



## **Follow Up of Patients, Surveillance and Its Significance in Head and Neck Cancer**

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### **Abstract**

This study aims to evaluate pattern of follow up visits among patients treated for head and neck cancers in our region. Follow-up in patients treated for head and neck cancer (HNC) is aimed at early detection of recurrence, metastases and second primary tumors. Various modalities for the routine follow-up of patients with HNC have been proposed and studied in the literature. Consequently, practicing head and neck surgeons and

oncologists all over the world use different guidelines and protocols to follow-up their patients. These guidelines involve follow-up intervals of varying intensity and schedule an assortment of investigations. This review summarizes strategies for follow-up, imaging modalities and key investigations. In this review, we have assessed studies in the literature that have addressed follow-up intervals, imaging tests,

tumors markers, endoscopy and thyroid function tests as a part of the routine post-treatment surveillance in HNC patients. Studies analyzing the cost benefit of such surveillance have also been addressed. Based on the evidence presented, we have compiled definitive recommendations for effective surveillance/post-treatment follow-up in patients with HNC.

## **Introduction**

Follow-up in head and neck cancer (HNC) is essential to detect and manage loco regional recurrence or metastases, or second primary tumors at the earliest opportunity. A variety of guidelines and investigations have been published in the literature. Follow up of patients is also essential for the management of impairments after tumor therapy, the psychological care of the patients and the evaluation of the efficacy of therapy [3]. Various modalities have been proposed in literature for the routine follow up of patients with HNC and practicing head and neck surgeons and oncologists all over the world. Timely identification of locoregional recurrence or metastasis can help in institution of definitive treatment with curative intent.<sup>1</sup> In addition, post-treatment follow-up has an important role to play in the evaluation of disease control, rehabilitation of functional loss, pain management, impact on psychological and emotional well-being of the patient, and quality of life. Second primary tumor's in patients with tumor's of the upper aero digestive tract occur at a rate of about 10–20% overall lifetime risk<sup>2,3</sup> or about 5% per year as a result of tobacco abuse.<sup>4,5</sup>

Head and neck surgeons across the globe use a variety of interventions (such as office clinical examinations including endoscopies, imaging studies, blood examinations and tumour markers) in the follow up of HNC patients. These various protocols often lack a clear evidence base and carry significant cost

implications. The investigations and interventions have to be used effectively to detect recurrences as early as possible to institute appropriate treatment<sup>6</sup>

## **Methods**

### **Inclusion criteria**

To evaluate various surveillance strategies in post-treatment head and neck cancer patients, we reviewed literature available from 1980 to 2020. Articles fulfilling the following criteria were included for the review: Articles describing surveillance strategies in post-treatment HNC patients, articles describing the use of any evaluation modality for surveillance, all type of related studies published in the English language. To make it more comprehensive we also included studies published in other languages with abstracts in English describing methods for follow-up of patients with head and neck cancer.

### **Search strategy**

A comprehensive literature searches of PubMed, Embase<sup>TM</sup>, CINAHL<sup>®</sup> (Cumulative Index to Nursing and Allied Health Literature) and the Science Citation Index was performed for surveillance in patients with HNC. Keywords used were head and neck cancer, surveillance, follow-up study and recurrence. The reference lists from the relevant articles were also inspected and cross-referenced and any other pertinent publications were added to the review. A total of 48 articles or book chapters that satisfied the inclusion criteria were reviewed.

## **Results**

There were twelve publications with recommendations on follow-up strategies for HNC and nine with site-specific recommendations on follow-up. Three studies evaluated the efficacy of chest x-ray in the follow-up period: one compared the efficacy of chest computed tomography (CT) over chest x-ray and

two were on the efficacy of chest CT alone. Four of the included studies were on the efficacy of post-treatment CT in routine follow-up. Four studies were on the role of positron emission tomography in the post-treatment surveillance of patients with HNC. Four studies were reviewed on the role of routine endoscopy as a part of follow-up. Five of the studies related to tumour markers in HNC. Five studies studying the utility of thyroid function tests were included in the study.

Frequency of visits Published recommendations for the follow-up of patients with HNC can be site-specific or applicable to all sites (generic). The recommended numbers of office visits vary from 8 to 27 and around 18 chest radiographs are recommended for the first years after treatment.<sup>7-18</sup> There is a wide variation in the strategies for the specific sites.<sup>6,19-26</sup>

In 1996 the American Head and Neck Society recommended an average of 28 office visits and 5 chest radiographs in the five years after treatment.<sup>26</sup> The other recommended tests varied across the sites. Practice care guidelines published in the *European Journal of Surgical Oncology* in 2001 advised a 4–6 week follow-up schedule in the first 2 years, 3-monthly follow-up for the third year, 6-monthly follow-up in years 4 and 5, and annual visits thereafter.<sup>27</sup>

A survey conducted among members of the American Society of Head and Neck Surgeons (SHNS) reported 73% agreement among respondents for offering monthly follow up in the first year after surgery, 2–3 monthly visits for the second year and 4–6 monthly visits in years 3–5 after surgery.<sup>13</sup> Chest radiography was used by a majority. Seventy per cent of the respondents felt that patients with TNM (tumors, nodes, metastasis) stage 1 and forty per cent felt that those with stages 2–4 would benefit from the follow-up strategy. In another survey conducted among members

of the SHNS it was found that 70% of the respondents had the same follow-up strategy irrespective of the TNM stage.<sup>28</sup>

The authors concluded that follow-up is not indicated three years after completion of treatment and should only be routine for patients who still have a treatment option left. They estimated that about a third of the follow-up consultations could be dropped without a reduction in the number of early recurrences detected. The main implications from this study are that patients for whom a salvage treatment option exists should have a strict follow-up regimen for the first three years and that in patients who have been treated with combined modality therapy the focus should be on providing care and support rather than on detecting recurrence.

### **Post-treatment imaging**

Imaging is crucial for the detection of recurrences. However, imaging modalities such as CT, MRI and ultrasonography have poor specificity in differentiating post-treatment soft tissue changes from recurrence in the post-treatment period.<sup>32,33</sup>

Chest radiography is performed as a part of routine follow-up of HNC to detect lung metastasis and second primary tumours in the lung. The authors concluded that chest CT should be used instead of chest radiography as a screening tool in patients of advanced head and neck squamous cell carcinoma.

Accurate interpretation of CT is necessary to differentiate between post-treatment and residual or recurrent disease.<sup>32</sup> Baseline CT or MRI performed 3–6 months after treatment should be obtained, especially in high-risk HNC patients. These modalities can be very useful in drawing a comparison with subsequent imaging for earlier detection of recurrent/residual disease.<sup>31-32</sup>

The ability of MRI to detect recurrence is dependent on the individual interpreting the study. MRI is preferred in patients with sinonasal, skull base and nasopharyngeal tumours and in whom there is any suspicion/evidence of early perineural or intracranial spread.

Physiological and metabolic changes occur prior to anatomic changes in tissues. Hence anatomical imaging techniques are unable to identify the fibroblasts which replace the tumour tissue without significant change in tumour volume.<sup>38</sup> Fludeoxyglucose positron emission tomography (FDG-PET) has found widespread acceptance for initial staging, restaging and detection of second primary tumours in HNC. However, FDG-PET has been shown to produce a high false positive result in patients with recurrent HNC. This was to some extent reduced by the introduction of PET in combination with CT, known as PET-CT. Distant lesions can be detected by PET-CT as it is a whole body scan from the vertex up to the mid-thigh.<sup>21</sup>

Ong *et al* studied 65 patients undergoing chemo-radiotherapy for HNC by FDG-PET-CT performed not later than 6 months post-therapy.<sup>30</sup> They showed it had a negative predictive value of 98% for excluding viable cancer in neck nodes. The combination of PET with CT reduced the false positive rates by >50% compared to CT alone.

### **Endoscopy**

During the initial workup of HNC patients a panendoscopy is usually performed for ruling out the presence of second primary tumours. In a meta-analysis of second primary tumours of the head and neck it was found that overall prevalence of second primary tumours was 14.2% in 40,287 patients.<sup>43</sup> A significantly higher detection rate was seen for prospective panendoscopy studies. The authors recommended

routine endoscopic evaluation within two years of completion of treatment and clinical surveillance beyond five years to detect second primary tumours.

### **Tumour markers**

A variety of tumour markers have been studied for their role in diagnosis, prognosis and treatment of HNC. These markers, however, lack sensitivity for use with HNC. In order to evaluate the value of tumour makers, such as squamous cell carcinoma antigen (SCCAg) by using radioimmunoassay, lipid-associated sialic acid, carcinoembryonic antigen (CEA) and cancer antigen 125 (CA-125), 101 patients and 88 controls were studied. It was seen that squamous cell carcinoma radioimmunoassay was the most sensitive marker with 47.5% sensitivity in detecting recurrent/residual disease. The authors concluded that none of the available markers was adequate for diagnostic purposes in HNC.<sup>28</sup> In another study of the tumour markers (serum SCCAg, CEA, cancer antigen 19-9 and CA-125) in 121 patients with oral cancer, it was found that only SCCAg correlated with tumour burden and showed an exponential increase 1–2 months prior to a relapse.<sup>29</sup>

### **Hypothyroidism**

The reported incidence of hypothyroidism after radiation to the thyroid gland is between 3% and 44%.<sup>47</sup> In a study of 378 patients receiving radiotherapy for HNC, it was seen that hypothyroidism affected only patients treated by surgery and radiotherapy.<sup>48</sup> The authors concluded that thyroid function tests should be performed in these patients prior to and 3–6 months after completion of therapy. In a study by Garcia-Serra *et al*, the authors concluded that serum thyroid stimulating hormone (TSH) should be checked at six-monthly intervals for the first five years and yearly thereafter in patients receiving radiotherapy to the low neck region.<sup>19</sup> They also felt that thyroid hormone

replacement therapy should be initiated if the TSH value was more than 4.5miu/l.

#### Cost–benefit analysis

The cost of a follow-up strategy is often very difficult to calculate accurately as any true estimate would have to include the cost of each visit to the physician, the cost of travel, the cost of investigations ordered as a part of the follow-up, the cost of treatment (including complications) if recurrent disease was found and the cost incurred due to loss of productivity of the patient. In a study analysing different strategies for the follow-up period, Virgo *et al* found that there were no data to demonstrate greater efficiency for higher cost strategies.<sup>12-18</sup> They recommended a minimalist approach towards follow up but also added that their analysis was not done on actual patients and prospectively studied.

#### Recommendations

The first clinical evaluation should take place 4–8 weeks after treatment completion. This should include a thorough clinical history for symptoms and clinical examination. In the first visit the patients' response to the treatment has to be evaluated, with specific reference to the detection of persistent disease, the management of adverse effects and the provision of psychological and emotional support. Endoscopy is indicated in patients with symptoms. A rigid or flexible nasal endoscopy may be performed in patients with nasopharyngeal carcinoma within 4 months of completion of treatment. No reliable serum tumour markers are available. CT or MRI is to be obtained 3–6 months after treatment to provide baseline images for later reference. PET imaging may be done if there is a discrepancy between the physical findings and the initial imaging studies. An FDG–PET–CT may be useful at 12 months after treatment, but further studies

are required to clarify this issue. Follow-up of N0 necks which have been untreated should be done with the help of clinical examination and, where suspicion exists, US-FNAC. Chest CT should be done in symptomatic patients. Blood investigations should be done in patients with symptoms at clinical follow-up. Psychological support, advice on hygiene and risk factors are an integral part of follow-up. Surveillance should be more intense in the first three years as this is the time period in which most recurrences occur. Patients should be educated about symptomatology and the need for additional visits if new symptoms arise. Surveillance of patients for whom additional therapeutic options are available should be more intense. All patients with cancer of the UADT are at a higher risk for developing second primary tumours. Follow-up studies for second primaries must include an endoscopy doubting the event of worrying symptoms. Patients with larynx cancer are at higher risk for developing second primaries in the lung, while location of the primary in the hypopharynx is associated with increased risk of second primaries in the oesophagus. Chest radiography to detect metastases in the lung is not necessary unless the patients' clinical situation warrants aggressive management of the lung disease. Chest CT can be done in patients with suspected lung metastasis. Patients with bone pain and hypercalcaemia suspicious of bone metastasis should be investigated with radiographs, isotope bone scans and CT scans. PET scans are more sensitive for detecting occult bone metastasis. TSH values should be checked six-monthly in patients who have received radiotherapy to the lower neck. Non-oncological components such as swallowing function, voice rehabilitation, morphological changes, neuromuscular alterations, cosmetic sequelae and psychological support have to be catered for during

routine surveillance. Time-tagged visual flow-chart for surveillance in post-treatment head and neck cancer patients.

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