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MRI of radiation-induced tumors of the head and neck in post-radiation nasopharyngeal carcinoma

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Abstract The aim of this study was to document the sites and MRI features of radiation-induced tumors (RITs) in the head and neck following treatment for nasopharyngeal carcinoma (NPC). The MRI examinations and clinical records of 20 patients with 21 RITs were reviewed retrospectively. RITs developed 3-30 years after radiotherapy and included eleven squamous cell carcinomas, six sarcomas, two neuroendocrine carcinomas, one mucoepidermoid carcinoma and one meningioma. RITs arose in the maxillary region (9), oro/hypopharynx and oral cavity (5), external auditory canal (4), nasopharynx and sphenoid sinus (2) and brain (1). Radiation-induced carcinoma and sarcoma had MRI features that were useful to distinguish them from recurrent NPC. To improve early detection of RITs, the check areas on an MRI of a patient with previous NPC treated by radiation should always include the maxillary region, tongue, and external auditory canal/temporal bone.

Keywords MRI · Nasopharyngeal carcinoma · Sarcoma · Squamous cell carcinoma · Radiation-induced tumor

Introduction

Radiotherapy (RT) forms the cornerstone of treatment for nasopharyngeal carcinoma (NPC), which is a common tumor in the southern Chinese population. The 5-year cancer-specific survival rates are high, in the region of 80% [1]. However, longer survival results in an increased opportunity for the complications of RT to develop. These complications include radiation-induced tumors (RITs), which although rare, have been reported in several case series with an incidence ranging from 0.04 to 7% [2–11]. The radiologist should be aware of the common sites of RITs so these can be scrutinized on follow-up scans, and be aware of their radiological appearances. The aim of this study was to review the radiological features of RITs on magnetic resonance imaging (MRI) following RT treatment for NPC.

Materials and methods

Patients with second malignancies were identified from a review of the MRI reports of patients with a history of NPC previously treated by RT. The clinical records were

reviewed to determine histology, latency period, and clinical presentation. The inclusion criteria for RIT were (1) tumor arising within the radiation field, (2) tumor histology that was different from the undifferentiated carcinoma of NPC, and (3) latency period of 3 years or more after RT treatment. These criteria were adapted from those for radiation-induced sarcoma, described by Cahan et al. [12] and Arlen et al. [13]. The MRI examinations of patients meeting the criteria for an RIT were reviewed by consensus by two radiologists to determine the site or origin and signal characteristics as well as extent of disease including invasion into bony, vascular, and neural structures. In addition lymphadenopathy was evaluated. Where available, history of alcohol and tobacco use was noted to identify other known risk factors for head and neck cancers.

Patients underwent MRI on a 1.5T MR whole-body system unit, either a Philips Gyroscan (Netherlands), Philips Intera (Netherlands), or Siemens Medical Systems Magnetom Sonata (Germany), using a head coil and a neck coil or a combined head and neck coil. The imaging protocol in all patients included an axial fat-suppressed T2weighted sequence (TR/TE 2,500/100 ms, echo train length of 15, field of view 22 cm, slice thickness 4 mm, with no interslice gap, and matrix size 256×202), coronal T2-weighted turbo spin-echo (repetition time of 2,500 ms, echo time of 100 ms, echo train length 14, 22 cm field of view, 4 mm slice thickness with no interslice gap and a 256×202 matrix), axial T1-weighted spin-echo (repetition time of 500 ms, echo time of 20 ms, 22 cm field of view, 4 mm slice thickness with no interslice gap, and a 256×202 matrix). Following a bolus injection of 0.1 mmol/kg of either gadolinium dimeglumine (Schering AG Germany) or gadoteric acid (Dotarem; Guerbet, Aulnay, France), highresolution contrast-enhanced T1-weighted spin-echo images using a 512×512 matrix were acquired in the axial and coronal planes. In addition to the standard protocol above, most patients underwent a T1-weighted sequence post-contrast with fat saturation, and some sequences were also performed in the sagittal plane.

Results

The MRI reports of 884 patients with previously treated NPC were reviewed and 21 RITs in 20 patients (15 males and 5 females, age range 37–79 years with a mean of 55 years) were identified, including 3 patients reported previously [6]. MRI was performed at the time of first presentation (n=19) or at recurrence (n=2) of the RIT. The largest histological group was the squamous cell carcinomas (SCC) (n=11), followed by the sarcomas (n=6), and a miscellaneous group comprising neuroendocrine carcinoma (n=2), mucoepidermoid carcinoma (n=1), and meningioma (n=1) in a patient with SCC. The site of origin was localized to five regions: maxilla (including the maxillary

sinus, alveolar process, and palate) and nasal cavity (n=9), oro/hypopharynx and oral cavity (n=5), external auditory canal (n=4), nasopharynx and sphenoid sinus (n=2), and brain (n=1). The MRI and clinical findings of tumors in each group are shown in Table 1.

The average latency period from the time of radiation therapy to the time of diagnosis of the RIT was 12.6 years (range 3–30 years). SCC presented at a mean of 12.5 years after RT, whereas sarcomas presented sooner, 8.8 years after RT. SCC in the oral cavity and pharynx had shorter latency periods (mean of 7.7 years) compared to SCC in the ear (mean of 21 years). In six patients with SCC, there was a history of alcohol abuse and smoking in three patients (RITs in the maxillary sinus, hypopharynx, and EAC) and no such history in three patients [RITs in the tongue (n=2) and palate], while for the remaining 14 patients, no data were available.

Discussion

The most common location for RITs was the maxillary region, including the maxillary sinus, alveolar process, palate, and adjacent nasal cavity. Although the radiation field for each individual patient was not reviewed in the study, the maxillary region is usually covered by the highdose radiation field for NPC, which encompasses at least the posterior half of the maxillary sinus and adjacent nasal and oral cavity. Radiation-induced tumors encountered in this region included both sarcomas and carcinomas (Figs. 1, 2, 3, and 4). In many of these cases, the palate and alveolar process of the maxilla were involved while larger tumors involved adjacent regions and spread into the maxillary sinus, as well as into the oral cavity and pharynx. While the epicenter of most of these tumors was located in the inferior aspect of the maxilla, a minority arose more medially in the nasal cavity.

From the results of this study and a review of the literature, the sinonasal region is emerging as one of the most common sites of RIT following RT for NPC. A study by Liu et al. [8] showed that of 15 sarcomas in the head and neck, 8 arose in the maxilla or nasal cavity and paranasal sinuses, while Lee et al. [3] reported 2 cases and Dickens et al. [14] 4 cases of osteosarcoma of the maxilla. Malone et al. [9] reported a case of adenocarcinoma in the maxillary sinus and hard palate and a literature review revealed 11 further sinonasal RITs, which included a study by Ko et al. [4] with 8 malignant fibrous histiocytomas arising in the nasal cavity or maxillary sinus.

After the maxillary region, the two most frequent regions for RIT in this series were the oral cavity and oro/ hypopharynx, and the external auditory canal. In the oral cavity and oro/hypopharynx, all RIT were SCC, the most common site being the tongue base, which lies in the high radiation field of NPC treatment (Fig. 5). The increased incidence of tongue carcinoma and its relationship to RT

Region	Site (epicenter)	Histology	Clinical details	MRI features
Maxilla (including maxillary sinus, al- veolar process, and palate) and nasal cavity	Palate	SCC, moderately differentiated	NPC stage N/A. Ulcer in the soft palate 8 years after RT	1.5×1.0 cm tumor confined to the right side of the soft palate. Signal intensity see below ^a
	Palate	Mucoepidermoid carcinoma	NPC stage N/A. Tumor in the soft palate, uvula, naso- pharynx, and oropharynx 25 years after RT	Irregularly shaped infiltrating tumor destroying the soft palate and ex- tending to the oropharynx, nasophar- ynx, and skull base. V3 nerve appears involved but no definite evidence of perineural spread. Signal intensity similar to SCC, see below. ^a Meta- static lymphadenopathy present
	Maxillary sinus/ palate	SCC, moderately differentiated	NPC stage N/A. Palatal mass and right facial swelling 21 years after RT	7.0×6.5 cm tumor in the right maxil- lary antrum and soft and hard palate extending into the subcutaneous soft tissues, nasal cavity, and alveolar process of the maxilla. V3 nerve engulfed by the tumor. Signal inten- sity see below ^a with the exception that the T2 signal intensity was mildly heterogeneous. Metastatic lymphadenopathy present
	Palate	High-grade sarcoma (fibro-, leiomyo-, and angiosarcomatous elements)	NPC stage N/A. Nodule in the hard palate 4 years after RT. CT revealed a 6-cm mass destroying the palate, right side of the alveolar process of the maxilla, and posterior wall of the maxillary sinus. Tumor resected but recurred 1 year later in the skull base	4.5×3.0 cm tumor recurrence invad- ing the right side of the skull base, sphenoid sinus, cavernous sinus, and middle cranial fossa. Signal intensity homogeneous low/intermediate T1, intermediate mildly heterogeneous T2, and moderate homogeneous enhancement
	Maxillary sinus/ nasopharynx	Spindle cell sarcoma	NPC T2bN1M0. Nasal ob- struction 10 years after RT	4.0×3.5 cm tumor centered on the posterior wall of the maxillary sinus and pterygoid process with extension anteriorly into the maxillary sinus and posteriorly into the nasopharynx. Signal intensity heterogeneous of mixed intermediate and high T2 and mixed low and intermediate T1, and heterogeneous enhancement. The tumor grew rapidly over the follow- ing 6 months despite treatment
	Alveolar process of the maxilla	Undifferentiated sarcoma	NPC T2N0M0. Nasal discharge and exophytic growth from the maxilla 5 years after RT	4.0×3.0 cm tumor destroying the left alveolar process of the maxilla, hard palate, and maxillary sinus. Signal intensity homogeneous low T1, mildly heterogeneous intermediate T2 and heterogeneous contrast en- hancement with a central area of necrosis

Region	Site (epicenter)	Histology	Clinical details	MRI features
	Nasal cavity	Osteogenic sarcoma	NPC T2aN0M0. Nasal mass in the left middle turbinate 7 years after RT. Underwent resection with no residual tumor on MRI performed 3 months after treatment but rapidly growing tumor re- currence 1 month later	4.0×2.0 cm polypoidal tumor in the left side of the nasal cavity. Signal intensity homogeneous low/interme- diate T1 and high T2, with marked contrast enhancement
	Maxillary sinus	Neuroendocrine carcinoma	NPC T3N3M0. Maxillary sinus tumor 23 years after RT	4.1×4.7 cm tumor in the left maxillary sinus with invasion of the nasal cavity, hard palate, alveolar process of the maxilla, and buccal space. Signal intensity similar to SCC, see below ^a
	Nasal cavity	Neuroendocrine carcinoma	NPC T2N2M0. Right nasal mass 6 years after RT	7.5×5.0 cm tumor arising from the right nasal cavity and extending into the left nasal cavity, bilateral ethmoid air cells and frontal sinuses, right orbit and anterior cranial fossa. Signal intensity is mildly heterogeneous intermediate T2, homogeneous low/intermediate T1 with mild homogeneous enhancement
Oral cavity and oro/hypopharynx	Tongue	SCC, well- differentiated	NPC T4N1M0. Fungating mass in the tongue 4 years after RT	3.5×3.5 cm tumor in the oral tongue and left side of the tongue base extending into the pre-epiglottic fat and floor of mouth. Signal intensity see below. ^a Metastatic lymphadenopathy present
	Tongue	SCC, moderately differentiated	NPC T3N3M0. Left-sided tongue base mass 6 years after RT	2.5×1.5 cm tumor confined to the tongue base. Signal intensity see below ^a
	Tongue	SCC, high grade	NPC stage N/A. Right-sided tongue ulcer 3 years after RT	4.0×2.5 cm tumor confined to the right side of the oral tongue. Signal intensity see below ^a
	Palatine tonsil	SCC, high grade	NPC T2N0M0. Left palatine tonsil and tongue base mass 3 years after RT	4.5×2.0 cm tumor in the left palatine tonsil extending to the soft palate and tongue. Signal intensity see below. ^a Metastatic lymphadenopathy present
	Hypopharynx	SCC, well- differentiated	NPC T2N3M0. Dysphagia and hoarse voice 9 years after RT	4.5×2.0 cm tumor in the hypopharynx centered in the right pyriform sinus with glottic spread and invasion of the thyroid lamina and strap muscles. Signal intensity see below ^a
External auditory canal	External auditory canal	SCC, moderately differentiated	NPC stage N/A. Bloody otorrhoea and mass in the right external auditory canal 30 years after RT	2.7×1.5 cm tumor filling and confined to the right external auditory canal with early erosion of the bony walls. Signal intensity see below ^a
	External audito- ry canal	SCC, moderately differentiated	NPC T4N0M0. Discharge, pain, and reduced hearing in the left ear 10 years after RT	4.0×3.0 cm tumor filling the medial aspect of the left external auditory canal, middle and inner ear, Eustachian tube with extensive bone destruction of the petrous temporal bone and

invasion into the middle cranial fossa, parapharyngeal region, and parotid gland. Signal intensity see below^a

Table 1 (continued)				
Region	Site (epicenter)	Histology	Clinical details	MRI features
	External audito- ry canal	SCC, high grade	NPC stage N/A. Ulcerating mass of the left ear 30 years after RT	8.5×7.5 cm tumor in the pinna, left external auditory canal, middle and inner ear, and Eustachian tube with bony destruction of the petrous tem- poral bone and invasion into the middle cranial fossa and temporal lobe and parotid gland. Signal intensity mildly heterogeneous inter- mediate T2, homogeneous low/ intermediate T1 with very heteroge- neous contrast enhancement
	External audito- ry canal	SCC, high grade	NPC stage N/A. Fungating mass and hearing impair- ment in the right ear 14 years after RT	3.5×1.5 cm tumor in the external auditory canal and middle ear. Signal intensity see below ^a
Nasopharynx and sphenoid sinus	Sphenoid sinus/ roof of naso- pharynx	Spindle cell sarcoma	NPC T3N0M0. Mass in the nasopharynx 9 years after RT	2.5×2 cm sphenoid sinus tumor extending into the roof and along the posterior wall of the nasopharynx, clivus. Signal intensity homogeneous low/intermediate T1, heterogeneous mixed T2 and heterogeneous enhancement
	Nasopharynx/ skull base	High-grade undiffer- entiated sarcoma	NPC stage N/A. Numbness in the R V2 region 18 years after RT	4.3 cm×2.6 cm enhancing soft tissue mass in the right lateral NP wall with extension to right skull base, orbital fissures and apex, right cavernous sinus with leptomeningeal enhance- ment. Signal intensity mildly heterogeneous intermediate T2, homogeneous intermediate T1 with mild homogeneous enhancement
Brain	Anterior cranial fossa	Meningioma	NPC stage N/A. Additional finding on MRI for SCC of the right external auditory canal 30 years after RT (patient listed above)	2.0×1.5 cm heavily calcified tumor in the midline of the floor of the anterior cranial fossa with nonag- gressive features that remained un- changed in size over 7 years

RT Radiotherapy, NPC nasopharyngeal carcinoma

^aSignal intensity of SCC was homogeneous low/intermediate T1 and intermediate T2, and homogeneous moderate contrast enhancement

were first reported by Teo et al. [5], since which time there have been several other reports showing the tongue to be at risk after treatment for NPC [9, 10]. Two patients in this study had SCC in the pharynx, one involving the palatine tonsil and the other the pyriform fossa in the hypopharynx. These are common sites for SCC in the general population, and it is possible that they were not directly related to RT, one patient having a history of alcohol abuse and smoking, which can predispose to these cancers. On the other hand, the association with radiation is supported by an analysis of cancer registries by Scélo et al. [10], which showed that patients with the undifferentiated form of NPC have an increased risk of carcinoma in the upper aerodigestive tract (excluding the tongue) after RT.

The external auditory canal lies in the low radiation zone of treatment for NPC. All RITs there were SCC, which together with the four cases from a series by Goh et al. [15], suggest that this is the most common histological type of tumor to arise at this site, although there have been a few case reports of radiation-induced sarcomas [6, 11, 15] in the region of the temporal bone. Interestingly most SCC of the external auditory canal arose many years after RT, with a range of 10–30 years and a mean of 21, which is similar to the results of Goh et al. [15]. The prognosis for patients



Fig. 1 Radiation-induced SCC 21 years after radiotherapy. Axial T1-weighted post-contrast image of a large radiation-induced SCC in the maxillary sinus, palate, and alveolar process of the maxilla (*arrows*)

with nonradiation-induced SCC of the external auditory canal is excellent (5-year survival of 100%) when the tumor is limited to the canal and can be completely resected [16]. One patient in this series underwent successful surgical resection to remove a small tumor that was localized to the external auditory canal. The prognosis drops significantly to around 40% once there is infiltration beyond the temporal bone [16]. In these cases it may not be possible to distinguish if they are arising in the external auditory canal or in the temporal bone. This appears to be the category in which most patients with radiation-induced SCC fall.

In this series, two patients had large RIT that had spread superficially to involve regions such as the pinna of the ear and parotid gland, and deeply to destroy the petrous temporal bone and invade the parapharyngeal region and cranium (Fig. 6), while the tumors in the series by Goh et al. [15] also were advanced at diagnosis, leading to a poor prognosis. This highlights the importance of inspecting the external auditory canal in all patients who undergo followup MRI after treatment for NPC, in order to try to detect the RIT in the early stages. The nasopharynx and sphenoid sinus receive the full dose of radiation but surprisingly, with the exception of the brain, this was the least frequent region to develop an RIT. Finally the mandible has been cited as a common site for RIT, especially sarcomas [8, 9], but no cases were recorded in this study.

When RITs are considered from the histological perspective, there were two main forms of cancer, carcinoma and sarcoma. Overall the carcinomas, particularly SCC, were the most common cancer, an observation that has been made previously [7]. Carcinomas arising in the

mucosal linings are thought to be related to regions that receive lower doses of radiation. A study by Hall et al. [17] highlighted the concern that the shift towards conformal RT, such as IMRT, will lead to larger volumes of normal tissue being exposed to lower doses, which may in turn lead to a higher incidence of radiation-induced SCC in patients treated for NPC in the future. In this series, SCC arose in low-radiation-dose regions, such as the external auditory canal, but also in the high-radiation-dose regions, such as the maxilla and tongue base. The SCCs in the lowdose regions developed much later than either the SCCs or sarcomas in the high-dose regions.

From the radiology perspective, the MRI features of radiation-induced SCC were no different from the nonradiation-induced SCC or recurrent NPC. Most of these cancers were fairly homogeneous tumors of low/ intermediate T1 and intermediate T2 signal with moderate homogeneous enhancement (Fig. 1). The distinction between recurrent NPC and radiation-induced SCC therefore relied on location. Recurrent NPC usually arises in or around the margin of the original tumor, while the radiation-induced SCC in this series arose peripheral to the sites of primary tumor recurrence.

Radiation-induced sarcomas of this region were less common than carcinomas. Radiation-induced sarcomas



Fig. 2 Radiation-induced neuroendocrine carcinoma 23 years after radiotherapy. Coronal T1-weighted post-contrast image of a large tumor in the maxillary sinus invading the nasal cavity, palate, and alveolar process of the maxilla (*arrows*). The right-sided submental node was reactive in nature



Fig. 3 Radiation-induced undifferentiated sarcoma 10 years after radiotherapy. Axial T1-weighted post-contrast image of a heterogeneous sarcoma in the maxillary sinus that extended into the nasal cavity, nasopharynx, and parapharyngeal region (*arrows*)

tend to arise in the high-radiation-dose region, and it is known that a total dose of 55 Gy or above increases their risk [18]. Patients undergoing a full course of RT for NPC received a dose equivalent to about 66 Gy or more, and most sarcomas in this series arose in the maxillary region, the middle and posterior part of which received this full radiation dose. The development of sarcomas after radia-

tion exposure for both benign and malignant conditions is well established in the head and neck with a reported latency period from a few months to 65 years [19, 20]. For those arising after treatment for NPC, the reported range is 6-27 years with a mean of 13 years [8], although in this series they arose after 4-18 years. In this study most sarcomas were large with extensive local invasion at the time of MRI. This is partly because they were very aggressive tumors that often grew rapidly as illustrated by the case of the recurrent nasal osteosarcoma that grew rapidly over a month (Fig. 4a-c) and the spindle cell sarcoma in the maxillary sinus that grew rapidly over 6 months despite treatment. The large size, extensive local invasion with bony destruction, and the predilection for the maxillary region were the main clues to the diagnosis. The signal characteristics of sarcomas were variable reflecting the wide range of histological subtypes, but when they were compared to radiation-induced carcinomas and recurrent NPC, they were often more heterogeneous with more contrast enhancement (Fig. 3) and solid areas of high T2 signal intensity (Fig. 4b).

One other potential difficulty for differential diagnosis was the distinction of a radiation-induced sarcoma from nonmalignant polyps and masses, especially those in the sphenoid sinus [21]. The prognosis for RIT of the head and neck is poor. Complete surgical resection provides the only chance of a cure, but most tumors are not resectable because of their deep-seated location and advanced stage at the time of diagnosis. The recurrence rate is usually high, and residual tumors do not respond well to RT and chemotherapy.



Fig. 4a–c Radiation-induced osteogenic sarcoma 7 years after radiotherapy. a Coronal T2-weighted image 3 months after resection of the osteogenic sarcoma in the left nasal cavity. b Coronal T2-weighted image 1 month later showing rapid regrowth of the

sarcoma, which is of high T2 signal (*arrows*). **c** Axial T1-weighted image showing marked contrast enhancement in the recurrent sarcoma (*arrows*)

1204



Fig. 5 Radiation-induced squamous cell carcinoma 6 years after radiotherapy. Axial T1-weighted post-contrast image showing an SCC in the left side of the tongue base (*arrow*)

The other histological types of RIT in this series were less common. Two patients developed neuroendocrine carcinomas in the nasal cavity and maxillary sinus, 6 and 23 years after RT, respectively. To the authors' knowledge, these are the first two reported cases of a head and neck neuroendocrine carcinoma in patients irradiated for NPC, although one gastric neuroendocrine tumor has been reported [7]. An extensive literature search also revealed a lone report of a neuroendocrine carcinoma that developed in the thymus of a patient 16 years after local irradiation in infancy [22].

A mucoepidermoid carcinoma arose in the minor salivary tissue of the palate in one patient. The association between radiation and development of mucoepidermoid

carcinoma has already been established. It was initially suspected by Rice et al. [23], who reported 23 mucoepidermoid carcinomas in the salivary glands after radiation exposure, and the incidence was also found to be high in survivors of the atomic bomb [24]. Since then there have been several case series of mucoepidermoid carcinoma arising after radiation exposure including eight by Modan et al. [25], nine by Stites et al. [26] after irradiation for childhood cancer, and nine by Beal et al. [27] of which two patients had received RT for NPC. Meningiomas are well known complications of cranial irradiation [28] but are rarely reported in NPC with only two other reported cases of meningiomas in the literature [9]. This is rather surprising given that the inferomedial temporal lobe is included in the radiation field and is itself a common site of radiation injury.

A few limitations are identified in this study. Firstly, the prevalence was not provided as our data do not reflect the true number of RITs in post-RT NPC patients. This is because some patients undergo MRI examinations in other institutions while some at our institution undergo CT scan examination. Secondly, it is acknowledged that some of the carcinomas may have been second primary tumors rather than radiation-induced tumors although our arguments for believing they are related to radiation have been discussed. Thirdly, this study focused on the imaging aspects of RITs and did not attempt to document the treatment regimes or clinical outcome.

In conclusion, the radiologist should be aware of the common sites of RIT so that these sites can be scrutinized on follow-up scans, and be aware of their radiological appearance so they are not confused with a recurrent NPC. SCC and sarcomas were the two most common forms of RIT. They both had a predilection for arising in the high-dose maxillary region (alveolar process of the maxilla, maxillary sinus, palate, and nasal cavity), and in addition SCC arose more frequently in the high-dose region of the tongue and the low-dose region of the external auditory canal. SCC often had a similar homogeneous appearance to recurrent NPC and so the differential diagnosis was

Fig. 6a, b Radiation-induced SCC of the external auditory canal 10 years after radiotherapy. a Coronal T1-weighted image post-contrast showing a large radiation-induced squamous cell carcinoma involving the left external auditory canal (*arrows*). b Axial T1-weighted image post-contrast showing the tumor invading the petrous temporal bone and parapharyngeal region (*arrows*)



dependent on location, being away from the site of the original NPC. Sarcomas tended to be more heterogeneous with more variable signal intensity, including high T2 signal intensity and marked contrast enhancement when compared to recurrent NPC. RIT often presented late, especially the SCC in the ear, while the sarcomas resulted in a poor prognosis.

In an attempt to improve early detection of RIT, the check areas on MRI should always include the maxillary

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