Results of excision of cerebral radionecrosis: experience in patients treated with radiation therapy for nasopharyngeal carcinoma

Clinical article


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Object. In theory, the purpose of the treatment of cerebral radionecrosis (CRN), a nonneoplastic condition, is to minimize loss of brain function by preventing the progression and reversing some of the processes of CRN. In a practical sense, factors for achieving this purpose may include the following: removal of a CRN lesion that is causing mass effect, control of brain edema, prevention of recurrence of CRN lesions, minimization of adverse effects from treatments, and achievement of reasonably long and good-quality survivals. Based on these practical issues, the authors performed a retrospective study to evaluate the results of excision for the treatment of CRN.

Methods. The authors retrospectively reviewed the results of excision of CRN lesions in a group of patients with temporal lobe CRN due to radiotherapy for nasopharyngeal carcinoma. Patients who had undergone surgery at the authors’ institution between January 1998 and November 2008 were analyzed. Surgical results were evaluated by assessing postoperative resolution of brain edema, recurrence of temporal lobe CRN, surgery-related complications, and postoperative functional status and survival.

Results. Twenty-four patients were included (age range 39–69 years; in 23 patients nasopharyngeal carcinoma was in remission). All patients underwent craniotomy for excision of the contrast-enhancing region. The indications for operation were temporal lobe CRN lesions with a mass-occupying effect beyond the temporal lobe. There were 32 craniotomies in all (mean postoperative follow-up 40 months). It was found that brain edema resolved rapidly postoperatively. The recurrence and reoperation rates were 6.3 and 3.1%, respectively. There were no surgery-related deaths. The median survival was 72 months, and 67% of the patients had a Karnofsky Performance Scale score of ≥ 70% at the time of their last follow-up.

Conclusions. In a specific group of patients with CRN of the temporal lobe in whom the CRN lesions were causing a mass-occupying effect beyond the temporal lobe, excision of the contrast-enhancing region was safe and could achieve prompt resolution of brain edema and a low incidence of recurrence of CRN. (DOI: 10.3171/2010.1.JNS091039)

Key Words: cerebral radionecrosis • surgical treatment • craniotomy • nasopharyngeal carcinoma

Abbreviations used in this paper: CRN = cerebral radionecrosis; KPS = Karnofsky Performance Scale; NPC = nasopharyngeal carcinoma; 2D-RT = conventional 2D radiotherapy.
to the extent of a CRN lesion. For example, in patients with temporal lobe CRN, it has been shown that the total volume of the white matter lesion (that is, cyst and brain edema) correlated significantly with their cognitive deficits. Because neurological dysfunctions due to brain edema may be reversible, controlling brain edema is one of the treatment goals in patients with CRN. Other factors for achieving that purpose may include the following: treatment effects should be persistent; adverse effects, if they occur, should be mild in nature and low in incidence; and patients should have a reasonable length and quality of survival.

At our hospital, the most common group of patients with CRN consists of those with temporal lobe CRN due to radiotherapy for NPC. This is because of the following factors: (1) NPC is a common malignancy in Southeast Asia; (2) radiotherapy remains the mainstay treatment; (3) the proximity of the temporal lobes to the nasopharynx; and (4) the high radiation dose needed to control NPC.

To evaluate the results of surgical removal for the treatment of CRN, we retrospectively reviewed the outcomes in this group of patients with temporal lobe CRN due to radiotherapy for NPC.

Methods

Study Design

All patients with NPC who had received cranial surgery at Tuen Mun Hospital between January 1998 and November 2008 were evaluated retrospectively. Patients treated with cranial surgery for temporal lobe CRN were included. Histological confirmation of NPC and temporal lobe CRN was required. Data were collected by reviewing patients’ hospital records, outpatient clinic records, imaging studies, radiotherapy planning records, and slides of histopathological specimens. Patients with incomplete hospital or outpatient clinic records were excluded, and individuals with NPC who underwent cranial surgery solely for brain abscesses were also excluded. Histopathological specimens of excised temporal lobe tissues were reviewed, with a focus on the types of histological changes.

Evaluating the Results of Surgical Treatment of Temporal Lobe CRN

In clinical practice, relief of mass effect on the adjacent brain regions is usually obvious after excision of a lesion, but it is technically demanding to quantify it; we did not evaluate this aspect specifically. In this study, the following 4 parameters were used to evaluate the results of excision. 1) The resolution of brain edema after craniotomy was assessed. Complete resolution of brain edema was defined by resolution of hypodensity on CT scans of the brain, or by T2-weighted hyperintense signals on MR images of the brain, but allowing an arbitrary 1.5-cm margin along the resection cavity to account for the changes seen with encephalomalacia. Another imaging parameter used to differentiate brain edema from encephalomalacia is expanded gyri, with obliteration of sulci in patients with brain edema. Besides, imaging changes compatible with encephalomalacia were limited to the temporal lobe.

2) Recurrence of temporal lobe CRN was assessed using hemorrhage or recurrence of brain edema, contrast-enhancing lesion, or cyst as end points. 3) Intraoperative and postoperative complications were assessed. 4) Postoperative functional status according to the KPS and overall survival were evaluated. Because of the retrospective nature of this study, for surviving patients the last follow-up functional status was used, whereas for deceased patients the functional status before the event leading to death was used.

Statistical Analysis

Overall and median survival were estimated using the Kaplan-Meier method. Overall survival was calculated from the date of craniotomy for temporal lobe CRN (the first craniotomy for those who had bilateral operations). The Student t-test was used to detect any significant difference in time to first diagnosis of temporal lobe CRN between groups. MedCalc statistical software (MedCalc Software) was used for statistical calculations.

Results

Patient Characteristics

Twenty-four patients with NPC in whom temporal lobe CRN developed and who received cranial surgery were included. The male/female ratio was 23:1, and the patients’ ages ranged from 39 to 69 years (mean 49 years). Treatments for their NPC before their clinical presentation with temporal lobe CRN are summarized in Table 1. In 23 patients, their NPC was in remission when they underwent cranial surgery for temporal lobe CRN, and only 1 of these 23 patients had recurrence of NPC during follow-up. That patient had a neck lymph node recurrence and underwent curative radical neck dissection.

Temporal lobe CRN occurred unilaterally in 7 patients and bilaterally in 17. For the 16 patients with repeat irradiation (Table 1), the interval from repeat irradiation to initial diagnosis of temporal lobe CRN on imaging studies ranged from 5 to 109 months (mean 33 months). For the 8 patients who underwent radiotherapy only once (that is, did not undergo repeat tumor irradiation), the interval from completion of radiotherapy to initial diagnosis of temporal lobe CRN on imaging studies ranged from 21 to 354 months (mean 122 months). The difference in the mean interval was 89 months (p = 0.0081).

Before their first craniotomy, 19 patients had received steroid therapy for temporal lobe CRN (Table 2). Fourteen of them had received pulse steroid therapy, with or without a long course of dexamethasone, and 5 of them just received a long course of dexamethasone. In all patients, the steroid therapy was discontinued after their first craniotomy.

Surgical Treatment for Temporal Lobe CRN

Sixteen patients had a unilateral craniotomy, whereas 8 patients required bilateral operations. For all patients with bilateral craniotomies, the second surgery was per-
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formed in a separate hospitalization. The clinical presentations leading to their first craniotomy are summarized in Table 3. The indications for craniotomy were temporal lobe lesions with a mass-occupying effect extending beyond the temporal lobe, characterized by compression of the brainstem and shift of the diencephalon across the midline.

All patients underwent craniotomy for excision of the contrast-enhancing region, with a margin of the adjacent gliotic temporal lobe tissue. Because 8 patients required bilateral craniotomies, there were 32 operations in all. Only 2 patients had temporary catheter drainage of large cysts before undergoing craniotomy. The length of follow-up from their first craniotomy ranged from 2 to 113 months (mean 40 months, median 30.5 months), and the follow-up rate was 100%.

Results of Surgical Treatment for Temporal Lobe CRN

Resolution of Brain Edema. In 15 patients, postcraniotomy CT and/or MR imaging films were available for review. All of these patients underwent operation after 2003. Three of them had bilateral surgeries; thus, 18 craniotomies were analyzed for the resolution of brain edema after craniotomy. In all 18 surgeries, there were early postoperative imaging studies showing a marked decrease in the extent of brain edema. In 8 of these 18 craniotomies (Group 1), imaging studies showed complete resolution of brain edema before postoperative Week 4 (Fig. 1). Those imaging studies were obtained between postoperative Days 9 and 23 (median Day 16). On the other hand, in the other 10 craniotomies (Group 2), early postoperative imaging studies (postoperative Days 2–10; median Day 4) showed a marked decrease in the extent of brain edema, but this fell short of a complete resolution. No imaging studies were performed for these 10 craniotomies in the intermediate period after the early imaging studies. However, in these 10 craniotomies, the later imaging studies all demonstrated complete resolution of brain edema (postoperative Days 36–201; median Day 83) (Fig. 2).

Recurrence of Temporal Lobe CRN. The follow-up period for these 32 craniotomies ranged from 2 to 113 months (mean 40 months, median 30.5 months). Only 1 patient required a repeat operation, which occurred at 14 months after the initial surgery. Another patient had a small hemorrhage at 66 months postoperatively, which was followed with serial imaging for 17 months, with no symptoms. Therefore, the failure rate and the reoperation rate were 6.3 and 3.1%, respectively. In both patients, there was a residual contrast-enhancing region documented on postoperative MR imaging, implying incomplete excision of contrast-enhancing regions.

Intraoperative and Postoperative Complications. There were no surgery-related deaths. One patient developed an ipsilateral chronic subdural hematoma, and this was drained at 5 weeks postcraniotomy. One patient had ipsilateral subdural effusion, which was treated with a subdural-peritoneal shunt at 2 months postcraniotomy. One patient (the only case of repeat operation, mentioned earlier) had a superficial wound infection, which was treated successfully with antibiotics. Three patients developed postoperative chest infection; 2 recovered with the aid of antibiotics, and 1 required mechanical ventila-
tion for 2 days. No patient developed new neurological deficits, although routine visual perimetry studies were not performed.

**Postoperative Functional Status and Overall Survival.** These 24 patients' last scores on the KPS were ≥ 70% in 16; 60% in 2; 50% in 2; 40% in 3; and 20% in 1. All but 1 of the patients with a score of ≥ 50% had undergone surgery in 2000 or before. Twelve patients died within the follow-up period and the causes of death were as follows: chest infection (related to oropharyngeal complications of radiotherapy) in 4; head injury in 2; and brain abscess, spontaneous subarachnoid hemorrhage, severe epistaxis, cardiac cause, stomach carcinoma, and unknown cause in 1 each. The overall survival of the whole group was 61.6% at 5 years postcraniotomy; the median survival was 72 months (Fig. 3).

**Histopathological Findings in Excision Specimens**

Histological changes in the gray matter consisted of zones of fibrinoid necrosis surrounded by gliosis (Fig. 4A). Hemosiderin deposits were prominent at the periphery, and capillary telangiectasia occurred in the interior of the necrotic zones (Fig. 4D). Focally, endothelial prolifera-

![Fig. 1. Illustrative case. Early postoperative CT scans obtained without contrast showing rapid, complete resolution of brain edema in a patient with CRN. A: Immediately preoperative CT scan. B: Postoperative Day 3 CT scan. C: Postoperative Day 5 CT scan showing markedly diminished brain edema. D: Postoperative Day 22 CT scan showing complete resolution of brain edema.](image)

![Fig. 2. Graph showing resolution of brain edema after craniotomy. Group 1: 8 craniotomies with imaging studies showing complete resolution of brain edema before 4 weeks postoperatively. Group 2: 10 craniotomies with early postoperative imaging studies showing marked resolution of brain edema, but falling short of a complete resolution. In these 10 craniotomies, the later imaging studies all demonstrated complete resolution of brain edema. The time needed for complete resolution of brain edema in each of these 10 craniotomies lay somewhere between those 2 imaging studies.](image)

**Illustrative Case**

In this 44-year-old man, who had been treated with radiotherapy in 2003 (2D-RT) and 2006 (intensity-modulated radiotherapy), NPC was in remission. The MR imaging studies obtained in January 2007 demonstrated features of left temporal lobe CRN (Fig. 5A and B). In May 2007, the patient was admitted to a general medical ward for a convulsion. A plain CT scan demonstrated marked left temporal lobe edema, suggesting progression of temporal lobe CRN (Fig. 5C). Dexamethasone (16 mg daily for 2 weeks) was given. In June 2007, the patient received 1 course of pulse steroid (intravenous infusion of methylprednisolone; 1000 mg daily for 3 days) for persistent temporal lobe CRN (Fig. 5D). In July 2007, he was admitted to our neurosurgical ward for head injury after a convulsion. At that time, an MR imaging study demonstrated marked left temporal lobe edema, suggesting progression of temporal lobe CRN (Fig. 5C). Dexamethasone (16 mg daily for 2 weeks) was given. In June 2007, the patient received 1 course of pulse steroid (intravenous infusion of methylprednisolone; 1000 mg daily for 3 days) for persistent temporal lobe CRN (Fig. 5D). In July 2007, he was admitted to our neurosurgical ward for head injury after a convulsion. At that time, an MR imaging study demonstrated marked left temporal lobe edema, suggesting progression of temporal lobe CRN (Fig. 5C). Dexamethasone (16 mg daily for 2 weeks) was given. In June 2007, the patient received 1 course of pulse steroid (intravenous infusion of methylprednisolone; 1000 mg daily for 3 days) for persistent temporal lobe CRN (Fig. 5D).
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Discussion

Cerebral radionecrosis is a nonneoplastic but potentially devastating complication of radiation exposure of the brain after radiation therapy for a variety of intracranial as well as skull base tumors. Whether endothelial or glial cell damage is the major pathophysiological mechanism of the observed necrosis of brain parenchyma is still under dispute, but endothelial damage seems to play a greater role. On imaging studies, CRN consists of various extents of brain edema, contrast enhancement, and cystic change. To evaluate the results of different treatment options for a disease, a theoretical goal or purpose of treatment that is often ideal is first defined. In practice, some realistic and practical goals are often needed. In the present study, we assessed the results of excision for the treatment of CRN by using several clinically assessable parameters; namely, resolution of brain edema after craniotomy, recurrence of CRN, intra- and postoperative complications, postoperative functional status, and overall survival.

Current treatment options for CRN include observation, medical therapy, and surgery. Medical therapies consist of corticosteroids, anticoagulation agents, hyperbaric oxygen, and some newer agents with limited efficacy. In the present study, 79% of patients had tried steroid therapy before undergoing craniotomy, but their CRN lesions progressed, with increased mass effect. Concerning the efficacy of surgery, evidence in the literature is limited to case reports and small case series. Besides, in the literature, it appears that the indications for surgery are large masses and complications such as hemorrhage and abscess formation. The results are not encouraging, and this leads to a generally pessimistic view of surgery for CRN among clinical oncologists.

In the present study, we found that the results of excision of CRN were more favorable. First of all, brain edema resolved promptly after surgery. The time factor is important, because it has been demonstrated that brain edema is also associated with a structural injury that may be potentially irreversible, and thus interventions with prompt effects may be better. By combining data from the 2 groups (presented in Fig. 2), it seemed that complete resolution of brain edema after excision of a temporal lobe CRN lesion very probably occurred within 4 weeks postoperatively. We observed that excision of mainly the contrast-enhancing region of temporal lobe CRN lesions could result in resolution of brain edema. This is very likely to be the case, because the major culprit for brain edema is actually the same tissue that gives rise to contrast enhancement; that is, masses of abnormal vessels with disrupted blood-brain barrier.

Intraoperatively, we often found that the major blood supply of these masses of abnormal vessels was actually from the middle cranial fossa dura mater. Macroscopically, these masses were much firmer and were well demarcated from the surrounding temporal lobe tissue, and were thus identifiable under the operating microscope. This observation is in concordance with the features observed histologically. Therefore, excision of contrast-enhancing regions is a relatively straightforward operation, and is likely to be effective in controlling brain edema in patients with similar CRN lesions. Besides, the origin of cystic change is probably closely related to contrast-enhancing regions; thus, removing these regions is also likely to be effective in controlling the recurrence of cystic change. Evidence in favor of our views is the relatively low failure and reoperation rates in our small series. On the other hand, for the control of contrast-enhancing regions, their incomplete excision, apart from the persistence of contrast enhancement, might also lead to recurrent hemorrhage. From the aforementioned observations, although imaging changes of CRN are heterogeneous, it is likely that not all imaging changes are directly caused by radiation and necrosis.

Based on these results we inferred that excision could achieve the purpose of treatment of CRN, that it reversed part of the processes (as evidenced by resolution of brain edema), and that it halted CRN progression (as evidenced by the low recurrence rate). Having said that, we are aware that the results of excision presented in this article are for a selected group of patients with CRN—a cohort of patients with NPC who had temporal lobe CRN. They were referred to our neurosurgical unit after failed medical treatment (that is, steroid therapy), and were admitted through our emergency department after acute neurological deterioration, or came to us because they refused medical treatment. However, all of these patients underwent craniotomy because their temporal lobe CRN lesions were causing significant mass effect, which we defined as a mass-occupying effect beyond the temporal lobe. Although subject to some limitations, we think our results may also be valid in patients with similar imaging changes.

Although in our patients, complete excision of contrast-enhancing regions appears to be adequate to control temporal lobe CRN lesions, one may ask, at what stage can one be sure that the surrounding brain tissue will not become contrast enhancing (that is, masses of abnormal vessels)? Using one of our patients (the illustrative case) as an example, the patient underwent craniotomy at 6 months after the appearance of contrast enhance-
ment, and there was no recurrence of contrast enhancement at 21 months after craniotomy. Thus, it appears that if regions of a particular irradiated brain parenchyma are going to become contrast enhancing, this will all occur within months of the appearance of the first region. How-

ever, to have a concrete answer, we definitely need further information on the natural history of CRN, which is still lacking in the literature.

A question with a theme similar to the previous one is whether excision should be advocated earlier.
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ing at it from a slightly different perspective, in theory, imaging changes within the high-dose region are more likely to be directly due to irradiation, and may be considered as inevitable damage. On the other hand, imaging changes beyond the high-dose region are, in theory, more likely not to be directly caused by irradiation, and may be considered preventable, provided that the culprit for their progression is removed in an earlier stage. Thus, it is important for further studies of CRN to take into account the relationship of a CRN lesion to the radiation isodose lines. As a practical matter, an obvious advantage of early excision of CRN lesions is the avoidance of the side effects of steroid therapy.

In addition, in the management of CRN we should bear in mind that this is a group of patients with a primary neoplastic disease, and that they have received radiotherapy. Apart from CRN, they do have other problems, such as the control of their primary neoplastic disease, and other postirradiation sequelae in the head and neck region. Therefore, in the management of CRN, each patient’s overall clinical condition is an important consideration. In our study, most patients (23 of 24) were in remission of their primary malignancy. Also, most patients did have a long period of functional survival after operation, as reflected by the following observations: 1) 16 patients (67%) had a KPS score of ≥ 70% at the time of their last follow-up; and 2) the overall survival of the whole group was 61.6% at 5 years postcraniotomy.

A final consideration is that, as with other pathological conditions involving the brain, the location of CRN, especially in so-called eloquent regions, affects clinical management. One of the drawbacks of this study is that all CRN lesions were within the temporal lobe, and thus the results may not be universally applicable to CRN lesions in other regions. However, there is also a specific issue with temporal lobe lesions, in that the risk related to surgery in patients with bilateral temporal lobe CRN was thought to be tremendous. However, in our opinion, bilateral temporal lobe CRN per se should not be considered as an absolute contraindication for surgery, because only nonfunctional tissues (that is, contrast-enhancing regions) are the targets of excision. Besides, in our patients, contrast enhancement usually first appeared at the medioinferior region of the tip of the temporal lobe, which is more anterior and lateral to the parahippocampal gyrus (Fig. 5). This may be the reason for the preserved memory function in our illustrative case. This leads to another question that remains to be answered: should earlier surgery be advocated before contrast enhancement extends to the parahippocampal gyrus? The answer to this question, however, can only be derived from a properly designed prospective study. This highlights another drawback of our study’s retrospective nature.

Conclusions

In a specific group of patients with CRN of the temporal lobe, in whom the CRN lesions were causing a mass-occupying effect beyond the temporal lobe, excision of the contrast-enhancing region was safe and could achieve prompt resolution of brain edema and a low incidence of recurrence of CRN. However, for better management of CRN, further studies on the natural history of this disease and the evolution of CRN lesions in relation to the radiation dosimetry are important.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: ST Wong. Acquisition of data: KT Loo. Analysis and interpretation of data: ST Wong, KT Loo, KY Yam, KF Fok. Drafting the article: ST Wong, KF Fok. Critically revising the article: KY Yam. Reviewed final version of the manuscript and approved it for submission: ST Wong, KT Loo, KY Yam, WM Hung, KF Fok, SC Yuen, D Fong. Statistical analysis: WM Hung. Study supervision: D Fong.

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