Recurrence and Follow-up in Head and Neck Cancer



J. Kasaboglu [1]

1.Department of ENT , University Hospital "Queen Joanna"-ISUL , Sofia ,Bulgaria

Introduction

Head and neck squamous cell carcinoma (HNSCC) ranks as the seventh most prevalent cancer globally, with approximately 700,000 new cases reported annually [1]. This type of carcinoma can develop from the epithelial cells found in the oral cavity, oropharynx, nasal and paranasal cavities, larynx, and hypopharynx. The primary risk factors linked to HNSCC are the use of tobacco and alcohol, and their combined usage significantly amplifies this risk [2,3]. Tobacco smoking is also a critical prognostic factor, largely due to the elevated incidence of smoking-related second primary tumours. Furthermore, the mortality specific to the disease is considerably higher in individuals who are current or former smokers compared to non-smokers [4]. The human papillomavirus (HPV) is also a contributing factor in the development of oropharyngeal carcinomas (OPSCCs) [5]. OPSCCs that are HPV-positive display unique histopathological characteristics and an earlier onset age, and they tend to have a more favourable prognosis in comparison to those that are HPV-negative [6].

Determining the best treatment plan should involve a multidisciplinary tumour board and be tailored to the specific disease location, stage, viral association, and anticipated functional outcome.

For early-stage HNSCC, a single-modality treatment approach is recommended, either through surgery or radiotherapy, such as intensity-modulated radiation therapy or volumetric-modulated arc therapy. Conversely, locally advanced cases can be successfully managed using a combination of surgery followed by adjuvant chemotherapy-radiotherapy [(C)RT] or exclusive concurrent CRT [7].

In instances where multimodal treatment fails, local recurrence is the most frequently observed relapse, affecting about 40% of patients, primarily occurring within the first two years post-diagnosis [8]. The occurrence of distant metastases (DMs) is comparatively lower (10–20%) [9] and is closely associated with specific risk factors, which include having three or more positive pathological lymph nodes, extra nodal invasion, minimal invasion in jugular nodes, previous (loco)regional recurrences, primary tumours in the hypopharynx, advanced T-stage, and lymph node metastases greater than 6 cm [10]. The lung is the most common site for DMs, followed by bones, liver, and skin. Additionally, nearly 50% of DMs from HNSCC occur within the first eight months after treatment completion, after which the incidence gradually declines until reaching a plateau around 24 months [11].

These findings highlight the vital importance of follow-up care, which currently involves a combination of clinical evaluations, endoscopy, and imaging studies, tailored to the tumour site, clinical stage, and treatment administered [12]. Regrettably, due to the absence of randomized clinical trials, there is no consensus on the optimal follow-up strategy for locally advanced HNSCC, including both the timing and methods, leading to controversial practice recommendations.

The role of radiological follow-up is particularly debated, as it may detect locoregional or distant recurrences and second primary tumours earlier than follow-ups based on clinical symptoms, although it remains uncertain whether this advantage translates into improved survival rates for patients [13].

Management of Recurrence of Head and Neck Cancer

The recurrence of head and neck cancer (HNC) poses significant challenges, necessitating a comprehensive and tailored management approach. Recurrences can occur locally, regionally, or distantly, and the management strategies depend largely on the site of recurrence, previous treatments, patient health status, and the characteristics of the recurrent tumour. This overview discusses the key management strategies for handling the recurrence of head and neck cancer.

1. Surgical Interventions

Surgery remains an essential cornerstone in the management of recurrent head and neck cancers, particularly for localized recurrences. The primary goals are to achieve complete resection of the recurrent tumour while preserving as much surrounding healthy tissue as possible. [14].

- Surgical Resection: Surgical removal of the recurrent tumour is often the first-line treatment. Surgeons typically evaluate the extent of recurrence and the feasibility of achieving clear margins. In some cases, reconstructive surgery may be necessary to restore form and function.
- Neck Dissection: If regional lymph nodes are involved, a neck dissection may be indicated to remove affected lymph nodes. This can be particularly important in cases of recurrent cervical lymphadenopathy.

2. Radiation Therapy

Radiation therapy can be employed either as a standalone treatment or as an adjunct to surgical interventions[15-16].:

- Post-Surgical Radiation: For patients whose tumours have recurred following surgery, adjuvant radiation therapy may be recommended, especially if positive margins or extra-nodal extension is noted.
- Palliative Radiation: In cases where curative intent is not feasible due to the extent of disease or patient health, palliative radiation may help manage symptoms, such as pain or obstruction, and improve quality of life.
- Reirradiation: For selected patients with previously irradiated areas, it may be possible to consider reirradiation, often using advanced techniques like intensity-modulated radiation therapy (IMRT) to minimize damage to surrounding tissues.

3. Chemotherapy

Chemotherapy plays a significant role in the management of recurrent head and neck cancer, especially for patients with distant metastases or who are not surgical candidates:

- Systemic Chemotherapy: Chemotherapy may be administered systemically to treat recurrent disease, often as part of a combination regimen. Agents such as cisplatin, carboplatin, and taxanes are commonly used in these settings.
- Targeted Therapies: For specific tumour characteristics, targeted therapies such as cetuximab (an EGFR inhibitor) may be used. These therapies can enhance treatment efficacy and sometimes lead to improved outcomes in recurrent disease.
- Immunotherapy: As promising new approaches, immune checkpoint inhibitors like pembrolizumab and nivolumab are increasingly utilized in cases of recurrent or metastatic head and neck squamous cell carcinoma, particularly in patients expressing PD-L1. [17, 18].

Multidisciplinary Management

An effective management strategy for recurrent head and neck cancer generally involves a multidisciplinary approach:

- ***Team Collaboratio***n: A team including oncologists, surgeons, radiation oncologists, and supportive care specialists collaborates to design a comprehensive treatment plan tailored to the patient's individual needs.
- ***Nutritional Support***: Given the impact of treatment on nutrition and swallowing, dietitians play an important role in managing nutritional status. Ensuring that patients maintain adequate nutritional intake can significantly affect treatment tolerance and overall health.
- ***Psychosocial Support***: Addressing the emotional and psychological needs of patients is essential. Mental health professionals or support groups can provide valuable assistance in coping with the stress and anxieties associated with recurrence.

5. Palliative Care

For patients with advanced recurrence where curative treatment may no longer be an option, palliative care focuses on improving quality of life and managing symptoms effectively:

- ***Symptom Management***: Palliative care involves addressing pain, dysphagia, and other debilitating symptoms. Medications, lifestyle adaptations, and supportive therapies are used to ensure comfort.
- ***Advanced Care Planning***: Discussions regarding goals of care and advanced directives are important in enabling patients and families to make informed decisions that align with their values and preferences.

Follow-Up Surveillance

Following treatment for recurrence, close follow-up and surveillance are crucial for early detection of any further recurrences:

Radiological follow-up:

At present, post-treatment surveillance for head and neck squamous cell carcinoma (HNSCC) utilizes a mix of morphological and functional imaging methods. Morphological imaging methods consist of computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US). In contrast, functional imaging techniques involve positron emission tomography (PET)-CT). CT is the most utilized imaging method for evaluating therapy response and detecting distant metastases in oncological radiology, as it is a relatively cost-effective and quick option for monitoring head and neck squamous cell carcinoma (HNSCC).

MRI is the preferred choice for clinical staging of most HNSCC subtypes due to its superior contrast resolution, allowing for excellent visualization of soft tissues among various imaging modalities.

Ultrasound (US) has a limited application in HNSCC imaging, primarily because it struggles to assess deeper structures effectively. However, it can be advantageous in identifying pathological lymph nodes and evaluating superficial lesions in specific, accessible areas, such as the oral cavity. Additionally, US is frequently employed to assist with fine needle aspiration and core biopsy procedures. PET-CT provides valuable functional information about cancer with high specificity, though its sensitivity for detecting post-treatment recurrence is only moderate. Therefore, it should be combined with morphological imaging techniques and clinical assessments for optimal evaluation. PET-CT is particularly beneficial in clarifying uncertain radiological or clinical findings, offering a high negative predictive value. Despite its widespread use in HNSCC surveillance, there is currently no evidence to suggest that it improves survival outcomes.

It is important to note that PET-CT scans should not be conducted immediately after treatment; instead, they are ideally performed 8 to 12 weeks post-therapy. This delay is necessary due to the increased uptake of (18)F-fluorodeoxyglucose (FDG) observed in both inflammatory and tumour tissues during this period.

Clinical Follow-up:

Clinical follow-up is crucial for patients with head and neck squamous cell carcinoma (HNSCC) for several reasons. First, it enables the evaluation of treatment response, helping healthcare providers determine the effectiveness of the selected therapeutic strategy. Second, regular follow-up visits allow for the early identification of late adverse events that may occur as a result of the treatment. Additionally, clinical follow-up offers extensive support to both patients and their caregivers, ensuring their well-being throughout the recovery journey.

To achieve effective follow-up, routine visits should involve a multidisciplinary team that includes ear, nose, and throat (ENT) surgeons, oncologists, radiation oncologists, nuclear medicine specialists, speech and swallowing therapists, nutritionists, and dentists. This collaborative approach promotes a comprehensive understanding of the patient's condition, addressing various aspects of their health and wellness.

The duration and frequency of the follow-up program should be customized for each patient, considering individual characteristics related to their health and cancer type. Typically, specialized follow-up for head and neck squamous cell carcinoma (HNSCC) can be concluded five years after

diagnosis. However, for specific cancers such as adenoid-cystic carcinomas, HPV-positive oropharyngeal squamous cell carcinoma (OPSCC), and head and neck neuroblastomas, follow-up should extend to ten years due to their heightened risk of late recurrence.

According to clinical practice guidelines from the European Laryngology Society (ELS), the European Head and Neck Society (EHNS), the European Society for Medical Oncology (ESMO), the European Society for Radiotherapy and Oncology (ESTRO), and the National Comprehensive Cancer Network (NCCN), clinical follow-up is recommended every 2 to 3 months for the first two years. This should then shift to every 3 to 6 months during years three to five, followed by annual visits thereafter. [1]

Following initial assessments, a thorough endoscopic evaluation is essential for examining the entire mucosal lining. The choice of endoscope depends on the specific location of the disease: a high-resolution flexible endoscope is recommended for laryngeal or hypopharyngeal conditions, while a rigid endoscope is appropriate for assessing issues in the oral cavity, sinonasal region, or nasopharynx. For patients with oropharyngeal cancer, particularly those with a history of smoking, both types of endoscopes may be utilized to ensure optimal visualization of the affected area and to screen for potential second primary tumours.

All endoscopies should utilize White and Narrow Band Imaging (NBI) to improve the visualization of mucosal and submucosal microvascular patterns. NBI employs narrow-band optical filters to enhance the view of the mucosa and the microvascular patterns within the submucosa. [18]. Since the depth of light penetration varies with wavelength, NBI filters target blue and green light (wavelengths of 415 and 540 nm, respectively), which align with haemoglobin absorption peaks. A suspicious lesion in NBI is characterized by a well-defined brownish area, marked by thick dark spots, winding vessels, and an afferent hypertrophic vessel.

Distant metastasis and recurrence:

The development of distant metastases in head and neck squamous cell carcinoma (HNSCC) shows a swift increase within the first 8 months following treatment, followed by a gradual rise from months 8 to 24, and then a significant plateau between months 24 and 84, indicating a low likelihood of late metastases. The overall incidence of diagnosed distant metastases in HNSCC is low, at less than 5% at the time of diagnosis and approximately 10–20% overall, with most cases being asymptomatic.

However, certain factors can elevate the risk of distant recurrence, particularly in advanced cases. These factors include advanced T classification of the primary tumour in the pharynx, the presence of a second primary HNSCC, having three or more neck lymph node metastases, bilateral lymph node involvement, radiological or histological evidence of extra nodal extension (ENE), and nodal metastases that are 6 cm or larger, as well as high-grade tumours, high tumour volume, lymphovascular invasion, and regional recurrence. Despite these increased risks, there is no evidence that early diagnosis of distant metastases significantly impacts prognosis. While patients with oligometastatic disease may benefit from targeted treatment, it remains challenging to predict who will develop this recurrence pattern.

The lungs are the most common site for distant metastases, occurring in about 75-80% of cases, followed by bones and the liver in 15-39% and 10-30% of cases, respectively. For metastatic patients, integrating locoregional and distant evaluations through endoscopic and radiological imaging, including assessments of the chest and abdomen, is essential. Systemic staging may occasionally reveal second primary tumours, with an incidence rate of 2% to 4% per year. Currently, there are no specific guidelines that recommend routine screening for potential second malignancies in patients diagnosed with head and neck squamous cell carcinoma (HNSCC). The only exception to this is for heavy smokers, defined as those with a smoking history of more than 20 pack-years, for whom a chest CT scan is advised even at an early stage to monitor for possible lung cancer.

The Neck Imaging and Reporting Data System (NI-RADS):

The Neck Imaging and Reporting Data System (NI-RADS) is a structured reporting template cre-

ated by the American College of Radiology (ACR) to facilitate the evaluation of potential recurrence in head and neck cancer after initial treatments like surgery and radiotherapy. [19].

NI-RADS enhances communication between radiologists and clinicians, ensuring standardized assessment and recommendations in the management of head and neck cancer recurrence.

Categories of NI-RADS:

1. NI-RADS 0: Incomplete evaluation due to lack of previous imaging for comparison.

2. NI-RADS 1: No suspicion of recurrence. This indicates either the resolution of previous findings, absence of new findings, or mere post-treatment changes like fibrocystic tissue with minimal enhancement or FDG uptake.

3. NI-RADS 2: Low suspicion of recurrence. This may include findings that are ambiguous or changes that are consistent with post-treatment changes rather than malignancy, such as:

- Intermediate signal findings
- Soft tissue lesions differing from pathological tissue
- Reduced tumor mass
- Heterogeneous enhancement in residual lymph nodes with mild-to-moderate FDG uptake
- Mucosal lesions that are likely post-treatment outcomes.

Follow-up: Recommended at 3 months, which could include PET scanning if not previously conducted.

4. NI-RADS 3: High suspicion of recurrence. Signs include:

- Nodular lesions resembling the primary tumor
- High FDG uptake (if PET is performed)
- Newly identified lymph nodes with necrosis, irregular margins, or intense FDG uptake
- Residual lymph node tissue exhibiting high uptake.

Next steps: Biopsy examination is indicated in this category.

5. NI-RADS 4: Definite evidence of relapse based on radiological or histopathological findings. This situation necessitates clinical management and a multidisciplinary approach to determine the appropriate treatment pathway.

Conclusion

The recurrence of head and neck cancer presents significant clinical challenges requiring a comprehensive and individualized management approach. By employing a combination of surgical, radiation, and chemotherapy strategies, along with multidisciplinary care and palliative support, healthcare providers can enhance patient outcomes and maintain quality of life. Continuous follow-up and patient education are pivotal in the long-term management of this complex condition. Ongoing research into novel therapies and best practices continues to improve our understanding and management of recurrent head and neck cancer.

References

1. Machiels, J.-P.; Leemans, C.R.; Golusinski, W.; Grau, C.; Licitra, L.; Gregoire, V. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2020, 31, 1462–1475. [CrossRef] [PubMed]
2. Sankaranarayanan, R.; Masuyer, E.; Swaminathan, R.; Ferlay, J.; Whelan, S. Head and neck cancer: A global perspective on epidemiology and prognosis. Anticancer Res. 1999, 18, 4779–4786.
3. Gislon, L.C.; Curado, M.P.; López, R.V.M.; de Oliveira, J.C.; de Podestá, J.R.V.; von Zeidler, S.V.; Brennan, P.; Kowalski, L.P. Risk factors associated with head and neck cancer in former smokers: A Brazilian multicentric study. Cancer Epidemiol. 2022, 78, 102143. [CrossRef]
4. Varela-Lema, L.; Ruano-Ravina, A.; Crespo, M.J.; Barros-Dios, J. Tobacco consumption and oral and pharyngeal cancer in a Spanish male population. Cancer Lett. 2010, 288, 28–35. [CrossRef]
5. Blot, W.; Mclaughlin, J.; Winn, D.; Austin, D.; Greenberg, R.; Prestonmartin, S.; Bernstein, L.; Schoenberg, J.; Stemhagen, A.; Fraumeni, J. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res. 1988, 48, 3282–3287. [PubMed]
6. Duffy, S.A.; Ronis, D.L.; McLean, S.; Fowler, K.E.; Gruber, S.B.; Wolf, G.T.; Terrell, J.E. Pretreatment Health Behaviors Predict Survival Among Patients With Head and Neck Squamous Cell Carcinoma. J. Clin. Oncol. 2009, 27, 1969–1975. [CrossRef]
7. Osazuwa-Peters, N.; Boakye, E.A.; Chen, B.Y.; Tobo, B.B.; Varvares, M.A. Association Between Head and Neck Squamous Cell Carcinoma Survival, Smoking at Diagnosis, and Marital Status. Arch. Otolaryngol. Neck Surg. 2017, 144, 43–50. [CrossRef]

8. Jégu, J.; Binder-Foucard, F.; Borel, C.; Velten, M. Trends over three decades of the risk of second primary cancer among patients with head and neck cancer. Oral Oncol. 2013, 49, 9–14. [CrossRef]
9. Hobbs, C.; Sterne, J.; Bailey, M.; Heyderman, R.; Birchall, M.; Thomas, S. Human papillomavirus and head and neck cancer: A systematic review and meta-analysis. Clin. Otolaryngol. 2006, 31, 259–266. [CrossRef]
10. Saulle, R.; Semyonov, L.; Mannocci, A.; Careri, A.; Saburri, F.; Ottolenghi, L.; Guerra, F.; La Torre, G. Human papillomavirus and cancerous diseases of the head and neck: A systematic review and meta-analysis. Oral Dis. 2014, 21, 417–431. [CrossRef]
11. Lechner, M.; Liu, J.; Masterson, L.; Fenton, T.R. HPV-associated oropharyngeal cancer: Epidemiology, molecular biology and clinical management. Nat. Rev. Clin. Oncol. 2022, 19, 306–327. [CrossRef] [PubMed]
12. Pfister, D.G.; Spencer, S.; Adelstein, D.; Adkins, D.; Anzai, Y.; Brizel, D.M.; Bruce, J.Y.; Busse, P.M.; Caudell, J.J.; Cmelak, A.J.; et al. Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J. Natl. Compr. Cancer Netw. 2020, 18, 873–898. [CrossRef] [PubMed]
13. Lee, M.H.; Cho, K.-R.; Choi, J.W.; Kong, D.-S.; Seol, H.J.; Nam, D.-H.; Jung, H.A.; Sun, J.-M.; Lee, S.-H.; Ahn, J.S.; et al. Immune Checkpoint Inhibitors for Non-Small-Cell Lung Cancer with Brain Metastasis: The Role of Gamma Knife Radiosurgery. J. Korean Neurosurg. Soc. 2021, 64, 271–281. [CrossRef] [PubMed]
14. Eckardt, A.; Barth, E.; Kokemueller, H.; Wegener, G. Recurrent carcinoma of the head and neck: Treatment strategies and survival analysis in a 20-year period. Oral Oncol. 2004, 40, 427–432. [CrossRef]
15. Pignon, J.-P.; le Ma.tre, A.; Maillard, E.; Bourhis, J.; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother. Oncol. 2009, 92, 4–14. [CrossRef]
16. Gr.nh.j, C.; Jakobsen, K.K.; Jensen, D.H.; Rasmussen, J.; Andersen, E.; Friborg, J.; von Buchwald, C. Pattern of and survival following loco-regional and distant recurrence in patients with HPV+ and HPV− oropharyngeal squamous cell carcinoma: A population-based study. Oral Oncol. 2018, 83, 127–133. [CrossRef]
17. Beswick, D.M.; Gooding, W.E.; Johnson, J.T.; Branstetter, B.F. Temporal patterns of head and neck squamous cell carcinoma recurrence with positron-emission tomography/computed tomography monitoring. Laryngoscope 2012, 122, 1512–1517. [CrossRef]
18. Piazza, C.; Del Bon, F.; Paderno, A.; Grazioli, P.; Perotti, P.; Barbieri, D.; Majorana, A.; Bardellini, E.; Peretti, G.; Nicolai, P. The diagnostic value of narrow band imaging in different oral and oropharyngeal subsites. Eur. Arch. Oto-Rhino-Laryngology 2016, 273, 3347–3353.
19. Aiken, A.H.; Farley, A.; Baugnon, K.L.; Corey, A.; El-Deiry, M.; Duszak, R.; Beitler, J.; Hudgins, P.A. Implementation of a Novel Surveillance Template for Head and Neck Cancer: Neck Imaging Reporting and Data System (NI-RADS). J. Am. Coll. Radiol. 2015, 13, 743–746.e