Surgical Neurology International
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Original Article

Palliative stereotactic-endoscopic third ventriculostomy for the treatment of obstructive hydrocephalus from cerebral metastasis

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Received: 31 March 11 Accepted: 16 May 11 Published: 15 June 11

This article may be cited as:
Chen CC, Kasper E, Warnke P. Palliative stereotactic-endoscopic third ventriculostomy for the treatment of obstructive hydrocephalus from cerebral metastasis. Surg Neurol Int 2011;2:76.
Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2011/2/1/76/82083

Abstract

Background: Endoscopic third ventriculostomy (ETV) is increasingly used in the treatment of obstructive hydrocephalus. The literature supporting its use in the setting of metastatic disease, however, remains limited.

Methods: Between 2005 and 2010, 16 patients underwent ETV for treatment of obstructive hydrocephalus secondary to cerebral metastasis. Efficacy of symptomatic palliation and associated complications were reviewed. The results were compared to reported data for ventriculoperitoneal shunt placement in adult brain tumor patients. Patient selection criteria for ETV are reviewed.

Results: Eleven of the 16 patients experienced symptomatic improvement after ETV (69%). Patients who presented with headache associated with nausea, vomiting, or lethargy were more likely to respond to treatment relative to patients presenting with headache alone. Of the 16 ETV patients, one suffered a wound infection and another underwent external ventricular drainage for assessment of intracranial pressure, yielding an overall complication rate of 12.5%.

Conclusions: In select patients with obstructive hydrocephalus related to cerebral metastasis, ETV constitutes a minimally invasive palliative option. The efficacy of ETV in this population is comparable to those reported for obstructive hydrocephalus secondary to primary cerebral neoplasm or other non-neoplastic causes. Patients receiving chemotherapy close to the time of ETV may be at increased risk for infection.

Key Words: Cerebral metastasis, endoscopic third ventriculostomy, palliation

Access this article online
Website: www.surgicalneurologyint.com
DOI: 10.4103/2152-7806.82083
Quick Response Code:

INTRODUCTION

Cerebral metastases constitute an ongoing therapeutic challenge in neuro-oncology. It is estimated that approximately 20%–40% of patients afflicted with cancer will eventually develop cerebral metastases.[31] In the USA, this estimate translates into roughly 170,000 new cases of cerebral metastases each year.[6] Because of the aging population, improved treatment for systemic diseases, and failure of many therapeutic cancer agents to cross the blood–brain barrier,[31] the incidence of cerebral metastases is expected to rise.

The prognosis of patients afflicted with cerebral metastases is poor.[14] The median overall survival for untreated and treated patients is approximately 1 and 4 months, respectively.[34] The mainstay treatment for cerebral metastases involves radiation (whole brain or focal radiation) with or without preceding surgery.[14,32] Prognostic factors conferring a more favorable prognosis have been identified and include the following: younger age, absence of significant neurocognitive dysfunction, and systemic disease status.[4] The Radiation Therapy Oncology Group (RTOG) integrated these variables into an ordinal scale termed Recursive Partitioning Analysis (RPA) class. RPA class I is defined by age < 65 years and absence of significant neurocognitive function (as assessed by Karnofsky Performance Score [KPS] > 70), controlled systemic disease, and no extracerebral metastasis; RPA class III is defined by KPS < 70; all other patients are defined as RPA class II. The respective median survival for RPA class I, II, and III are 7.1, 4.2, and 2.3 months, respectively. In recent series, longer-term survivors have been noted in a subset of RPA class I patients.[17,33]

Given the inherent poor prognosis associated with cerebral metastases, management from a surgical perspective requires judicious considerations—factoring the potential benefit, efficacy of competing and less invasive modalities (such as radiosurgery[19]), time required for functional recovery,[8,30] and anticipated patient survival.[4] With the exception of patients with a single cerebral metastasis, surgical excision generally does not significantly contribute to an improvement in overall patient survival.[2]

For patients with multiple cerebral metastases, poor RPA class, or medical condition prohibitive of general anesthesia, the major goal for surgical intervention is palliation. In this setting, oncologic neurosurgeons are sometimes faced with management of obstructive hydrocephalus secondary to cerebral metastasis. Historically, these patients have been treated with standard ventriculoperitoneal shunting (VPS).[3,10,21,24] However, such approaches are plagued with risks of shunt failure, infections, injury to the abdominal viscera, metastatic seeding of the peritoneal cavity, over- or underdrainage,[3,10,21,24] and postoperative discomfort associated with extensive subcutaneous tunneling and catheter placement.[29] While these risks are generally low, the impact on the patient's quality of life may be dramatic in patients with metastases, particularly given the already poor prognosis. In 1999, Nguyen *et al*. reported a small case series of 7 patients with obstructive hydrocephalus related to cerebral metastasis treated with endoscopic third ventriculostomies (ETV).[20] Since this proof-of-principle series, there have been no other published reports to substantiate the use of ETV in the metastatic population. Here we reviewed our institutional experience with ETV as treatment for obstructive hydrocephalus in patients afflicted with cerebral metastases. Our results collaborated the results of Nguyen *et al*.,[20] and extend their work by (1) setting forth criteria for patient selection, and (2) highlighting management issues related to metastatic patients undergoing ETV.

MATERIALS AND METHODS

Patient selection and outcome evaluation. Clinical information was obtained after Institutional Review Board approval. We reviewed the records of surgical cases performed at our institution between the years of 2005 and 2010 and identified 56 third ventriculostomy procedures. The medical records from these patients were reviewed to identify patients that 1) presented with cerebral metastasis and 2) underwent third ventriculostomy for palliation of hydrocephalus related to cerebral metastasis. Sixteen such patients were identified. This constitutes less than 2% of BIDMC patients who underwent surgery for symptoms related to cerebral metastasis during the 5 year period. Prior to surgery, the indications for performing the third ventriculostomy were reviewed by two independent neurosurgeons (CC and PW). Assessment of outcome was determined by review of medical record documenting neurologic and functional status. Success of ETV was defined as partial or complete relief of symptoms. Failure was defined as no change or deterioration in condition. Outcome was assessed in the immediate postoperative period after ETV, and, when possible, at 1-month follow-up. Patients who complained of persistent symptoms at this time were further evaluated by CINE phase contrast magnetic resonance imaging (MRI) for patency of the ventriculostomy site.[7,11] Conventional MRI was also performed to assess interval changes in ventricular size. The results were reviewed with the attending neuroradiologist. Intracranial pressure (ICP) monitoring through an external ventricular drain was performed in patients in whom the cerebrospinal fluid (CSF) flow studies showed no or equivocal flow through the ventriculostomy site after ETV and unchanged ventriculomegaly.

Surgical technique. To be successful, ETV requires an intact CSF resorption capacity. To ensure such capacity, patients with the following history or radiographic findings were excluded in terms of consideration for ETV: previous history of ventricular hemorrhage, hemorrhagic metastasis, meninigitis, leptomeningeal metastasis, and radiographic findings of dilated subarachnoid space.

With one exception, all ETVs were performed under general anesthesia with endotracheal intubation. One procedure was performed under Monitored Anesthesia Care (MAC) because the patient was riddled with extensive pulmonary metastases and was at risk for failure of extubation.[16]

All third ventriculostomies were performed under image-guidance employing frame-based stereotaxy. After induction of anesthesia, a Riechert/Mundinger stereotactic head frame (Inomed GmbH, Emmendingen, Germany) was secured onto the patient's cranium. A 1.25 mm slice-thickness contrast-enhanced computed tomography (CT) imaging of the head was subsequently acquired using an intraoperative scanner (Ceretom, Neurologica, MA, USA). CT images were processed to yield three-dimensional reconstructions using software by Inomed (STP3, Germany). Using these reconstructions, an optimal trajectory through the Foramen of Monroe, offering an en-face view of the floor of the third ventricle, was planned. The basilar tip was identified, and a target position was selected to avoid contact with the basilar tip. Care was also taken to avoid trajectory intersection with any visualized vessels. The aiming bow was then mounted onto the stereotactic head frame. A burr hole was then placed as the entry point based on the planned trajectory. A 4.0 mm introducer sheath was inserted along the trajectory into the lateral ventricle under guidance of the rigid frame. Entry into the lateral ventricle was verified by the withdrawal of CSF. An oval Oi HandyPro endoscope (4.0 × 2.6 mm, Storz, Tuttlingen, Germany) equipped with three channels for instrument, suction, and irrigation was then advanced into the lateral ventricle with stereotactic guidance. Under direct vision, the neuroendoscope was then further advanced into the third ventricle. A disconnected monopolar electrode was used to perforate the thinnest portion of the floor of the third ventricle, just anterior to the two mammillary bodies. The perforation was enlarged using a Fogarty No. 4 balloon catheter inflated to a diameter of approximately 5 mm. Pertinent illustrations of surgical techniques are as shown in Figure 1. The procedures were performed by CC and PW.

In one patient, ETV was done prior to an endoscopic pineal biopsy of a lung metastasis. Two distinct trajectories were used to perform the ETV and the endoscopic biopsy.

RESULTS

Patient population. Between 2005 and 2010, we treated 16 patients with palliative ETV for symptomatic obstructive hydrocephalus secondary to cerebral metastases. Patient characteristics are as shown in Table 1. There were 6 men and 10 women. The age of the patients ranged from 46 to 81 years, with a median age of 61 years. At the time of presentation, all of the patients had failed firstline chemotherapy and suffered active disease at the primary site. By RPA classification, all patients were either class II (10/16, 63%) or III (6/16, 37%). The primary metastatic tumors in this series originated from breast (n = 5), lung (n = 4), melanoma (n = 3), esophagus (n = 2), and renal (n = 2) cancer. Expectedly, only two patients survived beyond a year. Of note, a quarter of the patients in this series (4/16) expired within a month of palliative ETV secondary to systemic disease progression. One patient presented with lung metastases and pulmonary dysfunction prohibitive of general anesthesia. In this patient, palliative ETV was performed under MAC. The cerebral metastases in all patients were treated with radiation; 11 patients were treated with whole brain radiation therapy (WBRT); five RPA class 2 patients were treated with radiosurgery. Thirteen of the patients harbored multiple cerebral metastases. The three patients suffering from single metastases were medically too tenuous to undergo surgical resection.

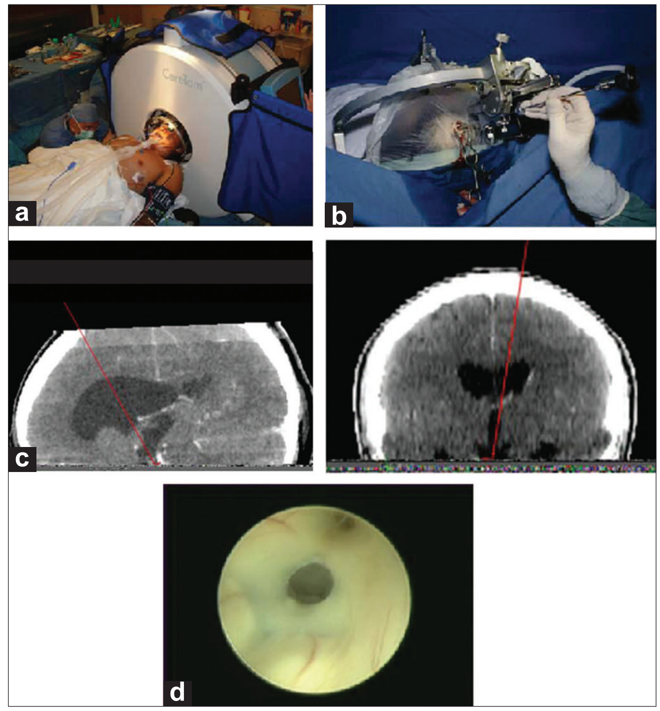

Figure 1: (a) Intraoperative head computed tomography for stereotactic planning of endoscopic third ventriculostomy (ETV) trajectory. (b) ETV performed under stereotactic guidance using the Riechert/Mundinger frame. (c) Stereotactic trajectory with en-face view of the floor of the third ventricle. (d) Completion of ETV

Indications and outcomes. All 16 patients complained of either isolated headache or headache with various other symptoms, including, nausea, vomiting, and lethargy. All patients had imaging workup demonstrating obstruction of CSF flow tract by cerebral metastases, ventriculomegaly, and no evidence of leptomeningeal disease. Symptomatic improvement was observed after palliative ETV in 11 of 16 patients (69%). A breakdown of the specific symptoms is as shown in Table 2. Five procedures were performed for severe headache without associated symptoms. Three of these patients (60%) reported improvement from headache post-ETV. Four procedures were performed for patients who presented

Table 1: Clinical summary of the 16 patients who underwent third ventriculostomy

Case	Age/sex	RPA class	Primary site	Location	Indication	Systemic disease	Symptomatic improvement	Survival
1	54 M	3	Melanoma	Cerebellum	Incapacitating HA	Active	Yes	17 days
2	52 F	2	Melanoma	Cerebellum	HA; Parinaud	Active	No	5 mo
3	46 F	2	Breast	Cerebellum	HA; N; V	Active	Yes	6 mo
4	52 F	2	Lung	Cerebellum	Incapacitating HA	Active	No	3 mo
5	69 M	3	Renal	Midbrain	HA; N; V	Active	Yes	1 mo
6	61 F	2	Breast	Cerebellum	Incapacitating HA	Active	Yes	3 mo
7	65 F	2	Breast	Cerebellum	HA; dysmetria	Active	No	11 mo
8	52 F	3	Breast	Cerebellum	HA; right facial palsy	Active	No	25 days
9	72 M	2	Lung	Pineal	HA; concurrent biopsy	Controlled	Yes	13 mo
10	67 M	2	Esophageal	Cerebellum	HA; lethargy	Active	Yes	1 mo
11	56 F	3	Breast	Cerebellum	HA; N; V	Active	Yes	22 days
12	49 F	2	Melanoma	Cerebellum	HA; N	Active	Yes	19 mo*
13	65 M	2	Esophageal	Cerebellum	HA; N	Active	Yes	11 mo
14	59 M	2	Renal	Cerebellum	HA; N	Active	No	4 mo
15	81 F	3	Lung	Cerebellum	HA; N	Active	Yes	3 mo
16	78 F	3	Lung	Cerebellum	Incapacitating HA	Active	Yes	6 days

HA: Headache, N: Nausea, V: Vomiting, RPA: Recursive Partitioning Analysis, *Alive at the time of manuscript preparation

with headache and nausea. Three of these patients (75%) reported improved symptoms post-ETV. Three procedures were performed for patients who presented with headache, nausea, and vomiting. All three patients demonstrated symptomatic improvement after ETV (100%). One patient with a 3-month history of headache whose family noted increased lethargy regained baseline alertness after ETV (100%). Three patients presented with headache associated with a focal neurologic deficit (Parinaud syndrome, right facial palsy, and dysmetria) but no complaint of nausea and vomiting. Of these patients, only the one with the Parinaud syndrome experienced headache relief after ETV. In this patient, the Parinaud syndrome also resolved post-ETV. The two remaining patients remained unchanged, with persistent headache and neurologic deficit.

Overall, patients who presented with headache associated with nausea, vomiting, or lethargy were more likely to benefit from ETV. Seven of eight such patients experienced relief of symptoms after ETV (87.5%). Four of the eight patients with headache without such associated symptoms experienced resolution of symptoms after ETV (50%). The difference between these groups was significant by Student's t test ($P = 0.037$). The likelihood of symptomatic improvement did not correlate to the ventricular size. We also attempted to correlate the likelihood of symptomatic improvement to the opening pressure observed during surgery. However, the opening pressure was not consistently reported in the operative note. Thus, there was insufficient data point for this analysis.

Complications. Of the patients whose symptoms did not improve after ETV, CINE phase contrast MRI was performed to assess patency of the ventriculostomy site.[7,11] Ventricular size was also assessed by conventional gadolinium-enhanced MRI.[15,26,27] Of the five patients whose symptoms did not significantly improve after ETV, three had CSF flow studies demonstrating patency of ventriculostomy site. One patient was made "comfort

Table 2: Summary of indications, efficacy, and morbidity

Presenting symptoms	Total number of patients	Patients with improved symptoms postoperatively	Percentage of patients with symptomatic improvement
Headache	5	3	60
Headache and nausea	4	3	75
Headache, nausea and vomiting	3	3	100
Headache, lethargy	1	1	100
Headache, neurologic deficit	3	1	33
Overall	16	11	69
Complications			
Wound infection		1/16 (6.3%)	
Ventricular drain placement		1/16 (6.3%)	
Overall		2/16 (12.6%)	

measures only (CMO)" due to rapid systemic disease progression. The CSF flow study was equivocal for one patient. The patient subsequently underwent ICP monitoring through external ventricular drain placement, and ICP was found to be within the normal range. Furthermore, the symptoms were not improved with CSF drainage. As such no further neurosurgical procedure was performed.

We recognized the possibility that a subset of patients may benefit from VPS despite a patent ventriculostomy if it was insufficient to restore normal CSF dynamics.[7] Empiric ICP monitoring and CSF drainage through an external ventricular drain were offered as therapeutic options to the three patients with patent ventriculostomy and persistent symptom at follow-up. The procedure was declined either due to systemic disease progression, inability to tolerate intensified chemotherapy, or patient preference.

One patient of this series suffered an infection of the incision site requiring debridement. Of note, this patient was likely immune-compromised from chemotherapeutic agents administered approximately 1 week prior to surgery. While the white blood count (WBC) was acceptable at the time of ETV (9.1×10^9 cells/L), the count dropped precipitously to the range of $2–3 \times 10^9$ cells/L approximately 3 days after the procedure, and the patient presented with a wound infection 1 week after the procedure.

DISCUSSION

The inherent prognosis of most patients afflicted with cerebral metastasis is poor and mostly unaffected by excision. Thus, the risk of surgical intervention needs to be carefully weighed against the potential harm.[22] Factors that would favor surgical resection of cerebral metastasis include: younger age, good KPS, controlled systemic disease, solitary metastasis located in favorable surgical anatomy, and absence of comorbidities that compromise surgical safety. In patients failing these criteria, the major goal for intervention should be palliation. It is in this context and given the proof-of-principle publication by Nguyen *et al.*,[20] demonstrating the feasibility of ETV for treating hydrocephalus related to cerebral metastasis, that we incorporated this practice into our oncologic care.

Along the line of comfort and palliation, it seems reasonable to raise the question of whether any surgical intervention is warranted in this population—particularly in light of the observation that a quarter of our patient population failed to survive a month after ETV. We believe that surgical intervention can be justified on two fronts. First, based on our clinical experience, headache related to hydrocephalus is severe, incapacitating, and extremely resistant to medical management. If symptomatic relief and improved quality of life is achievable with a minimally invasive surgery, we believe this to be justified—even if it is for a brief period. Second, while there are long-term survivors of cerebral metastasis, it is currently impossible to accurately identify them given the current prognostic tools. Treatment of hydrocephalus in the acute setting may thus yield meaningful survival gain for some patients.

In terms of surgical intervention, VPS is the most commonly used modality for the treatment of obstructive hydrocephalus secondary to cerebral metastases in poor surgical candidates. Overall, VPS is a good option for this indication. Modern series of palliative VPS for elevated ICP in the adult metastatic population yield a complication rate of 10%–30%. Approximately 70%–80% of the patients demonstrated symptomatic improvement postprocedure.[3,10,21,24] While abdominal spread of malignant cells has been reported,[5] the incidence of such seeding seems low enough in this population that it was not observed in several case series, totaling over 200 studied patients.[3,10,21,24]

The clinical efficacy of palliative ETV in our experience compares favorably to those reported for VPS. Overall, 69% of the patients experienced symptom relief after the procedure (compared to approximately 70% for palliative VPS). Therapeutic success seemed less likely for patients who presented with isolated headache or headache associated with neurologic deficits relative to those that presented headache without nausea and vomiting. The complication rate of ETV in our series (13%) is also comparable to those reported for VPS (10%). In our opinion, the major advantages of ETV over VPS for palliation in the metastatic population are fourfold: (1) the procedure obviated the risk and discomfort associated with subcutaneous tunneling and surgical manipulation of the abdomen; (2) palliative ETV can be performed under MAC in patients with tenuous pulmonary function.[16] Because of the extensive tunneling through pain-sensitive structures and surgical manipulation required in VPS placement, the procedure requires general anesthesia; (3) ETV minimized the risk of over- or underdrainage relative to VPS; (4) in cases of infection, debridement in an ETV patient constitutes a less invasive procedure as it does not require implant removal.

In addition to VPS and ETV, another palliative option in the treatment of obstructive hydrocephalus involves the insertion of an Ommaya reservoir followed by serial CSF removal. This last approach is limited by the risk of infection from repeatedly accessing the reservoir. Furthermore, discharge from hospital is difficult since nonphysicians are typically unfamiliar with the appropriate technique for Ommaya reservoir access. Finally, the amount of CSF and the periodicity of CSF removal through the Ommaya is unlikely physiologic.

As such, the palliative effect will be limited. For these reasons, we do not favor Ommaya reservoir placement unless the patient is not a candidate for ETV or VPS.

It is important to note that the patients included in this ETV series were highly selected. All patients reported here exhibit anatomy amenable to ETV (classic triventricular hydrocephalus with sufficient dilatation of the third ventricle for surgical access). Patients with history of ventricular hemorrhage, hemorrhagic metastasis, meningitis, and leptomeningeal metastasis were excluded for consideration of ETV because of concern for decreased CSF resorption capacity.[7] Similarly, patients with radiographic findings of dilated subarachnoid space were also excluded. We believe that patient with diseases processes that compromise the CSF resorption capacity should be treated with VPS rather than ETV.

Another major limitation of this study involves the small sample size and mixed patient population. Because of our stringent selection criteria, utilization of ETV constituted <2% of our metastatic patients who underwent surgical treatment during the five-year period. Realizing the small sample size, we nevertheless performed an analysis in hopes of assessing efficacy and safety of this practice in the metastatic population.

In our case series, all ETV were performed under stereotactic guidance. In doing so, we believe that we maximize the precision of our trajectory to the third ventricle and minimize manipulation of the cerebral parenchyma. Planning the trajectory to avoid contact of existing venous and arterial structures (including the basilar tip) also minimizes the risk of vascular injury.

The literature for ETV in metastatic patients is extremely limited. While studies of ETV have been reported for primary brain tumors[18] and pediatric tumors,[25] the only report in the metastatic population to date was the proof-of-principle series by Nyguen *et al.*,[20] where five of the seven patients with obstructive hydrocephalus related to cerebral metastases reported improved symptoms after ETV (71%). One patient required VPS for failed ETV. Our study is the only follow-up to the Nyguen *et al.* report and largely validated their results. The results of ETV in the metastatic patients are largely comparable to those reported for treatment of hydrocephalus secondary to primary brain tumors,[18] pediatric tumors,[25] and nononcologic indications.[1,9,12,13,28]

A review of the one case of wound infection raises an issue pertinent to patients afflicted with metastatic disease. Many of these patients may suffer cerebral metastases and related hydrocephalus while receiving chemotherapy that compromises the immune system.[23] Surgical procedures in this population are likely associated with an increased risk of infection. Identification of these patients may not always be straight forward. In our study, one patient had a complete normal preoperative workup, including WBC in the normal range (9.1×10^9 cells/L) but subsequently developed a wound infection. Detailed record review revealed that the patient had received chemotherapy a week prior to ETV. The patient had suffered persistent low grade fever postoperatively, prompting a workup that revealed WBC in the range of $2–3 \times 10^9$ cells/L. The patient developed a wound infection requiring surgical debridement thereafter. Given this case, careful deliberation of the timing of ETV relative to chemotherapeutic regimen is warranted.

CONCLUSION

Since proof-of-principle series by Nguyen *et al.*,[20] in 1999, there have been no reports to substantiate the use of ETV in the metastatic population. Here we reviewed our institutional experiment and corroborated the results of Nguyen *et al.*[20] In select patients with obstructive hydrocephalus related to cerebral metastases, ETV constitutes a minimally invasive option for symptomatic palliation. An overall efficacy of 69% was observed in this case series of 16 patients. Our work further reveals the new finding that the likelihood of ETV success was higher for patients experiencing headache associated with nausea, vomiting, or lethargy relative to those who presented without the associated symptoms. This finding suggests criteria for patient selection. Further, our study highlighted issues related to the immunocompromised nature of patients suffering from metastatic disease. Finally, we emphasize that the selection of patients for ETV versus VPS requires careful scrutiny of the pertinent radiographic anatomy as well as medical history.

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