

Clinical Management of Metastatic Cervical Cancer of Unknown Primary

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ABSTRACT

Metastatic cervical cancer of unknown primary (MCCUP) constitutes a challenging clinical entity for head and neck surgeons, which represents 3-5% of the total head and neck squamous cell carcinomas and 2-10% of the cases that proceed with palpable cervical lymph nodes. Usually, older male patients present with an asymptomatic, progressively enlarging neck mass, usually near the jugulodigastric lymph nodes. Despite the advancement of diagnostic modalities, such as PET/CT, endoscopy, US-FNAC, and biomarkers, some patients still have occult primary cancer with a controversial clinical management algorithm that is usually based on risk stratification. Early-stage disease is confronted with a single-modality treatment, preferably surgery, due to the staging potential, while advanced stages often require chemoradiation. The MCCUP treatment algorithm may shift toward precision medicine in the future, which offers accurate and individualized therapeutic outcomes.

Keywords: Oral cancer, neck dissection, unknown primary, neck metastasis, occult metastasis

DIAGNOSIS

The subset of patients whose malignant cells from the cervical lymph nodes did not allow the identification of the primary tumor, despite the meticulous assessment, suffer from metastatic cervical cancer of unknown primary (MCCUP) [1]. In most cases, those tumors arise in the upper aerodigestive tract, whereas primary subclavicular tumors can also cause MCCUP, such as lung and gastrointestinal malignancies [2,3]. The typical presentation of MCCUP is an asymptomatic palpable cervical lymph node in elderly males, whereas epistaxis and throat discomfort may be met, a fact that depends on the primary location of the tumor, nasopharynx or oropharynx, respectively [2,3]. A logical consequence of the multimodality diagnostic pathway should be executed to exclude an identifiable primary location of tumors [1].

An advanced laryngeal endoscopic study plays a pivotal role in assessing minor mucosal abnormalities, especially when assisted by narrow-band imaging (NBI), which allows for the accurate identification of superficial microcarcinomas in occult locations, such as the tongue base and piriform sinuses [4,5]. When conventional, non-intervening imaging modalities (CT, PET/CT, or MRI) are not diagnostic in identifying the primary tumor, blind

biopsies during pharyngeal endoscopy, tongue base mucosectomy, or tonsillectomy may be implemented to reveal the primary tumor location [1].

The final characterization of MCCUP is based on histopathologic assays with specific immunohistochemical stains, with p16 detection and EBER-ISH testing to identify HPV-positive oropharyngeal or EBV-nasopharyngeal squamous cell carcinoma, respectively [6]. On the contrary, adenocarcinomas are further divided based on the detection of thyroglobulin (Tg) and cytokeratins, such as CK7 and CK20, to identify thyroid, breast, lung, or salivary gland primary neoplasms [7].

TREATMENT

MCCUP with squamous cell features is treated with primary surgical dissection of the neck or definitive radiotherapy [1]. Cervical nodal status is the cornerstone of clinical management of MCCUP, as a reasonable therapeutic algorithm may avoid the accumulated adverse effects of combined treatment modalities (surgery, radiotherapy, systemic therapy) [8]. An early-stage, unilateral neck mass, without extranodal extension, can be treated with surgery or radiotherapy alone, while an advanced-stage MCCUP, often combined with unfavorable histopathologic characteristics, may require a multimodal treatment strategy, in a pattern that definitive or post-operative chemoradiotherapy constitutes the standard of care [9]. Nowadays, intensity-modulated radiotherapy (IMRT) allows targeting of highly suspicious mucosal surfaces while the adjacent mucosa remains intact, eliminating the adverse effects of radiotherapy [8].

Favorable long-term survival outcomes are observed in patients with MCCUP and positive p16 immunodetection, indicating that human papillomavirus (HPV) involvement acts as a prognostic biomarker [10]. The future perspective of MCCUP management may highlight the need for precision medicine that can refine the therapeutic algorithm adjusted in an accurate pattern to the individual needs of a patient, improving survival rates [11].

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