Original research article

Surgical techniques in radiation induced temporal lobe necrosis in nasopharyngeal carcinoma patients

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ABSTRACT

Background: Radiation induced brain injury ranges from acute reversible edema to late, irreversible radiation necrosis. Radiation induced temporal lobe necrosis is associated with permanent neurological deficits and occasionally progresses to death.

Objective: We present our experience with surgery on radiation induced temporal lobe necrosis (RTLN) in nasopharyngeal carcinoma (NPC) patients with special consideration of clinical presentation, surgical technique, and outcomes.

Method: This retrospective study includes 12 patients with RTLN treated by the senior author between January 2010 and December 2014. Patients initially sought medical treatment due to headache; other symptoms were hearing loss, visual deterioration, seizure, hemiparesis, vertigo, memory loss and agnosia. A temporal approach through a linear incision was performed for all cases. RTLN was found in one side in 7 patients, and bilaterally in 5. 4 patients underwent resection of necrotic tissue bilaterally and 8 patients on one side.

Results: No death occurred in this series of cases. There were no post-operative complications, except 1 patient who developed aseptic meningitis. All 12 patients were free from headache. No seizure occurred in patients with preoperative epilepsy. Other symptoms such as hemiparesis and vertigo improved in all patients. Memory loss, agnosia and hearing loss did not change post-operatively in all cases. The follow-up MR images demonstrated no recurrence of necrotic lesions in all 12 patients.

Conclusion: Neurosurgical intervention through a temporal approach with linear incision is warranted in patients with radiation induced temporal lobe necrosis with significant symptoms and signs of increased intracranial pressure, minimum space occupying effect on imaging, or neurological deterioration despite conservative management.

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1. Introduction

Nasopharyngeal carcinoma (NPC) is the most malignant nasopharyngeal tumor. It occurs more frequently in Southern China, specifically in the Canton province. The incidence of NPC in Canton province is 25 times higher than that in the rest of the world, thus NPC is often called Canton cancer. NPC is also found in some parts of Southeast Asia, the Mediterranean basin, and Alaska [1]. According to a study by Cao et al., the incidence NPC is as high as 27.2 per 100,000 person-years in men in China [2]. Radiation therapy is the most effective treatment. With a radiation dose between 66 and 70 Gray(Gy), 5 years survival rate may reach 80% [3]. The most frequent complication of the radiation is brain necrosis, with an incidence of approximately 2–4% [4]. This complication does influence patient quality of life. Many regions of the supra or infratentorial can be affected by radiation, such as the temporal lobes, frontal lobes, brain stem, and cerebellum. Patients who harbor temporal lobes necrosis are particularly at risk for transtentorial herniation given the limited space of the middle cranial fossa.

According to the time symptoms emerge, radiation induced temporal lobe necrosis (RTLN) can be divided to three stages [5]: 1 – acute phase: symptoms appear within one month of radiation therapy, 2 – subacute phase: symptoms appear in 1–6 months, 3 – chronic phase: symptoms appear more than 6 months after radiation therapy.

There two types of therapeutic treatment for RTLN in NPC patients. The first method is conservative, which is indicated for most patients or in medically unstable patients. Conservative treatment includes: steroids, osmotic diuretics such as mannitol and furosemide, hyperbaric oxygen therapy, Bevacizumab (Avastin) and anticoagulation (heparin, warfarin, antiplatelets), etc. If conservative management does not change the symptoms or they become more severe, suggesting brain herniation, surgery is the most effective tool. In spite of the simplicity of the RTLN operation, careful patient selection is very important. Because the majority of these patients are old or systemically ill, timing of surgery and the extension of the resection while preserving the functional areas of the temporal lobe are mandatory too.

In this study we present our experience with surgery of RTLN in NPC patients with non-life threatening edema or occupying mass effect with special consideration of clinical presentation, surgical techniques, and outcomes.

2. Materials and methods

2.1. Patient population

We retrospectively reviewed the data of 12 NPC patients with RTLN treated by the senior author (L.F.C.) in our neurosurgical center between January 2010 and December 2014. We excluded radiation induced brain necrosis due to other skull and brain pathology, e.g. AVM, glioma, meningioma, etc. The diagnosis of RTLN in NPC patients was established based on tumor histopathology, which was initially performed by transnasal endoscopy in the Ear, Nose and Throat (ENT) department prior to radiation therapy. Our cohort included 12 patients; all are males, aged 42–64 years (mean, 53.5 years). The initial radiation dose ranged between 66 and 75 Gy, (mean, 70 Gy). There were no repeated radiation therapy cases due to NPC recurrence. Radiotherapy was performed using two-dimensional radiotherapy (2DRT) or intensity-modulated radiotherapy (IMRT) in our institute or others. With an interval time between last course of radiation therapy and initial symptoms of 2–17 years (mean, 7.6 years). The initial symptom for which they sought medical help was headache, sometimes accompanied by vomiting; other symptoms were hearing loss, visual deterioration, seizure, hemiparesis, vertigo, short and long memory loss and agnosia. The most important demographic and clinical features of the patients included in this study are outlined in Table 1.

2.2. Neuro-imaging studies

Radiographic evaluation included brain Magnetic Resonance Imaging (MRI) scans as well as Computed Tomography (CT). The nature of the RTLN, its extensions and relationship to neighboring structures were studied using MR images, as MRI appears to have higher sensitivity than CT in diagnosing RTLN. CT scans, with the aid of bone algorithm, were obtained for analysis of bone involvement. Magnetic resonance spectroscopy (MRS) and Diffusion Weighted MRI (DWI) are best suited to differentiate between RTLN and recurrence of NPC, post radiation second primary intracranial malignancies, hematogenous cerebral metastasis and brain abscess.

2.3. Surgical technique

The patient is placed in a supine position and the ipsilateral shoulder is raised with a cushion to facilitate head rotation. The head is fixed in a three-pin Mayfield head holder with a single pin placed in the frontal area to allow free manipulation during the procedure.

After precise orientation, the borders of the craniotomy and incision are marked with a sterile pen. We use a straight line incision 1 cm in front of the tragus to avoid injury to the neurovascular structure of the pre-auricular region. The inferior border of this incision starts at the level of the zygomtic arch and the upper border ends ~2–3 cm above the pinna with a small anterior curve to facilitate retraction of the edges of the skin incision with the temporalis muscle for wide exposure later.

A craniotome is used to create a 34 mm (width) × 55 mm (height) bone flap. In intradural stage, for cystic lesions, we began by tapping and aspirating the fluid inside the cyst with a ventricular cannula. We then resected the inferior temporal lobe along the inferior temporal sulcus to the Sylvain fissure. Our resection of the normal temporal lobe tissue did not exceed 4 cm in the dominant side and 5 cm in the non-dominant side, to prevent any post-operative complications. We removed some, not all, of the cystic wall and tried to ensure communication the cyst with neighboring ventricles or arachnoid cisterns (ambient cistern) to prevent reformation of the cyst and reaccumulation of the fluid causing relapse of the cyst. For solid tumors, we resected the inferior temporal lobe as in cystic lesions, and tried to remove all necrotic tissue and enhanced lesion found on MRI to prevent

Case no.	Sex	Age	Past radiation history (Years)	Total dose (Gy)	Initial symptoms	Imaging
1	M	57	17	66	Headache, seizure	Bilateral temporal lobe, right frontal lobe necrotic cysts.
2	M	63	2	68	Headache, vomiting, hearing loss	Left side temporal lobe irregular enhancement, midline shift to the right.
3	M	52	4	75	Headache, hearing loss	Left side temporal lobe necrotic cysts with edema.
4	M	64	12	68	Headache, hemiparesis	Bilateral temporal lobes necrotic cysts, edema, midline shift.
5	M	59	2	72	Headache, memory loss, seizure	Left side temporal lobe irregular enhancement with severe edema.
6	M	48	13	70	Headache, hearing loss, vertigo	Bilateral temporal lobes necrotic cysts.
7	M	52	11	75	Headache, vomiting	Left side temporal lobe irregular enhancement with edema.
8	M	48	7	68	Headache, hemiparesis	Right side temporal lobe necrotic cysts with edema.
9	M	53	9	75	Headache, agnosia, hearing loss	Right side temporal lobe necrotic cyst.
10	M	42	3	75	Headache, memory loss	Bilateral temporal lobes, irregular enhancement nodules.
11	M	55	6	70	Headache	Left temporal lobe necrotic cyst.
12	M	50	6	66	Headache, blurred vision, memory loss, weakness in lower limbs	Bilateral temporal lobes necrotic cysts, midline shift compressing midbrain.

Table 1 – Demographic and clinical features of 12 NPC patients with RTLN.

postoperative edema or recurrence. When dissecting necrotic tissue from the Sylvain fissure, we were careful not to injure the middle cerebral artery (MCA). Some residual necrotic tissue was left to adhere to vessels to prevent postoperative infarction. Similarly to cystic lesion, we aimed to communicate cisterns with each other, by opening the crural and ambient cisterns and the Sylvian fissure. For patients with preoperative epilepsy, intraoperative electrocorticography may be used to guide resection of electrically abnormal areas.

3. Results

With the exception of case 1, who was intubated by tracheostomy due to severe trismus and skull base osteoradionecrosis, all patients were orally intubated. Our imaging studies showed unilateral RTLN in 7 patients and bilateral in 5 patients. For patients harboring bilateral temporal lobe necrosis with mass effect (cases 1, 6 and 12), one stage operation was done for both sides. For all other cases, we operated on the side with mass effect, with close postoperative follow up. There was no operative mortality. There were no postoperative complications, except in case 12, who developed aseptic meningitis, which was treated by steroids and continuous lumbar drainage for 3–5 days. Postoperative follow up ranged from 5 to 47 months (mean, 20.6 months). All patients survived without operation-related morbidity. All 12 patients were free from headache, and no seizures occurred in the patients with preoperative epilepsy. Other symptoms such as hemiparesis and vertigo improved in all patients. Agnosia, memory and hearing loss did not change following surgery. The follow-up MR images demonstrated no recurrence of necrotic lesions in all 12 patients. For surgical descriptions and outcomes, see Table 2.

3.1. Illustrative case report (Patient No. 11, Fig. 1)

A 55-year-old man underwent radiotherapy for nasopharyngeal carcinoma (NPC) in 2007. He presented in January 2013 with headache. On magnetic resonance imaging (MRI), a 5.6 cm × 4.1 cm cystic lesion was found in the left temporal lobe with minimal compression of the left ventricle and the basal ganglia, within the area previously irradiated. He proceeded with left side temporal cystic lesion resection through a temporal approach. The patient was placed in a supine position. After definition of the craniotomy, the skin was prepped and draped in standard fashion. A vertical straight epifascial skin incision was made at the level of the zygomatic arch. After elevation of the temporalis muscle, a 34 mm (width) × 55 mm (height) bone flap was created. After opening the dura in cruciate fashion, the necrotic cyst wall was partially removed and communicated with lateral ventricle and crural and ambient cisterns. Postoperative histology revealed coagulative and fibrinoid necrosis, ischemic neurons, hyalinized blood vessel walls, telangiectasia, chronic inflammatory cells and reactive gliosis, suggesting radiation induced temporal lobe necrosis. The postoperative course was uneventful and the patient recovered quickly; follow up MRI did not show any recurrence (Fig. 1).

4. Discussion

Regaud and Schmincke first described NPC as a separate entity in 1921 [6,7]. NPC is arising from the epithelial cells that cover the surface and line the nasopharynx. NPC is a frequent head and neck cancer in southern China and Southeast Asia, such a geographical distribution suggests that NPC has a strong environmental factor possibly linked to nutrition, such as nitrosamine contaminated fishes [8]. In addition to

Case No.	Operation	Anesthetic Intubation	Treatment Outcome	(Karnofsky Scale)	Follow Up (Months)
1	Bilateral	Tracheostomy	Improve	80	10
2	Left	Oral	Improve	90	24
3	Left	Oral	Improve	80	22
4	Right	Oral	Improve	80	13
5	Left	Oral	Improve	90	47
6	Bilateral	Oral	Improve	80	12
7	Left	Oral	Improve	80	36
8	Right	Oral	Improve	90	25
9	Right	Oral	Improve	80	16
10	Bilateral (2 stages)	Oral	Improve	80	23
11	Left	Oral	Improve	90	12
12	Bilateral	Oral	Improve	80	5

Table 2 – Surgical description, outcome and follow up in 12 RTLN patients.

environmental factor, Epstein–Barr virus (EBV) infection has been associated with the etiology of NPC; this is supported by the finding that EBV is detected in all undifferentiated NPC cells [9]. However, some researchers hold the theory that a specific inheritable genetic factor influence on the development of the disease [10]. The prognosis of NPC in early stage is favorable, with 10 year survival of more than 40% [11]. NPC has extensive skull base invasion or cavernous sinus involvement in 70% of grade 3 to 4 patients [12]. Because of the proximity to the nasopharyngeal cavity, the medial and inferior temporal lobes are inevitably delineated in the target volume of irradiation, which increases the risk of temporal lobe necrosis, a late stage complication after radiotherapy in NPC. RTLN responds poorly to treatment, and is associated with permanent neurological deficits and occasionally progresses to death.

The treatment of NPC is based on radiotherapy and chemotherapy. Radiotherapy alone has been the first curative treatment of NPC. Many radiotherapy techniques have been applied in treating NPC patients, such as 2-dimensional (2D)
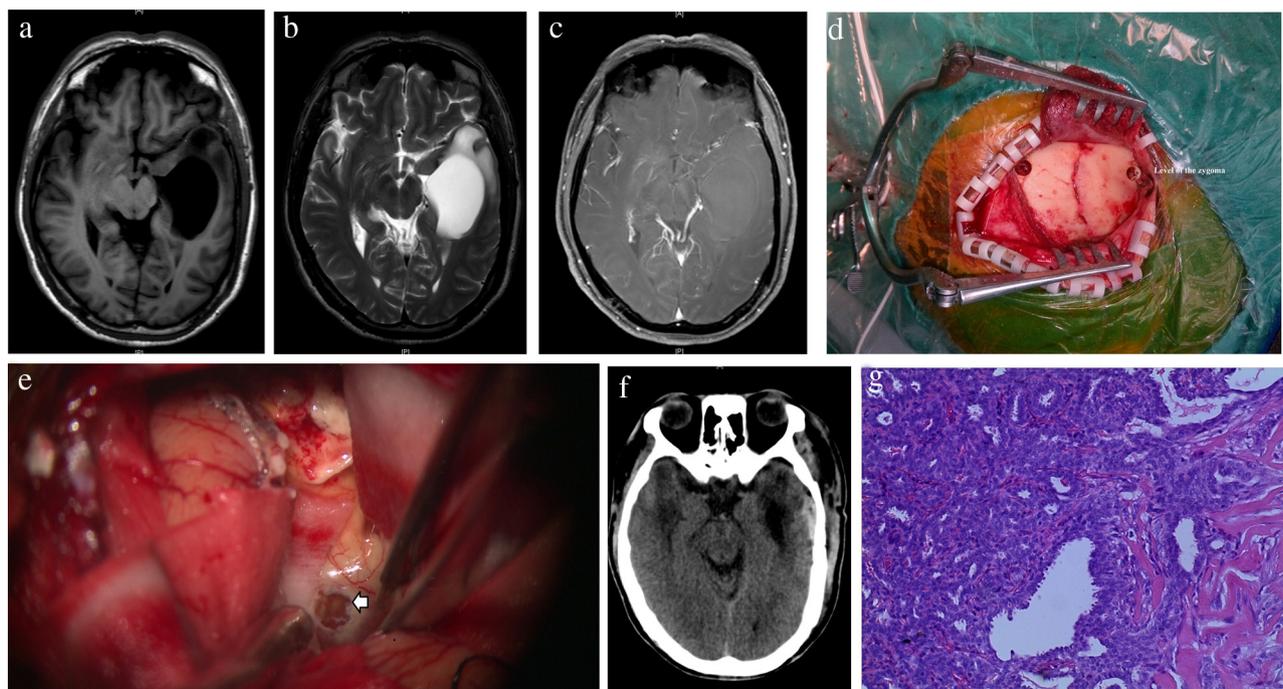
Fig. 1 – Preoperative axial T1 (a), T2 (b), T1 with contrast (c) images demonstrating a 5.6 cm × 4.1 cm cystic lesion in the left temporal lobe. Intraoperative views show the linear incision and the elevated temporalis muscle exposing the squamous bone (d), after opening the dura and aspirating the cystic fluid. The cystic wall was partially resected and fenestration involves the creation of an opening between the cystic lesion and lateral ventricle (white arrow), and the cyst was communicated with basal cisterns (e). Postoperative CT(f). The postoperative histopathological examination (hematoxylin and eosin staining, original magnification × 100) revealed coagulative and fibrinoid necrosis, ischemic neurons, hyalinized blood vessel walls, telangiectasia, chronic inflammatory cells and reactive gliosis, suggesting radiation induced temporal lobe necrosis(g).

and 3-dimensional (3D) radiotherapy. 3D radiotherapy techniques such as 3D conformal radiotherapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) is a new technique developed in the last 2 decades that achieves good results in terms of overall survival, locoregional control, as well as the late toxicity profile comparing to 2D radiotherapy which has suboptimal target coverage and excessive dose to normal structures [13].

Tumor control for NPC has been highly correlated with higher doses of radiation delivered to the tumor. A definitive radiation dose between 66 Gy and 70 Gy needs to be given to the gross tumor volume (GTV), and 54–60 Gy to the clinical target volume (CTV). Patients with NPC experienced irradiation-induced late complications including radiation-induced temporal lobe necrosis (RTLN). Factors associated with an increased risk of RTLN are young age [14], re-irradiation, total radiation dose [15], fraction schedule, administration

of chemoradiotherapy and type of radiotherapy technique [16].

The mechanisms of RTLN are not completely understood. The most accepted theories suggest that radiation necrosis is a continuous process from endothelial cell dysfunction to tissue hypoxia and necrosis, with the concomitant release of inflammatory factors, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) [17], and vasoactive compounds, such as the vascular endothelial growth factor (VEGF), which can lead to progressive blood–brain barrier dysfunction and brain edema [18,19].

Pathologically, in its early stage, RTLN is characterized by demyelination of oligodendrocytes associated with axonal edema due to damage of the blood–brain barrier [20,21], while in late stages; it is characterized by coagulation, fibrinoid necrosis and dissolving or disappearing of nerve cells in the irradiation field, with reactive glial cell proliferation. Finally,
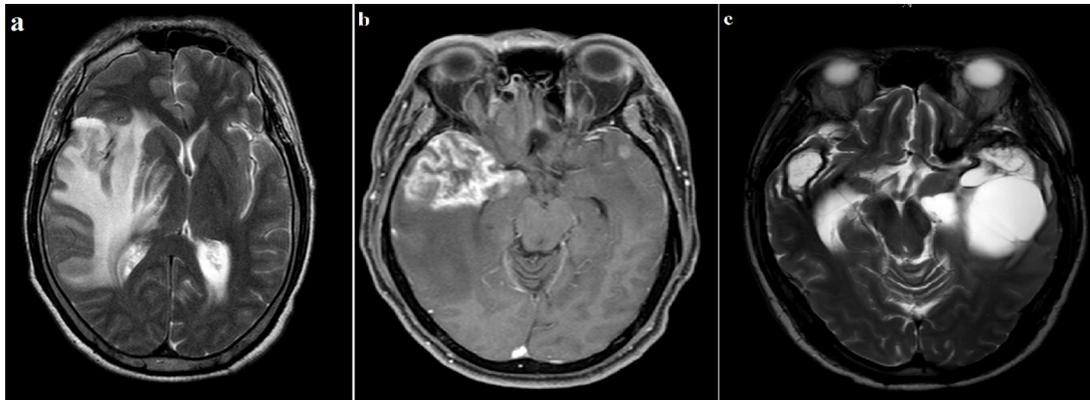
Fig. 2 – The three most common features of RTLN on MRI, finger-like edema on T2 (a), flower lace on T1 + C (b), and soap bubble on T2(c).
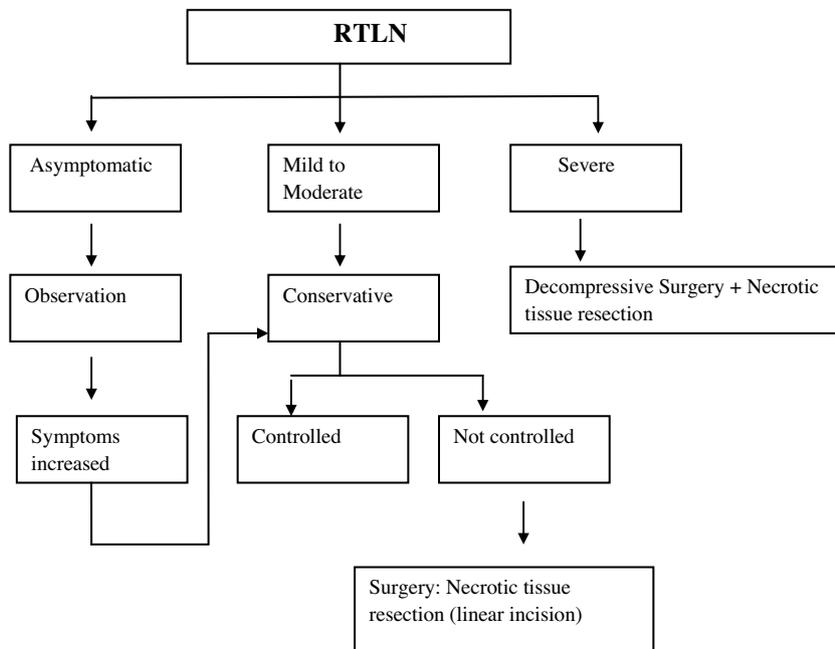
Fig. 3 – Flow diagrams for treatment of RTLN patients.

1- In spite of conservative management, there is progressive neurological dysfunction

2- Long-term dependence on corticosteroid therapy

3- Severe edema with mass effect on CT/MRI

4- Establishment of histopathologic diagnosis

Fig. 4 – Indications for surgical intervention in RTLN patients in our center.

the whole process results in a cystic lesion, as seen in Fig. 6, case 12. The progressive impairment of the endothelium induced by radiation may lead to the thickening of the microvascular wall, which ultimately leads to changes in cerebral white matter demyelination [22,23].

In a study by Greene-Schloesser et al. [24] clinical presentations of RTLN were divided into acute and late stages, with acute stage being characterized by headache, nausea, vomiting due to high intracerebral pressure, seizure, fever, and even acute changes in spiritual consciousness. Almost of these symptoms are reversible through conservative treatment. In the late stage, the symptoms are more profound and irreversible, including cognitive impairments like memory loss, hearing loss, aphasia and blurred vision, even blindness. Some patients will develop temporal lobe transtentorial herniation due to severe edema around the necrotic lesions, which represents a medical emergency and requires surgical intervention.

MRI is more sensitive than CT in diagnosing RTLN. The features of RTNL on MRI are irregular finger-like areas representative of reactive white matter edema, or ''soap bubble'' which represents multiple cystic lesions on T2, and ''Flower lace'' which can be seen on contrast images, such as that in Fig. 2 [25–27].

The differential diagnosis of RTLN includes recurrence and extension of NPC cranially, hematogenous metastasis and primary tumors such as glioma [24]. A diagnostic dilemma sometimes arises when trying to differentiate RTLN from intracranial extension of recurrent NPC. Recurrent NPC is entirely located in the extradural space and is rarely associated with cerebral edema, whereas RTLN is found in intraaxial lesions and cerebral edema is common early sign [24]. Magnetic resonance spectroscopy (MRS) is a noninvasive means of quantifying various metabolites and studying their distribution in different tissues, and is helpful in differentiating between RTLN and primary tumors. In case of RTLN, N-acetyl aspartate (NAA), creatine (Cr), choline (Cho) are remarkably decreased, while with primary tumors, Cho is elevated and NAA levels are diminished or lost entirely [28,29].

The treatment of temporal lobe necrosis depends on clinical assessment, as depicted in Fig. 3. Observation may be the only treatment needed in asymptomatic patients. Conservative treatment, including corticosteroids, osmotic diuretics such as mannitol and furosemide, hyperbaric oxygen therapy, Bevacizumab (Avastin, anti-vascular endothelial growth factor (VEGF)), anti-inflammatory agents, and anticoagulation (heparin, warfarin, antiplatelets), should be applied for patients with mild to moderated edema with minimum brain space-occupying effect. Neurosurgical RTLN resection can be indicated in cases that failed to respond to conservative management, involve progressive neurological dysfunction or long-term dependence on corticosteroid therapy (which carries the risk of immunosuppression and extensive infections), show the MRI or CT shows severe edema with mass effect on MRI or CT, or require establishment of a histopathologic diagnosis due to nonspecific imaging manifestations of the temporal mass in irradiated patients with NPC (Fig. 4). Neurosurgical resection of RTLN is performed through a temporal approach. Preoperative evaluation of the airway in RTLN patients has significant value in determining the type of intubation that will be used. Nasotracheal intubation assisted by flexible fiber-optic bronchoscopy is the preferred option for

Fig. 5 – Case 11. The patient presented with headache and memory loss. MRI showed bilateral temporal lobe necrosis with edema. The right side edema was more severe than the left side (a, b). Patient underwent right side temporal lobe necrotic lesion resection. 5 months later, the patient began to have a headache. MRI showed severe edema on the left temporal side (c, d), he underwent resection of the left temporal lobe necrotic tissue.

patients with trismus, and tracheostomy is preferred for patients with damaged or necrotic skull base damaged due the radiation. Most of our cases were intubated orally; only case 1 was an exception. In most of our cases, the temporal lobe necrosis was resected through a liner incision. If RTLN involved both temporal lobes, the side with significant mass effect was operated on first (Fig. 5, case 10). When both sides have the same degree of mass effect, both sides were operated on in one stage operation, as in case no 12 (Fig. 6). We resected all the necrotic tissues and enhanced lesions on MRI, as well as some part of the cyst wall, and tried to communicate cystic lesions with all neighboring cisterns or the lateral ventricle to prevent postoperative reformation of the cystic lesion. For solid lesions, we also tried to open the cisterns and the Sylvain

fissure following the removal of necrotic lesions. Resection of the normal temporal tissue cannot exceed 4 cm in the dominant side and 5 cm in the non-dominant side. For patients with preoperative epilepsy, intraoperative electro-corticography may be used to guide resection of electrically abnormal areas.

In conclusion neurosurgical intervention through a temporal approach with a linear incision becomes warranted in patients with RTLN with significant symptoms and signs of increased intracranial pressure, minimum space occupying effect on imaging, or neurological deterioration despite conservative management. RTLN patients are systemically ill, and preoperative patient selection is critical to have obtaining successful outcomes.
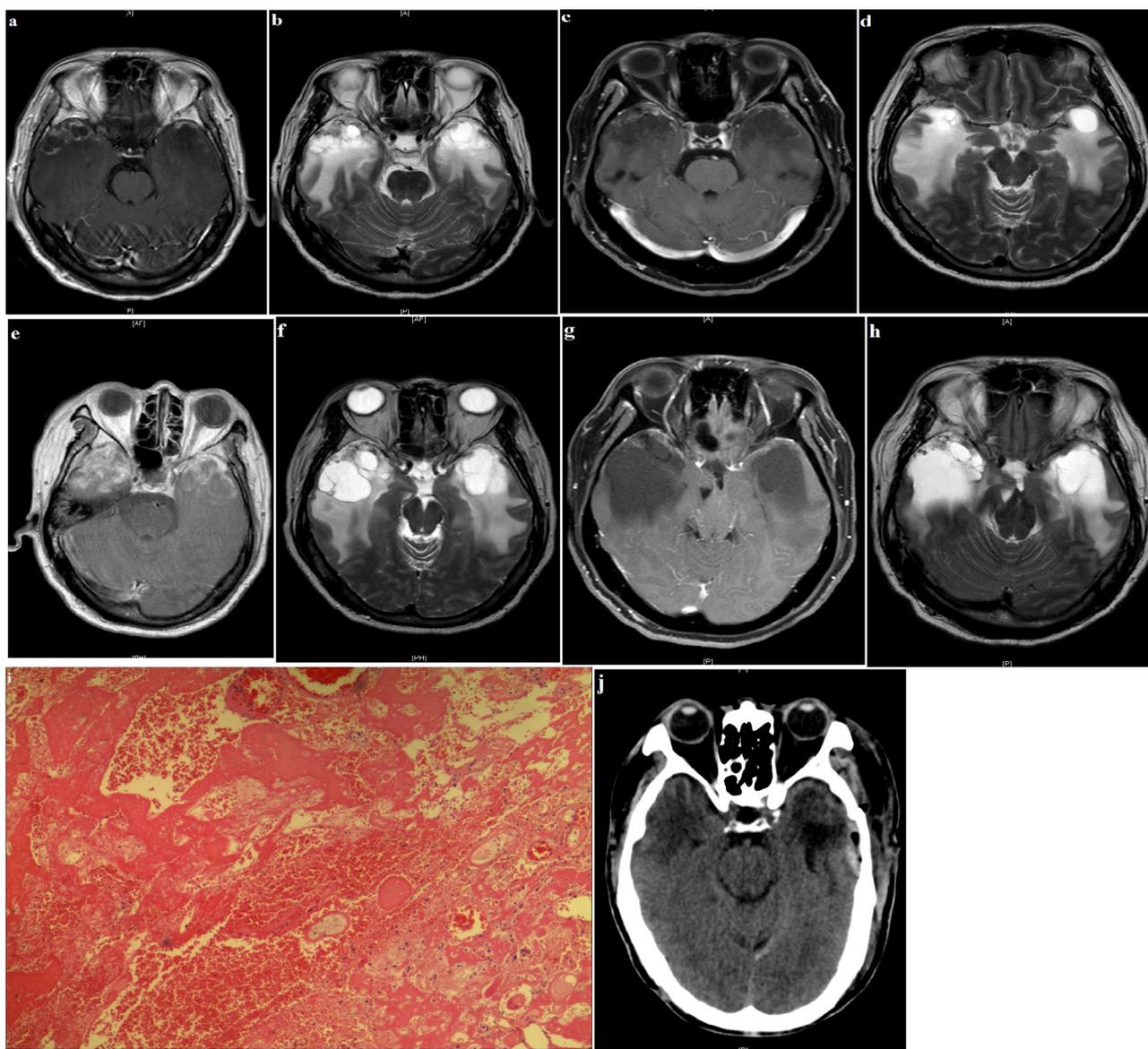
Fig. 6 – The process of solid necrosis tissue changing to cystic lesion in a 50 year old patient (Case 12). Images at the time of diagnosis of bilateral RTLN (a,b), 4 months later (c,d), one year later (e,f), and 16 months later (g,h). The patient underwent bilateral resection of temporal lobe necrotic tissues in one staged operation through a linear incision as described for Case 11. Postoperative histopathologic examination (hematoxylin and eosin staining, original magnification × 100) revealed vascular proliferation and ectasis and extensive necrosis (i). Postoperative CT (j).

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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