



Surveillance tools for detection of recurrent nasopharyngeal carcinoma: An evidence-based review and recommendations

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Abstract

Objective: Nasopharyngeal carcinomas (NPC) are tumors arising from epithelium of the nasopharynx. The 5-year survival rate of primary NPC is 80% with significant risks of recurrence. The objective here is to provide an evidence-based systemic review of the diagnostic value of different modalities in detecting local, regional, and distal recurrent NPC, as well as the associated costs with these modalities.

Methods: MEDLINE, EMBASE, and the Cochrane review database were queried. Two hundred and twenty-three abstracts were generated using the inclusion criteria: patients >18 years of age; histopathological reference standard; and modalities pertaining to imaging or microbiology.

Results: Twenty-four manuscripts fulfilled the inclusion criteria and 5 surveillance tools identified: endoscopy, MR, FDG-PET, Tc-99m MIBI and ²⁰¹Tl SPECT, and EBV DNA.

Conclusions: For local surveillance, endoscopy is the gold standard recommendation, with increased efficacy if Narrow Band Imaging or contact endoscopy are utilized. MRI and FDG-PET is also recommended to help with local to distal spread; however, Tc-99m MIBI and ²⁰¹Tl SPECT are options as well. EBV DNA is recommended as a cheap and accessible adjunct surveillance tool if an available as an option.

KEYWORDS

EBV DNA, FDG-PET Imaging, MR, Endoscopy, Recurrent Nasopharyngeal Carcinoma

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is the umbrella term for a group of tumors arising from the epithelium of the nasopharynx. Approximately 86 000 new cases of NPC are diagnosed per year globally,¹ but the incidence of NPC follows a distinct geographic distribution, with 25–50 per 100 000 of population reported in Southeast Asia, North Africa, and part of the Mediterranean basin.² Additionally, a

greater risk of NPC carries over with migration to non-endemic regions.³ While there is a decreased risk of incidence in these migrant populations, their risk is still 10–30 times greater than their counterparts of other races (1 per 100 000).^{3–5}

The 5-year survival rate of primary NPC is 80%, however there is a significant risk of recurrence in 15%–85% of patients.^{6,7} The majority of recurrences will occur within 3 years of initial treatment (52% within 2 years, 39% from 2 to 5 years).⁷ The

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5-year survival for locoregional recurrence is about 41%. A North American based study found 3-year overall survival (OS) for locoregionally recurrent NPC treated with IMRT was 49%, with 37% of patients experiencing late toxicities.⁸ A China based study found similar rates of OS (46%) but with higher rates of late toxicities (53%).⁹ Loco-regionally recurrent disease can be treated in a variety of modalities including re-irradiation with or without chemotherapy or surgical resection or a combination thereof. Currently, there is a lack of level I evidence-based management of recurrent disease; nevertheless, early detection and treatment are well known to correlate with improved disease control and overall survival.^{2,10} However, an accurate modality and timing of surveillance techniques to capture recurrent NPC (rNPC) remains controversial. There is a lack of consistency between facilities in endemic and non-endemic regions, as well as in between clinical practice guidelines (CPGs) for NPC follow-up.^{11,12} The objective of this review is to provide an evidence-based approach for the diagnostic value of different modalities in detecting local, regional, and distant rNPC. Based on the level of evidence and evaluation of benefit to harm, recommendations for surveillance techniques to monitor rNPC are provided.

METHODS

This article was written in an online iterative process for evidence-based systematic reviews following the protocol outlined by Rudmik and Smith.¹³ A systematic review of the literature on the surveillance of recurrent NPC was performed using MEDLINE, EMBASE, and the Cochrane Review Database up to January 2nd, 2020. The keywords used in the search included: "recurrent nasopharyngeal carcinoma", "MR", "PET-CT", "CT", "EBV serology", "EBV DNA", and "HPV" up to January 2nd, 2020. A total of 223 abstracts were reviewed and 5 surveillance tools were identified in the diagnosis of recurrent NPC (Table 1).

Two reviewers (A.X.Y and K.H.T) independently reviewed all eligible studies following the inclusion criteria: patients > 18 years old; reference standard with histopathology; and modalities pertaining to imaging or microbiology. Studies in contention were resolved by a third reviewer (B.J) independently and the majority opinion was used for further analysis. After applying these filters, 24 studies were included in this review: 3 on endoscopy, 5 on magnetic resonance

imaging (MR), 5 on Fluorodeoxyglucose Positron Emission Tomography (FDG-PET), 6 on Tc-99m MIBI and ²⁰¹Tl single photon emission computerized tomography (SPECT), and 5 on Epstein-Barr virus (EBV) DNA.

Each article deemed to fulfill the inclusion criteria were reviewed and summarized. Articles are assigned a level of evidence and recommendation as per the strategy outlined by the American Academy of Pediatrics Steering Committee on Quality Improvement and Management (Table 1).¹⁴

RESULTS

Endoscopy

Traditional diagnostic approaches in primary NPC involve nasopharyngeal endoscopy confirmed with a definitive biopsy of the primary tumor site.¹⁵ However, assessment of the nasopharyngeal space for recurrent disease may be confounded by post-radiation changes or obstructed by secretions and crusting. Improvements to the flexible nasopharyngoscopy have been developed such as narrow-band imaging (NBI), a novel optical technique that enhances the image of capillary vessels on the surface mucosa.¹⁶ In this review, three studies evaluating the effectiveness of enhanced endoscopy methods such as NBI and contact endoscopy were identified.¹⁷⁻¹⁹

Flexible endoscopes allow for the visualization of the texture, color, and the extent of mucosal lesions; however unlike contact endoscopy they lack the ability to provide histopathological data during clinical examination.¹⁸ Contact endoscopy for the detection of primary NPC tumors has been verified previously and allows in vivo differentiation of normal and malignant cells of the nasopharynx by using in vivo microscopy that allow the evaluation of superficial cell layers of the epithelium.²⁰ Pak and colleagues were able to verify that this technique also extends to the surveillance of rNPC in patients treated with radiation for NPC.¹⁷ They reported a specificity and sensitivity of 100% in the detection of rNPC using contact endoscopy with a diagnostic accuracy of 92.1%. It should be noted, however, that only 5/64 patients enrolled in the study had recurrence and thus the sample size for verification of this technique is rather small. The authors recommended that contact endoscopy should be added as an intermediate procedure between nasal endoscopy and biopsy for patients with suspicious or normal nasal endoscopy results, to limit the need for more invasive biopsy and more accurate surveillance of rNPC.

In a case report presented by Lin and colleagues, they validated the effectiveness of NBI in rNPC surveillance for a 51-year old NPC patient treated with radiation.¹⁸ NBI was able to accurately detect recurrence at an earlier stage compared to nasal endoscopy when the patient did not present with clinical symptoms. Follow-up with MR imaging confirmed local rNPC and prompt treatment was initiated for the patient. The authors suggest that NBI may serve as the ideal surveillance tool in the early months post-radiation after NPC treatment as it uniquely

TABLE 1 Surveillance tools to diagnose recurrent nasopharyngeal carcinoma

Endoscopy
MRI
FDG-PET Imaging
Tc-99m MIBI and ²⁰¹ Tl SPECT
EBV DNA

detects lesion areas that are not visually apparent on nasal endoscopy alone. The authors themselves did not define what constituted the 'early post-radiation period' in this study. However, several other papers share the consensus that this period ranges up to 4 to 6 months post-treatment.²¹⁻²⁴ Wang and colleagues verified the effectiveness of NBI in monitoring rNPC in a case study of 106 patients with NPC, although the rate of false positives was quite high (25/106) using NBI.¹⁹ Thus, Wang and colleagues suggested a modified NBI technique coined NBI closer view where areas suspicious on NBI were followed with further endoscopic closer view. Using this modified technique, the authors reported a sensitivity, specificity, and accuracy of 87.5%, 87.8%, and 87.7%, respectively, and conclude that NBI closer view had lower rates of false positives due to inflammation, necrosis, or non-neoplastic brownish spots mistaken for recurrence.

Overall, while modified endoscopy techniques prove to be cost-effective and may aid in earlier detection of tumor recurrence in NPC, validation of NBI and contact endoscopy warrant multi-centre, randomized controlled trials to determine its efficacy. Furthermore, this technique is limited to evaluating nasopharyngeal mucosa alone, and not the parapharyngeal, or cervical node for recurrence (see Table 2A for summary of endoscopy review; see Table 2B for summary of endoscopy manuscripts).

- (1) Detection of local recurrence: We recommend using endoscopy for detecting recurrent/residual NPC at the local site. Clinician should be aware of submucosal rNPC and other modalities should be employed to detect rNPC. Limitation of detecting exophytic recurrences can be hampered by post-radiation fibrosis and mucositis.²¹
- (2) Detection of regional recurrence: Not recommended. Recurrent NPC can spread submucosal and into the parapharyngeal space or other submucosal pockets of the head and neck where endoscopy cannot assess.
- (3) Detection of distant recurrence: Not recommended.
- (4) Cost: Endoscopy is the cheapest diagnostic tool for detecting regionally recurrent/residual NPC as it only costs approximately \$80 USD.²⁵ However, it has a higher chance of yielding false

negatives, so we recommend utilizing it with other imaging modalities.

MR

In the background of post-radiation changes to the skull and submucosa after treatment, it has been argued that magnetic resonance imaging (MR) should be favored over conventional CT imaging because MRI has higher sensitivity for soft tissue structures. Indeed, in a prospective case series study performed by King and colleagues, the authors demonstrated that the specificity of MRI was equivalent to endoscopy with superior sensitivity in detecting primary NPC.²⁶ With respect to rNPC, five studies comparing the specificity, sensitivity, and accuracy of MRI to conventional imaging methods were identified.²⁷⁻³¹

In a case study performed by Gong and colleagues, 88 participants diagnosed with NPC were classified into either the control ($n = 16$) group if they had not yet received radiotherapy, or patient ($n = 72$) group if they had undergone radiotherapy.³⁰ The researchers then scanned each participant using both CT and MR imaging and characterized the signal intensity patterns of the MR images in patients with rNPC ($n = 29$). They concluded that MR images demonstrating signal intensity in T2, weighted, spin-echo pulse sequences were most accurate in distinguishing rNPC from fibrosis or primary NPC.³⁰ One drawback to the study is that it is fairly descriptive and qualitative in nature with no numerical data depicting accuracy rates or sensitivity and specificity values to compare and quantify the imaging modalities. In a 2013 case study, Lin and colleagues took a similar approach and used MR imaging in 108 patients to evaluate post-radiation changes 1, 3, and 6 months after treatment.²⁸ The authors also concluded that residual tumor shows enhanced signal intensity on T2-weighted images and the appearance of tumor after radiotherapy correlated with rNPC up to five years following treatment.

Two case studies by Comoretto et al.²⁹ and Ng et al.³¹ both compared the effectiveness of MR vs FDG-PET imaging to identify rNPC. Comoretto and colleagues retrospectively examined 63 patients

TABLE 2A Summary of endoscopy

Aggregate quality evidence	D (Level 4: 2 studies; Level 5: 1 study)
Benefit	Timely, convenient office based procedure. NBI and contact endoscopy adjunct allow for reliable detection of persistent or recurrent NPC even in normal-appearing nasopharynx. Utility for guiding site of biopsy at suspicious area.
Harm	Hindered by post-radiation changes. Reach is limited to accessible regions and visualization does not extend well beyond superficial mucosa.
Cost	Low cost (~\$80 USD) as standard equipment in Otolaryngologist office but associated moderate costs if adjunct endoscopy used.
Benefits-harm assessment	Preponderance of benefit over harm.
Recommendation level	Recommended - for detection of local recurrence.
Intervention	Perform endoscopy for detection of superficial tumours during routine clinical evaluations.

TABLE 2B Endoscopy

Study authors	Year	Study design	Subjects (n)	Study groups	Diagnostic protocol	Follow-up period after treatment	Reference standard	Results/Conclusion
Pak et al. ¹⁷	2002	Case Series	64	Patients diagnosed with NPC and treated with chemoradiation	Contact endoscopy was performed by staining the surface of the normal nasopharynx and nasopharyngeal tumors using 1% methylene blue. Contact endoscopic images were then compared to their corresponding H&E stained histological sections of the biopsied tissue.	7 weeks	Histopathologic results	Four patterns of contact endoscopic findings were identified: squamous metaplasia (n = 43), postirradiation atypia (n = 10), granulation tissue (n = 6), and malignancy (n = 5). Prediction of persistent and recurrent disease using contact endoscopy was 100% sensitive and specific.
Lin et al. ¹⁸	2011	Case report	1	Patient diagnosed with undifferentiated NPC treated with IMRT	Narrow-band imaging coupled endoscopy which uses a blue filter to enhance the image of capillary vessels on the surface mucosa	6 months	Histopathologic results	Narrow-band imaging coupled with conventional endoscopy successfully detected early rNPC before clinical symptoms emerged or MRI findings. Narrow-band imaging may serve as an ideal surveillance tool after treatment for NPC.
Wang et al. ¹⁹	2012	Case series	106	Patients diagnosed with primary NPC who had completed NPC treatment	Endoscopic examination of the nasopharynx using conventional white-light endoscopy followed by re-examination using a narrow-band imaging (NBI) system capturing one narrow band image and one closer view image.	36 months	Histopathologic results	NBI outperformed WL endoscopy in both sensitivity and specificity for rNPC diagnosis, with NBI closer view yielding the highest sensitivity (87.5% vs 37.5%) over WL alone. However, NBI is prone to false positives with a moderate specificity rate (87.8% vs 92.9% for WL). NBI can offer a timely and convenient assessment of mucosal rNPC.

who were deemed high risk of residual disease for recurrence or restaging.²⁹ They reported the MR outperformed FDG-PET at detecting residual or recurrent NPC at the primary site ($P = 0.16$, accuracy = 92.1% for MR vs 85.7% for FDG-PET) but was inferior compared to FDG-PET at detecting rNPC in patients in regional lymph nodes. The authors attributed the limited use of the field of view and distant metastases to the inferiority of MRI at distant sites, suggesting that expansion of the MR scan to include supraclavicular lymph nodes may aid with detection of distant rNPC in MR imaging.²⁹ Using whole body MR imaging in 179 patients at high risk of residual or rNPC, Ng and colleagues found that MRI was similar to FDG-PET at detecting local rNPC (96.8% and 96.1% specificity for MRI and FDG-PET, respectively).³¹ In contrast, whole body MR was superior to FDG-PET in detecting distant rNPC (99.7% and 97.5% specificity, respectively). Since specificity was comparable between the two imaging modalities, the authors concluded that whole body MR and FDG-PET complement each other across different body sites. Whole body MRI is preferred over FDG-PET for brain and splenic metastases, intracranial invasion, and necrotic adenopathy.³¹ Ng and colleagues could not recommend the routine use of either modality for routine detection of rNPC due to lack of cost effectiveness evaluation.

In a study by Huang et al.²⁷ the authors noted the value of dynamic contrast enhanced T1W perfusion MR imaging in the detection of local head and neck primary tumors. However, patients with a history of iodine allergy would not be suitable for intravenous uptake of the contrast agent. Using 27 patients diagnosed with rNPC and 35 patients treated for NPC with tumor free post-chemoradiation fibrosis, the authors compared the diagnostic value of diffusion weighted MR imaging based on turbo spin-echo (TSE) and echo-planar (EP) imaging techniques. The latter is prone to distortion and susceptibility artifacts especially in areas of the head and neck, including the nasopharynx. Huang et al. found that TSE-DWI showed superior image quality and greater diagnostic accuracy for rNPC compared to conventional EP-DWI. TSE-DWI was able to efficiently differentiate between rNPC and post-chemoradiation changes (area under curve of 0.932).

MRI has proven efficacy in the surveillance of rNPC, particularly in the early follow-up period where anatomical changes due to radiation therapy may confound more conventional techniques such as CT imaging. However, this technique demonstrates limitations in detecting recurrence at distant sites due to its limited image acquisition in the head and neck region. In instances where distant recurrence is suspected, whole body MRI may be beneficial although such techniques may be limited due to cost or resource availability (see Table 3A for summary of MR review; Table 3B for summary of MRI manuscripts).

- (1) Detection of local recurrence: MR is recommended in detecting local recurrence. There are some recognized limitations such as fibrosis, inflammation, and treatment-related edema that can alter the shape of the nasopharyngeal mucosal outline, which might be interpreted by MR as recurring/residual NPC even though they are harmless,³² but it is much more superior than endoscopy in assessing the submucosal spread of rNPC in the local and regional area.
- (2) Detection of regional recurrence: Recommended to detect for regional recurrence. Only one study was found that compared the diagnostic value of whole body MRI (WB-MRI) and FDG-PET-CT in identifying recurrent/residual NPC at a regional site.³¹ 14% of the patients in this study had regional nodal metastases (25 out of 179 patients) and the authors observed that WB-MRI and FDG-PET-CT were equally effective in detecting regional cancerous nodes (96.8% and 96.1% specificity, respectively).³¹ Combined interpretation of both modalities had a sensitivity of up to 96%. Since WB-MRI has been suggested to be a more cost-efficient and time-efficient alternative to conventional imaging modalities such as CT and PET, we recommend the use of MRI in monitoring rNPC at regional sites because its diagnostic accuracy is as equally effective as FDG-PET-CT whilst allowing healthcare costs to be reduced.³³ When an MR is ordered, it should include the nasopharynx and the neck.
- (3) Detection of distant recurrence: Ng and colleagues observed that WB-MR is the most accurate in detecting bone marrow and brain

TABLE 3A Summary of magnetic resonance imaging (MR)

Aggregate quality evidence	C (Level 3b: 2 studies; Level 4: 3 studies)
Benefit	High sensitivity to soft tissue structures. Ability to distinguish rNPC from fibrosis. Proven efficacy in detection of residual NPC in early post-radiation period. Utility in detection of rNPC at primary site and distant sites including lymph nodes.
Harm	Limited accessibility. High false positive and false negative rate earlier than 1-month post-radiation treatment. Risk of allergy to contrast agents.
Cost	Equipment, imaging, and associated costs very high (\$165–2 048 USD).
Benefits-harm assessment	Preponderance of benefit over harm.
Recommendation level	Recommended – for detection of local and regional recurrence. WB-MRI is recommended for detection of distance recurrence.
Intervention	Perform MR multiple times through surveillance period as it detects submucosal recurrence not detected by standard endoscopy.

TABLE 3B Magnetic resonance imaging (MRI)

Study authors	Year	Study design	Subjects (n)	Study groups	Diagnostic protocol	Follow-up period after treatment	Reference standard	Results/Conclusion
Gong et al. ³⁰	1991	Case-control	88	72 patients diagnosed with NPC and treated with radiotherapy; 16 patients diagnosed with NPC before radiation treatment as control.	MR was performed with TOMIKON BMT 1100 operating at 0.282 T	13 months	Radiologic diagnosis using CT of having soft-tissue mass in the nasopharynx	MRI was superior to CT for assessment of local rNPC as differentiation between fibrosis and tumour tissue could be differentiated in the majority of cases using signal intensity differences.
Comoretto et al. ²⁹	2008	Retrospective case series	63	Patients treated with combined chemotherapy + radiation therapy for nonkeratinizing, undifferentiated or poorly differentiated NPC: stage III (n = 25); stage IV (n = 21)	1.5 T MRI (Signa, GE Medical Systems, Milwaukee, WI)	2-14 months	Histopathologic results or radiologic follow up	MR had overall accuracy of 92.1% in depicting residual and/or rNPC at primary site and 90.5% at regional lymph nodes
Ng et al. ³¹	2010	Case series	179	Patients diagnosed with NPC at high risk of residual disease or with suspected recurrence	Whole body MRI performed using a 3 T MRI scanner (MAGNETOM Trio with Tim, Siemens Medical Solutions, Germany) as well as a dedicated MR of the head and neck region obtained in axial projection.	3.1-56.1 (average of 14.2) months	Histopathologic results	The sensitivity, specificity and diagnostic capability of whole body MR was 90.9%, 91.1%, and 0.929, respectively. Residual/rNPC was detected in 46/55 patients by whole body MRI. 3 T whole-body MRI provides a feasible comprehensive imaging technique for evaluation of residual/rNPC, and when compared to FDG-PET-CT offered similar diagnostic capability.
Lin et al. ²⁸	2013	Retrospective case series	108	Patients diagnosed with NPC who underwent radiotherapy	MRI scans were obtained using a 1.5 T MRI scanner (Gyrosan Interna, Philips, Netherlands)	12-96 months	Histopathologic diagnosis	MRI was useful in detection of residual tumour 1- and 3-months post radiotherapy treatment and correlated with tumour recurrence in year 2 and 3 following treatment. MRI is useful in the progressive management of NPC patients post-treatment and should patients should be periodically monitored using MRI in the first 5 years following treatment.

TABLE 3B (Continued)

Study authors	Year	Study design	Subjects (n)	Study groups	Diagnostic protocol	Follow-up period after treatment	Reference standard	Results/Conclusion
Huang et al. ²⁷	2019	Case-control	62	Patients diagnosed with recurrent NPC (n = 27); post-chemoradiation fibrosis group treated for NPC but remained disease free throughout study.	MRI performed on T3 imager and a 20-channel neuromuscular transceiver coil. Head and neck protocol included axial and sagittal T1W imaging, axial and oblique coronal T2W imaging, and axial and oblique coronal T1W imaging after contrast injection.	12 months	Histopathology	TSE-DWI showed superior image quality and greater diagnostic accuracy for recurrent NPC compared to conventional EP-DWI. Comparison between recurrent NPC group and post-chemoradiation fibrosis group showed area under curve higher in TSE (0.932) than EPI (0.835).

metastases whereas FDG-PET-CT (another imaging modality that has a similar diagnostic accuracy as WB-MR) is more effective in detecting bowel or peritoneal malignant lesions, distant nodal metastases or lung metastasis.³¹ The authors further noted that when WB-MR is used in conjunction with FDG-PET-CT, they have a combined sensitivity of up to 94.5%.³¹ Thus, we recommend either the use of WB-MRI or FDG-PET-CT for better assessment of distal rNPC. Combination is superior but may not be cost-effective.

- (4) Cost: Using data from 171 hospitals in Florida, United States, Siström and McKay discovered that the average cost per scan for MRI can range from \$165–2048 USD, making it one of the most expensive surveillance tools for detecting rNPC.²⁵

FDG-PET

Radiation therapy is a mainstay component of NPC due to anatomical constraints and the high radiosensitivity of NPC.³⁴ However, long-term post-radiation changes are often observed such as crusting, mucositis, or varying degrees of trismus,³⁵ which compromise results using conventional techniques such as flexible endoscopy or CT imaging. Fluorodeoxyglucose positron emission tomography (FDG-PET) bypasses traditional imaging techniques by identifying head-and-neck malignancy through regions of increased glucose metabolism. FDG-PET has been shown to be sensitive and specific at detecting residual or recurrent tumors from post-radiation changes.^{36,37} In this review, 5 studies evaluating the effectiveness of FDG-PET were identified.^{21,23,24,29,38}

The mainstay imaging modality for identifying mucosal recurrence has traditionally been MRI but arguments have been made for the effectiveness of FDG-PET, particularly in patients with indeterminate MRI findings. In case series by Tsai et al.²⁴ and Ng et al.,²³ patients who underwent radiotherapy and subsequently had non-conclusive MRI findings 4 months after completion of therapy were re-scanned using FDG-PET. Half of the patients (n = 14) enrolled in Tsai et al.'s study presented with recurrence, all which were accurately identified using FDG-PET, with only one false positive finding. Ng et al. enrolled 37 patients and while FDG-PET correctly identified 17/19 patients with residual or recurrent NPC, the rates of false-positives (8) and false-negatives (2) were higher, yielding an overall specificity of 89.5% and sensitivity of 55.6%.

Al-Amro et al.³⁸ compared the accuracy of FDG-PET to conventional CT imaging and found that FDG-PET was superior to CT with respect to specificity and sensitivity of rNPC detection at both primary and nodal sites. Similarly, Comoretto and colleagues²⁹ directly compared rNPC detection using both MRI and FDG-PET and concluded that FDG-PET had higher sensitivity and specificity at regional lymph nodes and distant metastases whereas MRI fared better at the primary site. The authors also found that combining imaging results from both MRI and FDG-PET was more accurate than each modality independently. In line with these results, Chan et al.²¹

reported similar findings such that FDG-PET was superior to MRI at detecting tumor recurrence in patients with initial T4 disease but not early stage (T1-T2) disease. Authors from the Tsai et al., Ng et al., and Chan et al. studies noted that the accumulation of FDG in inflammatory tissue may have led to the false positive readings in recently irradiated patients.^{21,23,24} Almost all (6/8) false positive cases from the Chan et al. study showed regression on follow-up imaging 3 months after the initial false positive finding, indicating the less pronounced influence of post-irradiation inflammation on imaging studies over time.²¹ For this reason, the authors highlighted that FDG-PET may not be a suitable surveillance tool during the early post-radiation period (~4–6 months).

Overall, FDG-PET is superior to CT imaging in detection of rNPC but may be comparable to surveillance results yielded using MR imaging techniques. FDG-PET yields the best diagnostic accuracy when combined with MR imaging in NPC patients and may be warranted as a combined approach rather than stand-alone modality in the surveillance of rNPC (see Table 4A for summary of FDG-PET review; Table 4B for summary of FDG-PET manuscripts).

- (1) Detection of local recurrence: We recommend the use of ¹⁸F-FDG PET in conjunction with MRI to better localize the recurrent tumor because both modalities have similar diagnostic accuracies and can mutually complement one another.^{29,31} Unlike CT and MR, ¹⁸F-FDG PET does not detect cancerous tissues based on morphological changes.
- (2) Detection of regional recurrence: We recommend the use of either FDG-PET-CT or MRI of the nasopharynx/neck whenever possible for detecting regional rNPC. As described above, the information from both modalities will provide the clinician better understanding whether there is recurrence but MRI does provide additional morphological information to determine if salvage surgery is achievable.
- (3) Detection of distant recurrence: We recommend either the use of WB-MR or FDG-PET-CT for better assessment of distal rNPC. Combination is superior but may not be cost-effective.³¹
- (4) Cost: Based on data from 8 American health institutions, Berger and colleagues state that the average cost per scan for FDG-PET is \$1885–1898 USD, similar to the price of an MR scan.³⁹

Tc-99m MIBI and ²⁰¹Tl SPECT

Nuclear medicine techniques such as FDG-PET have shown to be highly sensitive and specific at distinguishing residual or recurrent NPC from post-radiation changes, but are relatively costly, have lower resolution, and have limited availability. The consideration of SPECT imaging using either Tc-99m MIBI or ²⁰¹Tl has been debated in the literature as alternatives or adjuncts to conventional endoscopy or imaging methods such as FDG-PET or MRI where conventional methods may fail due to post-radiation changes in the nasopharyngeal area. In this review, six studies were identified evaluating the specificity, sensitivity, and accuracy of Tc-99m MIBI or ²⁰¹Tl in surveillance of recurrent NPC.^{22,40–44}

In a prospective study of 18 NPC patients, Kostakoglu et al.²² compared the effectiveness of post-therapy evaluation for rNPC using ²⁰¹Tl, Tc-99m MIBI, and MR imaging at 3 and 6 months post-treatment. Whereas MR demonstrated early false positives at the 3-month follow-up scan (15% specificity, 100% sensitivity, and 39% accuracy), MIBI imaging was superior at both time points with regards to specificity, sensitivity, and accuracy (85%, 100%, and 89%; 93%, 100%, and 94%, respectively at 3 and 6 months).²² In the 18 patients studied by Kostakoglu and colleagues,²⁰¹Tl yielded the lowest diagnostic accuracy (72% and 71% at 3 and 6 months post-treatment). In a later study with a larger sample of 46 NPC patients, Sobic-Saranovic and colleagues presented differing results demonstrating that the specificity, sensitivity, and accuracy of ²⁰¹Tl was actually similar to that of MIBI SPECT imaging (88%, 78%, and 82% versus 86%, 77%, and 81%).⁴⁴ It is unclear, however, if these results can be directly compared to the earlier study performed by Kostakoglu et al. as patients in the latter study were subdivided into two groups to receive different imaging modalities (either MIBI SPECT or ²⁰¹Tl) rather than both imaging modalities due to the limited availability of tracers and high radiation exposure.

The effectiveness of ²⁰¹Tl imaging in detection of rNPC was further evaluated by two case series by Shiao et al.⁴² and Tai et al.⁴³ Shiao and colleagues presented a case study of 30 NPC patients with indeterminate CT findings,⁴² whereas Tai et al. applied ²⁰¹Tl imaging

TABLE 4A Summary of fluorodeoxyglucose positron emission tomography (FDG-PET)

Aggregate quality evidence	D (Level 4: 5 studies)
Benefit	Increased FDG uptake by tumor in irradiated field allows for differentiation of tumor from fibrosis or scar tissue. High sensitivity/specificity to residual or recurrent disease from post radiation changes.
Harm	Limited accessibility. Low dose radiation exposure. Imaging during early post-radiation period may produce false positives.
Cost	Equipment, imaging studies, and associated costs very high (\$1 885–1 898 USD).
Benefits-harm assessment	Preponderance of benefit over harm.
Recommendation level	Recommended – for detection of local, regional and distant recurrence and best when combined with MRI.
Intervention	Best used for distal spread if MRI is solely used for local and regional disease.

TABLE 4B Fluorodeoxyglucose positron emission tomography (FDG-PET)

Study authors	Year	Study design	Subjects (n)	Study groups	Diagnostic protocol	Follow-up period after treatment	Reference standard	Results/Conclusion
Tsai et al. ²⁵	2002	Case series	28	Patients diagnosed with NPC with indeterminate MRI findings	MR scans were acquired using a 1.5 T MRI scanner (Vision Plus, Siemens, Erlangen, Germany; Signa Instrument, GE Medical Systems, Michigan).	4 months	Histopathological diagnosis	The specificity, sensitivity, and accuracy of FDG-PET were 100%, 92.9%, 96.4% respectively in detecting rNPC in patients with indeterminate MR results.
Ng et al. ²⁴	2004	Case series	37	Patients diagnosed with NPC whose postirradiation follow-up MRI examination showed questionable residual or recurrent disease	Dual-phase ¹⁸ F-FDG PET acquired using a dedicated PET system (ECAT EXACT HR +, Siemens-CTI) while laying supine along the central axis of the PET table.	14 months	Histopathologic results	Sensitivity and specificity of ¹⁸ F-FDG PET for detection of rNPC was 91.6% and 76% respectively at the primary site; 100% + 90.6% at distant sites; 90% + 88.9% at nodal sites. PET added significant information to the MRI findings by offering true-negative findings (n = 18), revealing unexpected small metastatic adenopathy (n = 3), and disclosing distant metastatic foci (n = 5).
Chan et al. ²²	2006	Prospective case series	152	Patients diagnosed with NPC enrolled in 2 trials to evaluate suspected local recurrence or local treatment response 3 months post therapy	¹⁸ F-FDG PET obtained with ECAT EXACT HR + camera (CTI) while lying supine along central axis of PET table. MRI was obtained on 1.5 T MRI scanner (Vision, Siemens, Germany) using a spin-echo technique.	20.9 months	Histopathology or clinical imaging follow-up.	¹⁸ F-FDG PET is superior to MRI in detecting rNPC in patients with initial stage T4 disease (P = 0.04) but is not statistically different to detection of rNPC overall in patients.
Comoretto et al. ²⁹	2008	Retrospective case series	63	Patients treated with combined chemotherapy + radiation therapy for nonkeratinizing, undifferentiated or poorly differentiated NPC: stage III (n = 25); stage IV (n = 21)	Whole body PET/CT (Discovery LS; GE Healthcare, Milwaukee, WI)	2-14 months	Histopathologic results or radiologic follow up	FDG PET/CT had overall accuracy of 85.7% in depicting residual and/or rNPC at primary site and 96.8% at regional lymph nodes
Al-Amro et al. ³⁶	2009	Retrospective case series	55	Patients diagnosed with NPC	Imaging using CT and PET (Siemens, Hoffman Estates)	16 months	Histopathologic results	PET scan revealed significantly higher specificity and positive predictive value in detection of regional relapse (89% vs 47% respectively) and is useful in differentiating post radiotherapy fibrosis versus rNPC.

to 26 NPC patients with indeterminant MRI findings.⁴³ In both studies, the use of ²⁰¹Tl imaging yielded effective detection of tumor recurrence when traditional imaging modalities failed. Since these two imaging studies were performed by the same group, it is unclear if there was overlap between the patients included in both studies whom had both indeterminant findings on CT and MR – and whether these patients represent a unique subset of NPC patients with anatomical difficulties yielding poor radiographic findings that may be especially beneficial to non-traditional imaging such as ²⁰¹Tl imaging techniques.

Evidence for the effectiveness of MIBI SPECT was also further elucidated by Kao and colleagues in a case series.⁴¹ The authors compared the efficacy of MIBI SPECT to traditional imaging techniques (CT and FDG-PET imaging) in 36 NPC patients and found that MIBI SPECT demonstrated comparable specificity to CT imaging (both 73%), though MIBI SPECT had slightly higher sensitivity and accuracy than CT alone (88% and 83% sensitivity and accuracy for FDG-PET vs 96% and 89%, respectively, for MIBI SPECT).⁴¹ In contrast, MIBI SPECT was not superior to FDG-PET in detecting rNPC (100% specificity, 96% sensitivity, and 97% accuracy). The authors concluded that while MIBI SPECT was more effective than CT at identifying rNPC, congruence between MIBI SPECT and CT imaging yielded the best predictive results. In patients with incongruent imaging results on MIBI SPECT and CT, FDG-PET was still the most effective surveillance modality.⁴¹

It is currently unclear whether MIBI SPECT is more effective than ²⁰¹Tl, nevertheless there is evidence to support the use of SPECT imaging when conventional techniques such as CT and MR imaging yield indeterminant results (see Table 5A for summary of Tc-99m MIBI and ²⁰¹Tl SPECT review; Table 5B for summary of Tc-99m MIBI and ²⁰¹Tl SPECT manuscripts).

(1) Detection of local recurrence: Optional. Similar to FDG-PET, TC-99m MIBI and ²⁰¹Tl SPECT detect cancerous tissues based on metabolic activity (²⁰¹Tl accumulates in cells with high Na-K-ATPase activity whereas TC-99m MIBI concentrates in the mitochondria of tumor tissues) instead of morphological

changes.⁴⁴ For indeterminate MRI findings, TC-99m MIBI and ²⁰¹Tl SPECT can serve as an adjunctive alternative.⁴³

- (2) Detection of regional recurrence: Optional. ²⁰¹Tl SPECT and TC-99m MIBI had an 87% and 89% sensitivity in detecting cervical lymph node involvement, respectively.⁴⁴ For indeterminate MRI findings, TC-99m MIBI and ²⁰¹Tl SPECT can serve as an adjunctive alternative.⁴³
- (3) Detection of distant recurrence: Optional. We recommend using TC-99m MIBI for detecting lymph node and lung metastases but not for bone metastases because it had a 32% sensitivity for the latter.⁴⁰ Pui and colleagues further commented that most of the missed lesions were in the extremities, pelvis, ribs, and spine.⁴⁰ As for ²⁰¹Tl SPECT, nothing was found in the literature regarding its diagnostic accuracy and sensitivity for detecting metastatic rNPC.
- (4) Cost: Using data from a hospital in South Carolina, United States, Nightengale reported that a TC-99m MIBI kit costs approximately \$315 USD whereas a 9.9mCi vial of ²⁰¹Tl costs approximately \$250 USD.⁴⁵ These prices are for the radiopharmaceuticals only and does not take into account other cost variables such as the wages of the pharmacists and nuclear medicine technologists. We were unable to find an exact cost for these modalities in the literature. However, it has been noted that both TC-99m MIBI and ²⁰¹Tl SPECT are cheaper than FDG-PET.^{22,41,43}

Epstein-Barr Virus DNA

Several risk factors have been identified in NPC, in particular the association between Epstein - Barr virus (EBV) infection and NPC pathogenesis is considered crucial in the etiology of NPC.⁴⁶ Using real-time quantitative PCR (rt-qPCR), Lo and colleagues demonstrated both quantitative and temporal correlations with circulating cell-free levels of EBV DNA and tumor recurrence in NPC.⁴⁷ Circulating EBV DNA has been evaluated as an adjunct to endoscopy and imaging in the pre-, mid-, and post-treatment surveillance of patients with NPC.^{48,49} In this review, five studies were identified

TABLE 5A Summary of Tc-99m MIBI and ²⁰¹Tl single photon emission computerized tomography (SPECT)

Aggregate quality evidence	D (Level 3b: 1 study; Level 4: 5 studies)
Benefit	Offers alternative imaging for patients with post-radiation anatomical difficulties yielding poor radiographic findings from conventional imaging (i.e. MR, CT).
Harm	Radiation exposure. Limited availability of tracers. Spatial resolution of SPECT limits ability to detect lesions.
Cost	Radiopharmaceuticals alone cost ~\$250-315 USD, excluding imaging procedures.
Benefits-harm assessment	Preponderance of benefit over harm.
Recommendation level	Option – alternative for indeterminate MR findings for detection of local recurrence; option for detection of regional and distant recurrence.
Intervention	Perform Tc-99m MIBI or ²⁰¹ Tl SPECT for additional imaging studies during surveillance period if MRI and FDG-PET inconclusive.

TABLE 5B Tc-99m MIBI and ²⁰¹Tl single photon emission computerized tomography (SPECT)

Study authors	Year	Study design	Subjects (n)	Study groups	Diagnostic protocol	Follow-up period after treatment	Reference standard	Results/Conclusion
Kostakoglu et al. ²³	1997	Case series	18	Patients with confirmed NPC diagnosis.	Patients underwent whole-body MIBI imaging after administration of 111 MBq ²⁰¹ Tl and 555 MBq MIBI.	3, 6, 15 months	Histopathologic results	MIBI-SPECT outperformed MRI and ²⁰¹ Tl in detection of residual disease 3 months (89% vs 39% and 72%, respectively) and 6months post treatment (94% vs 71% and 71%).
Pui et al. ³⁷	1998	Case-control	64	21 healthy controls, 43 patients diagnosed with primary NPC	Anterior and posterior whole-body scans of Tc-99m MIBI using a large-field-of-view gamma camera (GCA901, Toshiba, Tokyo, Japan or Diacam, Siemens, Germany).	31.1 months	Histopathologic results or radiographic results	Moderate to intense uptake of Tc-99m MIBI was seen in 88% of patients with primary NPC and 77% of patients with residual or rNPC. Tc-99m MIBI SPECT is useful in the work-up of patients with after-therapy changes as submucosal NPC cannot be diagnosed with conventional fibroscope and distinction of tumour is difficult on CT and MRI.
Kao et al. ³⁸	2002	Case series	36	Randomly selected patients diagnosed with NPC that completed course of radiotherapy within 7 weeks of diagnosis	Patients were positioned supine on imaging table and given intravenous injection of Tc-MIBI using a commercial preparation (Cardiolite, DuPont Pharmaceuticals, Bellecra, MA, USA).	4 months	Histopathologic results	Tc-MIBI SPECT combined with CT demonstrated congruent results to FDG-PET in sensitivity, specificity, and accuracy for differentiating residual or rNPC lesions.
Shiau et al. ³⁹	2003	Case series	30	Patients with confirmed NPC diagnosis and treated with radiotherapy within 7 weeks of diagnosis and with indeterminate findings on CT for residual/rNPC	²⁰¹ Tl SPECT of the head and neck was performed 10-15 minutes after IV injection of 150 MBq Tl-201 chloride and scanned using a Vertex dual-head gamma camera (ADCA, Milphas, CA).	4 months	Histopathologic results	The sensitivity, specificity, and accuracy of ²⁰¹ Tl SPECT was 86.7%, 93.3%, and 90%, respectively in detection of residual or rNPC. In patients with indeterminate CT findings, ²⁰¹ Tl may serve as a non-invasive diagnostic tool to replace biopsy to detect residual or rNPC.
Tai et al. ⁴⁰	2003	Case series	26	Patients with confirmed NPC diagnosis and treated with radiotherapy within 7 weeks of diagnosis and with	²⁰¹ Tl SPECT of the head and neck was performed 10-15 minutes after IV injection of 150 MBq Tl-201 chloride and scanned using a Vertex	6 months	Histopathologic results	The sensitivity, specificity, and accuracy of ²⁰¹ Tl SPECT was 92.3%, 93.2%, and 92.3% respectively for detection of rNPC in patients with

(Continues)

TABLE 5B (Continued)

Study authors	Year	Study design	Subjects (n)	Study groups	Diagnostic protocol	Follow-up period after treatment	Reference standard	Results/Conclusion
Sobic-Saranovic et al. ⁴¹	2007	Case series	46	Consecutive patients with first-time diagnosis of undifferentiated NPC and divided into 2 groups to be scanned	indeterminate findings on MRI for residual/rNPC	indeterminate findings on MRI for residual/rNPC	dual-head gamma camera (ADCA, Milphas, CA).	indeterminate MRI findings. ^{201-Tl} SPECT may serve as a useful imaging modality in detecting patients with rNPC especially when MRI is indeterminate.
					^{201-Tl} imaging and Tc-99m MIBI SPECT was performed in half of the patients, respectively.	12 months	Histopathologic results	Both ^{201-Tl} SPECT and Tc-99m MIBI SPECT are useful in detection of residual/rNPC and lymph node involvement in patients with NPC especially when CT/MRI is ambiguous. The sensitivity, specificity, and accuracy of ^{201-Tl} SPECT and Tc-99m MIBI SPECT are 87%, 78%, 83% and 78%, 82%, and 82% respectively.

evaluating the effectiveness of EBV DNA detection in the surveillance of recurrent NPC.⁵⁰⁻⁵⁴

Leung and colleagues quantified and compared plasma EBV DNA levels from 189 patients with NPC (140 with primary NPC, 24 with rNPC, 25 with metastatic NPC) to evaluate the sensitivity of using EBV DNA as a surveillance tool for local recurrence.⁵³ They demonstrated that detection of plasma EBV DNA was significantly lower in sensitivity in patients with local rNPC (15 out of 24 patients) compared with patients with primary NPC (135 out of 140 patients) and even in patients with distant, metastatic rNPC (24 out of 25 patients). Among the rNPC tumors positive for plasma EBV DNA, the authors quantified the median EBV DNA level and reported significantly lower levels of EBV DNA in rNPC tumors compared to primary NPC tumors. Thus, the authors suggest that EBV DNA is only sensitive for the diagnosis of primary NPC and metastatic NPC but should not be used as a sole surveillance technique in rNPC detection, especially in local sites. Leung et al.⁵³ hypothesized that the clearance of EBV DNA in rNPC tumors may be due to post-radiation changes that are found locally and not at distant sites, resulting in metastatic rNPC sites still demonstrating high levels of EBV DNA.

In a 2004 case series by Shao and colleagues,⁵² the authors used a similar stratification of 149 patients (120 patients with primary NPC, 8 with rNPC, 20 with distant metastatic NPC) to compare the effectiveness of EBV DNA versus EBV immunoglobulin A/viral capsid antigen and early antigen in diagnosing and monitoring patients with NPC. They found similar patterns of plasma EBV DNA levels to the study performed by Leung et al.⁵³ such that quantitatively, EBV DNA levels were lowest in local rNPC tumors compared to primary and metastatic NPC. When comparing the methods of plasma detection of EBV DNA versus immunoglobulin detection, Shao and colleagues report that plasma EBV DNA is a more sensitive and specific marker such that patients in remission demonstrate negative testing on EBV DNA (0 copies/mL) but not EBV immunoglobulin A/viral capsid antigen (levels remained high in all patients groups). The authors suggest that serologic techniques to diagnose and monitor NPC are only semi-quantitative and plasma EBV DNA surveillance is a more superior and sensitive technique in monitoring patients with NPC. These findings demonstrating the superiority of plasma EBV DNA to serology techniques in surveillance of rNPC were also verified by Stoker and colleagues,⁵¹ in a case study to evaluate the application of nasopharyngeal brush to detect EBV DNA. Stoker et al. compared pre- and post-treatment EBV DNA levels and serology obtained from traditional blood samples in 72 patients to those obtained from their newer technique, the nasopharyngeal brush, which is minimally invasive and easier to perform in the clinic compared to biopsy. They found that pre-treatment, EBV DNA levels acquired using nasopharyngeal brush outperformed plasma EBV DNA levels in detection of NPC, however, post-treatment, plasma EBV DNA levels were more accurate in diagnosis of rNPC compared to nasopharyngeal brush. The authors also validated previous studies in confirming that EBV serology did not demonstrate any prognostic value in detecting persistent or recurrent NPC. Stoker and colleagues suggested that

monitoring EBV DNA levels using the nasopharyngeal brush is an effective technique in the early months after treatment for NPC and yields high prognostic value in distinguishing tumor from post-radiation damage. Using a smaller sample size of patients with rNPC (n = 14) and a control group (n = 15) of patients treated for NPC in clinical remission, Lam et al.⁵⁰ verified the nasopharyngeal brush technique as an additional surveillance strategy for rNPC. The authors found a statistically significant difference in Epstein Barr virus detection levels (EDL) between the recurrence group (mean = 2.38) and the control group (mean = 0.17). Further validation of this technique using a larger sample size is required in order to determine sensitivity, specificity, and accuracy.

Moreover, in a 2011 case study of 245 patients diagnosed with NPC, Wang and colleagues evaluated the effectiveness of the plasma EBV DNA assay prior to PET imaging for diagnosis of recurrence and treatment planning in rNPC.⁵⁴ Of the patients enrolled in the study, 41/245 developed rNPC. 36 out of 41 of these patients were accurately identified through the detection of abnormal EBV DNA levels, whereas 5/41 of these patients were falsely negative for EBV DNA but demonstrated clinical signs/symptoms suggestive of rNPC. Subsequent imaging with PET then revealed recurrence sites and guided treatment planning for these patients. The authors suggest that this surveillance approach using plasma EBV DNA assay prior to PET imaging yields high accuracy in detecting rNPC and should be used as a cost-effective measure in monitoring NPC patients as the EBV DNA assay is 77–88% less costly than PET imaging, without exposure to ionizing radiation, and did not identify any false positives. Nonetheless, clinical suspicion and expertise are still necessary as negative EBV DNA results (false negative) were obtained in 5 patients with rNPC. It should be noted that patients without recurrence identified by either EBV DNA levels or clinical signs/symptoms were not scanned with PET imaging in this study, and thus the true accuracy, sensitivity, and specificity of this tailored approach cannot be conclusively determined.

In addition to analysis for plasma EBV DNA, other EBV-derived genes involved in the immune response attributable to the pathogenesis of NPC have been shown to be promising tumor markers. These include the detection of EBV encoded latent

membrane protein 1 (LMP1) and rightward transcripts known as BART microRNAs. LMP1 has been useful in the diagnosis of local rNPC, especially in cases of suspected osteoradionecrosis.⁵⁵ Changes in LMP1 status at the time of NPC reoccurrence have been observed to manifest earlier (~11.9 weeks) than morphological changes detected by nasopharyngoscopy.⁵⁶ The potential utility of EBV miRNA BARTs has also been studied. Tissue EBV miRNA BART7 was shown to be useful for identifying a subgroup of patients with histologically clear margins who are at an increased risk of subsequently developing tumor reoccurrence compared to those with negative histological margins.⁵⁷ Another study which profiled circulating plasma BART miRNAs, identified that BART8-3p and BART10-3p had the greatest efficacy in discerning rNPC patients with undetectable EBV DNA from non-cancer controls.⁵⁸

The level of evidence for the use of plasma EBV DNA is strikingly positive in the surveillance of rNPC based on the papers evaluated in this review. Newer techniques such as the detection of EBV miRNA BARTs, and EBV encoded LMP-1 gene may aid in earlier detection of rNPC than plasma EBV DNA alone. By comparison, EBV serology (IgA, VCA) does not yield efficacy in detecting persistent or residual/recurrent disease in NPC and is not a recommended technique in the surveillance of rNPC (see Table 6A for summary of EBV DNA review; Table 6B for summary of EBV DNA manuscripts).

- (1) Detection of local recurrence: EBV DNA should not be used as a sole diagnostic tool for detecting locally rNPC but may provide some value as an adjunct tool based on the above evidence.
- (2) Detection of regional recurrence: EBV DNA should not be used as a sole diagnostic tool for detecting regional rNPC but may provide some value as an adjunct tool based on the above evidence.
- (3) Detection of distant recurrence: EBV DNA has more of a role in distant recurrences but similar to above, other modalities should be used and EBV DNA as only adjunct tool.
- (4) Cost: From a cost-perspective, EBV DNA analysis is the cheapest diagnostic tool for detecting rNPC as it only costs between \$30–58 USD.⁵⁹ However, the analysis requires testing labs that are not readily available.

TABLE 6A Summary of Epstein-Barr virus (EBV) DNA

Aggregate quality evidence	C (Level 3b: 3 studies; Level 4: 2 studies)
Benefit	Minimally invasive. Identifies patients at risk of recurrence and may reflect tumour burden.
Harm	EBV DNA not detected in all NPC cases. Sensitivity lower in irradiated sites. Access to EBV assay maybe difficult if prevalence low.
Cost	In clinic procedure and associated lab processing cost low if available (\$30–58 USD).
Benefits-harm assessment	Preponderance of benefit over harm.
Recommendation level	Recommended – as adjunct tool for detection of local, regional, and distant metastasis.
Intervention	If available, perform brushing or serum biopsy to assess EBV DNA load and associated EBV factors as a part of routine surveillance.

TABLE 6B Epstein-Barr Virus DNA

Study authors	Year	Study design	Subjects (n)	Study groups	Diagnostic protocol	Follow-up period after treatment	Reference standard	Results/Conclusion
Leung et al. ⁴⁹	2003	Case control	189	Patients with postirradiation local recurrence of NPC (n = 24); newly diagnosed NPC patients (n = 140); distant metastatic relapse patients (n = 25).	Plasma samples were collected and subjected to DNA extraction using a QIAmp blood kit (Qiagen, Hilden, Germany). Plasma EBV-DNA was measured using rt-qPCR.	48 months	Histopathologic results	Postirradiation locally recurrent tumors were associated with significantly lower rate of detectable plasma EBV DNA compared to radiation-naïve tumors of comparable stage and distant metastatic recurrences. Locally recurrent tumors also demonstrate a significantly lower median EBV DNA level compared to radiation-naïve tumors. EBV DNA cannot be relied on as the sole surveillance tool for detection of local relapse since the sensitivity of EBV DNA from tumors regrowing from an irradiated site is much lower than a radiation-naïve site.
Shao et al. ⁴⁸	2004	Case-control	294	Patients with primary NPC (n = 120); control individuals (n = 47); patients with non-NPC malignant tumors (n = 38); patients with NPC in clinical remission (n = 60); patients with distant metastasis (n = 21); patients with NPC that locally recurred after completion of treatment (n = 8)	Peripheral blood was collected and DNA from plasma samples were extracted with the QIAmp Blood Kit (Qiagen, Hilden, Germany). Serum antibody titers of EBV VCA/IgA were detected using the ELISA method. EBV DNA was extracted using rt-qPCR.	12 months	Histopathologic results	Plasma EBV DNA levels were high in patients with primary + locally recurrent + distant metastatic NPC. Plasma EBV DNA levels declined to 0 copies/mL in patients with clinically remissive NPC + patients with non-NPC tumors + controls. In contrast, EBV VCA/IgA titers remain high in all NPC groups. Plasma EBV DNA levels are significantly higher in patients with advanced TNM staging. Plasma EBV DNA detection is more sensitive and specific than serum IgA/VCA titer and may be beneficial for monitoring recurrence and metastasis of NPC tumors.
Wang et al. ⁴⁷	2011	Case series	245	Patients diagnosed with NPC who previously received treatment and were in state of remission	Plasma DNA extraction using QIAmp DNA Blood MiniKit (Qiagen, Hilden, Germany). Plasma EBV DNA levels measured using rt-qPCR assay	60 months	Histopathologic results or radiologic follow up or clinical follow up	All patients (n = 36) who had detectable plasma levels of EBV DNA had demonstrable NPC recurrences. Screening for EBV DNA improves diagnostic yields and can offer a cost-effective strategy of pre-screening prior to further imaging such as PET.

TABLE 6B (Continued)

Study authors	Year	Study design	Subjects (n)	Study groups	Diagnostic protocol	Follow-up period after treatment	Reference standard	Results/Conclusion
Stoker et al. ⁴⁷	2016	Case series	72	Patients diagnosed with EBV positive NPC planned for curative intent treatment or a history of EBV positive NPC	4 ml peripheral blood was collected by intracubical vein puncture. Brushing of the nasopharynx was formed, if necessary, under local lidocaine spray anesthesia whereby a sample was taken via a tubing catheter by extruding and rotating the brush at the site of the suspected tumor or site where the tumor was located previously before treatment. DNA was extracted using an isolation procedure from BioMerieux (Boxtel, the Netherlands) and EBV DNA load was determined using rt-qPCR (LightCycler 480, Roche, Penzberg, Germany).	25 months	Histopathologic results	EBV DNA load in blood and in nasopharyngeal brushes had the best discriminating power post-treatment (PPV 39% + NPV 97%; PPV 75% + NPV 99% respectively). Assessing EBV DNA load in blood has significant prognostic value and the EBV DNA load in the brush may improve early detection of local failures post-treatment.
Lam et al. ⁴⁶	2016	Case-control	29	14 patients with confirmed diagnosis of rNPC and a control group of 15 patients with NPC in clinical remission	Transoral nasopharyngeal brushing, endoscopic examination, as well as MRI was performed in all patients. Quantification of EBV DNA using qPCR was performed.	67 months	Histopathologic results	There was a statistically different level of EBV DNA detected using qPCR using transoral brush biopsy in the control group with a mean EDL of 0.17 (range, 0-1.0) versus the patient group with a mean EDLof 2.38 (range, 1.4-3.3).

CONCLUSION

Early detection of recurrent nasopharyngeal carcinoma is paramount to disease control. Surveillance systems must circumvent post-radiation changes in order to accurately and efficiently detect rNPC. This review found there are limitations in the endoscopy, but authors recommend it as it is low risk, cost effective tool that should be combined with other surveillance modalities. One option is to improve the surveillance efficacy with NBI or contact endoscopy but a better adjunct to the endoscopy is the MRI and FDG-PET on a routine basis. The MR and FDG-PET are costly and can be less accessible, which may make routine assessments difficult but should be done at least once during the surveillance period. We recommend this modality be used more than once during the surveillance period. EBV assays are also recommended as a cost effective and accessible aid during routine follow up to prompt for additional imaging or increased clinician awareness but access to such assays are limited and should not be used as a standalone surveillance technique. While all modalities have a preponderance of benefit over harm, depending on the health care system and access, authors recommend a multimodal surveillance method to assess for exophytic/local, regional and distal recurrence by doing a routine endoscopy (approximate every 3 months the first two years, 4–6 months the next two years and every 6 months in the last year) and at least one form of imaging modality at 3 months post-treatment and another one throughout the 5-year surveillance stage. If available, the EBV testing should be included. In terms of detecting locally and regionally rNPC, we recommend the combined use of ¹⁸F-FDG PET and MRI whenever available because both modalities have similar diagnostic accuracies and yield >95% sensitivity when combined. As for rNPC metastases, we recommend using FDG-PET-CT for confirmation. A WB-MRI can be done if morphological information is required. There is a need for randomized control trials, and a greater number of well-designed cohort and case control studies to increase the quality of evidence for each surveillance modality and the timing of such interventions.

FINANCIAL DISCLOSURES

None

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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