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Efficacy of Cingulotomy for Refractory Malignant Cancer Pain: A Case Series

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Abstract

Purpose: Poorly controlled pain is a significant quality of life issue for patients with advanced cancer. Patients often suffer from uncontrolled pain or intolerable side effects of treatment despite receiving multi-modal care with stepwise escalation of opioids. Interventional procedures impacting central pain pathways have demonstrated promise in treating pharmacologically intractable cancer pain and may be underutilized, especially in patients with escalating opioid use. The aim of this study was to assess effectiveness of bilateral anterior cingulotomy a minimally invasive neurosurgical procedure in patients with refractory malignant cancer pain through describing opioid use trends pre- and post-procedure and by comparing pain scores.

Methods: This is a retrospective review of a case series of six patients with refractory malignant pain who underwent bilateral anterior cingulotomy. Response to procedure was measured by percent change of pain scores and average daily opioid dose reduction. In addition, demographics, oncologic history, discharge disposition, survival time post-procedure, and complications were reported.

Results: Six unique patients underwent seven total procedures between 2019-2022. Average daily OME (oral morphine equivalent) dose 48 hours prior to procedure was 4411 mg. At discharge, average daily OME dose was 250 mg, an 89% dose reduction from 48 hours prior to procedure. Pain scores reduced by 43% during this same time period.

Conclusion: Cingulotomy effectively reduced pain scores with a concurrent reduction in opioid dosing in our cohort of patients with medically refractory malignant cancer pain. Further research is warranted to identify advanced cancer patients who may benefit most from this procedure and inform clinical adoption.

Keywords: Cingulotomy • Cancer pain • Opioid reduction • Palliative care • Neurosurgery

Introduction

Advanced cancer patients often suffer from diffuse pain secondary to metastatic disease that is inadequately treated with medications alone [1-3]. Intractable pain is a common complication of cancer, occurring in up to 75% of patients with advanced disease or about nine million patients annually. An estimated 30% of these patients do not receive adequate pain relief [4]. Patients with worsening pain on multimodal pain regimens, including high doses of opioids, are at risk for drug-related toxicity and side effects that can diminish quality of life. In cases where multimodal therapy was insufficient to relieve pain or resulted in harmful side effects, interventional procedures such as nerve blocks, intrathecal pain pumps, neuromodulation devices, and lesioning procedures have been used [2]. Anterior cingulotomy is the creation of lesions in the anterior cingulate cortex, a brain region involved in cognitive control and higher order sensory processing integration, and the procedure has been shown to improve pain control and quality of life [5,6]. In particular, patients who have widespread, nonspecific pain of both malignant and nonmalignant origin, as well as patients who have a significant affective component to their pain, seem to benefit most from cingulotomy [7]. This procedure has been performed *via* both noninvasive techniques such as stereotactic radiosurgery and focused ultrasound, and minimally invasive techniques such as radiofrequency ablation and laser interstitial thermal therapy.

Prior to procedure, patients undergo magnetic resonance imaging (MRI) of the brain for target planning by the surgeon. A total of four to six trajectories are planned, two to three on each side. On the day of surgery, patients are induced under general anesthesia and prepped and draped under sterile technique. An intraoperative surgical robot assists with incision, trajectory, and target navigation. Small linear incisions are planned and made. A drill is then used to access the skull and a radiofrequency probe is passed through the burr hole and advanced to the planned target. Next, ablation is initiated, with temperature set to 85°C for 60 seconds. The probe is retracted and reheated to enlarge the lesion. This is repeated to create two to three lesions on each side (Figure 1). Once lesioning is complete, the probe is then fully retracted, and skin is closed. A post-operative CT is obtained to visualize the lesions and evaluate for hemorrhage (Figure 1).

Since its initial development and application to treat chronic pain, anterior cingulotomy has shown variable efficacy in reducing medically refractory chronic pain [7,8]. The rate of meaningful pain relief in cancer patients who undergo cingulotomy reported in the literature varies widely but averages between 60-70%. Viswanathan and colleagues performed a literature review of cingulotomy for treatment of malignant pain and included eight studies that found 32-83% of patients had meaningful pain relief with minimal cognitive changes and rare side effects [9]. Anterior cingulotomy is a safe and promising, yet seemingly underutilized, treatment option for select patients with medically refractory cancer pain.

In this article, we present a retrospective, single institution case series of six patients with advanced cancer suffering from medically refractory, diffuse, malignant pain that underwent bilateral anterior cingulotomy by minimally invasive surgical approach (Table 1).

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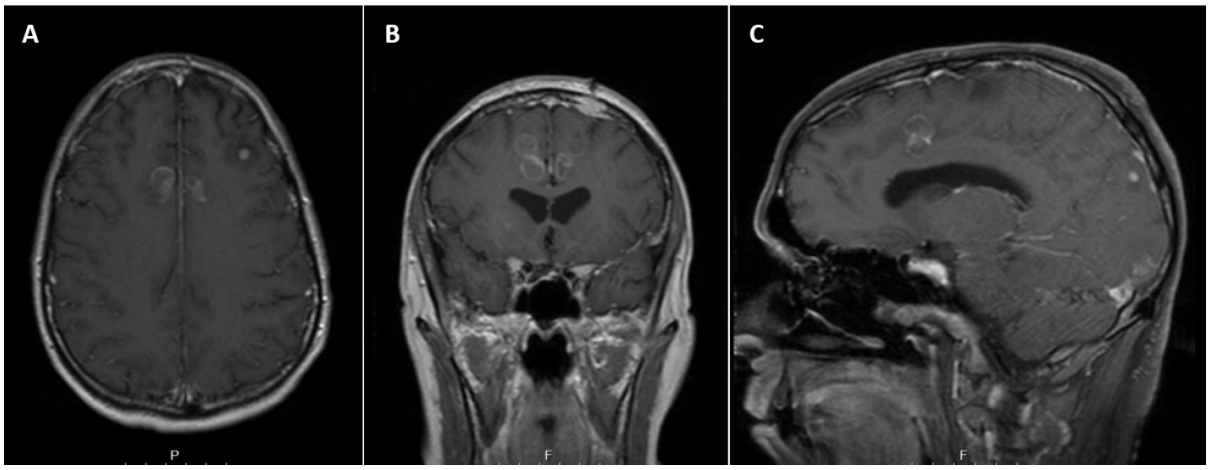

Figure 1. (A) T1 post-contrast MRI in axial, **(B)** Coronal and **(C)** Sagittal. Orientations depicting post-operative cingulotomy lesions in an example patient from our cohort.

Table 1. Describes demographics, oncologic diagnoses and treatments, pain regimen, functional status, disposition, and survival.

Subject	1	2	3	4	5	6
Age	55	59	69	62	50	33
Gender	Female	Male	Male	Male	Male	Female
Race	White	White	White	Black or African American	White	White
Insurance	Private/ Commercial	Medicare	Medicare	Private/ Commercial	Private/ Commercial	Private/ Commercial
Cancer Type	Renal Cell Carcinoma	Merkel Cell Carcinoma of External Auditory Canal	Renal Cell Carcinoma	Ampullary Carcinoma	Renal Cell Carcinoma	Rectal Adenocarcinoma
Sites of Metastasis	Bone, viscera	Lymph	Bone, viscera, lymph	Bone, viscera, lymph	Bone, viscera, lymph	Viscera, lymph
Cancer Treatments	Chemotherapy, immunotherapy, radiation, surgical resection	Chemotherapy, immunotherapy, radiation	Chemotherapy, immunotherapy, radiation, surgical resection	Chemotherapy, surgical resection	Chemotherapy, immunotherapy, radiation	Chemotherapy, immunotherapy, radiation, surgical resection
Pain Medications 48h Pre-op	Opioid, muscle relaxant, steroid, acetaminophen	Opioid, neuropathic agent, muscle relaxant	Opioid, neuropathic agent, steroid, acetaminophen, NMDA-receptor antagonist	Opioid, neuropathic agent, steroid, acetaminophen	Opioid, neuropathic agent, steroid, muscle relaxant	Opioid, steroid, acetaminophen, neuropathic agent, NMDA-receptor antagonist, muscle relaxant
Interventional Pain Procedures?	Yes (radial nerve neurolysis)	No	Yes (trigger point injections, thoracic medial branch blocks, radiofrequency ablation)	No	Yes (kyphoplasty, cordotomy)	No
Referral Source (Location)	Orthopedic Surgery (Outpatient)	Oncology (Inpatient)	Anesthesiology (Outpatient)	Oncology (Inpatient)	Oncology (Inpatient)	Oncology (Inpatient)
ECOG 3 Months Prior to Procedure	2	2	3	3	3	3
ECOG at Discharge	3	3	3	3	4	4
Number of Procedures	1	1	1	1	2	1
Complications	Affect change	None reported	None reported	None reported	None reported	Headache
Hospital Length of Stay (Days)	33	4	15	16	80	14
Time to Discharge from Procedure (Days)	6	4	3	2	43	4
Discharge Services	Home hospice	Home without new services	Home hospice	Home hospice	Home hospice	Home hospice
Survival Post-op (Days)	49	23	11	27	26	Alive at 90 days
Subject	1	2	3	4	5	6
Age	55	59	69	62	50	33
Gender	Female	Male	Male	Male	Male	Female
Race	White	White	White	Black or African American	White	White
Insurance	Private/ Commercial	Medicare	Medicare	Private/ Commercial	Private/ Commercial	Private/ Commercial
Cancer Type	Renal Cell Carcinoma	Merkel Cell Carcinoma of External Auditory Canal	Renal Cell Carcinoma	Ampullary Carcinoma	Renal Cell Carcinoma	Rectal Adenocarcinoma
Sites of Metastasis	Bone, viscera	Lymph	Bone, viscera, lymph	Bone, viscera, lymph	Bone, viscera, lymph	Viscera, lymph

Cancer Treatments	Chemotherapy, immunotherapy, radiation, surgical resection	Chemotherapy, immunotherapy, radiation	Chemotherapy, immunotherapy, radiation, surgical resection	Chemotherapy, surgical resection	Chemotherapy, immunotherapy, radiation	Chemotherapy, immunotherapy, radiation, surgical resection
Pain Medications 48h Pre-op	Opioid, muscle relaxant, steroid, acetaminophen	Opioid, neuropathic agent, muscle relaxant	Opioid, neuropathic agent, steroid, acetaminophen, NMDA-receptor antagonist	Opioid, neuropathic agent, steroid, acetaminophen	Opioid, neuropathic agent, steroid, muscle relaxant	Opioid, steroid, acetaminophen, neuropathic agent, NMDA-receptor antagonist, muscle relaxant
Interventional Pain Procedures?	Yes (radial nerve neurolysis)	No	Yes (trigger point injections, thoracic medial branch blocks, radiofrequency ablation)	No	Yes (kyphoplasty, cordotomy)	No
Referral Source (Location)	Orthopedic Surgery (Outpatient)	Oncology (Inpatient)	Anesthesiology (Outpatient)	Oncology (Inpatient)	Oncology (Inpatient)	Oncology (Inpatient)
ECOG 3 Months Prior to Procedure	2	2	3	3	3	3
ECOG at Discharge	3	3	3	3	4	4
Number of Procedures	1	1	1	1	2	1
Complications	Affect change	None reported	None reported	None reported	None reported	Headache
Hospital Length of Stay (Days)	33	4	15	16	80	14
Time to Discharge from Procedure (Days)	6	4	3	2	43	4
Discharge Services	Home hospice	Home without new services	Home hospice	Home hospice	Home hospice	Home hospice
Survival Post-op (Days)	49	23	11	27	26	Alive at 90 days

Table 2. Pain scores and opioid dosing.

Subject	Pain Score 3 Months Pre-op	Pain Score 48 Hours Pre-op	Pain Score at Discharge	Daily OMEs 3 Months Pre-op	Daily OMEs 48 Hours Pre-op	Daily OMEs at Discharge
1	7	7	3	480	1174	60
2	5	6	1	90	480	0
3	8	6	6	540	1776	22.5
4	7	6	4	293	1683	140
5[1]	7	2.5	1	200	1470	676
6	8	8	6	600	19882	600
Average	7	6	4	367	4411	250

OME=Oral Morphine Equivalent
[1]Patient 5–listed pain scores and OME dose averaged from both procedures

Table 3. Post-operative changes.

1	1174	790	404	60	-33	-49	-95	-57
2	480	38	8	0	-92	-80	-100	-83
3	1776	50	53	23	-97	5	-99	0
4	1683	240	200	140	-86	-17	-92	-33
5[1]	1470	1333	1500	676	-9	13	-54	-60
6	19882	1440	960	600	-93	-33	-97	-25
Average	4411	648	521	240	-68	-20	-89	-43

[1]Patient 5 – listed pain scores and OME dose averaged from both procedures

Case Presentation

We conducted a retrospective chart review of all patients who underwent bilateral anterolateral surgical cingulotomy for intractable oncologic pain conducted at a single academic quaternary care center with over 1,000 beds, located in a large metropolitan city in the southeastern United States between May 1, 2019 and May 9, 2022. Data collected from the electronic medical records (EMR) included: patient demographics, Eastern Cooperative Oncologic Group (ECOG) scores, oncologic history, types of pain medications prescribed, patient-reported pain scores on a numeric 10-point scale, prior interventional pain procedures performed, referral source, discharge disposition, survival time post-procedure, length of stay (LOS), and complications. Major complications were defined as paralysis, brain hemorrhage, and seizures. Minor complications were defined as headache, change in affect, and post-operative confusion. Data was de-identified and stored in a password-protected, HIPAA-compliant REDcap database.

Pain regimens and daily oral morphine equivalent dose were determined from review of outpatient supportive care, palliative care, or oncology notes and inpatient admission documentation from the EMR. The authors used the same equianalgesic table for all opioid conversions. All data and opioid conversions were independently reviewed by three authors to ensure consistency of data and dose conversions. In the event of discrepancies, all three authors reexamined the EMR to achieve consensus. Institutional review board approval was obtained. This study was deemed exempt.

Results

A total of six unique patients had seven total procedures performed. One

patient (subject 5) underwent cingulotomy twice due to inadequate pain relief following the initial procedure. The age of the patients in our cohort ranged from 33 to 69. 67% (4/6) were male. Five patients were white, and one patient was black. 50% (3/6) of our cohort was diagnosed with renal cell carcinoma. The three remaining patients had diagnoses of Merkel cell carcinoma of external auditory canal, ampullary adenocarcinoma, and rectal adenocarcinoma. All patients had metastatic cancer, with only one patient having metastasis limited to the lymphatic system (subject 2). The remainder had a combination of lymphatic, visceral, and bony metastases. Prior to cingulotomy, all patients had received chemotherapy, and all but one (subject 4) received immunotherapy and radiation. 50% (3/6) of our cohort had received some type of interventional pain procedure prior to pursuing cingulotomy, such as cordotomy and/or nerve blocks. Pain for all patients in our cohort was treated with an average of three adjuvant medications in addition to an opioid. 67% (4/6) of patients were referred for a cingulotomy procedure while inpatient status. 67% (4/6) were referred for cingulotomy by oncology specialists.

83% (5/6) of patients discharged home with hospice services. One patient (subject 2) discharged home with home health services and at next outpatient follow-up transitioned to home hospice. Prior to procedure, 67% (4/6) of patients had an ECOG score of 3, and 33% (2/6) had an ECOG score of 2. Post procedure, 67% (4/6) had an ECOG score of 3, and 33% (2/6) had an ECOG score of 4. 67% (4/6) of patients in our cohort had a survival time post-procedure of less than 30 days. One patient died 49 days post-procedure, and one patient was alive at 90 days. There were no major complications in our cohort. Minor complications included affect change (subject 1) and headache (subject 6). Table 2 describes average daily patient reported pain (ADPRP) scores and daily OME dose three months prior to cingulotomy, 48 hours prior to procedure, and at discharge. Average daily OME dose three months prior to cingulotomy, 48 hours prior to procedure, and at discharge were 367 mg, 4411 mg, and 250 mg, respectively (Table 2).

Table 3 lists daily OME dose by post-operative day (POD) and percent change of daily OME dose. There was a 43% reduction in ADPRP score from 48 hours prior to procedure to discharge, with a concomitant reduction in average daily OME dose of 89%. The greatest reduction in average OME dose occurred on POD 1 with a 68% reduction in average daily OME dose as compared to 48 hours prior to procedure. Average LOS in our cohort was 27 days. Average time to discharge post-procedure was 10 days (Table 3).

Discussion

All patients reviewed had metastatic, terminal cancer with substantial opioid dose escalations in the three months prior to procedure, reflecting uncontrolled pain despite multimodal pain regimens. This is not surprising given that inadequately controlled pain is unfortunately an ongoing issue for cancer patients at the end of life [10]. We believe the short survival time and decrease in ECOG scores post-procedure reflect advanced disease at time of referral and not complications due to the actual procedure, as no patient in our cohort suffered a major complication and all patients had metastatic disease with poor functional status measured by ECOG score at time of referral. This does highlight the question of timing of the procedure, as it had positive impact on pain scores and opioid use, without significant complications.

In our case review, cingulotomy resulted in a 43% reduction in ADPRP score that correlated with a dramatic 89% reduction in total daily opioid dose at time of discharge as compared to 48 hours prior to procedure. The greatest reduction in daily OME use occurred immediately post-operatively and decreased daily until discharge. This is consistent with previously published studies [11]. Given that 20-30% of cancer patients do not achieve adequate pain control with pharmacotherapy alone, cingulotomy should be considered as an effective therapy to optimize pain control [12,13]. Our results are consistent with other case reviews showing success of cingulotomy for cancer-related pain [5,11]. Our series suggests that cingulotomy, with its resulting opioid dose reduction, may provide an effective alternative to opioid dose escalation that both controls pain while minimizing toxicity and/or side effects [14].

We were not surprised that one patient in our cohort underwent repeat procedure due to incomplete pain relief from the initial procedure. This, too, is consistent with published literature. Harim and colleagues reported a re-operation rate of 7.6% in their review of 224 patients who underwent cingulotomy [5,15]. While most patients still required opioids post-operatively for pain control, the total average OME dose decreased by almost 90% compared to just before procedure. Of the five patients discharged on opioids, average OME dose at discharge was 240 mg (median 100 mg); one patient discharged without an opioid. This is an important finding given that the current opioid epidemic in the United States has been fueled in part by the volume of opioid prescriptions written across the country [16]. Patients enrolled in hospice have been targets of opioid diversion, with nearly a third of hospices reporting in a national survey at least one episode of confirmed diversion within 90 days [17].

Cingulotomy in our cohort carried minimal risk. All complications in our study were minor. One patient experienced a change in affect; another experienced a headache. Changes in affect and attention have been described as mild and transient in more recent literature [11-19]. This complication can be treated with steroids. Change in affect should be considered in the larger context of the known impact high dose opioids have on mood. It has been well established that opioids, particularly at higher doses, affect mood and arousal and carry the risk of sedation [20,21]. We would argue that when clinical teams counsel patients on potential complications like affect change that they explain this complication may be offset by improvement in mentation due to dramatic reduction in opioid usage [9,22]. Because this was a retrospective review, our analysis does not guide clinicians on the timing of referral for cingulotomy as a pain intervention. Given the dramatic opioid dose reduction in our cohort whose LOS post-procedure was short, we believe cingulotomy may have facilitated discharge home with hospice in patients whose opioid needs would otherwise have required ongoing hospitalization versus inpatient hospice care. Thus, cingulotomy even within last month of life is worth considering.

Conclusion

We acknowledge the following limitations of our study: Our sample size was small, there were limited cancer types represented, all procedures were performed at a single institution, and the study design was a retrospective review. In our study, cingulotomy was an effective, minimally invasive procedure for patients with refractory pain due to advanced cancer. It was associated with minimal risks and successfully reduced ADPRP scores by 43% and resulted in an 89% average total daily opioid dose reduction at discharge compared to 48 hours prior to procedure. Further research is warranted to identify which advanced cancer patients may benefit most from this procedure and optimize timing of this intervention.

Acknowledgment

None.

Conflict of Interest

None.

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