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The role of transoral surgery in the diagnosis of the carcinoma of unknown origin of the head and neck

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Abstract

Purpose of review: The aim of this article is to update readers on the most recent evidence on the role of trans oral surgery (TOS) in the diagnosis of carcinoma of the unknown primary of the head and neck.

Recent findings: Tongue base mucosectomy has an important role in identifying the primary in patients who have had negative imaging, PET CT scans and ipsilateral tonsillectomy. In patients with bilateral nodal disease, tongue base mucosectomy should precede tonsillectomy. There are several unanswered questions that remain regarding sequencing of operations and use of intraoperative frozen section.

Summary: An evidence based approach to diagnosis is important to ensure the highest detection rates, and least morbidity, in patients with head and neck carcinoma of the unknown primary.

Key words: carcinoma of unknown primary, head and neck squamous cell carcinoma, tongue base mucosectomy, tonsillectomy

Objectives of article

The aim of this article is to update readers on the most recent evidence on the role of transoral surgery (TOS) in the diagnosis of carcinoma of the unknown primary of the head and neck.

Introduction

Carcinoma of the unknown primary (CUP) is defined as a patient presenting with lymphadenopathy of the head and neck, without an obvious primary tumour on initial examination and non-invasive investigation (1). The exact incidence of this condition is not clear, especially in more recent times with the increase in human papilloma virus (HPV) – mediated head and neck cancer (HNC) in some regions of the world. Previously incidence was reported to be between one and 7% of all HNC patients. (2). One study found that incidence was increasing over time in the US NCDB database – with 296 cases during 2004-2009, versus 668 cases during 2010-2015,mirroring the increase in HPV-mediated HNC (3). In a single centre study there was also an increase in the detection rates of the primary over time - 50.0% vs 64.9%, from calendar periods 2005-2008 to 2012-2014 (*P* = .38) - albeit statistically non-significant.(4) A systematic review in 2015 found that 36% of 659 CUPs that were reported were p16 and HPV DNA positive (5).

One may ask why it is important to identify the primary site in this clinical circumstance. The reason is that by identifying the primary site is associated with better survival. (6) This may be partly due to the fact that those cases which were identified are more likely to be HPV positive, and so may have better survival. However, identification of the primary site is also associated with more targeted treatment which is likely to result in less toxicity, long-term functional deficit, and be more cost-effective. The same retrospective study showed that identifying the primary site resulted in savings between $5774 and $8619 per patient, compared to when no primary site was identified. This was partly because in a few patients were spared radiotherapy altogether and up to 30% received lower doses or were spared radiotherapy to the contralateral side of the oropharynx. (6)

Initial investigations

The investigation of CUP proceeds from the simple to the more complex. As always, a thorough history and clinical examination should be undertaken. Where available, an

examination with narrowband imaging should be undertaken, if routine examination does not identify an obvious primary site. A recent metanalysis demonstrated the detection of a primary site in 35% of patients undergoing narrow band imaging when normal clinical examination had not revealed the primary. (7). Recently a group in Japan described transoral flexible endoscopy in the clinic for patient with CUP. They found that patients tolerated the procedure well, and that it increased the detection of oropharyngeal primaries, and so this may be a promising additional investigation in future.(8*)

The confirmation of the pathology of the CUP should be undertaken by sampling of the involved lymph node. This is most effectively done by a core biopsy, especially if guided by ultrasound. Core biopsy has been found to provide higher detection rates than FNA, because it provides substantially more material for analysis, especially because often metastatic lymph nodes in HPV-mediated disease are cystic, and therefore yield a lot of fluid on FNA. (9,10). A sequential approach has also been described where if any biopsy is performed, followed by immediate assessment by a cytopathologist, and proceeding to a core biopsy, if the FNA results are negative (9). Open biopsy of involved nodes should not really be done, if at all possible.

The material should then be tested for p16 immunohistochemistry , as this will aid the localisation of the primary tumour. Several studies show that p16-positivity of nodal metastases correlates strongly with oropharyngeal origin. For example, in a study by Jakscha et al, 77% the 31 oropharyngeal tumours were p16 positive, compared to only 1 of 37 (3%) non-oropharyngeal tumours ($P < 0.001$; Fisher's exact) (11). If positive on p16 IHC, the sample should then be routinely tested for HPV DNA or RNA, especially in regions with low attributable fractions, and/or heavy smokers. The confirmatory HPV testing identifies cases where tumours are p16 positive, but HPV negative, as they may have poorer prognosis than p16 positive/ HPV positive tumours (12*)

Where the nodal metastasis is negative for p16 IHC, consideration should be given to EBV DNA testing, especially in patients with level IV or V, or bilateral nodal disease. This is, of course, especially important in regions with high EBV mediated HNC. (13)

This should then be followed by imaging studies; the most common modality being CT scanning or MRI. Both modalities appear to have similar efficacy in detecting the primary site in this specific setting. (14-16). Additionally, both modalities can identify gross nodal extracapsular extension, albeit MRI is reported to have a slightly better accuracy compared to CT scan in this regard in some studies (17).

An alternative imaging modality that is increasingly being used is FDG-PETPET CT scan. Two meta analyses have shown demonstrated the utility of PET CT scan in in the detection of the primary site, with detection rates of 24.5% (18) and 37% in the more recent meta-analysis of 433 patients (19). A recent study showed that the benefit from the use of PET CT scan in patients where the primary site is still not evident after clinical examination and cross-sectional imaging was only 7% (95% CI 2–21%) (20). So, in agreement with the ASCO guidelines, we would recommend sequential use of pet CT scan only if the primary site remains undetected by CT or MRI.

Indications for surgical evaluation

If, after the above meticulous evaluation of a patient, the primary site remains undetected, then surgical evaluation should be considered. This begins with a panendoscopy and examination under anaesthesia. During that, a careful examination and palpation of the base of tongue and tonsils should be undertaken, and where possible examination by NBI. In addition, assessment by microscopy has been shown to identify a significantly higher number of primary tumours in the base of tongue compare to rigid oesophagoscopy (94% versus 25% respectively) (21)

If the primary site still remains to be elusive at that point, random biopsies should be avoided as they have low yield rates (approximately 3.2% vs 29.6%, $p<0.0002$) compared to tonsillectomy (22).

At this point, there is a decision to be made about whether to do tonsillectomy first or tongue base mucosectomy?

Unilateral nodal disease

The majority of patients will have unilateral nodal disease. In these cases, the first operation would be an ipsilateral tonsillectomy, because this would identify a further 31% (16-45%) of patients (23), and it is technically an easier and less expensive operation than tongue base mucosectomy.

If the ipsilateral tonsillectomy is negative, then undertaking an ipsilateral TBM is recommended. A recent meta-analysis determined that overall tongue based mucosectomy identify the primary in 64% of cases were no primary had been identified by clinical examination and imaging. This rose to 78% when there was a negative work up even after palatine tonsillectomy (23). Similar rates have been identified by other systematic reviews (24, 25).Detection rates are much lower in HPV-negative cases with a detection rate of only 13% reported in one recent study (26). This has been recently confirmed in a recent meta-analysis with detection rates of 82% in HPV-mediated CUP, compared to 12% in HPV-negative CUP cases (25).

Bilateral TBM with bilateral tonsillectomy should be avoided due to risk of circumferential stenosis, especially after radiotherapy. Therefore, if ipsilateral tonsillectomy and TBM are negative, there is some debate as to whether one undertakes further surgery, and whether that should be a contralateral tonsillectomy or contralateral TBM. The meta-analysis (23) found that bilateral primaries in the tonsil were identified in 0.69% of cases, and in the contralateral tonsil in 0.23% of cases. On the other hand, contralateral TBM primaries were identified in 1.85% cases and bilateral TBM tumours in 0.23% of cases. It is therefore a judgement call as to whether to do a further procedure. All things being equal, I favour contralateral TBM as this may yield a marginally higher detection rate.

Bilateral nodal disease

In this situation, it is more likely that the primary is in the tongue base. Therefore TBM of the side of the tongue with the heavier burden of nodal disease should be undertaken. If this is negative, then TBM of the contralateral side should be undertaken, and if this is also negative, followed by ipsilateral tonsillectomy. Again bilateral TBM and bilateral tonsillectomy should be avoided due to risk of circumferential stenosis.

Tissue processing, reporting and involved margins

It should be noted that in all cases the tissue samples must be clearly oriented , marked and submitted entirely for serial sectioning and histological examination, whether during frozen section or histologically. Staining with p16 immunohistochemistry can improve detection rates. Margins should be clearly reported. In a limited systematic review, clear margins were reported to be obtained in 60% (range 0%-85%) of resected occult tumours (24).

Complications of transoral surgery

In terms of complications, haemorrhage is the most commonly reported complication, with an incidence of 4.8% in a meta-analysis of the published literature (23). Other rare complications include gastrostomy , alteration of tongue sensitivity and swelling, chest infection, pulmonary embolus, readmission due to pain and dehydration. Another study found that the average weight reduction was 2.5 ± 4.3 kg as a result of TBM.

The reported mean length of stay varied between 1.4 and 6.3 days (27). It should be noted that TORS TBM results in significantly less acute morbidity than therapeutic base of tongue TORS, with OR of 0.39 (p=0.081) of moderate/severe dysphagia as determined by DIGEST overall scores for TBM compared to resection for a primary (28).

Some outstanding issues

Type of TBM

There appears to be no significant difference in the detection rates between transoral laser surgery and transoral robotic surgery. In the meta-analysis, the pooled proportion identified by TORS, based on 15 case-series, was 74% (95% CI, 68%, 79%), and by TLM (based on three studies) was 91% (95% CI 85%, 98%) (23). Similar findings were reported by a smaller more recent meta-analysis (25).

Sequencing

A debate arises around the sequencing of procedures, that is whether to do tonsillectomy and tongue base mucosectomy concurrently or sequentially. In those cases, where the two procedures were done concurrently, a primary site was identified in 73% of cases, with TBM identifying primary in 64% of cases (23). However, if TBM is done after a negative

tonsillectomy, detection rates rose to 78%. A further consideration is cost-effectiveness. Byrd et al (29) showed that concurrent procedures were associated with lower direct costs but, at the end higher overall expenses, approximately $2900 more per patient, resulting from higher pain levels, resulting in more complications rates and longer in patients stays to control the pain.

Use of intro-operative frozen section

Some centres use frozen section during the operation to determine whether to proceed to TBM after palatine tonsillectomy. In the meta-analysis (23), 8 studies utilised this protocol - the primary identification rate by TBM was 61% (95%CI 36-61). Using frozen section may have the benefit of reducing the number of TBMs undertaken, and so reducing pain and hospital stay. It also has the advantage of allowing immediate assessment of margins and re-resection of the areas where close margins exist to reduce the need for postoperative adjuvant therapy. However it does have disadvantages: there is an inevitable increase in the duration of surgery and costs. To date, there have no cost effectiveness evaluations of this paradigm. Furthermore, a recent study suggests that , whilst use of frozen section does improve sensitivity of margin assessment (from 82.8% to 88.9%), 11% of cases exhibited at least one 'non-diagnostic' margin, and the use of frozen section overcalls approximately 11% of margins as involved, which later are found to be negative on definitive histological assessment (30). This may result in removal of larger amounts of tongue base tissue than is absolutely required.

Future directions

HPV DNA testing of FNAs

As discussed above, HPV-mediated metastatic nodes can often yield hypocellular samples on FNA that are not sufficient to undertake p16 IHC (31). A recent study of 93 cases demonstrated the feasibility and relatively high accuracy of HPVDNA testing on FNA aspirates with positive and negative predictive values of 96.3% [95% CI 87.3-99.0%] and 74.2% [95% CI 59.9-84.7%] respectively, and a mean turn-around time of four calendar days. (32)

Enhanced intraoperative visualisation for detection of primary

Fluorescence lifetime imaging (FLIm) is a form of enhanced visualisation technology utilising the ability of tumour tissues to autoflouresce when exposed to ultrashort pulses of light. The technique depends on differences in the exponential decay rate of the photon emission of a fluorophore. A recent proof of concept study demonstrated that FLIm could identify all 3 patients that had primaries, and could also identify all 3 patients who did not have primaries, and hence holds promise for the future (33).

Key points

Identification of the site of the primary is important in patients presenting with CUP as it helps improve outcomes and reduce overtreatment and attending morbidity.

CUP patients should undergo a systematic, evidence based protocol of investigations, that initially should include clinical examination, narrow band imaging if available, cross-sectional imaging, and PETCT if available.

Surgical diagnosis with examination under anaesthetic, tonsillectomy and tongue base mucosectomy (TBM) is effective and indicated if nonsurgical investigations do not identify a primary.

CUP patients with unilateral nodal disease should undergo ipsilateral tonsillectomy and then ipsilateral TBM if tonsillectomy was negative. The sequencing of these procedures (separate or same sitting) is still under debate.

CUP patients with bilateral nodal disease should undergo ipsilateral then contralateral TBM, as a tongue base tumour is more likely.

All tissue samples must be clearly oriented, marked and submitted entirely for serial sectioning and histological examination.

Declaration of interest

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