

Update on the Management of Carcinoma Unknown Primary with Neck Metastases

Introduction:

Carcinoma of unknown primary (CUP) in the head and neck region remains a persistent and complex challenge for clinicians worldwide. Significant advances in diagnostic modalities—such as cross-sectional imaging, molecular diagnostics, robotic surgery, and positron emission tomography (PET)—have improved the ability to identify primary sites, especially within the oropharynx, notably HPV-related cancers.^{1,2} With the rising incidence of HPV-associated oropharyngeal carcinomas, the proportion of CUP cases presenting with regional metastases and occult primaries is also increasing, emphasizing the need for updated management strategies.³

Definition and Historical Background

CUP is a heterogeneous disease characterized by metastatic cervical lymph nodes with no identifiable primary tumor despite thorough evaluation's efforts.⁴ In many of these cases were presumed to involve 'branchiogenic carcinoma' - a controversial and largely unsupported concept—since many series failed to meet the classical criteria established by Hayes Martin.⁵ It is now recognized that a significant portion of patients represent metastatic carcinoma from occult primaries, primarily within the oropharynx.⁶

Incidence

The incidence of CUP in head and neck cancers ranged between 30% and 10%. However, with the implementation of standardized protocols incorporating PET-CT, these figures have decreased to approximately 5%.^{7,8} At Guy's & St Thomas' NHS Trust, the incidence declined from 8% to 4% over the last decade.⁸ The increasing prevalence of HPV-positive cancers suggests many of these occult primaries are located within the oropharynx, particularly the tonsils and tongue base.⁹

Nomenclature and Staging

The 8th edition of the AJCC and UICC staging manuals reflects significant updates. Notably, it redefines the T0 category for p16-positive oropharyngeal and other HPV-related cancers, recognizing the difficulty of locating the primary lesion.^{10,11} Demonstrating HPV or Epstein-Barr Virus

(EBV) status via cytology or tissue samples enables better localization, mainly implicating the oropharynx and nasopharynx as primary sites.¹²

Evaluation and Diagnosis

A comprehensive, systematic approach is essential. It begins with detailed history and clinical examination, including fiber-optic nasolaryngoscopy.¹³ Modern imaging techniques such as Narrow Band Imaging (NBI) significantly increase early detection of mucosal neoplastic changes.¹⁴ Cross-sectional imaging—covering CT, MRI, and FDG PET-CT—is crucial to localize occult primaries before invasive procedures.¹⁵ When initial assessments are inconclusive, panendoscopy with bilateral tonsillectomy, directed biopsies of the tongue base, and nasopharyngeal biopsies are recommended.¹⁶ The use of robotic tongue base mucosectomy has demonstrated success in detecting primaries in more than 50% of PET-negative cases.¹⁷

Positron Emission Tomography (PET) Scanning

FDG-PET-CT is a mainstay in the evaluation of CUP, with studies reporting a primary detection rate of approximately 37% and pooled sensitivities and specificities exceeding 84%.^{18,19} Performing PET-CT prior to biopsies helps prevent false positives caused by post-inflammatory uptake, thus optimizing diagnostic accuracy.¹⁹

NICE Recommendations

The UK's NICE guidelines endorse a multi-disciplinary, stepwise approach, including ultrasound-guided FNAC, PET-CT imaging, and guided biopsies.^{7,20} These protocols have been associated with improved primary tumor detection and more precise management.²¹

Clinical Management:

Management is dictated by nodal staging and disease extent. For early-stage disease (N1), single-modality treatments such as neck dissection or involved-field radiotherapy are effective.²² For advanced disease (N2/N3), particularly with extracapsular spread, combined modality treatment—surgery, radiotherapy, and chemotherapy—is standard.²³ Recent evidence supports PET-CT-guided active surveillance following chemoradiotherapy, which demonstrates

comparable outcomes to upfront neck dissection but with less morbidity.²⁴

Surgical Management of the Neck

While traditional management involves radical or modified radical neck dissection,²⁵ recent data suggest that PET-CT-guided surveillance can better identify residual disease, thereby reducing unnecessary surgeries and their associated morbidity.²⁶

Management of the Violated Neck

Current trends favor earlier, targeted intervention – either surgery or CRT – guided by multidisciplinary assessment and advanced imaging techniques. Centralized, protocol-driven management ensures adequate treatment delivery and improved outcomes.²⁷

Branchial Cyst Carcinoma

The existence of branchial cyst carcinoma, or ‘branchiogenic carcinoma,’ remains contentious. Many series have failed to meet the classical criteria outlined by Hayes Martin, raising doubts about its true existence.¹ Patients over 35 presenting with lateral neck cystic masses should be presumed to harbor malignancy until proven otherwise.² Such patients are recommended to participate in a carcinoma of unknown primary (CUP) investigation protocol, even if initial fine-needle aspiration cytology (FNAC) does not indicate metastasis.³

Radiation Therapy to the Neck and Putative Primary Site

The extent of radiotherapy remains a subject of debate. Some centers favor unilateral irradiation of the neck and the most probable primary site, whereas others advocate for bilateral neck irradiation, or “total mucosal irradiation,” aimed at eradicating occult primaries.^{6,28} Data suggest that bilateral neck irradiation enhances local control and disease-free survival but does not invariably translate into improved overall survival.²⁹ The increased morbidity associated with extensive irradiation – such as xerostomia, dysphagia, and feeding tube dependence – remains a concern. Intensity-modulated radiotherapy (IMRT) with bilateral coverage has demonstrated a reduction in both acute and late toxicity, becoming the standard in many countries.^{30,31}

Recommended Treatment Approaches

bcT0N1M0 and cT0N1M0 without ENE: Patients may be managed effectively with single-modality therapy either selective neck dissection or involved-field radiotherapy. Close surveillance of the upper aerodigestive tract mucosa is essential post-treatment.³²

PT1N0M0 with extracapsular extension (ENE): Post-operative radiotherapy (RT), especially if ENE is detected, is advised.³³

T0N2M0 and T0N3M0: These advanced cases should typically receive primary chemoradiotherapy (CRT) followed by PET-CT-guided surveillance or combined modality treatments (neck dissection with subsequent RT or CRT), tailored on a case-by-case basis.¹⁷

Treatment Outcomes

Most literature reports improved survival with combined modality treatments. Five-year overall survival (OS) varies with nodal stage, with figures ranging from 70–100% for N1 disease to 30–60% in N3 cases.^{34,35} A large retrospective series from a single institution recorded 100% survival for N1 and 60% for N2/N3 disease, consistent with data from the Memorial Sloan Kettering Cancer Center, where two-year survival rates for regional progression-free, distant metastases-free, and overall survival exceeded 85–90%.³⁶

Patterns of Failure

Recurrences are predominantly locoregional, especially if initial treatment involved radiotherapy alone; many recurrences are associated with extracapsular disease.³⁷ Distant metastases, particularly to the lungs, often occur within the first-year post-treatment. Recurrences in potential primary sites vary markedly ranging from 0% to 66% most frequently appearing within 24 months at sites such as the oral cavity, oropharynx, and nasopharynx.³⁸

Conclusion

The management of CUP has seen significant improvements with the advent of advanced diagnostic and therapeutic modalities. Currently, the incidence of true CUP is declining to fewer than 5%, primarily due to better detection techniques; however, the apparent rise in HPV-positive cancers may influence future trends.³⁹ A comprehensive workup – including panendoscopy, bilateral tonsillectomy, biopsies of the nasopharynx and tongue base, coupled with cross-sectional imaging such as CT, MRI, and PET-CT – remains essential.¹⁸ The use of molecular diagnostics can further enhance primary site detection, enabling tailored treatment strategies.

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