40	5 – –	Hospice	3 weeks (deceased)	3 weeks	Yes
10	56	F	Pancreatic Ca.	Abdominal; back pain	40	9 26 51	70	2 – –	Home	2 mo (deceased)	2 mo	Yes
11	31	F	Uterine cervix Ca.	Pelvis	60	9 32 48	60	9 33 50	Home	3 mo	1 mo	No
12	49	F	Lipo-sarcoma	Back	50	8 28 70	50	2 24 56	Home	3 mo	1 mo	Temporary
13	59	F	Non-small cell lung Ca.	Left hemibody	70	9.5 28 25	70	3 1 24	Home	3 mo (deceased)	3 mo	Yes

KPS, Karnofsky performance status; VAS, Visual Analogue Scale; BPI, Brief Pain Inventory; BPI-S, BPI severity; BPI-I, BPI interference; mo, months.

cided to perform 2 lesions on each side; the second lesion was performed more anteriorly, 16 mm behind the tip of the frontal horn.

We used standard stereotactic techniques. On the morning of the operation, a Leksell stereotactic frame was applied to the patient's head under local anesthesia. Then, a preoperative computerized tomography (CT) was done and fused to the MRI using iPlan software (Brainlab Inc.). The coordinates of the cingulate targets in both hemispheres were determined, and the trajectories were computed to the entry points approximately 1 cm in front of the coronal suture and 2.5–3 cm lateral to the midline avoiding blood vessels.

The patient was then transferred to the operating suite, where 2 frontal burr holes were created under local anesthesia. Through each burr hole, a radiofrequency thermocoagulating monopolar electrode was stereotactically inserted to the target. In the first 10 cases, we used a 4-mm exposed tip, 2-mm-diameter Cosman RF electrode, using 2–3 adjacent lesions in each trajectory (80°C for 80 s) to achieve sufficient coverage of the cingulate gyrus. In the last 4 cases, we switched to a 10-mm exposed-tip Cosman RF electrode, which can achieve complete coverage of the cingulate gyrus with a single lesion (Fig. 1).

Postoperative Follow-Up

Patients were kept overnight in the neurosurgical intensive care unit for observation. It is our departmental routine to perform postoperative head CT without contrast enhancement to rule out intracranial bleeding. Postoperative MRI was performed within 48 h after the operation to verify lesion location. Patients were evaluated during the immediate postoperative hospitalization for a general assessment of the response to the procedures in terms of pain relief and mobility, and their discharge destination – home, rehabilitation center, or nursing care.

Patients were then usually seen 2 weeks after the procedure for a routine checkup and then at 1 and 3 months. At the 1-month follow-up visits, patients completed pain questionnaires (VAS, BPI, and POS) and were reevaluated by a neuropsychologist.

Results

Thirteen patients (10 women and 3 men) underwent 14 stereotactic bilateral anterior cingulotomy procedures for intractable oncological pain after having failed medical treatment. Their average age at surgery was 54 ± 14 years (range 31–78). All patients suffered from severe pain refractory to conventional treatments due to widespread metastatic disease; individual patient data are presented in Table 2. The mean preoperative pain score was 9 ± 0.9 (range 7–10) on the 10-point VAS. Ten patients completed preoperative short BPI questionnaires (Table 2). Pain locations varied but mainly involved the back, abdomen, and pelvis (Table 2). The median preoperative period of pain was 5 months (range 1–48), during which patients had received various analgesic regimens by their primary care physicians and pain experts, including high doses of opioid medications.

Eight patients were admitted electively for surgery after being evaluated in our interdisciplinary clinic, while 6 patients were referred after being hospitalized for prolonged periods (range 4 weeks to 3 months) due to intractable pain. The first 3 patients were referred by the palliative care service of our hospital; thereafter, we received 8 referrals from other hospitals and home hospice care. The median preoperative Karnofsky performance status was 50, ranging from 30 to 70 (Table 2).

Postoperative Course

All patients reported significant pain relief immediately after the operation in the recovery room (mean VAS 0.9 ± 1.3). In the postoperative hospitalization period (1–7 days), there was a decrease in the need for opiate analgesics, and patients that were hospitalized for intravenous morphine preoperatively could be weaned off within a few days and discharged home on oral medications.

Fig. 2. Average Visual Analogue Scale (VAS) pain score before, immediately after, and 1 and 3 months after cingulotomy.

Our routine is to initially decrease the opioid dose by approximately 25% per day and to continue tapering down slowly, as tolerated [16].

The 8 patients that arrived electively for surgery from home were discharged home 1–2 days after the procedure. Out of the 6 preoperatively bedridden patients, 3 could start ambulating and participate in physiotherapy after the operation and were sent to rehabilitation, 2 were discharged home and 1 patient to hospice care.

Pain and Functional Outcome

Eleven patients were available for the 1-month follow-up. Eight of the 11 patients (72.7%) reported significant pain relief (>50%), and 1 patient (9%) reported partial improvement. In 2 patients, pain returned to its original severity. One month after the operation, the average VAS score was 4 ± 2.7 (range 0–9), resulting in a statistically significant decrease in 5.1 points of VAS ($58 \pm 28\%$; $p = 0.003$; Wilcoxon signed-rank test; Fig. 2). Upon specific questioning, patients reported that they still felt the pain, but the level of suffering was significantly reduced. Family members reported that the patients were more relaxed, less anxious, and were able to function better. The median postoperative Karnofsky performance status at 1 month significantly improved to 60 (range 40–70; $p = 0.041$, Wilcoxon nonparametric test).

Seven patients completed the 1-month postoperative BPI pain severity and pain interference questionnaires (Table 2). Both scores were significantly decreased 1 month after operation, with an average percent decrease of $48 \pm 40\%$ ($p = 0.028$) and $28 \pm 27\%$ ($p = 0.043$; Wil-

Fig. 3. Brief Pain Inventory (BPI) severity (a) and interference (b) scores before and 1 month after cingulotomy.

Fig. 4. Kaplan-Meier curves for cumulative survival (a) and pain relief (b) after cingulotomy (time to failure).

coxon signed-rank test), respectively (Tables 2, 3; Fig. 3). Further analysis of the mood and sleep subcategories of the BPI interference score showed that 1 month after cingulotomy, patients reported that mood and sleep were significantly less affected by pain: 29% ($p = 0.027$) and 54% ($p = 0.028$; Wilcoxon signed-rank test).

The median survival after surgery was 3.8 months (range 0.6–13 months). Seven patients were available for the 3-month follow-up. Five of the 7 patients (71%) reported sustained pain relief. The median duration of pain relief after cingulotomy was 3 months by the Kaplan-Meier analysis (Fig. 4).

Six patients completed the neuropsychological assessment before and after surgery, each of them showing some changes in cognitive functions following the proce-

cedure (Table 4). As a group, no statistically significant cognitive changes were detected. The global cognitive performance score before the procedure was 90 ± 15 compared with 86 ± 17 postoperatively (nonsignificant, Wilcoxon nonparametric test).

Complications and Adverse Effects of the Procedure

We had no cases of surgical mortality or procedure-related morbidity, such as surgical site or central nervous system infections, intracranial hemorrhages, or permanent neurological deficits. Transient confusion or mild apathy was observed in 4 patients (30%) postoperatively; in 2 patients, it resolved within 1 week following the procedure and in 2 patients it lasted for ~1 month. These patients seemed to have some flattening of their affect and

Table 3. Summary of pre- and postoperative (1-month) pain and functional scores

<i>VAS score</i>	
Preoperative	9±0.9 (7–10)
Postoperative	4±2.7 (0–9)
Δ	–5.1 (–58%)
<i>p</i> value (Wilcoxon)	0.003
<i>BPI severity score</i>	
Preoperative	29±4 (23–40)
Postoperative	16±12 (0–33)
Δ	–15 (–48%)
<i>p</i> value (Wilcoxon)	0.028
<i>BPI interference score</i>	
Preoperative	55±12 (25–70)
Postoperative	37±15 (20–56)
Δ	–17 (–28%)
<i>p</i> value (Wilcoxon)	0.043
<i>BPI mood interference score</i>	
Preoperative	7.6±3.0 (2–10)
Postoperative	5.4±3.8 (0–10)
Δ	–2.2 (–29%)
<i>p</i> value (Wilcoxon)	0.027
<i>BPI sleep interference score</i>	
Preoperative	7.4±3.6 (1–10)
Postoperative	3.4±3.2 (0–8)
Δ	–4 (–54%)
<i>p</i> value (Wilcoxon)	0.028
<i>BPI joy interference score</i>	
Preoperative	8.7±2.2 (4–10)
Postoperative	5.4±3.8 (0–10)
Δ	–3.3 (–38%)
<i>p</i> value (Wilcoxon)	0.068
<i>POS score</i>	
Preoperative	14±6 (7–23)
Postoperative	12±6 (4–20)
Δ	1 (12%)
<i>p</i> value (Wilcoxon)	0.416
<i>Postoperative improved ambulation, n</i>	
	6 (46%)
<i>Postoperative pain relief</i>	
Immediate, <i>n</i> (%)	14 (100%)
At 1 month, <i>n</i> /total <i>n</i> (%)	9/11 (82%)
At 3 months, <i>n</i> /total <i>n</i> (%)	5/7 (71%)
<i>Median KPS (range)</i>	
Preoperative	50 (30–70)
Postoperative	60 (40–70)
<i>p</i> value (Wilcoxon)	0.041

Means ± SD (ranges) are shown unless indicated otherwise. Δ, mean change; VAS, Visual Analogue Scale; BPI, brief pain inventory; POS, Palliative Care Outcome Scale; KPS, Karnofsky performance status.

Table 4. Summary of neurocognitive test scores

<i>Global neurocognitive Mindstream Score</i>	
Preoperative value	90±15
Postoperative value	86±17
<i>p</i> value (Wilcoxon)	0.207
<i>Memory</i>	
Preoperative value	85±18
Postoperative value	90±18
<i>p</i> value (Wilcoxon)	0.5
<i>Immediate verbal memory</i>	
Preoperative value	82±20
Postoperative value	85±32
<i>p</i> value (Wilcoxon)	1
<i>Delayed verbal memory</i>	
Preoperative value	91±25
Postoperative value	93±25
<i>p</i> value (Wilcoxon)	0.317
<i>Immediate nonverbal memory</i>	
Preoperative value	87±23
Postoperative value	86±23
<i>p</i> value (Wilcoxon)	0.581
<i>Delayed nonverbal memory</i>	
Preoperative value	92±18
Postoperative value	87±14
<i>p</i> value (Wilcoxon)	0.465
<i>Executive functions</i>	
Preoperative value	93±14
Postoperative value	87±24
<i>p</i> value (Wilcoxon)	0.462
<i>Problem solving</i>	
Preoperative value	101±12
Postoperative value	98±15
<i>p</i> value (Wilcoxon)	0.343
<i>Attention</i>	
Preoperative value	89±13
Postoperative value	80±19
<i>p</i> value (Wilcoxon)	0.249
<i>Information processing speed</i>	
Preoperative value	87±22
Postoperative value	78±12
<i>p</i> value (Wilcoxon)	0.285
<i>Naming</i>	
Preoperative value	94±14
Postoperative value	82±11
<i>p</i> value (Wilcoxon)	0.109
<i>Motor skills</i>	
Preoperative value	90±22
Postoperative value	92±22
<i>p</i> value (Wilcoxon)	0.157

Means ± SD.

minor personality changes per family members. Two of these 4 patients also developed transient urinary incontinence that resolved within 1 week.

Discussion

We describe our initial experience with stereotactic bilateral cingulotomy for the treatment of intractable pain in oncological patients. Our results demonstrate the efficacy and safety of the procedure in the palliative care of these complex and often frail patients. We elected to begin our clinical experience with patients in advanced stages, and, therefore, our follow-up is relatively short. Significant pain reduction was achieved in 82% of the patients at 1 month and in 72% of the patients available for follow-up at 3 months. Due to the short survival of patients in our cohort, the median duration of pain relief was 3 months, as determined by the Kaplan-Meier method. This was accompanied by a decrease in opioid consumption immediately after surgery. Reports using modern MRI-guided stereotactic techniques are limited to small case series [17–20]. Despite the difficulty in comparing results of small series, our results are in the range of previously published series. The most recent series were published by Yen et al. [17, 18] in 2005 and 2009, who reported their results in 2 series of 15 and 10 cancer patients, respectively. They reported significant pain reduction in 60–80% of the patients at 1 month, which dropped to 55% at 3 months and 50% at 6 months.

We are currently performing 2 lesions on each side – 24 and 16 mm behind the tip of the frontal horn (Fig. 1). Other series have mostly performed a single lesion on each side approximately 24 mm behind the tip of the frontal horn. We started performing double lesions after early recurrence of pain in one of our initial cases (Table 2 – patient 2). The drive for this policy change was that since cingulotomy is a palliative procedure for terminally ill cancer patients, we wish to maximize the chances for long-term effects and avoid the need for recurrent operations in these fragile patients. This is also supported by studies of stereotactic cingulotomies for obsessive-compulsive disorder performing 3 lesions on each side without increased risk for neurocognitive adverse effects [21, 22].

To better characterize the domains in which pain improvement is achieved, we used the BPI and POS questionnaires in addition to VAS. BPI is intended to assess cancer-associated pain by measuring its severity and interference with function components. Since cingulotomy

is thought to affect the emotional component of pain, we hypothesized that the BPI interference score would be more sensitive to improvement after the procedure, even if the VAS score did not change significantly. From our initial experience, both VAS and BPI scores have shown statistical changes in pain assessment levels following cingulotomies. In addition, by analyzing subcategories of the BPI interference score, we showed that cingulotomy not only decreases the severity of pain but also its influence on other dimensions of well-being, including mood and sleep. These results are in line with the known conception that cingulotomy affects the perception of pain and its emotional consequences.

Adverse Events

We did not have any mortality or significant complications. Similar to previous reports regarding MRI-guided cingulotomy, we had 4 cases of transient “frontal” apathy and urinary incontinence that spontaneously resolved within a few days. In 2005, Yen et al. [17] reported 2 cases of transient postoperative confusion in their series of 15 patients with no mortality or significant morbidity. In a review of 800 cingulotomies performed at the Massachusetts General Hospital, no deaths were reported and only 1 case of permanent neurological morbidity [21].

Despite evidence linking the cingulate cortex with neurocognitive functions and some reports associating cingulotomy with the development of “frontal-type” syndrome of apathy, studies have generally not reported significant cognitive disturbances after surgery. However, this notion has long been based on subjective clinical observations by physicians or families. In our study, neuropsychological evaluations were performed 1 day preoperatively and 1 month postoperatively. No significant effects on cognitive functions were detected at the 1-month follow-up evaluation. However, because mild changes in several domains were noted (Table 4) that did not reach statistical significance, maybe due to the small number of patients, we suggest that further evaluation in a larger cohort of patients is needed to determine the full effect of cingulotomy on specific cognitive functions. Similar findings were reported by Yen et al. [18] in 2009, who analyzed the impact of bilateral cingulotomy on cognition in 10 patients with intractable oncological pain. We are continuing to evaluate the neurocognitive performance of patients before and after surgery.

This study adds to the accumulating evidence regarding the safety and efficacy of stereotactic cingulotomy for refractory cancer pain. Further research is needed to delineate the biological mechanisms of the procedure as

well as its neuropsychological effects. Prospective studies may assist in profiling the more favorable candidates for cingulotomy, who might benefit more from earlier interventions rather than during the terminal stages of their disease.

Limitations

Our cohort included only patients with a short overall survival. This is attributed to the fact that we have introduced an innovative approach to cancer pain management in our institution. Patient selection was naturally directed towards patients who failed all other treatment modalities first. Therefore, generalizability of this study to patients with longer survival is limited, especially with

regard to the durability of the effect. Future patient selection will have to include patients earlier at the trajectory of their illness.

Conclusion

Stereotactic cingulotomy is a safe procedure, and when applied for the appropriate indications in carefully selected cases, it can contribute substantially to the palliation of pain and quality of life of cancer patients with refractory pain. Future studies are needed to define the true role of cingulotomy in patients with longer survival.

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