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Review

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Contemporary surveillance of sinonasal malignancy in adults

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Abstract

Sinonasal malignancies are a unique subset of head and neck cancers that necessitate close monitoring due to high local recurrence rates. Surveillance consists of a combination of endoscopy, imaging, and patient-reported symptomatology, but no standardized surveillance protocols currently exist. Strategies historically have been based on guidelines for other head and neck malignancies; however, the unique anatomical and histologic presentation of sinonasal malignancies presents challenges. This review discusses the literature surrounding the utility of each of the different surveillance modalities and highlights techniques under investigation to aid clinicians in optimizing the surveillance of sinonasal malignancies.

Keywords: Sinonasal cancer, sinonasal squamous cell carcinoma, sinonasal adenocarcinoma, sinonasal endocrine carcinoma, sinonasal malignancy, sinonasal undifferentiated carcinoma, surveillance

INTRODUCTION

Sinonasal malignancies make up less than 5% of all head and neck cancers, but while outcomes of many other head and neck cancers have increased dramatically over the last ten years, outcome metrics in sinonasal malignancy have remained relatively stagnant by comparison[1,2]. Even for resectable lesions with negative margins, recurrence rates are between 30%-50% for sinonasal malignancies with the vast majority

being local recurrences[3,4]. Despite the clear need for investigation into optimal treatment strategies for sinonasal malignancies, patients with these diagnoses have been excluded from most clinical trials testing novel therapeutic agents for head and neck cancer patients[5]. In treatment guidelines, sinonasal cancers are frequently combined into the greater category, head and neck cancers, and surveillance guidelines often follow these generalized recommendations.

There are limited studies examining optimal posttreatment surveillance strategies for sinonasal pathologies. Patients often present at an advanced stage, thought to be due to the large potential space of the sinuses where tumors can grow, and early symptoms, such as nasal obstruction, are often attributed to benign causes[6]. Additionally, post-operative and post-radiation mucosal inflammation of the paranasal sinuses can endure for much longer in the soft tissue of the skull base than in other regions of the head and neck for reasons that remain unclear[7]. Sinonasal malignancies possess many features that distinguish them from other head and neck malignancies, and there are potential pitfalls to not considering these unique features when planning posttreatment surveillance for these patients.

This review focuses on surveillance following primary treatment for the most common malignancy of the sinonasal tract: sinonasal squamous cell carcinoma (SNSCC), as well as malignancies occurring solely in the sinonasal tract, including sinonasal adenocarcinoma (SNAC), sinonasal neuroendocrine carcinoma (SNEC), sinonasal undifferentiated carcinoma (SNUC), and olfactory neuroblastoma. In addition, the review also covers other rarer malignancies that can occur in the sinonasal tract, such as primary mucosal melanoma (PMM), nuclear protein of the testis (NUT) carcinoma, and extranodal neural killer cell (Nk)/T-cell lymphoma. Due to the unique anatomic presentation, nasopharyngeal carcinoma is not included here. The goal of this work is to review current recommendations, guidelines, and caveats in the surveillance of the above malignancies of the sinonasal tract following primary treatment.

SURVEILLANCE OF MALIGNANCIES IN THE SINONASAL TRACT

When achievable, surgical resection is often the standard of care for sinonasal malignancies, which is then followed by close post-operative surveillance given the high recurrence risk for these patients. The landmark study by de Visscher and Manni in 1994 first highlighted the importance of surveillance and follow-up for patients with squamous cell carcinoma (SCC) of the head and neck by demonstrating a significant improvement in survival when recurrence in asymptomatic patients is detected at routine visits preceding self-referral[8]. Subsequently, additional studies have made efforts to identify predictors of recurrence, including neural invasion, orbital extension, and histologic subtype for patients with sinonasal malignancies to guide surveillance following treatment[9-11]. According to National Cancer Comprehensive Network (NCCN) head and neck cancer guidelines, patients with sinonasal malignancies (specifically SNSCC) who complete multimodal therapy should undergo endoscopy and radiologic imaging for a minimum of five years due to the high recurrence risk[12]. However, the optimal timing of endoscopy and imaging for cancers of the sinonasal tract is poorly defined. Approximately 70% of physicians follow the NCCN guidelines, but the frequency of surveillance should be individualized based on histology, grade, and other risk factors[13]. The following sections will review the existing surveillance modalities for monitoring for recurrence in patients with sinonasal malignancies and highlight new information and emerging strategies for the surveillance of different malignancies of the sinonasal tract.

ENDOSCOPY

Posttreatment endoscopic examination is an important part of the current standard of care for surveillance of patients with sinonasal malignancy. Endoscopy allows for the assessment of the surface of the nasopharynx and nasal cavity; however, complicated surgical resection and radiation can not only make

endoscopic examination more difficult but can also complicate identifying recurrence by exam[14]. Khalili *et al.* found that while endoscopy has a lower sensitivity for the detection of recurrences compared to imaging (25% *vs.* 75%), they had similar specificity (89% *vs.* 90%)[15]. Kahlili *et al.* also demonstrated that the positive predictive value (PPV) of endoscopy is significantly higher when used to evaluate recurrence in symptomatic *vs.* asymptomatic patients (83% v*s.* 13%, $P = 0.008$). Endoscopy also appears to be better at identifying recurrences amenable to re-treatment with surgery as the recurrences tend to be small and superficial[15,16].

In patients with recurrence following treatment for sinonasal malignancy, suspicious findings on endoscopic examination are often correlated with surveillance imaging and biopsy. The low PPV of endoscopic examination in asymptomatic patients has been reported to lead to unnecessary biopsies. Additionally, these unnecessary biopsies can be difficult as a result of tissue inflammation, cerebral spinal fluid leaks, and osteonecrosis[17]. Studies have found that routine biopsy of asymptomatic patients in the setting of normal ear-nose-throat (ENT) examination and endoscopy results in no survival benefit during the surveillance of sinonasal malignancies[18].

Endoscopy plays a particularly important role in the surveillance of patients with a subset of rare sinonasal malignancies. Patients with SNAC and low-grade SNEC are much more likely to have local recurrence as opposed to distant metastases[19]; as a result, it is particularly important that these patients undergo interval endoscopy for monitoring disease recurrence. For patients with SNEC, the optimal surveillance strategy may vary based on tumor grade. Low-grade tumors may be followed with endoscopy, whereas high-grade tumors, such as the small cell variant, should also be monitored by serial imaging in order to detect distant metastasis[19]. These recommendations mirror the surveillance guidelines for small cell carcinoma in the lung due to a deficiency of prospective studies of surveillance for patients with SNEC. In addition to sinonasal symptoms, patients with PMM may present with a pigmented lesion on ENT examination that can be visible on endoscopy. Rarely, a lesion that is nonpigmented may be seen[20]. On exam, PMM macules are irregular and asymmetric, which can differentiate PMM macules from melanosis.

IMAGING

Posttreatment surveillance imaging plays an essential role in care of the patient with a sinonasal malignancy. Computerized tomography (CT), magnetic resonance imaging (MRI) or ^{18}F-fluorodeoxyglucose (^{18}FDG) positron emission tomography (PET)/CT are frequently used in combination, and certain modalities have been reported to have different advantages. Surveillance imaging for sinonasal malignancies can be challenging to interpret, given that edema of scarred mucosa following surgical resection and enhancement near a tissue flap can last for many months after primary treatment[21]. It is important that imaging choices encompass all areas of possible recurrence, including all areas of potential distant metastasis, and should take into account the varying risk of distant metastasis for diverse subtypes of sinonasal malignancies. Despite the fact that most recurrences are local, studies have shown that imaging frequently diagnoses more recurrences of sinonasal malignancy than endoscopy alone. As a result, biopsies driven by imaging have improved sensitivity, accuracy, and PPV compared to biopsies performed solely following suspicious findings on endoscopy (PPV 72% *vs.* 43%)[15,16]. However, the utilization of endoscopy to clinically correlate imaging findings is often useful. Imaging has a high negative predictive value (NPV) in monitoring for recurrence of sinonasal malignancy (91%)[15,22]. The high NPV suggests that negative surveillance imaging can be helpful in identifying patients in remission, particularly in the surveillance of asymptomatic patients without concerning endoscopic findings. The following sections will discuss the different imaging types used in the surveillance of sinonasal malignancies, highlighting recent advances and unique advantages of different modalities.

MRI

MRI is thought to be the gold standard for assessing the recurrence of sinonasal malignancies. Generally, a baseline MRI of the brain and sinonasal cavity will be performed at 3-4 months following primary treatment[23-25]. Compared to other imaging modalities, MRI has been shown to have a higher PPV (46% to 84%) in monitoring for recurrence of sinonasal malignancies[15,26]. T2-weighted images are often employed in signal discrimination, while T1-weighted images are frequently used with postcontrast comparison[21]. Although MRI is a powerful and informative imaging modality, the interpretation of MRI images can be variable; individual providers and various institutions may have different criteria for evaluating findings suspicious of recurrence of sinonasal malignancy on MRI, leading to considerable discrepancies in findings considered suspicious for recurrence.

New techniques for MRI have attempted to help refine and standardize the detection of recurrence of sinonasal malignancy. Dynamic postcontrast-enhanced MRI has proven to be useful in distinguishing post-radiation fibrosis from tumor recurrence, which can demonstrate similar enhancement on standard MRI[22,27]. Diffusion-weighted imaging (DWI) MRI may also have utility in differentiating posttreatment inflammation from tumor recurrence. As a result of the complex bone-air-fat interface, DWI has high-susceptibility artifacts that can reveal variations on enhancement for particular sinonasal malignancy subtypes, particularly intestinal-type adenocarcinoma[21]. Because the diffusion of water molecules is limited in solid tumors with hypercellularity, higher apparent diffusion coefficient (ADC) values can be indicative of hypocellular tissue with apoptosis or necrosis[28]. As a result, DWI has been investigated as a tool that could allow for earlier surveillance imaging of patients with head and neck cancers[29,30]. With additional research, innovative techniques to assess for recurrence that can be distinguished from posttreatment inflammation and fibrosis will continue to emerge, further improving MRI, the gold standard imaging modality for surveillance of sinonasal malignancies.

COMPUTED TOMOGRAPHY

Computed tomography (CT) has largely been overtaken by MRI as the primary imaging modality for monitoring the recurrence of sinonasal malignancies; however, a few factors could warrant the use of CT for surveillance imaging. CT can have higher utility in assessing for acute intracranial complications in the post-operative period[21]. Because of its high spatial resolution, CT can be particularly valuable in assessing the resorption of thin bony structures and could play a role in surveillance imaging for tumor subtypes with a particular predilection for bony involvement. CT imaging has been suggested to be equivalent to MRI for a few subtypes of sinonasal malignancy, namely SNUCs and extranodal Nk/T-cell lymphoma. SNUCs are characteristically noncalcified on CT and MRI, making recurrence difficult to evaluate on either modality[31]. NUT carcinoma has distinct findings on CT, including hypoattenuation, heterogeneous enhancement, and infiltrative mass with not well-defined margins[32]. NUT carcinoma also exhibits necrosis and calcification with invasion into nearby structures, often in central airways and vascular structures, which can be assessed on CT and MRI[33]. In younger patients, surgeons should consider the risks of secondary malignancy from repeated CT radiation when choosing optimal imaging modality[34]. Overall, CT is most useful when combined with ^{18}FDG-PET imaging.

PET/CT

The NCCN guidelines recommend ^{18}FDG-PET/CT for surveillance following completion of primary treatment for the head and neck cancer[12]. Multiple studies have demonstrated that PET/CT can identify approximately 95% of recurrences that are asymptomatic in the first two years following completion of primary treatment[12,22,35] and has a higher sensitivity when compared to CT/MRI alone[36]. PET/CT also has the powerful advantage of the ability to detect distant metastases as unexpected areas of

hypermetabolism[37]. However, it is characteristically not specific for cancerous cells because immature granulation tissue, macrophages and fibroblasts all avidly uptake ^{18}FDG, particularly following radiotherapy[38,39]. As a result, PET/CT is very reassuring when negative with a high NPV, but has poor specificity, particularly in the context of sinonasal malignancy[21]. Studies have demonstrated that specificity falls to ~40% and PPV to ~50% for sinonasal malignancies, most likely due to the nonspecific radiotracer update in the inflammatory environment in the posttreatment sinonasal cavity[27,39]. Many centers that care for patients with sinonasal malignancy will perform ^{18}FDG-PET between one and four times per year, but this must be balanced with costs and reduced quality of life for patients as a result of false positives[40,41].

Generally, for head and neck cancer patients, practice guidelines recommend a three-month PET/CT following completion of primary treatment[22,42-44]. A retrospective study of PET/CT in surveillance of sinonasal malignancy between 2000 and 2015 demonstrated that compared to head and neck cancers overall, sinonasal tumors have a prolonged hypermetabolic period[17]. The team found that the specificity and PPV of PET/CT were improved when performed at baseline and then at least six months posttreatment, consistent with previous findings[45]. The prolonged period of hypermetabolism in the posttreatment sinonasal skull base may warrant reevaluation of the general recommendation that patients with head and neck cancer have a PET/CT completed by 10-12 weeks following primary treatment[17,45]. Although the optimal timing of surveillance PET/CT may remain unclear, the lack of pathologic FDG uptake on the first PET/CT following treatment was associated with improved overall survival (OS) for patients with SNSCC[46]. However, increasing the total number or frequency of scans during the first year has not been associated with reduced time to recurrence. Overall, at least one surveillance PET/CT should be performed for patients with sinonasal malignancy, although the optimal timing for PET/CT is still under investigation[47,48].

^{18}FDG-PET/CT can play a particularly important role in the surveillance of patients with some subtypes of rare sinonasal malignancies. For patients with high-grade SNEC, recurrence can present locoregionally or distantly metastasis, perhaps warranting closer surveillance of these patients with ^{18}FDG-PET/CT[49,50]. There are no definitive recommendations regarding the use of Gadolinium-DOTATATE PET/CT for SNEC, but a few reports have evaluated its utility for diagnosing low-grade SNEC where no radiotracer uptake was found on FDG PET/CT[51]. There have also been evaluations on the use of Gadolinium-DOTATATE PET/CT for the evaluation and surveillance of olfactory neuroblastomas, given that 99% of these tumors are positive for SSTR2 expression[52]. Additionally, SNUC is an aggressive disease with a partial neuroendocrine profile that confers a poor prognosis, and Gadolinium-DOTATATE PET/CT may be able to assist in the close surveillance of these patients. However, the use of Gadolinium-DOTATATE PET/CT for the surveillance of SNUC remains under investigation[48]. SNUCs are often locally recurrent and frequently metastasize, resulting in significant morbidity and mortality. Mucosal melanoma has a high recurrence rate with a tendency for distant failure (38%-57%) and demonstrates high FDG avidity, making PET/CT particularly useful[19,53,54]. FDG PET/CT is also recommended in patients with NUT carcinoma, given the particularly high risk for metastatic disease. PET/CT should be performed for optimal detection of metastases in patients with extranodal Nk/T-cell lymphoma[55]. Involvement of the bone marrow is rare, but aspiration and biopsy can be considered for evaluation, particularly given that PET/CT may also have the ability to detect bone marrow disease[56,57]. For patients with olfactory neuroblastoma, PET/CT is often not indicated except when symptomatic distant metastatic disease or pathology shows high-grade features. Somatostatin receptor-based methods can also be utilized because these tumors frequently express somatostatin receptors[58,59].

The World Health Organization (WHO) described human papillomavirus (HPV)-related multiphenotypic sinonasal carcinoma as an updated, new subtype of nonkeratinizing SCC of the sinonasal tract in 2017. HPV-related multiphenotypic sinonasal carcinoma is associated with greater five-year OS, including HPV-related oropharyngeal SCC, despite its aggressive histopathology[60]. Commonly defined by p16 overexpression, HPV-positive tumors are characterized by basaloid proliferation combined with focal areas of squamous differentiation on histopathology. Zupancic and Näsman performed a systematic review and found that 77 of 79 (97.5%) cases of HPV-related multiphenotypic sinonasal carcinoma occurred within the sinonasal cavity with no regional metastasis, while one occurred in the breasts, and one in the tonsils[61]. Additionally, given that approximately one-third of SNSCCs are HPV-associated[62], circulating HPV DNA (ctHPVDNA) is being investigated as a noninvasive biomarker of disease status both at diagnosis and throughout treatment[63]. Studies have demonstrated that HPV-associated SNSCC may have genotype distributions distinct from HPV+ oropharyngeal carcinoma, with HPV 16 being less common[64]. Further studies are needed to investigate the genotype distributions of HPV-related multiphenotypic sinonasal carcinoma and the utility of ctHPVDNA in the diagnosis and management of this disease. Although these findings could have implications for optimal surveillance timing for patients with HPV-related multiphenotypic sinonasal carcinoma, routine HPV testing for non-oropharyngeal head and neck primary tumors is not currently recommended by the College of American Pathologists given the lack of prospective trials and clear data determining prognostic significance[65].

EMERGING SURVEILLANCE STRATEGIES AND LIFETIME SURVEILLANCE

For patients with extranodal Nk/T-cell lymphoma of the sinonasal tract, in addition to endoscopy and symptom-guided imaging, disease surveillance can include plasma Ebstein-Barr Virus (EBV) DNA titers[66]. In one study, patients with EBV DNA levels were used to develop the prognostic index of natural killer lymphoma (PINK-E) score which risk stratifies patients into low, intermediate, and high-risk cohorts. Reports of late relapses, even up to three decades after remission, have been reported for extranodal Nk/T-cell lymphoma, making the role of EBV DNA titers for surveillance particularly important[67]. Patients with late relapses were found to have a prognosis comparable to that of patients with primary extranodal Nk/T-cell lymphoma, rather than those with the typically more aggressive relapsing disease[68]. These patients also have an increased risk of developing treatment-related acute myeloid leukemia[69]. Thus, for patients with extranodal Nk/T-cell lymphoma, lifelong surveillance is recommended.

Long-term surveillance beyond the standard five years is also recommended for patients with olfactory neuroblastoma, with local recurrence rates up to 20%-40% at ten years posttreatment[70]. Optimal surveillance of patients with olfactory neuroblastoma following primary treatment remains unclear; nevertheless, one protocol recommended MRI studies at baseline of both the brain and maxillofacial area every 2-4 months after treatment, followed by serial imaging studies at four or six-month intervals for five years, and then annual imaging studies for the lifetime of the patient[71]. The study recommends that examinations include endoscopy and overlap with the surveillance imaging timetable, and further imaging should be directed by patient-reported symptoms and examination findings.

CONCLUSION

Malignancies of the sinonasal tract are unique among head and neck cancers and require a nuanced approach to surveillance following primary treatment. Inflammation and postsurgical changes can persist appreciably longer than other head and neck cancers, which has implications for the ideal timing of surveillance imaging, particularly PET/CT. Endoscopy is an important part of surveillance following primary treatment and is most valuable when partnered with a thorough history and physical exam, probing for potential symptoms of recurrence. MRI is the gold standard imaging modality for surveillance for

sinonasal malignancy, but the great diversity of the biology and behavior of sinonasal cancers can make it difficult to construct broad guidelines or generalizable surveillance protocols. Risk factors, including staging, histology, tumor grade, and others, should direct the frequency and length of follow-up until more studies are conducted on sinonasal malignancies. Overall, physicians should be mindful that sinonasal malignancies are unique among head and neck cancers and often require a tailored and nuanced surveillance strategy for optimal patient care.

DECLARATIONS

Authors' contributions

Literature review, manuscript preparation, and manuscript revisions: Sell EA
Review design, literature review, manuscript preparation, and manuscript revisions: Panara K
Review design, manuscript preparations and revisions: Workman AD
Review conception, manuscript preparations and revisions: Adappa ND

Availability of data and materials

All referenced sources are available via Pubmed (https://pubmed.ncbi.nlm.nih.gov/).

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Conflicts of interest

All authors declared that there are no conflicts of interest.

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Consent for publication

Not applicable.

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