

Image-based diagnosis of residual or recurrent nasopharyngeal carcinoma may be a phantom tumor phenomenon

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Abstract

Some nasopharyngeal carcinoma (NPC) patients may present convincing radiological evidence mimicking residual or recurrent tumor after radiotherapy. However, by means of biopsies and long term follow-up, the radiologically diagnosed residuals/recurrences are not always what they appear to be. We report our experience on this “phantom tumor” phenomenon. This may help to avoid the unnecessary and devastating re-irradiation subsequent to the incorrect diagnosis.

In this longitudinal cohort study, we collected 19 patients of image-based diagnosis of residual/recurrent NPC during the period from Feb, 2010 to Nov. 2016, and then observed them until June, 2019. They were subsequently confirmed to have no residual/recurrent lesions by histological or clinical measures. Image findings and pathological features were analyzed.

Six patients showed residual tumors after completion of radiotherapy and 13 were radiologically diagnosed to have recurrences based on magnetic resonance imaging (MRI) criteria 6 to 206 months after radiotherapy. There were 3 types of image patterns: extensive recurrent skull base lesions (10/19); a persistent or residual primary lesion (3/19); lesions both in the nasopharynx and skull base (6/19). Fourteen patients had biopsy of the lesions. The histological diagnoses included necrosis/ inflammation in 10 (52.7%), granulation tissue with inflammation in 2, and reactive epithelial cell in 1. Five patients had no pathological proof and were judged to have no real recurrence/residual tumor based on the absence of detectable plasma EB virus DNA and subjective judgment. These 5 patients have remained well after an interval of 38–121 months without anti-cancer treatments.

Image-based diagnosis of residual or recurrent nasopharyngeal carcinoma may be unreliable. False positivity, the “phantom tumor phenomenon”, is not uncommon in post-radiotherapy MRI. This is particularly true if the images show extensive skull base involvement at 5 years or more after completion of radiotherapy. MRI findings compatible with NPC features must be treated as a real threat until proved otherwise. However, the balance between under- and over-diagnosis must be carefully sought. Without a pathological confirmation, the diagnosis of residual or recurrent NPC must be made taking into account physical examination results, endoscopic findings and Epstein-Barr virus viral load. A subjective medical judgment is needed based on clinical and laboratory data and the unique anatomic complexities of the nasopharynx.

Abbreviations: EBV = Epstein-Barr virus, MRI = magnetic resonance imaging, NPC = nasopharyngeal carcinoma, PET-CT = 2-Deoxy-2-[F18]fluoro-D-glucose (FDG)-positron emission tomography, T1WI = T1-weighted imaging.

Keywords: evaluation of treatment response, image diagnosis, nasopharyngeal cancer, phantom tumor, recurrence or residual tumor, reirradiation

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Treatment effect evaluation of nasopharyngeal carcinoma (NPC) requires a multi-dimensional approach including physical examination, nasopharyngoscopy, and imaging, to determine whether there is a complete or a partial response. Of all the evaluation tools, magnetic resonance imaging (MRI) plays a pivotal role. Image findings are often used as the main evidence to assess the response of cancer treatments in solid tumors.^[1–3] If the irradiated lesion does not regress completely, we consider there is a residual tumor. The diagnosis of a local recurrence is made with the appearance of new lesions after a certain period of tumor-free status. A residual or recurrent lesion may be found by physical examination or endoscopy, and then MRI provide detailed information about the size and extent of the disease. A lesion undetectable by physical examination or nasopharyngoscopy may also be revealed by a follow-up MRI. In either way, a biopsy is mandatory to confirm the diagnosis. However, the anatomy around the nasopharynx is complex and the accessibility is limited for a biopsy of a lesion at the skull base or the cavernous sinus. For these NPC patients, the diagnosis of residual tumor or

recurrence has to be made in the absence of histological confirmation.

During our practice of treating NPC patients, we have discovered that a remaining lesion of the original tumor may not be a genuine residual cancer, and a newly occurring lesion may not be a recurrence. In some patients, although images showed convincing findings, they were non-malignant lesions masquerading as cancer. We propose the term “phantom tumor” for this phenomenon. We present the image findings of these patients which may lead to an incorrect diagnosis resulting in re-irradiation of the false lesions, causing no benefits but severe late toxicities including skull base necrosis, brain necrosis and cranial nerve palsy. We also report on what these phantom lesions actually are histologically.

2. Materials and methods

2.1. Patients

Radiotherapy is the mainstay in the treatment of NPC. The use of chemotherapy varies by time in our institute. In brief, neoadjuvant or concurrent chemotherapy with mainly 5-fluorouracil and cisplatin were used in T3–4 patients before 1990. Since the year 1990, it is mostly concurrent cisplatin with or without adjuvant chemotherapy for T3–4 patients. After completion of treatment, NPC patients were followed up at both the Department of Radiation Oncology and the Department of Otolaryngology Head and Neck Surgery at the following intervals: 1 month after the completion of radiotherapy/chemoradiotherapy, 1 to 3 months during the first year, 3–6 months during the second to the 5th year, and then 6 to 12 months afterwards. At the follow-up clinics, fiberoptic nasopharyngoscopy and laryngoscopy were routinely conducted. Detailed physical examinations including cranial nerve functions were also conducted. MRI of the head and neck region was conducted at the first post radiotherapy follow-up, every 3–6 months during the first 3 years, every 6 months during the 4th and 5th years, and then every 12 months afterwards. Additional MRI scans may be ordered when considered needed. Plasma Epstein-Barr virus (EBV) viral load was also a routine test before and at the completion of radiotherapy and at 3 to 6 month intervals during the first 5 years and then annually. 2-Deoxy-2-[F18]fluoro-D-glucose (FDG)-positron emission tomography (PET-CT) was prescribed when further information was needed for differential diagnosis of suspicious lesions.

This is a longitudinal, observational cohort study. NPC patients followed up or presented at the department discussion sessions or the weekly multidisciplinary meetings during the period from Feb., 2010, to Nov, 2016, were screened. Those with all the following findings were included in this study: Diagnostic radiologist-reported presence of residual or recurrent lesions based on contrast MRI scans; alive and available for regular follow-up; undetectable EBV viral load; negative physical examination and endoscopy findings. The images were reviewed by a radiologist to confirm the image diagnosis. This cohort of patients was then closely followed up until June, 2019. The study was approved by the institutional review board and informed consents were obtained from the patients.

2.2. Magnetic resonance imaging protocols

MRI image findings were essential for the evaluation of treatment results and the diagnosis of residual and recurrent NPC. For this

cohort of patients, MRI was conducted with a shorter intervals than the non-studied patients. MRI study of the nasopharynx and neck was conducted with a 1.5 Tesla MRI unit. The patient was in supine position wearing a head and neck coil. The field view was 23 cm and the slice thickness was 3–5 mm. Gadolinium 0.1 mmol/kg was given intravenously on T1-weighted imaging (T1WI). Pulse sequences included:

- (1) Spin echo T1WI on coronal plane without and with fat saturation.
- (2) Spin echo T2-weighted images on axial plane.
- (3) Spin echo T1WI with fat saturation on axial and coronal planes and without fat saturation on sagittal.
- (4) Diffusion-weighted images on axial planes.

Lesions were measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations.

Once included in the study, follow-up contrasted MRI was conducted every 3 months for at least 1 year on until a biopsy confirmation of the absence of cancer. After the image findings were considered a phantom tumor phenomenon, the patients had MRI checks according to the department guideline for follow-up.

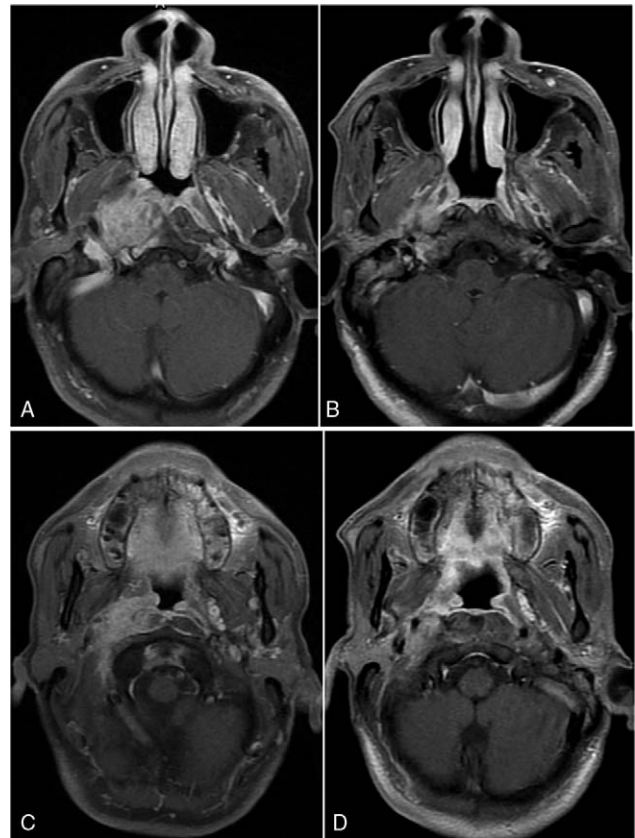


Figure 1. Magnetic resonance images of a 68-year-old male nasopharyngeal carcinoma patient, cT2N2M0, with histologically confirmed residual tumor. A & C: axial contrast-enhanced fat-saturated T1-weighted images before radiotherapy showing a large tumor at the right nasopharynx with posterior extension to the right para- and retropharyngeal space, carotid space, right prevertebral muscle, basal skull and clivus. B & D: axial fat-saturated T1-weighted images 23 months after completion of concurrent chemoradiotherapy and adjuvant chemotherapy, showing a residual, heterogeneously enhancing tumor (arrows) involving the right lateral recess of the nasopharynx, parapharyngeal space and infratemporal fossa. Biopsy was conducted and pathology report was undifferentiated carcinoma.

Figure 1 presents the MRI images of a patient with a histologically confirmed residual cancer.

2.3. Diagnostic criteria of residual and recurrent NPC

The MRI features of NPC include a lesion hypo- to isointense to muscle at T1WI and homogeneous enhancement at fat-saturated T1 with contrast. At T2-weighted imaging it shows hyperintensity compared to muscle. When a patient presented with residual or recurrent NPC based on MRI findings, a biopsy was mandatory. However, it was considered highly risky in some patents and was not conducted. If the EBV viral load was detectable, then the patient was diagnosed to have residual/recurrent NPC regardless of the biopsy results. For these patients, our retreatment policy inclines to the use of more intensive chemotherapy concurrently with low-dose re-irradiation with 3600 to 5000 cGy. If the EBV viral load was undetectable and physical examination and the nasopharyngoscopy showed no tumor, then the patient was considered unlikely to have residual/recurrent tumor. They were then put under close follow-up without anti-cancer treatments. There were no patients showing a positive biopsy for cancer and a negative EBV viral load test. Discussions of the patient diagnosis were conducted between radiation oncologists and head and neck surgeons or in a multidisciplinary team.

2.4. EBV viral load and PET-CT

EBV viral load has been a routine test for our NPC patients since 2009. The test methodology was previously described and the result was presented with EBV DNA copy number.^[4] It was a negative test when the copy number was undetectable (zero copy

of EBV DNA) and was positive otherwise. Positive results varied between 1 and several millions.

2-Deoxy-2-[F18]fluoro-D-glucose (FDG)-positron emission tomography (PET) PET-CT was performed using an integrated PET/CT scanner (Biograph BGO duo, Siemens Medical Solutions, Malvern, PA, USA). All patients fasted for at least 6h before an injection of 370 MBq FDG was given. Imaging began 1 h after the injection, followed by a low-dose (130 kVp, 50 mAs, 0.8 s tube rotation, 4 mm slice collimation, and pitch of 3) 2-slice CT scan of the entire body. It was conducted in all patients at least once with the hope to confirm the nature of the residual/recurrent lesions.

3. Results

During the period from Feb, 2010 to Nov. 2016, we treated 207 NPC patients, and the annual follow-up patients were about 360. The 5-year overall survival rate of NPC patients treated in our department with intensity-modulated radiotherapy is 80.1%.^[5] We collected 19 patients with an image diagnosis of residual or recurrent NPC who remained alive at the time of enrollment (Table 1). These patients showed radiological abnormalities typical of NPC, at varying intervals after completion of radiotherapy. Some of them were referred to radiotherapy department for re-irradiation, and some of them were diagnosed to have residual/recurrent NPC by the reporting diagnostic radiologists according to the MRI diagnostic criteria of the Diagnostic Radiology Department. Six of them had conventional radiotherapy and 13 had intensity-modulated radiotherapy (IMRT). Ten of the 19 patients had T4 diseases and 8 had radiotherapy-related cranial nerve palsy.

Table 1

Profiles of 19 patients with image diagnosis of residual/recurrent nasopharyngeal carcinoma who remained alive and/or without progression after long follow-up without treatments.

Case No.	Sex	Age	T	N	Stage*	IMRT	GTVnp dose	Latency (months)	Cranial neuropathy	NP [†] necrosis
1	1	30	4	0	4A	1	7600	0	0	0
2	1	42	4	1	4A	1	7400	0	0	0
3	1	40	1	1	2	1	7000	0	0	0
4	1	52	4	1	4A	1	7600	0	0	0
5	1	44	4	0	4A	1	7400	0	1	1
6	1	48	4	0	4A	1	7200	0	0	0
7	1	64	2	1	3	1	7000	6	1	1
8	1	45	2	1	2	1	7000	11	0	1
9	1	57	1	0	1	1	7000	24	0	0
10	1	51	4	0	4A	1	3000 [‡]	39	1	1
11	1	60	4	2	4A	1	7000	45	0	0
12	1	53	1	2	3	1	7000	49	1	1
13 [§]	1	56	1	0	1	1	7000	68	1	1
14	1	37	4	1	4A	0	7380	113	0	1
15	1	62	3	2	3	0	7000	120	0	0
16	0	35	1	1	2	0	7600	125	1	0
17 [§]	1	54	1	0	1	0	7000	125	1	1
18 [§]	0	46	4	0	4A	0	7000	136	1	1
19	1	44	4	0	4A	0	7740	206	0	1

GTVnp dose: Total external beam radiotherapy dose to the gross tumor of np in cGy. Latency: The time interval between the completion of radiotherapy and the appearance of abnormal MRI findings. Patients 1–6 showed residual tumors.

* AJCC 2010.

[†] NP=nasopharynx.

[‡] Dose of re-irradiation.

[§] All the 3 patients died of aspiration pneumonia.

Six patients showed residual tumors (Figs. 1 and 2) and 13 were reported to have recurrences (Figs. 3–5). For the 13 patients showing radiological evidence of recurrence, the lesions appeared after an initial complete tumor disappearance. The latency varied between 6 and 206 months after completion of radiotherapy (Table 1). All the image reports concluded that there were residual or recurrent nasopharyngeal cancers. Radiological disease progression was noted in the subsequent MRIs in most of the patients diagnosed to have recurrence. PET-CT images of all the patients showed abnormal FDG uptake compatible with the MRI findings.

Biopsy was considered for every patients. However, there were usually no visible lesions in the nasopharynx and the biopsy was done blindly. One patient underwent endoscopic biopsy of a pterygopalatine fossa lesion. Several patients had nasopharynx necrosis and had to undergo endoscopic, trans-nasal sequestration of the necrotic tissues to obtain tissues for histological examination. This is a surgical procedure with a risk of internal carotid artery damage, and in 2 patients a flap had to be used to cover the raw surface after the surgery. Two patients underwent craniotomy to obtain tissue samples from intracranial lesions. In summary, biopsy was made in 14 of the 19 patients including 4 of the 6 considered to have residual lesions and 10 of the 13 suspected recurrent patients. The number of biopsy or surgery of the nasopharynx/pterygopalatine fossa/skull base varies between 0 and 8 with a median of 1 (Table 2). All of the tissue specimens were shown to have no cancer histologically. The most common pathological diagnosis was necrosis/inflammation in 8 (57.1%), inflammation with fibrosis in 2, and granulation tissue with inflammation in 2, and reactive epithelial cells in 1 (Table 2). One patient who had craniotomy showed gliosis with hemorrhage and necrosis of the examined specimens. There were 5 patients who had no biopsy; the reason for all of the 5 patients was the poor accessibility of the suspected lesion and the high risk of morbidity associated with the biopsy procedure. We concluded that the image findings of these 5 patients did not support the diagnosis of residual/recurrent cancer. The decision was based on undetectable EBV viral loads, absence of visible lesion in the nasopharynx and the neck, and clinical judgments. We withheld any anti-cancer treatments throughout the follow-up period except low-dose oral endoxan and UFUR. These 5 patients, like the rest of the patients, have remained well after an interval of 38–121 months without anti-cancer treatments. Three of them died of aspiration pneumonia during follow-up, likely caused by palsy of the vagus nerve and the subsequent swallowing disorder (Table 2). There are 3 types of image patterns of these “phantom tumors.” The most common 1 is characterized by newly appearing extensive skull base lesions (10/19); the second 1 is a persistent or residual primary nasopharynx lesion (3/19); the third type is a hybrid of the former 2 and with lesions both in the nasopharynx and the skull base (6/19). These patients usually had other coexisting late side effects: nasopharyngeal necrosis was noted in 52.6% (10/19) of patients, cranial nerve palsy in 42.1% (8/19), and nasal bleeding in 2 patients. Four patients had no complaints.

4. Discussion

Our analysis shows that MRI false positivity can be a problem in NPC patients after radiotherapy, and images may be misleading for the diagnosis of a residual or recurrent tumor. Some patients had radiologically convincing tumor-like lesions in the nasopharynx and/or at the skull base after completion of radiothera-

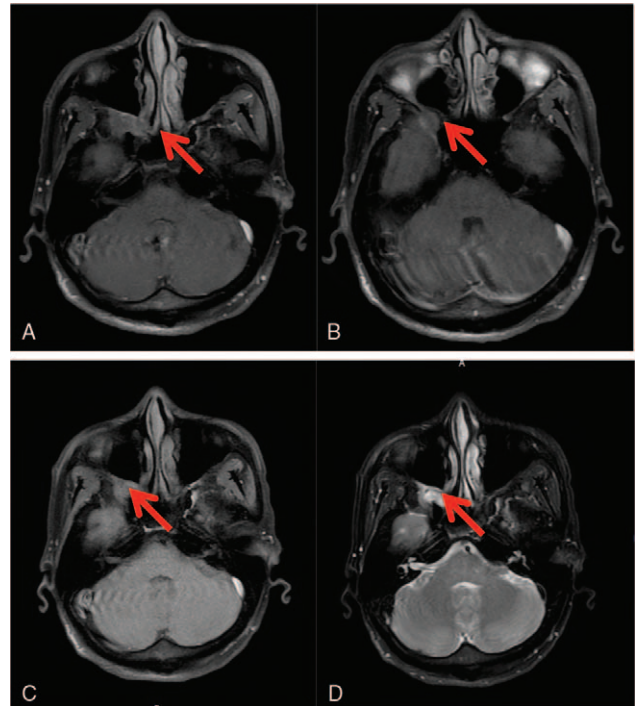


Figure 2. Patient 1: Magnetic resonance images of a 30-year-old male nasopharyngeal carcinoma patient, cT4N0M0. A-B: axial contrast-enhanced fat-saturated T1-weighted images before radiotherapy showing marked pterygopalatine fossa invasion (arrows). C-D: Axial contrast-enhanced fat-saturated T1-weighted (C) and T2-weighted images (D) 7 months after completion of concurrent chemoradiotherapy and adjuvant chemotherapy, showing a residual tumor (arrows) in the right pterygopalatine fossa and the sphenopalatine fissure. Pathology report was chronic rhinitis and bone tissue. The patient is alive and well 92 months after.

py. The lesions usually occurred in, though not limited to, T4 patients. The remaining bulk of a gross tumor after completion of treatment are, instead of residual cancer, benign changes after radiotherapy including inflammation or reactive epithelial cells. For the false recurrent cases, the MRI findings are usually progressive and extensive, and resemble recurrences so much that it is difficult to resist the diagnosis of recurrent cancer. The typical images of a false recurrent case show extensive skull base involvement at 5 years or more after completion of radiotherapy with undetectable EBV viral load. The histologic changes causing these radiological abnormalities are mainly inflammation, necrosis, and granulation. In an early study published in 1991 examining 72 NPC patients showing CT images of a nasopharyngeal soft tissue mass after radiotherapy, 40 had radiation fibrosis. 2 had inflammation and 1 had edema, as well as 29 proved local recurrence.^[6]

MRI findings are limited in the ability of differentiating a true cancer and a benign lesion partly because they are based mainly on dimensional and volume changes and do not take into account other parameters such as functional or metabolic changes that may occur following anti-cancer therapy. It has been observed that the traditional evaluation criteria of tumor size may be inappropriate for assessments of targeted therapy treatment responses. Other criteria including density changes and texture analysis may be needed in addition to tumor shrinkage.^[7,8] In the RESPONSE EVALUATION CRITERIA IN SOLID TUMORS

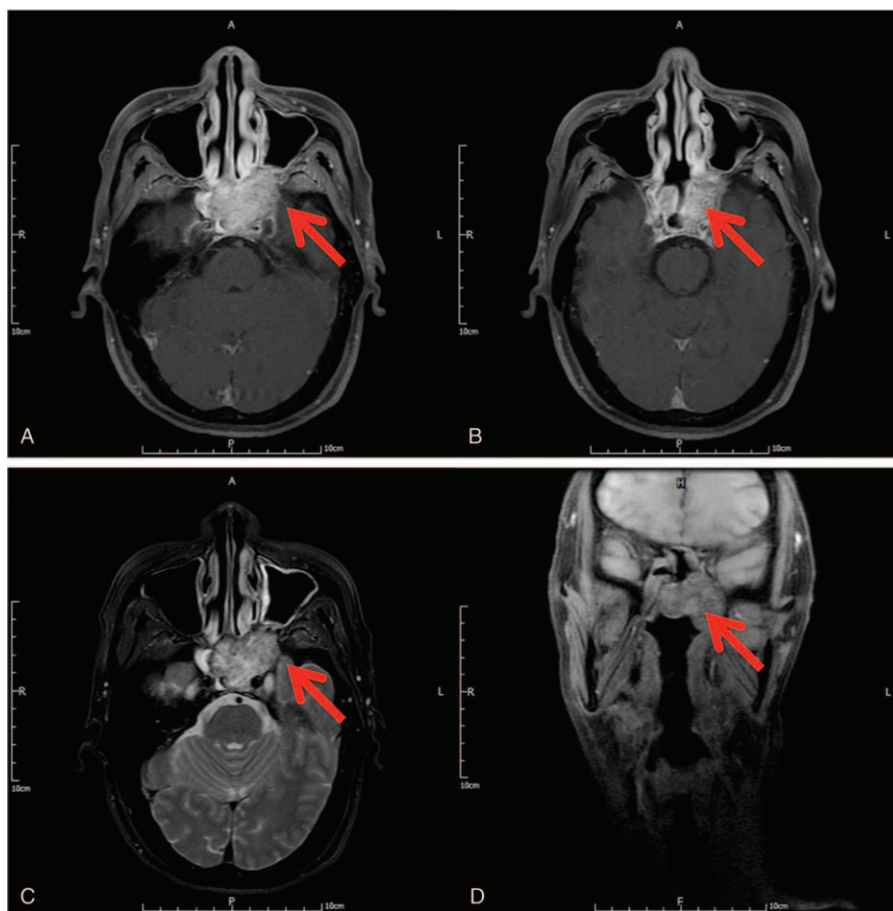


Figure 3. Patient 4: Axial contrast-enhanced fat-saturated T1-weighted images (A, B), axial fat-saturated T2-weighted image (C), and coronal fat-saturated T1-weighted image (D), of a 52-year-old male with an initial stage of cT4N1M0, showing a large residual tumor involving the nasopharynx, sphenoid sinus, bilateral cavernous sinuses, and left sphenopalatine fissure (arrows) 1 month after concurrent chemoradiotherapy. Pathology report shows reactive epithelial cells. He is alive and well 82 months after these images were taken.

guideline, measures other than tumor shrinkage has been mentioned, including serum markers and a special consideration of some specific anatomy sites with unique complexities.^[11] In our experience, the PCR-derived plasma EBV DNA copy number is a reliable differential test. EBV viral load has been reported to be highly accurate in predicting recurrences and long-term survival in NPC patients.^[9–12] In our hospital, we have routine EBV viral load checks for more than 10 years. EBV viral load demonstrates a high sensitivity and specificity; with undetectable EBV viral load, the possibility of a residual or recurrent NPC is very low regardless of the MRI findings.

Initially we had high expectation of PET-CT in differentiating recurrent cancer from inflammation. However, it turned out to be not a reliable diagnostic modality for residual/recurrent NPC. In a meta-analysis of the overall value of 18F-FDG PET/CT in the diagnosis of residual or recurrent nasopharyngeal carcinoma, the pooled sensitivity of 23 studies was 0.93. However, the positive likelihood ratio was 5.52, which is not high enough to correctly diagnose residual/recurrent NPC.^[13] We now still conduct PET-CT for suspected phantom tumour patients, but the results are carefully weighted with other clinical findings.

The incidence of phantom tumor is not clear, but the phenomenon seems to be not uncommon in NPC. Fujii M and Kanzaki J underwent an investigation of the MRI diagnostic accuracy of recurrent NPC. Of 87 patients studied, 13 had MRI and 6 showed MRI high signal which was considered a sign for recurrence, and eventually 5 were diagnosed to have recurrence with a false positive rate of 17%.^[14] Because only 13 had MRI with unspecified selection criteria, the genuine incidence of the phantom tumor is still not conclusive. In a study comparing the diagnostic accuracy of MRI and CT on NPC recurrence, MRI had a sensitivity of only 56%.^[15] In a paper describing post-radiotherapy images of NPC patients, the authors stated that a residual tumor is common for lesions at the parapharyngeal space, pterygopalatine fossa, inferior orbital fissure and intracranial area. However, there were no accompanying data or references to support this observation.^[16] Our analysis offers direct evidence showing the clinical presentation of the false positive MRI images which still exist in an era of much more sophisticated MRI imaging equipment and protocols than 2 decades ago when the earlier analyses were made. This has significant clinical implications, because once a recurrent/residual

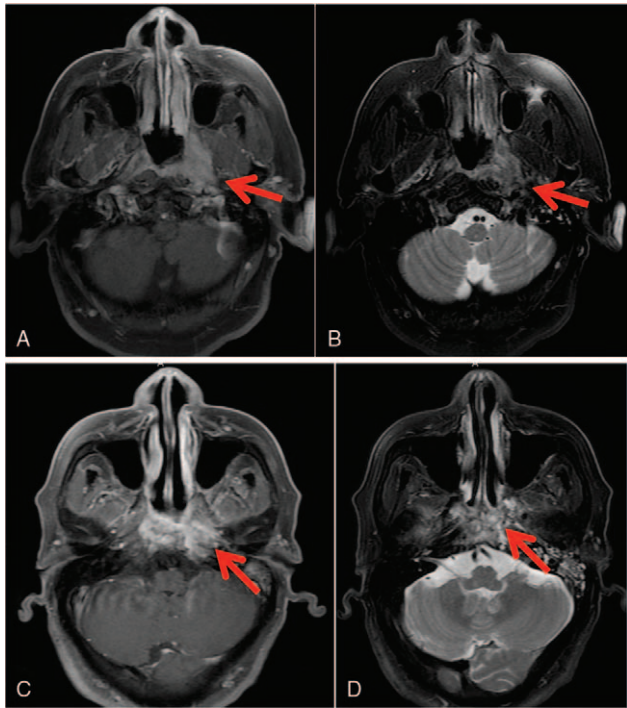


Figure 4. Patient 7: Magnetic resonance images (MRI) of a 64-year-old, male, cT2N1M0, NPC patient before radiotherapy including axial contrast-enhanced fat-saturated T1-weighted image (A) and axial fat-saturated T2-weighted image (B), showing a tumor (arrows) involving the left lateral nasopharynx with posterior and left lateral extension to the parapharyngeal space and prevertebral muscle. MRI obtained 10 months after completion of concurrent chemoradiotherapy plus adjuvant chemotherapy (C-D) show an ill-defined, heterogeneously enhancing lesion (arrows) involving the left hypoglossal canal, petrosal apex, central skull base including sphenoid floor, clivus, prevertebral muscles, and infratemporal fossa. Pathology report shows necrotizing inflammation with fibrosis and calcification. He is alive with stable disease 88 months after these images were taken.

NPC was diagnosed, re-irradiation is commonly considered a reasonable option. However, re-irradiation brings serious late toxicities.^[17] Several studies reported severe late adverse events in 48.1% of re-irradiated patients, including 31.5% with ulcer or necrosis of the nasopharyngeal mucosa, 20.4% with difficulty in feeding, 18.5% with temporal lobe necrosis, and 11.1% with massive hemorrhage.^[18,19]

To avoid these devastating damages, judicious differential diagnosis is crucial. Yet this may not be as easy as we imagine in NPC. It was reported that in head and neck cancer patients, differentiation between osteoradionecrosis and cancer recurrence may be difficult, and in average it requires 2.4 sequestrectomy procedures to confirm the diagnosis of osteoradionecrosis.^[20] Our study intends to increase the awareness of the phenomenon of phantom tumor in NPC. For the diagnostic radiologists, this awareness is important but the radiologists are limited in what they can do because image findings are relatively objective and radiologists report what they see. Facing this dilemma, a multidisciplinary approach is essential where diagnostic radiologists play a central role. Although image-based diagnosis of residual or recurrent nasopharyngeal carcinoma may be unreliable, an enhancing lesion at MRI has to be treated as real cancer until proved otherwise. However, the balance between under- and over-diagnosis must be carefully sought. Biopsy must be conducted with every effort to confirm a residual or recurrent cancer. Yet biopsy is sometimes not feasible due to the unique anatomy of the nasopharynx. Without a pathological confirmation, the possibility of a “phantom tumor” is not uncommon, and the final diagnosis must be made taking into account physical examination results, endoscopic findings and EBV viral load. A subjective medical judgment is needed based on clinical and laboratory data and experiences from careful observations.

There are 2 main limitations of this study. First, the magnitude of the “phantom tumor” cannot be ascertained from the present study. Some patients could have been re-irradiated due to the false positivity and therefore were not accounted for. Secondly, the validity of the 3 image groupings proposed by us needs to be tested in future analyses.

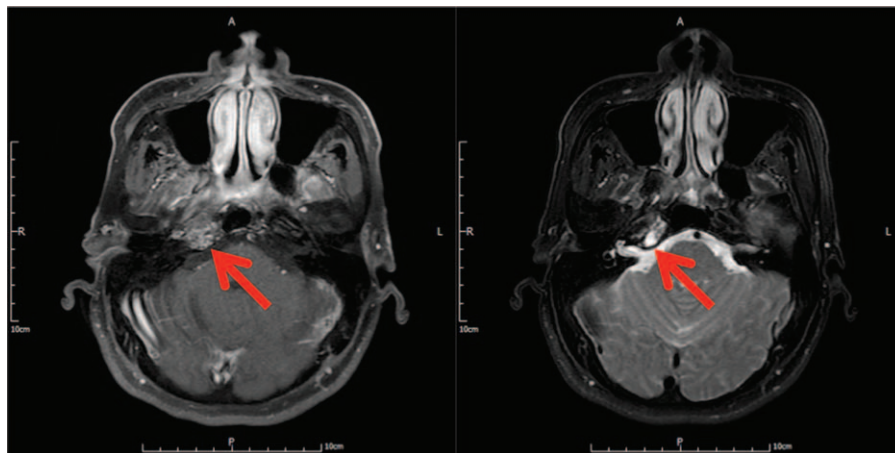


Figure 5. Patient 9: Magnetic resonance images including axial contrast-enhanced, fat-saturated T1-weighted image (A), and axial fat-saturated T2-weighted image (B), obtained 24 months after radiotherapy of a 57-year-old man with cT1N0M0 NPC. They show a focal lesion (arrows) with faint enhancement at the right petrosal apex. Pathology report shows chronic inflammation. He is alive and well 85 months after these images were taken.

Table 2**Features of the radiological lesions mimicking residual or recurrent nasopharyngeal carcinoma and the histological diagnosis and survival status.**

Case No.	Lesion sites	Pathology (No. biopsy)*	status	Survival after image diagnosis (mo)
1	Persistent primary at ppf, IOF, f. rotundum	Chronic rhinitis (1)	1	92
2	Persistent np, clivus, petrous, ppf, spf, jugular f., hypoglossal canal, itf	NA (0)	1	64
3	Persistent primary	NA (0)	1	75
4	Persistent primary	Reactive epithelial cells (1)	1	82
5	persistent tumor at bilateral ppf, f. ovale and rotundum, cavernous sinuses,	Degenerative bone,; extensive necrosis & inflammatory infiltrates; necrotizing inflammation; ulcer with mixed acute & chronic inflammatory cell infiltrates; fibrosis (3)	1	102
6	Persistent clivus, ppf, IOF, orbital apex, itf, cavernous sinus	Necrotizing inflammation (2)	1	146
7	clivus, petrous apex, ppf, itf, sphenoid base, hypoglossal canal, prevertebral m.	Necrotizing inflammation with fibrosis and calcification (5)	1	88
8	np, clivus, petrous, pterygoid m.	Chronic inflammation with ulceration & necrosis (1)	1	80
9	np & petrous apex	Chronic inflammation (1)	1	85
10	clivus, sphenoid sinuses, petrosal apex, cavernous sinus, temporal floor, ppf, IOF, f. rotundum, temporalis	Gliosis with hemorrhage, necrosis & hemosiderin-laden macrophage (2)	2a	84
11	np	NA (0)	1	54
12	skull base, cavernous sinus, masticator space, ppf	Acute inflammation with granulation; mixed acute & chronic inflammation (6)	1	86
13	clivus, C1, petrous apex, C5–6	Acute inflammation with necrosis (1)	2b	63
14	clivus, petrous apex	Acute inflammation with focal epithelial hyperplasia; mixed acute & chronic inflammation with focal necrosis & hemorrhage; necrotizing inflammation with bacterial & fungal infection (8)	1	91
15	clivus, temporal lobe	NA (0)	1	47
16	skull base, ppf, dura	NA (0)	1	111
17	np, clivus, petrous, ppf, cavernous sinus, dura, itf	Granulation tissue with necrotizing inflammation; necrosis (5)	2b	121
18	skull base, ppf	Chronic inflammation with candidiasis; acute necrotizing inflammation with bacterial colonies (6)	2b	60
19	np, ppf, sphenopalatine fissure	Necrotizing necrosis; necrosis with bacterial colonies; ulcer with hemorrhage & focal abscess formation (4)	1	46

f= foramen, iof = inferior orbital fissure, itf = infratemporal fossa, NA= histological diagnosis not available, np= nasopharynx, ppf= pterygopalatine fossa. Status: 1: alive with radiological evidence of disease; 2a: Died of intracranial abscess formation; 2b: Died of pneumonia.

*No. biopsy: numbers in the parenthesis indicate the number of biopsy or surgery of the nasopharynx/ppf/skull base to obtain tissue samples.

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