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Reducing the unknowns: A systematic review & meta-analysis of the effectiveness of trans-oral surgical techniques in identifying head and neck primary cancer in carcinoma unknown primary

Highlights

- Head & neck carcinoma unknown primary (CUP) is rare due to radiological advances
- Trans-oral surgical techniques in head & neck CUP work up are expanding
- Lingual tonsillectomy is effective with primary cancer identification rate of 45%
- Trans-oral laser & robotic surgery is effective but heterogeneity limit conclusions
- Largest systematic review and meta-analysis addressing surgery role in CUP work up and effects of human papilloma virus on the primary cancer detection rate.

Abstract

Objectives: The use of transoral robotic surgery (TORS), transoral laser microsurgery (TLM) and more recently reported transoral endoscopic electrocautery (TOEC) in identifying the primary cancer in head and neck Carcinoma Unknown Primary (CUP) patients have gained popularity. This review aims to assess the effectiveness of TORS, TLM and TOEC.

Materials & Methods: A systematic review and meta-analysis was carried out. EMBASE, MEDLINE and CINAHL databases were searched from inception to September 2020. All primary studies were considered for inclusion. Primary outcome measure was detection rates of primary cancer of the different techniques. Secondary outcome measures were complications and length of hospital stay.

Results: 289 studies were identified of which 30 met the inclusion criteria. The primary cancer was identified in 567 /777 patients (pooled results was 64% (95% CI 54-73). The primary identification rates were 45% and 32% in lingual (n=273) and palatine tonsillectomy (n=118) respectively. The primary cancer identification rates by surgical techniques are: TORS was 60% (95% CI 49-70), TLM was 80% (95% CI 0.58, 1.01), TOEC was 41% (95% CI 0.05, 0.76). 529/777 (68%) tumours were Human Papilloma Virus (HPV) related. The pooled data of studies that reported on detection rates relating to HPV status were 178/216 (82%) for HPV + ve and 7/59 (12%) for HPV- ve tumours. Coefficient of variation results suggest heterogenous data for TORS and TLM. The commonest complication was haemorrhage (5.3%). The length of reported hospital stay ranged from 1.4-7 days.

Conclusions: This is the largest systematic review in the subject. The quality of studies and heterogeneity of data limit conclusive findings. Lingual tonsillectomy is an effective procedure in CUP work up. Further larger, multicentre, prospective studies of PET CT negative CUP patients is needed to draw conclusive results.

Keywords: Head & Neck Carcinoma Unknown Primary, Trans-Oral Surgical techniques

INTRODUCTION

Carcinoma of Unknown Primary (CUP) in the Head & Neck (H&N) is a subset of H&N cancer with a biopsy proven cancer metastases of the neck lymph nodes containing squamous cell carcinoma (SCC), however, clinical assessment and radiological investigations including Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET) combined with Computed Tomography (CT) fail to identify a H&N primary cancer index site. This subset of H&N cancer patients represent a complex diagnostic dilemma for the H&N surgeon. Due to standardised diagnostic protocols, the incidence of H&N CUP as reported in the literature has subsequently reached a plateau over the last 10 years at around 5% of all types of H&N SCC [1-5]. The increased sophistication of diagnostic techniques including PET CT availability and new novel techniques such as PET MRI and diffusion weighted MRI meant that this condition has become increasingly rare. Despite the aforementioned investigations, studies have reported that in up to 43% of cases the primary cancer remains undetected radiologically [6].

With the aim of de-intensifying radiotherapy volumes, or obviating its need, and minimising side effects of total mucosal irradiation (Figure 1a vs Figure 1b radiotherapy volumes), recent surgical techniques using advances in technology and specifically optics have been used in an attempt to identify the primary cancer in H&N CUP patients. Trans-oral approaches include Trans-oral robotic surgery (TORS), trans-oral laser microsurgery (TLM), Trans-oral endoscopic UltraSonic Surgery (TOUSS) and more recently popularised trans-oral endoscopic electrocautery (TOEC) are used in oropharyngeal resections.

This systematic review and meta-analysis aims to incorporate the more recent evidence and update the systematic reviews by Farooq et al 2019 [5] and Meccariello et al 2019 [7] by including recent publications of the TOEC technique. The rationale for this study is to review the available evidence for the effectiveness of these surgical techniques. The primary outcome measure of this study is to systematically assess how effective TORS, TLM, TOUSS and TOEC are in identifying a primary index cancer in H&N CUP work up by measuring the identification rate of the primary cancer in Human Papilloma Virus (HPV) positive and negative tumours. Secondary outcome measures are reported complications and length of hospital stay.

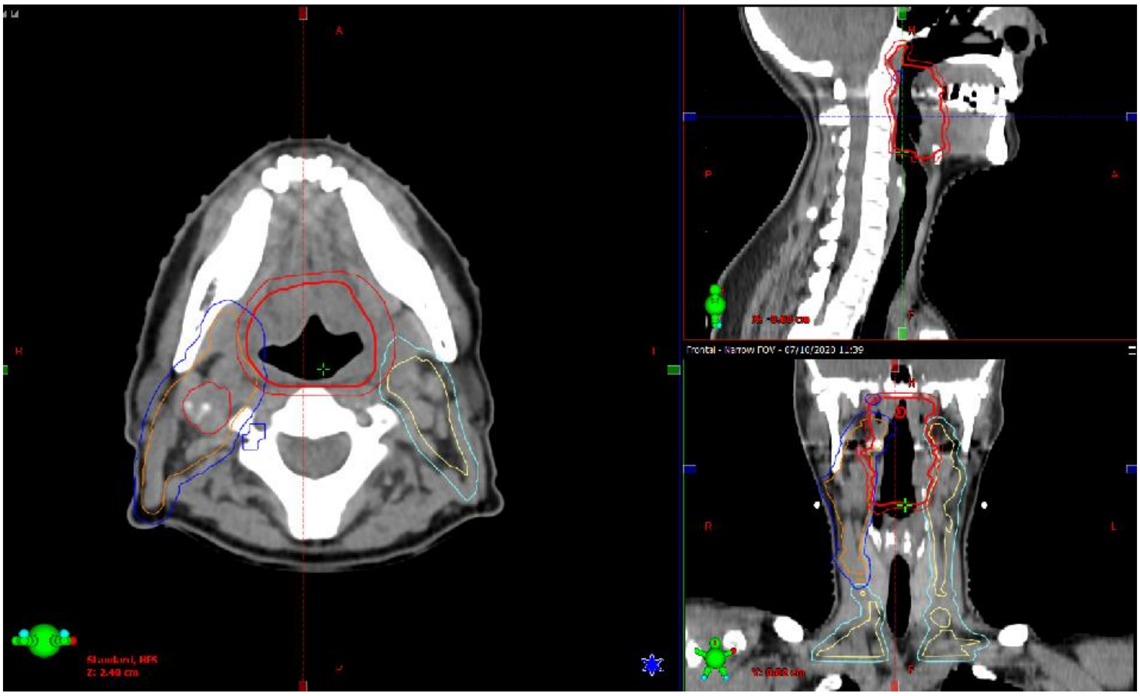

Figure 1a. Radiotherapy volumes in a H&N CUP patient where clinical, radiological, palatine tonsillectomy & lingual tonsillectomy did not identify a primary cancer in right neck CUP. The area covered by the red circle indicate Gross Tumour Volume of the primary and nodal disease which received 70 Grays.

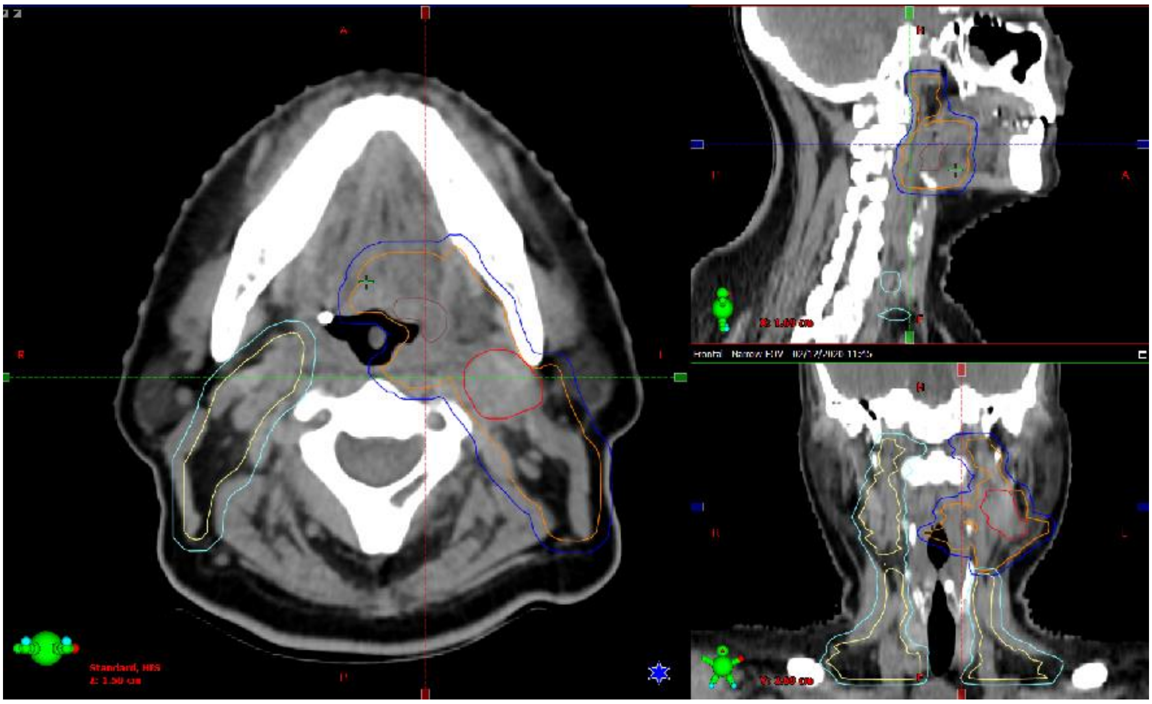

Figure 1b. Radiotherapy volumes in H&N CUP patient with negative clinical & radiological investigations. A concurrent palatine and lingual tonsillectomies identified a left base of tongue T1 10 mm SCC. Note the reduced Gross Tumour Volume in the left base of tongue receiving 70 Grays.

METHODS

A systematic review and meta-analysis using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting methodology of studies that addressed diagnostic surgical methods used to identify the primary H&N cancer in CUP work up was carried out. This project was undertaken as part of a master's dissertation. A study protocol was submitted prior to carrying out the systematic review which gained institutional approval.

Eligibility criteria

A) Types/characteristics of studies

- All primary studies of any design including randomised controlled trials (RCT), non-controlled trials, case series, case reports/studies and cross-sectional studies were eligible for inclusion

- All published articles in print, online or in press were included.

- All published English language articles from inception of the search databases until September 2020 were included. Non-English articles were excluded due to translation difficulty.

B) Population/participants

Studies included adult human patients only with H&N CUP diagnosis.

C) Intervention

Studies included have to report on transoral approaches (TORS, TLM, TOUSS & TOEC) to perform lingual and/or palatine tonsillectomy procedures used to identify the primary cancer of H&N CUP patients.

D) Settings

Any surgical centre including district general hospitals and tertiary centres carrying TORS, TLM, TOUSS & TOEC were included.

E) Comparators

TORS was considered the intervention arm and the comparators were TLM, TOUSS and TOEC if a RCT was found. Otherwise all studies reporting on transoral surgical approaches (TORS, TLM, TOUSS & TOEC) to perform the lingual and palatine tonsillectomy were included.

F) Outcomes

The included studies were assessed for the following outcomes.

Primary outcome:

- Primary cancer detection rates of the different transoral surgical techniques used in the study

Secondary outcomes:

- Post-operative complications (haemorrhage, need for gastrostomy (feeding tube) insertion, other complications, death).
- Length of hospital stay.

Information Sources

A systematic, computerised literature search of bibliographic databases using the following electronic databases were conducted:

- MEDLINE via Ovid (From inception to September 2020. last searched 28th of September 2020)
- EMBASE (From inception to September 2020. last searched 29th September 2020)
- CINAHL (From inception to September 2020. last searched 30th September 2020)

The databases used were in line with recent published systematic reviews literature to maintain consistency [5].

Search strategy

A search strategy was compiled using the aforementioned Population, Intervention, Comparators and Outcomes (PICO) analysis to guide its formation and exhaust all the potential terms as much as possible that eventually formed the Boolean operators to identify potential articles (Appendix 1).

The grey literature was searched by contacting other studies authors personally known to this systematic review authors to extract other relevant studies. References list of articles were also screened manually for inclusion of similar studies.

Study selection

Retrieved titles were first read by two reviewers (AA & CG), if relevant, abstracts were then screened. If necessary, full articles were screened to assess the suitability of the study to the inclusion criteria. Studies included in systematic reviews of similar population and intervention as this systematic review were included. The PRISMA flow diagram documentation was used for the study selection process and reasons for exclusion were noted.

Duplicate articles were removed. Non-English studies were excluded. Cadaveric studies were excluded. Studies that did not use transoral approaches were excluded. Studies that did not report the primary cancer identification rate were excluded. Studies that did not provide full data (study abstract and site of the primary head and cancer) were excluded.

Data collection process

Data extraction form was compiled and the data was collected and collated into a Microsoft Excel spreadsheet ®. The data extraction form was piloted for the first identified study and adjusted. Extracted data included demographics of the patients, design of the studies, investigations performed pre-operatively, primary tumour site identification using TORS, TLM, TOEC, adverse events post-operatively and length of hospital stay.

Human Papilloma Virus (HPV) data were extracted from the individual studies in terms of the total included HPV +ve and HPV-ve tumours. If the study included the detection rate individually of the HPV +ve and HPV -ve tumours this data was extracted for further analysis. HPV positivity were taken as either in situ hybridisation confirming HPV related tumours or P16 positivity as a surrogate marker for HPV.

Risk of bias

One reviewer (AA) performed the risk of bias analysis. Joanna Briggs Institute adopted criteria for case series and case reports were used [8]. The results of the assessment of bias of studies updates the assessment by Farooq at al [5] by incorporating recent publications. The results were tabulated (Appendix 2).

Summary measures & synthesis of results

The relevant data from the included full text articles were extracted. The results were tabulated and narratively described.

As studies were deemed to have similar patient and study characteristics, the proportions identified were pooled together and then subsequently separated for each surgical technique used (TORS vs TLM vs TOUSS vs TOEC) using random effect mixed model in meta-analysis in STATA (version 16). Mean length of hospital stays and post-operative complications were reported. PRISMA guidelines were used for reporting of results and a meta-analysis was performed [9].

Ethics

As this study is a systematic review of published literature and does not involve research on patients, NHS ethical approval is not necessary according to the University of Sheffield guidance.

RESULTS

Selection of studies

289 studies were retrieved and 32 duplicates and updated studies were excluded. After screening the records using titles and abstracts, a further 227 records were excluded as they were either not addressing the study questions or were systematic reviews of similar research question (but did not specifically address the surgical technique question as in this study). One further study was excluded as an updated publication from the same institution was found. Ultimately 30 studies with data relevant to the research question were included in this systematic review. Figure 2 shows the PRISMA flow chart.

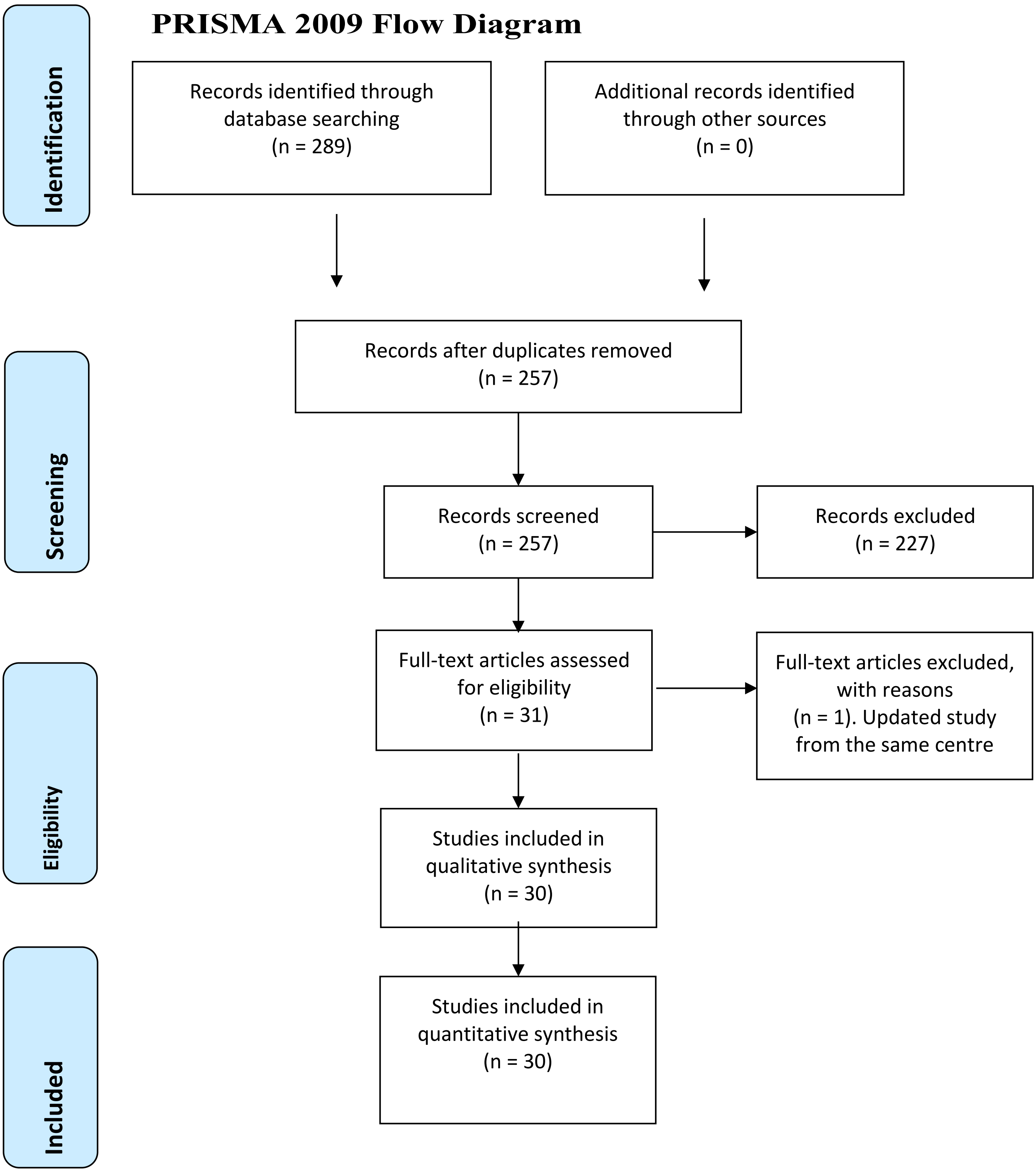

Figure 2. PRISMA flow chart

Study Characteristics

Design

The included studies are summarised in table 1. The publications period of the studies was from 2011 to 2020. There were 28 case series and 2 case reports with one prospective study [10], four multi-institutional studies [11-14] and 24 single institution studies [10, 15-38] and 2 studies did not declare their study settings [39,40].

Studies sizes

The case series sizes varied from 4 to 65 patients. For studies that only used one transoral surgical technique for lingual tonsillectomy, TORS case series size range was 4 to 64, TLM case series size range was 18 to 61 and 9 patients had TOEC. Two studies used more than one trans-oral surgical techniques ([16] had 16 patients and [38] had 65 patients). TOUSS publications did not mention it was used in H&N CUP work up.

Population

The number of patients included across 30 studies was 778 patients, who had biopsy proven metastatic squamous cell carcinoma in the neck without an apparent primary cancer. One patient was excluded from the data analysis due to incomplete data [18]. Of the studies that identified the gender of patients who had undergone surgery, 96% were male. The mean patients age in the studies that have clearly stated the mean age of CUP patient population was 57.3 years old. HPV related disease was present in 529 patients (68.7%). Neck nodal status was available for 597 (76.7%) of patients.

Intervention

The 30 studies included in this systematic review included a total 867 procedures on patients with CUP. As some patients had multiple procedures to attempt to identify the primary cancer (e.g. combined lingual tonsillectomy & palatine tonsillectomy), there were more procedures than the number of patients. TORS procedure was performed on 551 patients, 149 patients had TLM procedures and 12 patients had TOEC procedures. TOUSS was not performed. In the study by Graboyes et al, they did not differentiate between TORM and TLM [38]. There were 549 lingual tonsillectomies and 345 palatine tonsillectomies performed.

Comparisons

There were 23 studies that used the TORS technique to attempt to identify the primary cancer, and 4 studies only used the TLM technique [15, 18, 20, 33], whilst only 1 study used the TOEC technique [10]. In 2 case series multiple surgical techniques were used to perform the diagnostic procedure [16, 38] of which 1 series did not clearly differentiate between TORS & TLM in their results [38].

Lingual tonsillectomies were performed in 401/549 (73%) via TORS whilst 71 (12.9%) were performed by the TLM technique; only 12 (2.9%) were performed by the TOEC technique demonstrating its infancy compared to the more established former techniques. It was not possible to establish the surgical technique for 65 lingual tonsillectomies.

Palatine tonsillectomies were performed in 235/345 (68.1%) via TORS, 45 (13%) were via TLM and no palatine tonsillectomies were performed via the TOEC technique. It was not possible to establish the surgical technique for 65 palatine tonsillectomies. [38].

Outcomes

The overall pooled primary cancer identification rate was 64% (95% CI 54-73). The pooled primary identification rate for lingual tonsillectomy was 45% (95% CI 37-52) and 32% in palatine tonsillectomy (95% CI 21-43).Of the studies that differentiated between surgical techniques, the pooled rate of primary cancer identification for TORS was 60% (95% CI 49-70), TLM was 80% (95% CI 0.58, 1.01), and TOEC was 41% (95% CI 0.05, 0.76).

A further breakdown of the pooled identification by procedure shows that TORS had identified lingual tonsil primary in 45% (95% CI 36-55) and 50% (95% 33-66) of lingual tonsil primaries were identified by TLM. TOEC had the lowest pooled primary identification in the lingual tonsil 25% (95% CI 10-61). Amongst palatine tonsillectomies, TORS identified 26% (95% CI 14-38) of the primaries in this group whilst TLM identified 41% (95% CI 22-60). No TOEC palatine tonsillectomies were performed. One study [38] did not differentiate in the surgical technique used in lingual tonsillectomies and its findings were included in the lingual tonsillectomy detection rate only. Table 1 summarises the results of the identification rate of the different studies along with the findings of the lingual and palatine tonsillectomy.

Author	Detection rate by TORS/TLM/TOEC			Detection rate by Lingual tonsillectomy			Detection rate by palatine tonsillectomy	
	TORS	TLM	TOEC	TORS	TLM	TOEC	TORS	TLM
Mehta 2013	9/10 (90%)			9/10 (90%)				
Channir 15	7/13 (54%)			7/13 (54%)				
Patel 2013	34/47 (72%)			21/41 (51%)			13/47 (28%)	
Winter 17	17/32 (53%)			17/32 (53%)				
Durmus 14	17/22 (77%)			4/14 (28.5%)			13/17 (76.5%)	
Geltzeiler 2017	37/50 (74%)			32/50 (64%)			5/50 (10%)	
Hatten 17	48/60 (80%)			28/60 (47%)			18/60 (30%)	
Byrd 2014	19/22 (86%)			16/22 (73%)			3/22 (13.6%)	
Khan/Kass 2016	16/21 (76%)							
Blanco 13	1/4 (25%)			0/4 (0%)			¼ (25%)	
Krishnan17	5/7 (71%)			5/7 (71%)				
Patel 2017	26/35 (74%)			15/35 (42%)			13/35 (37%) 2 Cases of both lingual & palatin tonsils. 1 case of glossotonsillar sulcus	
Khan 2017	48/64 (75%)							
Wolford 11	4/9 (44%)			4/9 (44%)				
Newman 13	10/12 (83%)							
Abuzeid 13	1/1 (100%)			1/1 (100%)				
Mourad 13	0/1 (0%)			0/1 (0%)				
Lee 2020	4/8 (50%)			4/8 (50%)				
Al-Mulki20	23/29 (79%)							
Ryan 2018	8/14 (57%)			8/14 (57%)				
Kubik 2020	3/23 (13%)			3/23 (13%)				
Isenberg 20	23/48 (48%)			23/48 (48%)				
Nilsson 20	5/13 (38%			5/13 (38%				
Karni 2011		17/18 (94%)			11/18 (61%)			6/18 (33%)
Nagel 2014		31/36 (86%)			13/19 (68%)			
Kuta 2017		25/27 (93%)			12/27 (44%)			13/27 (48%)
Herruer 20		55/61 (90.2%)						
Graboyes 2015	No differentiation between TORS & TLM so analysed separately 61/65 (94%)			27/65 (41.5%)			34/65 (52%)	
Sudoko 2018	1/6 (16.6%)	2/7 (28.6%)	1/3 (33.3%)	1/6 (16.6%)	2/7 (28.6%)	1/3 (33.3%)		
Davies-Husband 2018			4/9 (44%)			4/9 (44%)		
Total pooled rate (95% CI)*	60% (49%, 70%)	80% (58%, 100%)	41% (5%, 76%)	45% (36%, 55%)	50% (33%, 66%)	25% (10%, 61%)	26% (14%, 38%)	41% (22%, 60%)

Table 1: TORS/TLM/TOEC primary tumour detection rate by lingual & palatine tonsillectomy
*Based on case series only (excluding Graboyes et al as unclear whether TORS or TLM used)

Human Papilloma Virus Effect

24 studies reported on the HPV status of the included patients. 13 studies gave further analysis of the primary identification rate in HPV positive and negative tumours. 529/777 (68%) were HPV +ve tumours. Further analysis on the primary identification rate in relation to HPV status in the studies that included this data showed a detection rate in 178/216 (82%) HPV +ve reported carcinoma of unknown tumours. 7/59 (12%) of the primary cancers in HPV -ve tumours were identified. Table 2 summarises the results of the included studies HPV data.

Study author	No. of patients	Technique	HPV status	Detection rate of HPV +ve CUP	Detection rate of HPV -ve CUP	Overall detection rate
Mehta 2013	10	TORS	80% HPV +ve 10% HPV-ve 10% unknown	8/8 (100%)	1/1(100%)	90%
Channir 15	13	TORS	54% HPV +ve 46% HPV -ve	7/7 (100%)	0/6(0%)	54%
Patel 2013	47	TORS	55% HPV +ve 17% HPV -ve 29% unknown	NS	NS	72%
Winter 17	32	TORS	72% HPV +ve 25% HPV -ve 3% unknown	NS	NS	53%
Durmus 14	22	TORS	73% HPV +ve 18% HPV -ve 9% unknown	NS	NS	77%
Geltzeiler 2017	50	TORS	92% HPV +ve 8% HPV -ve	NS	NS	74%
Hatten 17	60	TORS	92% HPV +ve 8% HPV -ve	NS	NS	80%
Byrd 2014	22	TORS	90% HPV +ve 5% HPV -ve 5% unknown	NS	NS	86%
Khan/Kass 2016	21	TORS	100% HPV +ve	16/21 (76%)	0/0	76%
Blanco 13	4	TORS	NS	NS	NS	25%
Krishnan17	7	TORS	86% HPV +ve 14% HPV -ve	5/6 (83%)	0/1 (0%)	71%
Patel 2017	35	TORS	51.4% HPV+ve 17.1% HPV-ve 31% unknwon	13/18 (72%)	0/6 (0%)	74%
Khan 2017	64	TORS	84.4% HPV+ve 3.1% HPV-ve 12.5% unknown	NS	NS	75%
Wolford 11	9	TORS	NS	NS	NS	44%
Newman 13	12	TORS	83% HPV +ve 17% HPV -ve	NS	NS	83%
Abuzeid 13	1	TORS	100% HPV +ve	1/1 (100%)	0/0	100%
Mourad 13	1	TORS	NS	NS	NS	0%
Lee 2020	8	TORS	NS	NS	NS	50%
Al-Mulki 20	29	TORS	100% HPV +ve	23/29 (79%)	0/0	79%
Ryan 2018	14	TORS	78.5% HPV +ve 21.5% HPV -ve	8/11 (72.7%)	0/3(0%)	57%
Kubik 2020	23	TORS	100% HPV-ve	0/0	3/23 (13%)	13%
Isenberg 20	48	TORS	91% HPV +ve 9% HPV -ve	21/48 HPV +ve	2/48 HPV-ve	48%
Nilsson 20	13	TORS	NS	NS	NS	38%
Karni 2011	18	TLM	NS	NS	NS	94%
Nagel 2014	36	TLM	86% HPV +ve 14% HPV-ve	29/31 (94%)	2/5 (40%)	86%
Kuta 2017	27	TLM	93% HPV +ve 7% HPV -ve	NS	NS	93%
Herruer 20	61	TLM	91.9% HPV +ve 6.5% HPV-ve 1.6% unknown	NS	NS	90.2%
Graboyes 2015	65	TORS & TLM	100% HPV+ve	61/65 (94%)	0/0	94%
Sudoko 2018	16	TORS, TLM & TLC	75% HPV+ve 25% HPV-VE	3/12 (25%)	1/4(25%)	25%
Davies-Husband 2018	9	TOEC	77.7% HPV+ve 11.1% HPV-ve 11.1% unknown	4/7 (57%)	0/1 (0%)	44%
Total	777		529 HPV +ve (68%)	178/216 (82%)*	7/59 (12%)*	

Table 2: HPV data *Isenberg et al excluded as extrapolation of percentages of HPV+ve/-ve/unknown not possible.

Post-operative complications and length of stay

Table 3 shows the reported complications and length of stay of the studies. 13 studies reported on all expected adverse events and 9 reported on selected adverse events. 21 studies reported on mortality rate. 1 death occurred due to a post-operative cardio-respiratory event [27]. 18 studies reported on haemorrhage rate with 29/544 (5.3%) of patients experienced bleeding post-operatively [11, 13, 14, 16, 18, 20, 25, 26, 27, 36, 38]. Gastrostomy tube requirement was 0.42% (2 /470) [24, 26]. Other complications included pain, tongue swelling and sensitivity, dehydration secondary to pain caused by fungal infection. Only six studies reported on the length of stay which ranged between 1.4 - >7 days [10, 18, 28 – 31]. The prolonged hospital stays were amongst patients who had concurrent neck dissection and their stay prolonged by high neck drain output.

Author	Surgical technique	Haemorrhage – Bleeding	Gastrostomy (Feeding tube)	Other	Deaths	Length of stay
Mehta 13	TORS	0	1	0	0	NR
Channir 15	TORS	1	0	1 (tongue sensitivity) 1 P.E.	0	NR
Patel 13	TORS	4	0	1- tongue swelling	0	NR
Winter 17	TORS	2	0	1- chest infection	0	NR
Durmus 14	TORS	NR	0	0	0	NR
Geltzeiler 17	TORS	2	1	0	0	NR
Hatten 17	TORS	3	0		1Cardiopulmonary event post-procedure	NR
Byrd 14	TORS	0	0	1-Pain and dehydration	0	1.4 days (mean)
Khan/Kass 16	TORS	NR	NR	0	0	1.7 days (mean range 1–3)
Blanco 13	TORS	NR	NR	0	NR	2.5 days (mean)
Krishnan 17	TORS	0	0	1-Candida – odynophagia	NR	6.3 days (mean) –four lengthened due to neck dissection
Patel 17	TORS	0	0	NR	0	NR
Khan 17	TORS	NR	NR	NR	NR	NR
Wolford 11	TORS	0	0	NR	NR	NR
Newman 13	TORS	NR	NR	NR	0	NR
Abuzeid 13	TORS	0	0	0	0	NR
Mourad 13	TORS	NR	NR	0	0	NR
Lee 20	TORS	NR	NR	NR	NR	NR
Al-Mulki 20	TORS	NR	NR	NR	NR	NR
Ryan 18	TORS	NR	NR	NR	NR	NR
Kubik 20	TORS	1	0	0	0	NR
Isenberg 20	TORS	5	0	0	0	NR
Nilsson 20	TORS	NR	NR	NR	NR	NR
Karni 11	TLM	NR	NR	0	0	NR
Nagel 14	TLM	1	0	0	0	NR
Kuta 17	TLM	NR	NR	NR	NR	NR
Herruer 20	TLM	1	0	NR	0	12/61 > 7 days LOS
Graboyes 15	TORS & TLM	6	NR	0	0	NR
Sudoko 18	TORS/TLM/TOEC	3 (19%). None related to lingual tonsillectomy	0	0	0	NR
Davies-Husband 18	TOEC	0	0	9 – Pain	0	1.4 nights

Table 3. Post-operative and length of stay. NR = Not recorded. P.E. = Pulmonary Embolism

Synthesis and analysis of results

Identification rate of the primary site by technique

TORS primary cancer identification rate was 66.4% (366/551), mean effect size 60% (CI 0.49, 0.70) and for TLM was 87.2% (130/149), mean effect size 80% (CI 0.58, 10.01). TOEC had the lowest pick up rate at 41.6% (5/12), mean effect size 41% (0.05, 0.76). A further breakdown of the identification rate by procedure shows TORS to have picked up a lingual tonsil primary in 50.6% of patients (203/401, mean effect size 45%, CI 0.36, 0.55) whilst TLM picked up 53.5% of lingual tonsil primaries (38/71, mean effect size 50% CI 0.33, 0.66). TOEC had the lowest primary identification rate in the lingual tonsil (41.6% (5/12, mean effect size 25% CI -0.1, 0.61)). With regards to palatine tonsillectomies, TORS identified 27.6% (65/235, mean effect size 26% CI 0.14, 0.38) of the primaries in this subsite whilst TLM identified 42.5% (19/45, mean effect size 41% CI 0.22, 0.60) when used.

The meta-analysis of the detection rates is shown in the forest plots for overall (Figure 3), lingual tonsillectomy (Figure 4) and palatine tonsillectomy (Figure 5).

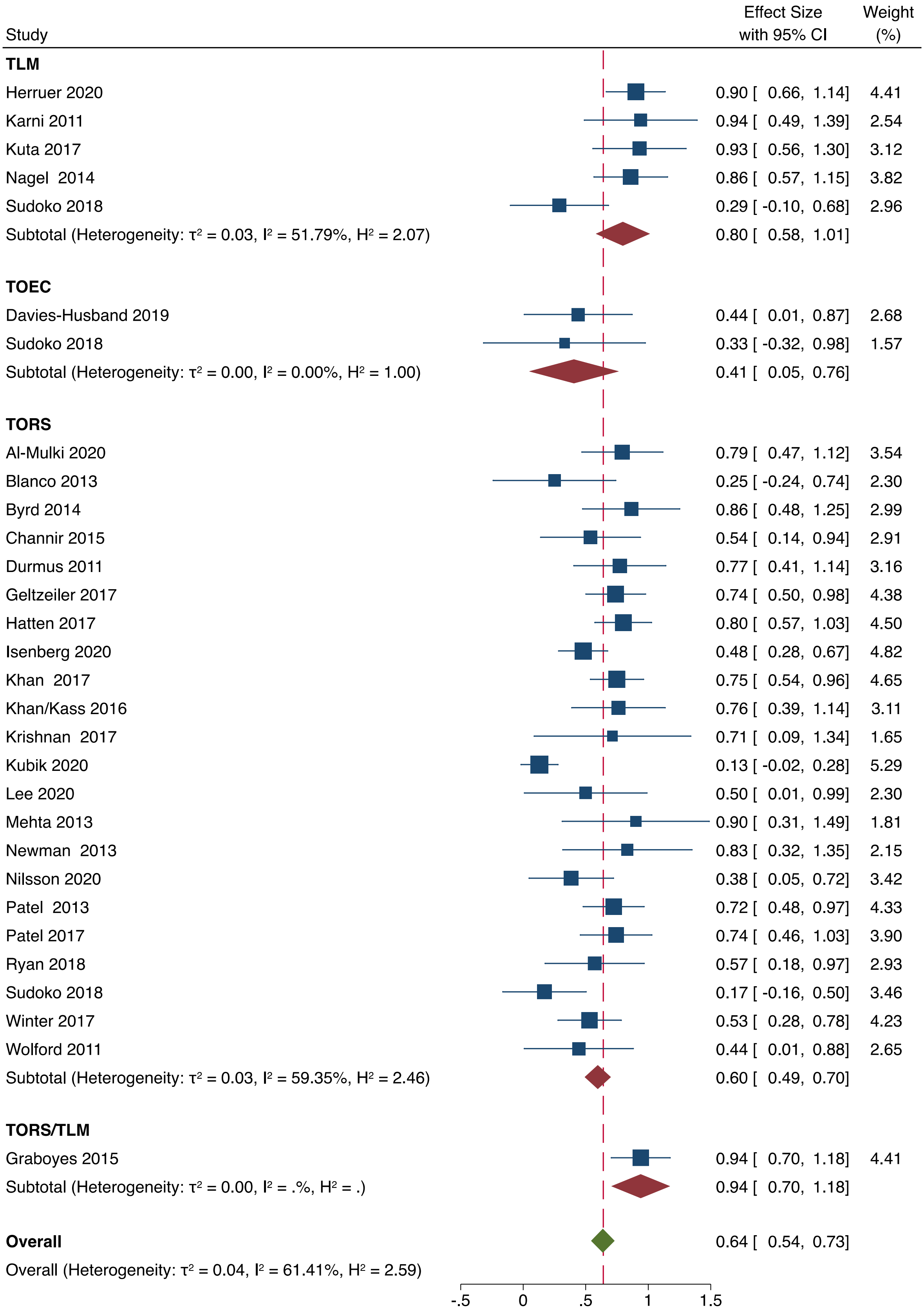

Figure 3: Overall forest plot of TORS, TLM and TOEC surgical techniques for both lingual and palatine tonsillectomies cancer identification

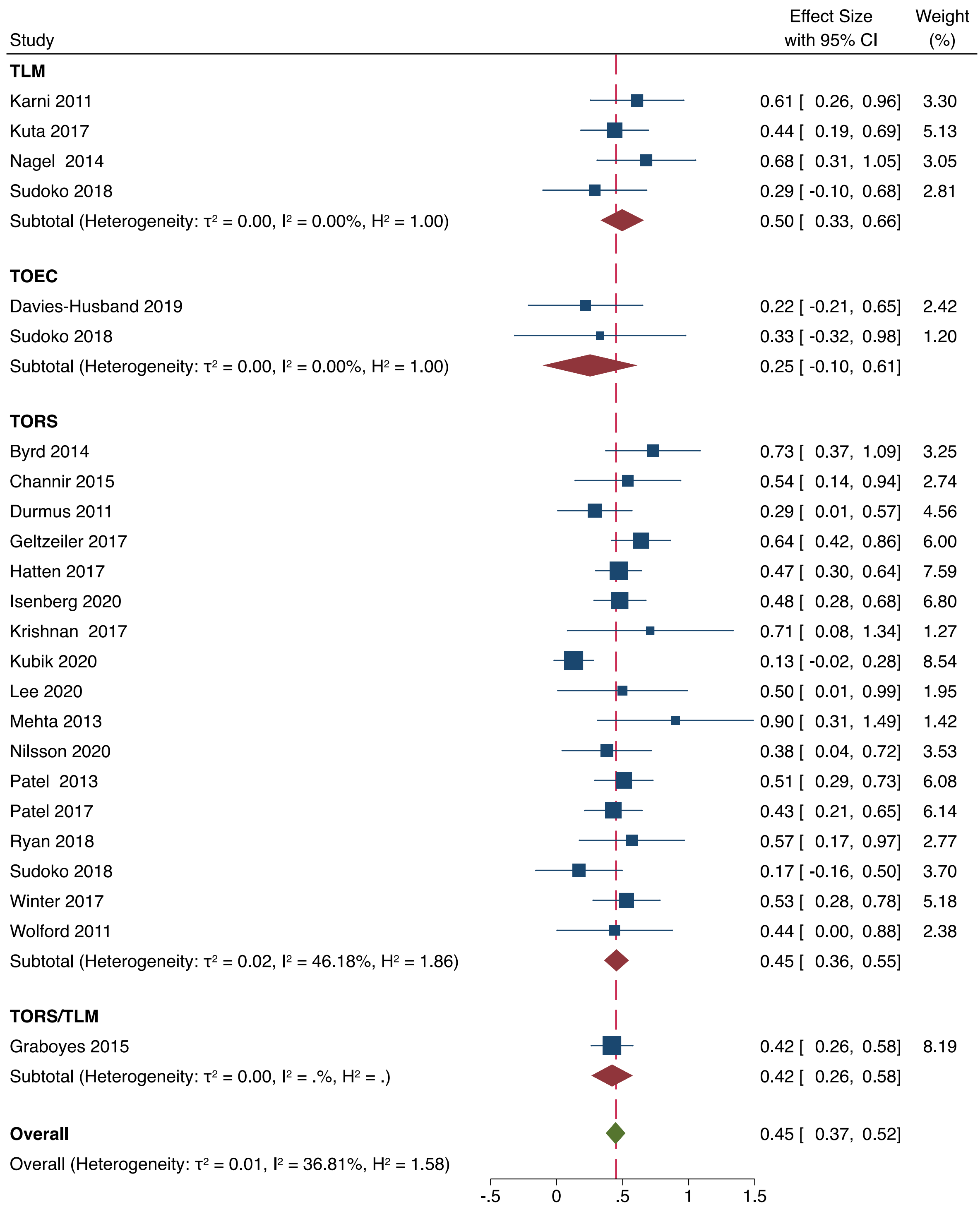

Figure 4: Lingual tonsillectomy forest plot for TORS, TLM and TOEC techniques cancer identification

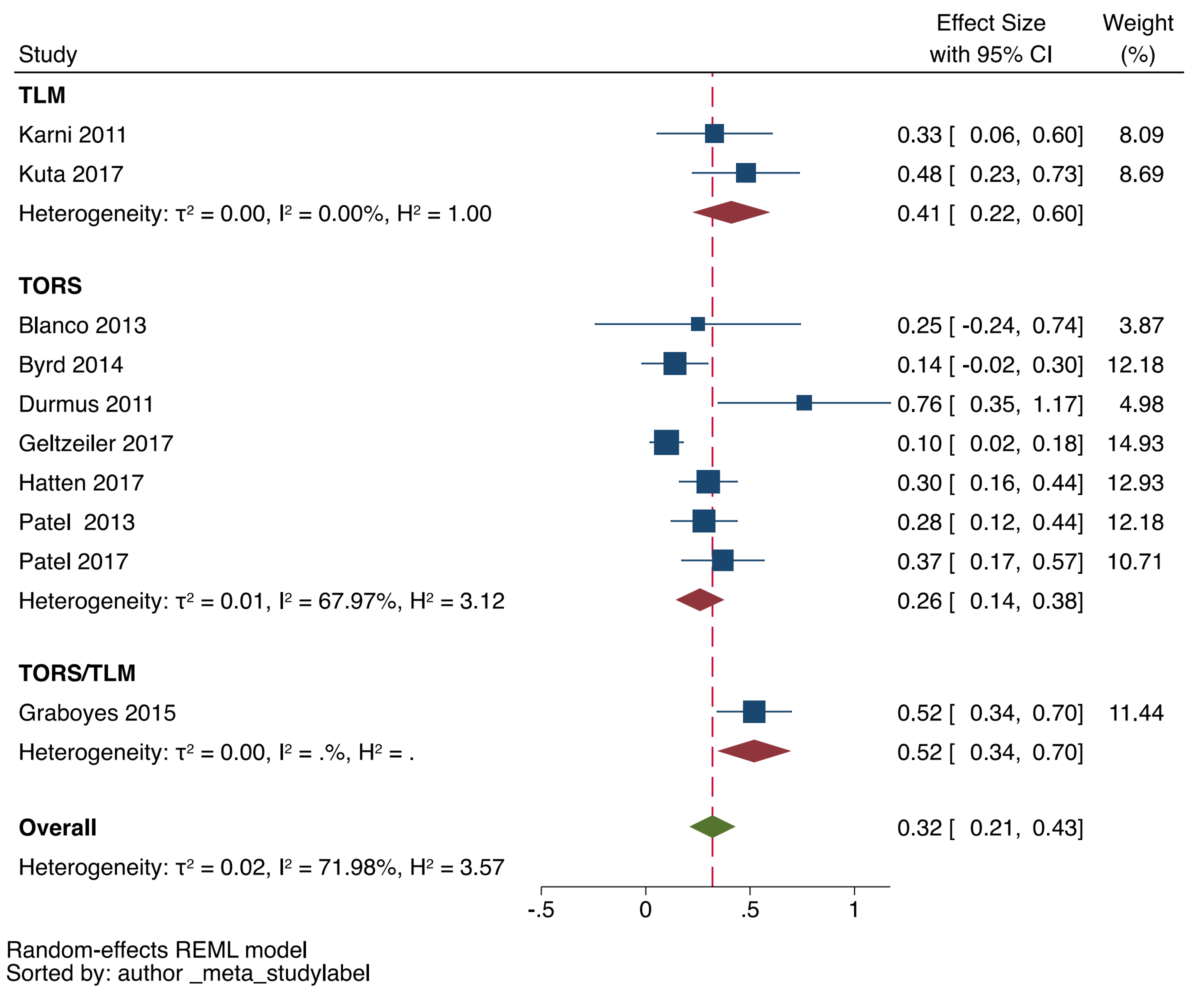

Figure 5: Palatine tonsillectomy forest plot for TORS and TLM techniques cancer identification

DISCUSSION

Summary of evidence

The primary objective of this review was to summarise the literature to assess the identification rates of the primary head and neck cancer in patients who present with cervical neck node metastases using the different published surgical techniques of TORS, TLM, TOEC and TOUSS. 30 studies (all within the last 9 years period) were identified reflecting the relative novelty of the technology used in the aforementioned surgical techniques. Overall, TLM primary H&N cancer in CUP patients pooled identification rate of 80% appears favourable compared for TORS (60%) and TOEC (41%). Further analysis with regards to the use of the newly adopted procedure of lingual tonsillectomy, the pooled rates of primary cancer identification were relatively similar between TORS (45%) and TLM (50%); TOEC was an inferior technique with a primary cancer pooled identification rate of 25%. Irrespective of the surgical technique used, the findings suggest lingual tonsillectomy is a useful adjunct in identifying the primary cancer in H&N CUP patients. Identification of the primary cancer in H&N CUP patients has the potential to improve survival benefit as well as reducing treatment related toxicity by reducing the need or volume of adjuvant treatment [15].

The results of this systematic review may suggest that TLM is superior compared to TORS with a higher primary pooled identification rate in the TLM patients. However, as highlighted by Farooq et al's systematic review [5], the evidence underpinning the TLM studies is limited by only 5 studies and 149 patients reported compared to the 24 studies and 551 patients who had TORS despite the use of laser in transoral surgery for a longer period compared to the newer TORS technique. This may reflect reporting bias in favour of TLM. To appreciate the role of surgical technology and its potential benefit, Nilsson et al [17] re-analysed its data for lingual tonsillectomy by excluding combined palatine & lingual tonsillectomy cases. They advocate that palatine tonsillectomy excision technique does not alter the detection rate. The small number of patients included in this review who had TOEC (12 patients) reflects the infancy of this technique and limits the conclusions that can be drawn. Davies-Husband [10] highlights that TOEC is safe, simple and has the potential of being cost-effective in financially retrained institutions. The I^2 values in the analysis suggest the heterogeneity of data used in the analysis of the three transoral surgical techniques.

The detection rate in 178/216 HPV +ve reported carcinoma of unknown primary tumours (82%) further supports the role of transoral approaches to attempt to identify the primary in HPV +ve patients. This has the potential to offer a surgical modality or de-intensify the radiotherapy volumes if that was the treatment modality intended if the primary was identified. The detection rate in 7/59 HPV-ve carcinoma of unknown primary tumours (12%) is disappointing. This is an important data to be borne in mind in multidisciplinary meetings when making the decision whether to perform tongue base mucosectomy taking into consideration the benefits vs morbidity risk and potential delay of the commencement of treatment. To our knowledge, this is the first systematic review that expands on the HPV data to include the detailed analysis of the impact of the HPV status on the detection rate of transoral approaches in CUP patients.

This systematic review is the largest study examining identification rates of the primary head and neck cancer in 778 patients from 30 studies with the incorporation of the recently published results of the TOEC techniques [10, 16]. This systematic review builds from the previously published systematic review by Farooq et al [5] which included 556 patients and 21 studies. However, there are limitations at both the included studies and at review level.

Limitations of the included studies

There is variation in the quality of the included studies. 3 studies did not report on patients' characteristics [31, 32, 40]. One study did not specify how they defined the patient as having H&N CUP in pre-operative investigations performed [36]. Another study had significant variability in the investigative work up of the included patients [13]. These factors have the potential to limit the studies internal validity.

There is the potential for introducing confounding, selection and detection bias with the inclusion of pre-operative cross-sectional radiological imaging with suspicious lesions and PET CT positive lesions in the data by the majority of studies which would potentially increase the detection rate of the primary cancer. The latter limitation is also highlighted by more recent publications [10, 17]. De Almeida [41] argues for the inclusion of patients with PET CT suspicious findings due to the high false positive rates of PET CT, however this inclusion criteria remains controversial in the literature.

In the 27 out of 28 case series included (the exception being the study by Davies-Husband on TOEC [10]) the data collection was retrospective in nature and may be influenced by recall bias and case selection bias. Also 11 out of 30 studies did not report their complications and thus the potential of under-reporting is present. In 4 out of 30 studies HPV status of the patients was not specified and this limits their external validity as HPV negative patients have a lower primary identification rate of 13% (3/23) [14].

Limitations of the review

The main limitation of this review was the data being derived from case series and case reports only as no RCTs addressed this subject currently exist. This resulted in a considerable heterogeneity and variation in the investigations carried out in the diagnostic work up of H&N CUP patients. In addition, there is likely considerable variability in the surgical technique due to lack of standardisation of how the operation was performed.

Despite the mentioned limitations, this is the largest systematic review specifically addressing the question of which is the most effective surgical technique in identifying the primary cancer in CUP work up. The results of this review can help surgeons performing these procedures in which technique to choose if they are trained and skilled in multiple techniques, and which technique to invest in terms of equipment and training if not already locally available.

Implications for clinical practice

The overall pooled primary cancer detection rate of 64% suggests the detection of a H&N primary should be pursued by a lingual tonsillectomy in addition to palatine tonsillectomy in CUP. This has superior primary identification rate compared to performing palatine tonsillectomy alone (32%). Lingual tonsillectomy is now recommended by the UK national guidelines [42]. Identifying the primary H&N cancer has clinical benefits and outcome with psychological comfort to patients. Furthermore, Karni at al [15] found that these patients have survival benefit. A de-intensified radiotherapy volume after primary cancer identification has the potential of less morbidity.

Due to the multiple factors involved in lingual tonsillectomy including surgeon's training and their institution financial constraints, there does not appear to be a single technique that would fit all purposes. The lingual tonsillectomy detection rate is comparable between TORS and TLM and further data is needed to assess the effectiveness of TOEC. This systematic review provides further evidence base to H&N multidisciplinary meetings to incorporate lingual tonsillectomy in CUP work up if they are not already adopting this procedure.

Implications for research

Study data that compares between patients with PET CT suspicious lesions and PET CT negative is needed to truly assess the difference in the detection rate between the different transoral surgical techniques.

The heterogeneity of the quality of the data in the studies included in this review advocate for a larger, multicentre, prospective study with improved standardisation of the clinical work up and investigations of the H&N CUP patients as well as surgical technique standardisation. This is the subject of a current study in Toronto, Canada [43] as well as the MOSES trial in the United Kingdom. Larger cohort of patients by a form of prospective study with strict inclusion criteria is needed to assess the TOEC technique effectiveness. However, a randomised data on cost-effectiveness and quantitative (as well qualitative) studies of the quality of life H&N CUP is much needed [44].

Conclusions

This is the largest systematic review addressing the results of different surgical techniques in identifying a primary H&N cancer in CUP patients. It is the only review to incorporate recently published new techniques of identifying the primary in the form of TOEC. It builds on the existing knowledge of the effectiveness of lingual tonsillectomy as a diagnostic procedure. The review highlights the need for further large, prospective studies with standardised clinical investigations work up for more definitive conclusions to be drawn.

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Appendix 1

Supplemental Table 1: Description of search strategy

MEDLINE, CINAHL, EMBASE

No.	Search term
1	Transoral (ti,ab)
2	Robotic (ti, ab)
3	Robotic surgical procedure/
4	Laser (ti,ab)
5	Microsurgery (ti,ab)
6	Endoscopic surgical procedure
7	Electrocautery
8	Lingual tonsillectomy (ti,ab)
9	Palatine tonsillectomy (ti,ab)
10	Tonsillectomy/
11	Mucosectomy (ti,ab)
12	tongue base biops*

13	(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12)
14	Head And neck (ti,ab)
15	Head And neck cancer/
16	tongue base (ti, ab)
16	Oropharyngeal (ti,ab)
17	(11 OR 12 OR 13 OR 14 OR 15 OR 16)
18	Occult (ti,ab)
19	Unknown primary (ti, ab)
20	Carcinoma of unknown origin (ti, ab)
21	Cancer of unknown primary site/
22	(18 OR 19 OR 20 OR 21)
21	(13 AND 17 AND 22)

Study	**Study design**	**Valid method for assessment of condition**	**Consecutive and complete? Inclusion of patients?**	**Clear reporting of patient characteristics**	**Clear reporting of adverse events?**	**Were outcomes reported for all patients?**
Mehta	**Case series**	Yes	Yes 2009-2011	Yes: age, gender, Tobacco, alcohol, Nodal status.	Yes	Yes
Channir	**Case series**	Yes	Yes 2013-2015	Yes- age, gender, HPV status, P16 status, TNM	**Yes**	**Yes**
Patel	**Case series**	Yes	Yes 2010-2013	Yes, age range, gender TNM, HPV	**Yes**	**Yes**
Winter	**Case Series**	Yes	Yes 2014-2016	Partial- gave an age range	**Yes**	**Yes**
Karni	**Case series**	Yes	yes 1997-2005	Partial- average age and gender	**Yes**	**Yes**
Durmus	**Case series**	Yes	Yes April 2008-2012	Partial, Gender included, age range included,	**Yes**	**Yes**
Nagel	**Case series**	yes	yes 1996-2011	Partial- not all aspects, has age range and gender	**Yes**	**Yes**
Geltzeiler	**Case series**	Yes	Yes 2010-2016	partial- mean age and gender	**Yes**	**Yes**
Hatten	**Case series**	Yes	Yes 2011-2015	Yes- age, gender	**Yes**	**Yes**
Graboyes	**Case series**	Yes	yes-2011-2015	Partial- mean age and gender	**Yes**	**Yes**
Byrd	**Case series**	Yes	yes 2001-2012	Yes	**Yes**	**Yes**
Khan/Kass	**Case series**	Yes	yes 2009-2012	partial-mean age, gender	**No**	**Yes**
Blanco	**Case series**	Yes	Yes 2010-2012	partial-mean age, gender	**No**	**Yes**
Krishnan	**Case series**	Yes	Yes-2008-2014	No	**Yes**	**Yes**
Patel	**Case series**	Yes	yes-2008-2014	Yes	**Yes**	**Yes**
Davies-Husband	**Case series, Prospective**	Yes	Yes May 2017 – June 2018	Yes age, gender, smoking, alcohol, HPV status, nodal status	**Yes**	**Yes**
Kubik	**Case series**	Yes	Yes 2012 to 2018	Yes, gender, smoking, alcohol, HPV status, nodal status	**Yes**	**Yes**
Isenberg	**Case series**	Not reported as CUP	Yes. May 2013-June 2017	No. Partial. HPV status only mentioned	**Yes**	**Yes**

		patients are included in the institution results of 205 patients				
Khan	**Case series**	Yes	yes 2010-2016	Partial- mean age and gender	**No**	**Yes**
Wolford	**Case series**	Yes	Yes-2007-2011	No	**Yes**	**Yes**
Newman	**Case series**	Yes	yes 2011-2012	No	**No**	**Yes**
Kuta	**Case series**	Yes	Yes 2013- 2016	Partial- gender excluded	**No**	**Yes**
Abuzaid	**Case report**	**Yes**	**N/A**	Yes, age, gender	**Yes**	**Yes**
Mourad	**Case report**	**Yes**	**N/A**	Yes, age, gender	**Yes**	**Yes**
Lee	**Case series**	**Yes**	Yes. January 2000 - December 2018.	Yes, age, gender, tobacco & alcohol intake, HPV status, nodal status	**No**	**Yes**
Al-Mulki	**Case series**	**Yes**	Yes. 2016 and March 2019	Yes, age, gender, HPV status, nodal status not included.	**No**	**Yes**
Ryan	**Case series**	Yes	Yes 2011 - 2018	Yes, age, tobacco intake, HPV status, nodal status	**No**	**Yes**
Herruer	**Case series**	Yes	Yes 2013 - 2018	Yes	Yes	No. One patient excluded as incomplete records
Nilsson	**Case series**	Yes	No. Non-consecutive 2008 - 2017	Yes	No	Yes
Sudoko	**Case series**	Yes	Yes. Feb 2010 - May 2017	Yes	Yes	Yes

Appendix 2. Risk of bias assessment. Adopted from the Joanna Briggs Institute Criteria