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The use of ultrasound in the search for the primary site of unknown primary head and neck squamous cell cancers

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SUMMARY

Background: Although human papillomavirus detection in cervical lymph nodes of head and neck squamous cell cancers (HNSCC) of unknown primary site (UP) is indicative of a primary tumor of the oropharynx (OP), localization can remain elusive. Therefore, we investigated ultrasonography (US) for the identification of the primary tumor.
Methods: Eligible cases had HNSCC of UP after evaluation by a head and neck surgical oncologist. Controls were healthy volunteers. Transcervical and intraoral ultrasonography was performed by a standard protocol using convex (3.75–6.0 MHz and 5–7.5 MHz) transducers. US findings were compared with operative examination (exam under anesthesia, direct laryngoscopy) and biopsies. The primary outcome of interest was the presence or absence of a lesion on US.
Results: 10 cases and 20 controls were enrolled. PET/CT scans were negative/nonspecific (9), or suspicious (1) for a primary lesion. On US, predominantly hypoechoic (9 of 10) lesions were visualized consistent with base of tongue ($n = 7$) or tonsil ($n = 3$) primary tumors. On operative examination, 5 of 10 were appreciated. Two additional primaries were confirmed with biopsies "directed" by preoperative US. This represents an overall diagnostic rate of 70%, which is 20% higher than our detection rate for 2008–2010. The three cases in which a suspicious lesion was visualized on US, yet remained UP despite further interventions, could represent false positives, misclassification or operator variability. No lesions were suspected among the controls.
Conclusion: Ultrasound has promise for detection of UPs of the OP and therefore warrants further investigation.

Background

Head and neck squamous cell cancers (HNSCCs) with unknown primary site (UP) represent approximately 5% of HNSCCs [1]. Historically, HNSCCs of UP were recognized to be a heterogeneous clinical entity with subclinical primary tumors of the nasopharynx, hypopharynx and oropharynx. In the era of rising incidence of human papillomavirus (HPV)-related oropharyngeal squamous cell cancer (OPSCC), the majority of squamous cell carcinomas of the neck that present with an UP arise from the oropharynx [2–4]. HPV-positive OPSCCs tend to have small primary tumors and advanced nodal disease [5,6]. Therefore, when individuals present with large nodal disease and no obvious primary lesion, the primary is likely to be hidden within the cryptic lymphoepithelium of the oropharynx which is difficult to examine [7]. Although the tonsil and base of tongue (BOT) are the two most common subsites of unknown primaries [8], identification of the primary site remains elusive in up to 60% of HNSCCs of UP [9].

The traditional diagnostic paradigm comprises of comprehensive clinical examination including indirect mirror exam and fiberoptic laryngoscopy, and imaging. Contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) are recommended in the evaluation of HNSCCs of UP and primary

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tumor detection rates range from 9% to 20% [10,11]. PET scans demonstrate a primary tumor in 25 to 35% of cases [10,12,13]. Operative exploration of the primary site occurs in a stepwise fashion, starting with an exam under anesthesia and direct laryngoscopy with biopsy, and thereafter continuing with "blind" biopsies directed at the most common sites of UPs and bilateral palatine tonsillectomies until the UP is identified [14]. Recent case series have proposed the addition of lingual tonsillectomies to the algorithm in the event of negative biopsies and palatine tonsillectomies [15,16]. While each operative component may increase the probability of identifying the primary tumor site, each has an inherent risk (e.g., bleeding and death), prolongs time under anesthesia and could require greater than one trip to the operating room.

Successful identification of the primary tumor can have significant therapeutic implications. For example, radiotherapy fields can be limited to the oropharynx and thus reduce treatment morbidity relative to irradiation of the entire pharyngeal axis in the case of an UP. Additionally, the identification of the primary site may provide patients with therapeutic alternatives, such as definitive surgical treatment including transoral resection of the primary tumor [16,17].

In a previous study, we demonstrated that ultrasound could be used to visualize and describe anatomic characteristics of BOT malignancies [18]. With this knowledge, we sought to investigate the potential of ultrasound to detect primary tumors within the oropharynx among patients who present with HNSCC of UP.

Methods

Cases and controls were prospectively enrolled. Eligible cases included patients with a pathological diagnosis of squamous cell cancer in a cervical lymph node without clinical identification of the primary site after examination by a head and neck surgical oncologist. Exclusion criteria included clinical suspicion of a cutaneous malignancy, prior head and neck radiotherapy, or neck surgery (incisional or excisional biopsy and/or neck dissection). Controls were healthy volunteers without known head and neck cancer. The study was approved by the Greater Baltimore Medical Center (GBMC) investigational review board and written consent was obtained from all study subjects.

Ultrasound examination was performed by investigators who were not blinded to clinical information (RGB, CF). A Toshiba ultrasound model SSA-580A was used. The transducer used for the transcervical examination was convex (3.75–6.0 MHz; Model PVQ-375A) and set at 6 MHz. For the intraoral examination, an endocavitary multifrequency convex probe (5–7.5 MHz; Model PVM-651VT) set at 7.5 MHz was used.

Ultrasound examination was performed by use of a standard protocol. Subjects were seated in an ENT exam chair. In a stepwise fashion, the following transcervical views were obtained: midline sagittal, bilateral parasagittal, and coronal. Before initiating the transoral exam, patients were sprayed with topical 1% lidocaine. The transducer surface was covered with ultrasound gel and wrapped with a disposable clingy wrap before initiating intraoral ultrasonography. To visualize each side of the pharynx (including palatine tonsils), the probe was placed on the dorsum of the tongue in superior/inferior, then medio/lateral orientation. For transcervical examination, the landmarks for the BOT were determined by identifying the central portions of the hyoid bone and the mandible and dividing this into thirds. The posterior third was considered the ultrasonographic base of tongue (Fig. 1). Doppler was used to visualize the lingual artery for tumors in the BOT and carotid artery for tumors in the tonsil.

Data were recorded using a standardized case report form at the time of ultrasound examination. An ultrasound impression was ascertained which captured the suspected location of tumor, size, anatomic extent (crossing midline, adjacent site involvement, distance to either lingual or carotid artery) and echogenic characteristics of the suspected lesion and margin (representative image

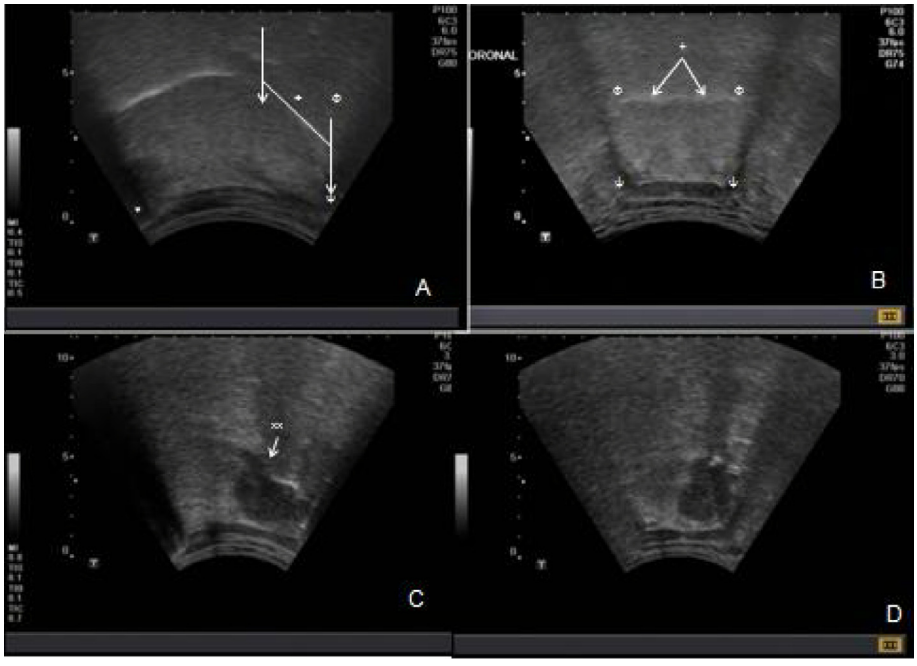

Fig. 1. Transcervical ultrasound examination of oropharynx. Parasagittal view (A) demonstrates intact hyperechoic oral mucosa of oral and base of tongue (+). The hyoid (ψ) and mandibular (∗) shadows are shown. The sonographic base of tongue is the posterior one third of the distance between the central portions of the mandible and hyoid annotated by (↓). The palatine tonsillar region is isoechoic (Φ). On coronal view (B) hyoid shadows are seen bilaterally (ψ). The oral mucosa is intact (+). The base of tongue musculature is noted to be symmetric. Panels C and D are images representative of a base of tongue lesion. On parasagittal view is a hypoechoic lesion, the majority of which is beneath the mucosal surface of the base of tongue, with a slight disruption of the mucosa (xx). The mass is also visualized in coronal view (D). Extent across midline is appreciated in coronal view.

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