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Editorial

Management of Carcinoma of Unknown Primary in the Neck: Changing Dynamics

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Although carcinoma of unknown primary of the neck (CUP) constitutes approximately 2-4% of the squamous cell carcinoma (SCC) of the head and neck, this ratio is expected to rise parallel to the increase in incidence of HPV related oropharyngeal SCC which in many instances present with a large metastatic neck lymph node but a very difficult to detect, small primary [1-3].

Identification of primary site in CUP is still a big challenge; with modern diagnostic options like positron emission tomography/computerized tomography (PET/CT), panendoscopy, tonsillectomy and directed biopsies, only 59.6% of primary tumors are identified. Most common primary site identified in the work up of CUP is oropharynx. After every effort, unidentified, true CUPs are treated with wide-field primary irradiation or chemoradiation with or without neck dissection. Even with latest improvements in radiation technology, there are significant morbidities and complications associated with wide field primary irradiation (RT) or chemoradiation (CRT) [4-9].

Advances in transoral laser microsurgery (TLM) and robotic surgery (TORS) allowed the otolaryngologist to better detect and even simultaneously treat the primary site in CUP with relatively good functional and quality of life outcomes [2,10,11]. These studies also demonstrated that the identified primary site is almost always palatine tonsils and base of tongue (95-100%). Just like the added benefit of palatine tonsillectomy, ability to do instantaneous lingual tonsillectomy with TLM or TORS also contributed in identification of primary site. HPV positivity and p16 protein expression were seen in 80.9% and 95.2% respectively.

Since the concordance with p16 and HPV positivity is very strong (96%) and both are associated with better prognosis [2], detection of p16 overexpression using immunohistochemistry became the test of choice in a more efficient, objective and relatively inexpensive way [3]. Detection of p16 positivity in fine needle aspiration biopsy (FNAB) specimens of the CUP directs the clinicians to focus more on possible oropharyngeal primary sites. Combination of these pathologic analysis with the findings of advanced imaging technologies (CT, MRI, and PET CT) and intraoperative, magnified, tridimensional TORS and TLM examination have lead the significant improvement in identification and also simultaneous removal of primary sites [2,10-12]. While identification means avoidance of wide field RT to entire upper aero digestive tract, complete removal with negative margin after identifications might even lead the avoidance of RT to primary site and concurrent chemotherapy completely too. These kinds of targeted transoral surgeries with the application of selective neck dissections have the potential to minimize the toxicity of adjuvant RT or CRT.

Future results of the latest clinical trials related to oropharyngeal cancer, including transoral surgical cooperative group's multicenter trials (ECOG 3311, RTOG 1221) might also open new horizons in the treatment of CUP since most of CUP is identified at oropharynx. Currently, scientific, high-quality evidence is insufficient for de-escalation of treatment regimens for human papillomavirus-associated oropharyngeal carcinoma. Even though, handful of single institutional experiences have already demonstrated improvement in identification and treatment of CUP with the use of contemporary radiologic, pathologic, molecular, and therapeutic methods in their systematic approach, future, randomized, controlled clinical trials are still essential to define a more targeted, and personalized treatment regimens while minimizing the adverse events, and morbidity associated with treatment modalities.

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