Indications for Oropharyngeal Biopsy in Head and Neck Squamous Cell Carcinoma of Unknown Primary - A Systematic Review (HNSCCUP)

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March 29, 2023

Abstract

Background Patients presenting with head and neck squamous cell carcinoma of unknown primary (HNSCCUP) remain challenging clinical scenarios as large variation exists in practices used to locate the primary. Objective To perform a systematic review of the literature and offer recommendations for oropharyngeal biopsies in HNSCCUP. Method Pubmed, Medline and Embase were searched to identify studies from inception to October 2021. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed. Results 483 articles were included and screened, 40 studies met the inclusion criteria, including over 3400 patients from the original articles and 1575 patients from 3 meta-analyses. The primary site identification rate following random biopsies or deep tissue biopsies is less than 5% in most studies. The mean detection rate following ipsilateral tonsillectomy is 34%; two pooled analyses indicate that the mean detection rate following tongue base mucosectomy is 64%, with this figure rising when the tonsils are negative. Conclusions High level evidence is lacking, with heterogeneity in the reported studies. Published meta analyses are based on retrospective data. There is little evidence supporting the practice of random/non-directed oropharyngeal biopsies. Available evidence supports palatine tonsillectomy and tongue base mucosectomy compared to deep tissue biopsies.

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Data sharing is not applicable to this article as no new data were created or analysed in this study.

The authors received no funding for the production of this article and have no conflicts of interest to declare.

Conflicts of Interest: None Declared

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Pubmed, Medline and Embase were searched to identify studies from inception to October 2021. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed.

Results

483 articles were included and screened, 40 studies met the inclusion criteria, including over 3400 patients from the original articles and 1575 patients from 3 meta-analyses. The primary site identification rate following random biopsies or deep tissue biopsies is less than 5% in most studies. The mean detection rate following ipsilateral tonsillectomy is 34%; two pooled analyses indicate that the mean detection rate following tongue base mucosectomy is 64%, with this figure rising when the tonsils are negative.

Conclusions

High level evidence is lacking, with heterogeneity in the reported studies. Published meta analyses are based on retrospective data. There is little evidence supporting the practice of random/non-directed oropharyngeal biopsies. Available evidence supports palatine tonsillectomy and tongue base mucosectomy compared to deep tissue biopsies.

Key points

- Random directed biopsies are not recommended
- Directed biopsies of clinically/radiologically suspicious areas on imaging findings are useful
- Ipsilateral Tonsillectomy should be performed as a minimum procedure; deep tonsil biopsies are not recommended
- Consideration should be given to bilateral tonsillectomy
- If imaging, EUA and tonsillectomies are all negative, further investigation in the form of tongue base mucosectomy (TBM) is recommended via any suitable surgical technique. Consideration should be given to bilateral TBM.

Introduction

Patients presenting with head and neck squamous cell carcinoma of unknown primary (HNSCCUP) pose a diagnostic conundrum. Cancer of unknown primary is defined as the "histological diagnosis of metastasis without the detection of a primary tumor"[1]. The cited incidence of HNSCCUP is between 2% to 5% of all head and neck squamous cell carcinoma (SCC)[2,3].

When clinical examination and imaging have failed to identify a potential primary site, traditional further investigation of HNSCCUP comprises examination under anaesthetic (EUA), evaluation of all subsites of the head and neck and either targeted and/or random biopsies. The typical biopsy sites are nasopharynx, tonsils, tongue base, and piriform fossa, although there is considerable heterogeneity and little high level evidence exists to support this routine[4,5].

The rationale for intensively searching for the primary site is as follows:

1. The majority of patients presenting with HNSCCUP will harbour primary sites in the head and neck[6].

2. There may be prognostic and therapeutic benefits to finding the primary site, by being able to precisely target the primary site and reduce the morbidity of treatment[7].

This systematic review identifies the indications and practice of oropharyngeal biopsy in HNSCCUP and focuses on the following:

1. Random versus direct biopsies

2. Management of the palatine tonsils

3. Management of the tongue base

4. Utility of surgical techniques

Methods

Search strategy

Bibliographic databases Pubmed, Medline and Embase search engines were searched to identify studies from inception to October 2021. Search terms used included "cancer of unknown primary" AND "tonsillectomy" OR "tongue base mucosectomy" OR "lingual tonsillectomy", "unknown primary tumour AND squamous cell carcinoma of head and neck", "oropharyngeal cancer AND biopsy".

Inclusion and exclusion criteria

All primary human studies were included regardless of study type. Exclusion criteria included individual case reports, non-original studies, studies with non-extractable data, or including large proportions of non-squamous cell carcinoma patients.

Within the literature, variability exists as to when individual authors' make a HNSCCUP diagnosis [8]. The heterogeneity results from the extent of the preceding workup prior to diagnosis. No meaningful adjustments could be made to standardise the workup and so no exclusions were made on this basis.

Study selection

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed[9] Titles and abstracts were independently screened by two reviewers (NK/RT). Disagreements were resolved by discussion with the senior authors (SL).

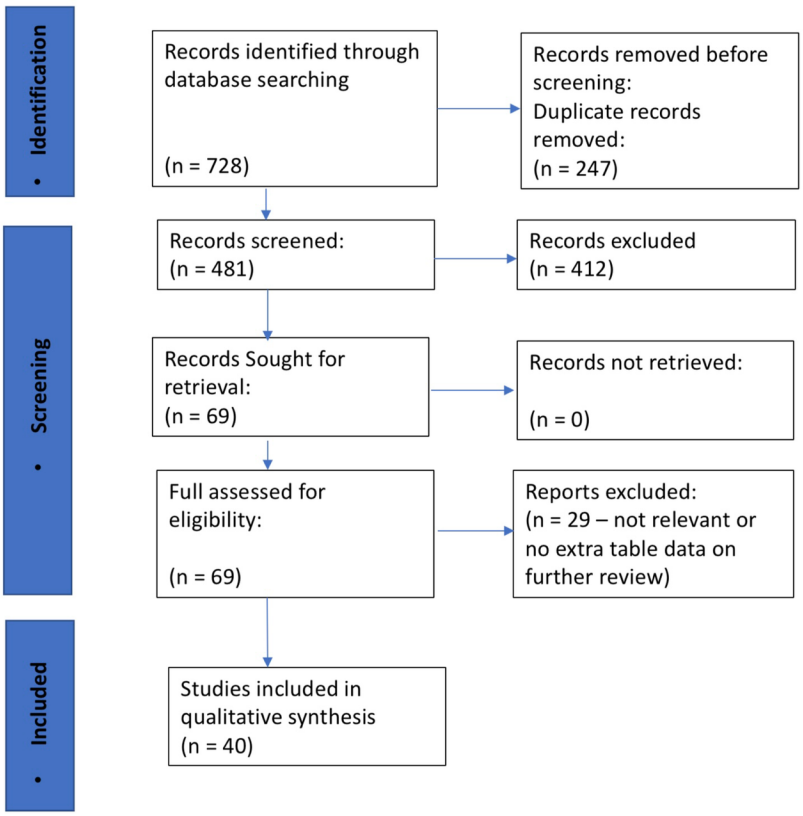

Figure 1 PRISMA Flow Diagram.

Data extraction

Data extraction was undertaken by three reviewers (NK/RT). Key article information was uploaded into Microsoft Excel. Data extracted included study type, number of patients, method of biopsy including tonsillectomy or tongue base mucosectomy, surgical technique used, number of primary tumours detected and their location, human papillomavirus (HPV) status and use of any additional techniques such as frozen section.

Results

Of the 483 articles that were included and screened, 40 studies met the inclusion criteria; these included over 3400 patients from the original articles, and 1575 patients from meta-analyses. The analysis is split into the four sections as set above.

Random Directed Biopsies: Location of Tumour

Two studies dispute the utility of random biopsies. Tanzler et al[5] included 156 patients who underwent deep tissue biopsies, and found the pickup rate to be 0% from the nasopharynx and piriform sinus (Table 1). A systematic review and meta-analysis of 673 patients recommends against random biopsies given pickup rates of often 0% in the literature[8].

Several studies have specifically reported on pickup rates from the practice of random directed biopsy[9,5,10,11] (table 1.1). Other authors have and have detailed the positive sites by location from their general workup including, but no limited to, random biopsies[1,12,13,14,15,16,17](table 1.2).

These studies call into question the utility of random biopsies, especially for two commonly targeted subsites, the nasopharynx and hypopharynx. In the nasopharynx the pickup rate ranged from 0-9.4%[5,11,9]. The highest pickup rate reported by Haas et al[9] is a retrospective study published in 2002, using data from a time before modern imaging was routinely utilised for workup preceding a biopsy. Similarly low pickup rates were observed in the piriform fossa alone, ranging from 0-4.2%[9,5,11,14]. When the entire hypopharynx is considered, a higher pick up rate is evident, ranging from 1.7% to 6%[15,13] (table 1.2, note that pickup rate here is of total number of CUP patients).

The studies demonstrate significant heterogeneity in their workup, as several include directed biopsies from sites considered suspicious on imaging, calling into question the nature of the biopsies as 'true random biopsies'. No studies have specifically performed biopsies following negative imaging and shown to be positive for cancer. Given the generally low pick up rates, in the era of cross-sectional imaging and PET-CT, the practice of random directed biopsies cannot be recommended.

1.1

	Tonsil	**BOT**	**Nasopharynx**	**Hypopharynx**	**Piriform sinus/fossa**	**Comment**
Haas[9]	No random Biopsies of tonsils. TE BL 14% (6/53)	7.6% (4/53)	9.4% (5/53)		0% (0/53)	Systematic and blind. 4 of 57 were not true CUP
Tanzler[5]	13% (7/54) (39%TE 28/71)	18% (10/85)	0% (0/77)		0% (0/53)	Random directed
Waltonen 2009[10]	3.2% 3/95 (29.6% 8/27 PT)	6.3% (6/95) (7.4% 2/27 PT)	1.1% (1/95)	1.1% (1/95) (Further 3.7% 1/27 from PT not random Bx)		Mainly tonsils. Some BOT and hypopharynx found with PT

McQuone 1998[11]	13% (2/15) TE 39% (9/23)	0% (0/34)	0% (0/34)		0% (0/34)	Tonsil mainly directed Bx
1.2	**Tonsil**	**BOT**	**Nasopharynx**	**Hypopharynx**	**Piriform fossa**	**Comment**
Issing et al 2003[1]	Overall: 4.2% 7/167 Bx: 2.9% (5/167) (TE 2/167) Overall primaries identified: 7/36	Overall 2.9% 5/167 Overall primaries identified: 5/36	Overall 2.4% (4/167) Overall primaries identified: 4/36	Overall 4.8% 8/167 Overall primaries identified: 8/36	Overall 3.6% (6/167) Overall primaries identified: 6/36	Overall Ix CUP 36 primaries found in 167 CUP's
Lee et al 2020[12]	Overall CUP 28.3% (51/180) Overall primaries identified: 51/92 (Tonsillectomy 28/87)	Overall CUP 20.1% (37/180) Overall primaries identified: 37/92 (Lingual tonsillectomy 4/8)	0.6% 1/180 (not all had NP Bx Overall primaries identified: 1/92			Tonsils via tonsillectomy and deep biopsy 92 primaries found in 180 CUP's
Waltonen 2009[13]	Overall CUP 18.6% (34/183) Overall primaries identified: 34/84	Overall CUP 15.3% (28/183) Overall primaries identified: 28/84	Overall CUP 2.19% (4/183) Overall primaries identified: 4/84	Overall CUP 6% (11/183) Overall primaries identified: 11/84		Deep biopsy or tonsillectomy 84 primaries found in 183 CUP's
Cianchetti 2009[14]	Overall CUP 25% (59/236) Overall primaries identified: 59/126 (35/79 from PT)	24.6% (58/236) Overall primaries identified: 58/126	0.4% (1/236) Overall primaries identified: 1/126		4.2% (10/236) Overall primaries identified: 10/126	Not all true negative workup 126 total primaries found in 236 CUP. Not all neg workup
Ryan 2019[15]	Overall CUP 23/110) Overall primaries identified: 23/59 38.9% (23/59)	Overall CUP 28/110 Overall primaries identified: 28/59 47.5% (28/59) TOR	Overall CUP 0/110 Overall primaries identified: 0% (0/59)	Overall CUPl 1/110 Overall primaries identified: 1.7% (1/59)		59 primaries found in 110 CUP's.. Some positive findings on workup. TORS OP 8.5% (5/59)
Nagel 2014[16]	Overall 11/52 Overall primaries identified: 25.7% (11/39)	Overall 26/52 Overall primaries identified: 66.7% (26/39) TLM	Overall 1/52 Overall primaries identified: 2.6% (1/39)	Overall 2/52 Overall primaries identified: 5.1% (2/39)		TLM 39 primaries found in 52 CUP's

Karni 2011[17]	Overall 7/30 Overall primaries identified: (7/20)	Overall 12/30 Overall primaries identified: 57.1% (12/20) TLM	Overall 1/30 Overall primaries identified: 4.8% (1/20)	Overall 1/30 Overall primaries identified: 4.8% (1/20)		20 primaries found in 30 CUP's TLM Inc synchronous as diff sites

Table 1.1 Random directed biopsies. Pickup rate as a percentage is of total number of patients who underwent biopsy of that location.

Table 1.2 Pick-up rates in location of total number CUP patients (includes directed biopsies and other methods).

PT: palatine tonsillectomy. BOT: base of tongue, OP:Oropharynx, NP: nasopharynx,Bx: biopsy, IL: Ipsilateral, BL: Bilateral, Ix :Investigation, TOR: transoral robot assisted surgery, TLM: transoral laser microsurgery

Diagnostic Procedures for the tonsils

The search identified 16 studies including over 2700 patients[5,10-14,18-27]. 11 studies documented detection rate with tonsillectomy[5,10-14,18,19-22] (table 2 & 3), 9 studies quoted the rates of synchronous tonsillar SCC[5,11,12,14,19,23-26] (not necessarily HNSCCUP[23,24]) (table 4) and 3 examined the role of HPV status in cancer detection following tonsillectomy[19,24,27] (table 5).

Deep tonsil biopsy versus tonsillectomy

Five studies investigated the efficacy of random tonsil biopsies versus tonsillectomy[5,10,11,18,19] (Table 2). The rate of positive findings on tonsil biopsy ranged from 0[19]-16.7%[18] in these studies, whereas positive findings on tonsillectomy ranged from 25.5[19]-44.3%[14] (table 2-5). Tanzler et al[5] recommend that random biopsies of the tonsil have a low pickup rate and tonsillectomy should be performed instead.

Di Maio et al[8] performed a large systematic review and meta-analysis specifically addressing the role of palatine tonsillectomy in the diagnostic workup of HNSCCUP.

Fourteen studies were included, involving 673 patients in total; 338 underwent tonsillectomy as part of examination under anaesthetic (EUA), and 78 underwent palatine tonsillectomy as part of TORS. The study identified 140 occult tonsil cancers. The authors performed a meta-analysis of 11 of these studies (n670) this gave an overall detection rate with tonsillectomy of 34% (99% confidence interval 0.23-0.46) and provides the current highest quality of evidence supporting the role of tonsillectomy in the investigation of HNSCCUP.

Authors	**Year**	**Origin**	**Study Design**	**N**	**Workup**	**Deep Tissue Biopsy**	**Tonsillectomy**	**Pickup tonsil Deep tissue**	**Pickup Tonsillectomy**
Tanzler et al[5]	2014	USA	RS	156	Negative Ex, Ix and PE	54	71	13% (7/54)	39% (28/71)

Berta et al[18]	2014	France	RS	45	Ex, CT, PECT (100%) then PECT (60%)	6	28	16.7% (1/6)	42.9% (12/28)
Waltonen et al[10]	2009	USA	RS	122	Ex, CT (81%), MRI (7%), PETCT (21%), PE	95 (BL)	27 (16 UL, 11 BL)	3.2% (3/95)	29.6% (8/27)
McQuone et al[11]	1998	USA	RS	37	Negative Ex and radiological, endoscopy	15	23 (7 IL, 16 BL)	13.3% (2/15)	39% (9/23)
Podeur et al[19]	2020	France	RS	63	Ex, CT, PET-CT, PE	10	47 (IL/BL)	0%	25.5% (12/47 IL/BL)

Table 2. Deep tonsillar biopsy versus tonsillectomy. IL: ipsilateral. BL: bilateral, CL: contralateral. PE: panendoscopy. Ix: Investigation. Ex: examination. BOT: base of tongue.

Authors	Year	Origin	Study Design	N	CT/MRI/PET	NTCT tonsillectomy	Tonsil Pickup	Overall Pickup	Complicatio
Podeur et al[19]	2020	France	RS	63	Negative Ex, CT, PETCT, endoscopy	47 (UL/BL)	26% (12) (59% if HPV positive)		6% haemorrhage for tonsillectomy -

Lee et al[12]	2020	USA	RS cohort	180	Negnegative ex and flexible laryn-goscopy/mirror HPV status. PETCT (73.9%) prior to direct laryn-goscopy with Biopsy	87 (36 BL/51 UL) some Biopsy (20 inc PT)	Tonsillectomy 32.2% (28/87) Overall tonsil: 51/92: 55.4%	51.1% (92/180) from surgery
Waltonen et al[13]	2009	USA	RS	183	CT/PETCT variable but negative. PE and biopsy negative. UL and BL tonsillectomy	Mix of BL and UL and directed Bx	40.5% (34)	45.9% (84). If PETCT, PE & Biopsy +/- tonsillec-tomy: 59.6%
Cianchetti et al[14]	2009	USA	RS	236	Negative Ex, CT/MRI.+/- FDG-DSPECT/FDG PET. Then PE directed biopsy. Mix negative and positive	72 IL BL 7 (79)	44.3% (35/79 PT) 46.8% (59/126 overall positive in Bx)	53.4% (126/236) (21/72 29.2% if all workup negative)

Mendenhall et al[20]	1998	USA	RS	130	CT/MRI/SPECT	34	CT	35.2% (12/34) Overall 43% (25)	43% (56/130) Positive PE & rad 65%	
Lapeyre et al[21]	1997	France	?PS	87	IL tonsillectomy performed during endoscopic workup	87		26% (23/87) (31% in those single cervical LN)		Non specific
Righi et al[22]	2005	USA	RS	19	Negative Ex, flex NE, CT, PE random Biopsy	IL 19		31.6% (6)		

Table 3: Utility of tonsillectomy in HNSCCUP cancer unknown origin. IL: ipsilateral. BL: bilateral. PE: panendoscopy. Ix: Investigation. Ex: examination. BOT: base of tongue, PT: palentine tonsillectomy, Bx: biopsy.

Contralateral and synchronous tonsil tumours

There is considerable heterogeneity between papers regarding the practice of unilateral or bilateral palatine tonsillectomy; variations on the theme included ipsilateral tonsillectomy only, ipsilateral tonsillectomy with contralateral tonsil biopsies, and bilateral tonsillectomy. Nine studies reported synchronous and/or contralateral cancer identification rates[5,12,11,14,19,23-26]. Four small retrospective studies specifically addressed the role

of bilateral palatine tonsillectomy [23-26]. Rokkajer et al[23] and Saber et al[24] reported rates of synchronous primaries in tonsil SCC, not solely HNSCCUP.

Di Maio et al's[8] meta-analysis reported rates of 1% contralateral and 10% bilateral synchronous tonsil primaries. The synchronous tonsil primary rates amongst these studies varied from 3.3%[23] up to 22.7%[25]. Contralateral rates ranged from 2%[12] to 12.5%[26]. Saber et al[24] found the majority of bilateral tonsil tumours were in patients with HPV positive disease (75%).

Given the possibility of contralateral tonsil cancers and rate of synchronous tonsil primaries there is a case for performing bilateral tonsillectomy in the workup of HNSCCUP. As a minimum, ipsilateral tonsillectomy should be performed and bilateral tonsillectomy should be considered.

Authors	Year	Origin	Study Design	N	Workup	N tonsillectomy	Tonsillectomy Pickup	Synchronous/Contralateral	Complications
Podeur et al[19]	2020	France	RS	63	Negative Ex, CT, PETCT, endoscopy	47 (UL/BL)	26% (59% if HPV positive)	CL 8.3%	6% for tonsillectomy - Haemorrhage - return to theatre
Lee et al[12]	2020	USA	RS cohort	180	Negative ex and flexible laryngoscopy/mirror HPV status. PETCT (73.9%) prior to direct laryngoscopy with Biopsy	87 (36 BL/ 51 UL)	Tonsillectomy 32.2% (28/87) Overall tonsil: 51/92: 55.4%	CL 2% (2) BL 6% (6) (location not specified)	
Rokkjaer & Klug[23]	2018	Denmark	RS	211	Tonsillar Ca pts	180 BL, 31 UL with CL Biopsy. 14 Biopsy		3.3% (7/211) Synchronous BL 2.3% (4/171) CL (2 had dysplasia)	

Saber et al[24]	2017	Denmark	RS	1119	Tonsillar Ca pts	12 Bi tonsillar SCC. 9 of which were CUP		Bilateral 9% (2012-2014 when tonsils totally embedded) particularly HPV. !% whole study time
Kothari et al[25]	2007	UK	RS	24	MRI if negative PETCT	BL tonsillectomy in 22		BL 22.7% (5/22) 2 had IL pos findings PETCT
Koch et al[26]	2001	USA	Case series	41			39% (16)	12.5% CL (2/16), 12.5% BL (2/16)
Tanzler et al[5]	2014	USA	RS	156	Negative Ex, Ix and PE	71	39% (28/71)	6% (2/34) BL (not all had CL sampled)
Cianchetti et al[14]	2009	USA	RS	236	Negative workup: Ex,CXR, CT/MRI.+/- FDG-DSPECT/FDG PET. Then PE directed Biopsy. Mix negative and positive	IL or BL 79	44.3% (35/79) Overall 46.8% (59/126)	4.76% (6/126) synchronous (2.8% BL tonsils 1/59 with tonsillar Cancer)

McQuone et al[11]	1998	USA	RS	37	Negative Ex and radiological, endoscopy	IL7, BL 16: 23	39% (9/23)	11.1% (1/9) BL with tonsillectomy, 9.1% overall (1/11)

Table 4. Synchronous and contralateral tonsillar tumours. IL: ipsilateral. BL: bilateral, CL: contralateral. PE: panendoscopy. Ix: Investigation. Ex: examination. BOT: base of tongue, PT: palatine tonsillectomy, TORS: trans-oral robotic assisted surgery, TBM: tongue base mucosectomy

Complications

When considering unilateral or bilateral tonsillectomy over biopsies, the incidence of complications is an important deciding factor. Overall there was a lack of documented complications. Podeur et al[19] noted a haemorrhage rate of 6% in their cohort of unilateral and bilateral tonsillectomies in 63 patients. This is in keeping with the national post-tonsillectomy bleed rate. Lapeyre et al[21] had no specific complications related to tonsillectomies. Low complication rates support the recommendation of bilateral tonsillectomy.

HPV related tumours

There were several studies which specifically looked at HPV or P16 positivity and detection rates in the palatine tonsils[27,19,24] (table 5). HPV positivity correlated with oropharyngeal primary in general. Due to the nature of HPV associated tumours, they are less likely to be picked up on random deep tissue biopsies. This pertains to the increased pickup rates associated with tonsillectomy. Vent et al[27] suggest that P16 can be used as a marker of oropharyngeal primary, directing investigation. Podeur et al[19] go further and suggest that the indication of an oropharyngeal primary in this subset of patients should prompt an extended investigation including bilateral tonsillectomy and possible tongue base mucosectomy (TBM) in these patients, but not in P16 negative patients.

However, it must be borne in mind that HPV positive tumours have been detected in the nasopharynx[28]. This topic will be re-visited in the management of the base of tongue and in particular the subgroup of patients where novel techniques can be used.

Authors	Year	Origin	Study Design	N	Workup
Vent et al[27]	2013	Germany	RS	47	CT/MRI, FDG-PET< Skeletal scintigraphy. PE- if Ix negative
Podeur et al[19]	2020	France	RS	60	Negative Ex, CT, PETCT, endoscopy
Saber et al[24]	2017	Denmark	RS	1119	BL tonsillar cancer pts

Table 5. HPV association. IL: ipsilateral. BL: bilateral. PE: panendoscopy. Ix: Investigation. Ex: examination. BOT: base of tongue, PT: palatine tonsillectomy, TBM: tongue base mucosectomy

Diagnostic Procedures for the Tongue Base

Table 6 shows the eight studies which specifically look at the approach to the tongue base[29-36]. Typically these patients have already undergone a negative tonsillectomy or have palatine tonsillectomy and tongue base sampling performed at the same time.

A variety of surgical techniques have been used in these studies, including frozen sections, used as a decision node for simultaneous palatine tonsil and tongue base procedures under one anaesthetic. Overall, there is a lack of high quality evidence. The studies are mainly retrospective and heterogenous in terms of

workup. However, the majority have had PETCT, EUA and biopsies, and often, where appropriate, negative tonsillectomy prior to tongue base mucosectomy (TBM).

The detection rate for tongue base mucosectomy ranged from 13[29]-90%[36]. This is higher than the pickup rates for random biopsies of 0[11]-18%[5] (table 1.1), suggesting TBM is more effective than deep tissue biopsies.

There is variable practice with regard to approach to the contralateral tongue base (table 5) but contralateral and/or synchronous rates is reported in several studies. The rate of contralateral tongue base SCC primaries ranged from 0[29,32]-12%[33](table 6). Durmus et al37 had an overall bilateral rate of 17.6% with palatine tonsil rate of 66% and lingual tonsil rate of 33%[40]37 using TORS (table 7).

Across the studies included in this systemic review TBM haemorrhage rates ranged between 0[32]-8.5%[38](table 6 and 7) most of which were managed conservatively. These include alternative techniques.

HPV/P16 positivity rate was reported in many of these studies (table 6 and 7). There was a high rate of HPV positive cancers in those patients with positive TBM. Several studies reported rates of up to HPV 100% positivity for those with a tongue base primary[32,34,35] As with tonsillar primaries, HPV positivity should prompt meticulous investigation of the oropharynx.

Authors	Year	Origin	Study Design	N CUP	Workup	BOT Pickup	Synchronous/Contralateral	HPV/P16 Rate	Complications
Kubik et a[29]	2021	USA/Denmark	RS	23	Negative (inc CT/PETCT).PE - IL PT and Biopsy. Then TORS BL TBM. 4/23 had positive PETCT, 1/4 correlating with positive Biopsy.	13% (3/23)	0%	Negative 100% (inclusion negative)	4.3% (1/23) Haemorrhage, managed conservative
Nilsson et a[30] May want to inc to TOR	2020	Sweden	Prospective	13	Negative PETCT & PE blind biopsy inc BOT, IL PT. Then TORS IL TBM	38%		Benefit may reduce HPV positive	No serious

Sudoko et al[31]	2018	USA	RS	16	Negative Ex, PETCT, PE and Biopsy, PT. Then TORS/TLM IL/BL TBM	25% (4/16) (1/6 TOR, 2/7 TLM, 1/3 TMC)		75%	19% bleeding "not related LT"
Davies-Husband[32] Endo-scopic cautery's put below	2018	UK	PS	9	Negative MRI/PETCT, PE and blind BOT Biopsy and PT. Then en-doscopic BL electrocautery	44.4% (4/9)	0%	77.8% all patients. 100% tongue primary	No surgical
Winter et al[33]	2017	UK	PS Multi-centre	32	Negative Ex, radio-logical and PETCT, and ex under anaes-thesia, PT, then TORS TBM	53% (17/32)	CL 12% (2/17)	72% positive	9% (66% of these post-op bleed - Cx)

Krishnan, Connell and Ofo[34]	2016	Australia	RS	7	Ex, CT/MRI, PETCT, PE PT and TORS IL/BL BOT. Not all workup negative	71.4% (5/7)	85.7% overall. 100% for BOT primary.	14.3% Candida. "No surgical"
Channir et al[35] May want to inc TOR	2015, [28-]	Denmark	RS	13	Full negative including PETCT, EUA inc random Biopsy BOT and BL PT. TORS BL BOT	54% (7/13)	69.2% overall. 100% BOT	30.8% Tongue sensitivity, difficulty breathing (ITU)/PE, bleeding, severe pain

Mehta et al[36]	2013	USA	RS	10	CT/MRI &/or PETCT (some positive), endoscopy, BL PT/Biopsy's. BOT/pharynx. Then TORS BL BOT	90% (9/10)	11.1% (1/9)CL	80% positive overall, 88.9% Positive BOT	10% gastrostomy

Table 6. Management of the Base of Tongue. IL: ipsilateral. BL: bilateral. PE: panendoscopy. Ix: Investigation. Ex: examination. BOT: base of tongue, TBM: tongue base mucosectomy, PT: palatine tonsillectomy TOR: transoral Robotic Assisted Surgery. TLM: transoral laser microsurgery, Dx: diagnosis, Tx: treatment

Novel Techniques

Several novel surgical techniques have been reported in the literature to perform TBM. These include TORS, TLM as well as other endoscopic cautery techniques. The majority of studies focus on outcomes following TORS or TLM (table 7 location percentage is percentage of total primaries found).

There were six studies[15,37-41] where 331 patients underwent TORS within the diagnostic workup and, 5 studies with 223 patients underwent TLM[16,17,42-44], (Graboyes et al used TLM but in two of 65 patients TORS was used for resection after TLM[44]). The were two meta-analyses: Meccarellio et al[45] and Farooq et al[46]. The primary studies are all retrospective studies with significant heterogeneity. There are no randomised controlled trials.

The meta analysis by Meccariello et al[45] looked at the use of TORS in HNSCCUP for 349 patients over 12 studies. They found an overall detection rate of 64% in the base of tongue using a TORS approach.

Farooq et al al[46] looked at patients undergoing TBM using either TORS or TLM in 556 patients over 21 studies. The pooled rate of positive TBM was 64% in those that had negative clinical examination and imaging (including PET). The detection rate went up to 78% in those patients who had also undergone an EUA and negative tonsillectomy prior to TBM. They also reported a higher detection rate for TLM (91%) versus TORS (74%) but this was based on very limited evidence in 81 total patients.

The current evidence suggests that TBM should be undertaken in the workup of HNSCCUP to increase the chances of primary site identification. There is no evidence to suggest one technique is superior to another. The detection rate is greater in patients who have already undergone a negative tonsillectomy. This does mean further general anaesthetic for those patients who go on to require TBM, or the potential risk of increased complications (theoretical risk of oropharyngeal stenosis) if the procedures are combined. The studies where they are combined often use frozen sections as a surgical decision node, an option not

routinely used in the UK. Therefore, the decision on a staged or a combined procedure would currently be based on surgeon preference and on the individual case (ie suspicious scans, or HPV positivity). Higher quality, prospective studies would be required to look at the potential risks and efficacy in primary pickup of combining these procedures in particular palatine tonsillectomy and TBM.

TORS

Authors	Year	Origin	Study Design	N	Workup	Primary Yield	BOT	Tonsil	Synchronous	HPV	Complica
Durmus et al[37]	2014	USA	PS	22	Negative flexible laryngopharyngoscopy and imaging. Then PETCT (some positive). TORS IL tonsillectomy, IL TBM (variable extent)	77.3% (17/22)	17.6% (3/17)	59.1% (10/17)	17.6% (2/3 PT, 1/3 BOT) BL.	80% HPV, 95% P16	T w H d r H a H C T v a c t I a T p n t n s

Patel et al[38]	2013	USA	RS	47	Ex, flexible scope, CT/MRI and PET. PE directed Biopsy, TORS UL or BL tonsillectomy, UL or BL TBM	72.3% (34/47) (TORS alone)	58.8% (20/34)	38.2% (13/34)	2.9% (1/34 BOT and palatine tonsil) synchronous	76.5% (28/34) positive	10.6% (5/47): Bleeding (4/5: 8.5%) with 50% RTT and tongue swelling (1/5).	T u a p i T r s F
Mistry et al[39]	2020	UK	RS	28	Negative Ex, imaging inc PETCT.	67.8% (19/28)	47% (9/19) (3 in BOT and tonsil)	37% (7/19)	16% (3/19) synchronous BOT and tonsil. 5% CL LT (3 in BOT and tonsil)	82.6% 100% in OP primary	10.3% (n=3) bleed - Cx	T T p i t r p h y V t a w r r
Ryan et al[15]	2019	USA	RS	110	PETCT, PE and Biopsy, tonsillectomy then TORS TBM (not all negative)	66% with TORS, 44% before	57% (8/14)	36% (17/47)	17% (2/12 BL TE) in palatine tonsils	73% (80/110)		S a p p r i t c t i t s l t a T T

Hatten et al[40]	2017	USA	RS	60	MRI/CT negative. PETCT. PE and Biopsy, IL tonsillectomy, then IL TBM. If HPV positive CL not resected.	80% (48/60)	58% (28/48)	38% (18/48)		92% (55/60) enrolled at least one marker	13% (8/60): 5% post-op bleed (6% of these RTT)	T a s e d u t r t i t a i T I i f p
Geltzeiler et al al[41]	2017	USA	RS	64	Negative Ex, flexible nasolaryngoscopy, CT &/or PETCT. DL, TORS LT UL/BL +/- PT UL or BL	80% (51/64) 74% (37/50) ID TORS alone 22% (14/64) DL alone	86.5% (32/37)	13.5% (5/37)	12% CL BOT (3/25 underwent BL BOT)	96% (n=48)	6% (3/50) 4% - RTT bleeding 2% peri-op feeding tube Further h 16% gastrostomy feeding 6/12	C l g a T e c l i p r S d i s c t r i c d r y a c i r t r r
TLM Authors	Year	Origin	Study Design	N	CT/MRI/PETCT	Primary Yield	BOT	Tonsil	Synchronous	HPV	Complicati	I

Herruer et al[42]	2020	Canada	PS	61	PETCT and intraoperative identification. TLM IL PT, IL TBM, CL tonsil, CL TBM	90.1% (55/61) combined PETCT and TLM.			91.9% (57/61)	27.9% (17 complications in 15 patients) overall - not all TLM TLM: 12 Delayed recovery swallow - 5 DC NGT, 1 OP bleed (Cx), 3 Neck haematomt 1 chyle leak.	

Kuta et al[43]	2017	Canada	PS	27	Ex negative. PETCT (not all negative). TLM Biopsy. IL PT and TBM	92.6% (25/27)	48% (12/25)	52% (13/25)		92.6% (25/27)		S d s t e c c P T p t d t t a t a p t p
Graboyes et al[44]	2015	USA	CS	65	Negative ex, CT/MRI &/or PETCT. Rigid pharyngoscopy and directed Biopsy. If negative IL PT, IL TBM and CL 1cm (Maj TLM small min TOR after microscopy)	89% (58/65)	41.5% (27/65)	52.3% (34/65)	5% (3/58) synchronous IL palatine and lingual tonsil n=2, BL palatine tonsil 1)	100% (65/65) inclusion criteria	16.9% (11) surgery related): 9.2% (n=6) post-op haemorrhage - surgery or embolisation 7.7% (n=5) shoulder weakness n=9: CRT complicatio	1 f P e (T s a p h e t a P p t P C a l f d f e

Nagel et al[16]	2014	USA	RS	52	Traditional approach inc. PT vs TLM approach IL tonsil, IL TBM then CL	Overall 75% (39/52). TLM protocol 86.1% (31/36) Traditional 50% (8/16)	65% (n=26)	27.5% (n=11)	2.3% (n=1 both palatine tonsils)	Lingual 92% Palatine 100%	2.8% haemorrhage requiring RTT (n=1). ?Temporary swallow dysfunctio	S a r U p r i T a t r i T c g e l h d i C
Karni et al[17]	2013	USA	RS cohort	30 (18 TLM)	TLM vs traditional (+/- PT) TLM: IL tonsil, IL TBM	94.4% TLM (17/18), 25% (3/12) traditional	60% (12/20)	35% (7/20)	1/20 in NP and HP (21 complete tumours)			T M c p r h d t r a h l I I a t

Table 7. Novel Techniques. TOR: transoral Robotic Assisted Surgery. TLM: transoral laser microsurgery, IL: ipsilateral. BL: bilateral. PE: panendoscopy. Ix: Investigation. Ex: examination. BOT: base of tongue. Dx: diagnosis, Tx: treatment, CRT: chemoradiotherapy, PT: palatine tonsil

Discussion

Limitations and strengths

Except for a very small number, most reports in this space are retrospective and single centre studies. The current literature suffers from heterogeneity and non-uniform reporting. Thus, the limitations relate to study quality. Multicentre prospective work is needed to confirm the veracity of these findings.

Comparisons to other studies

This systematic review pooled together a wide range of diagnostic approaches for the HNSCCUP scenario. While no dedicated meta analysis was performed, the findings reported here have allowed us to offer a global view of the date, encourage discussions and also make firm recommendations that have helped discussions at the national consensus day, leading to national guidelines

Clinical applicability and generalisability

Combined with the data from the national audit and the discussions emerging from the consensus day, the recommendations made from this review have been used to create the national guidelines, thus leading to applicability of the findings.

Conclusion

A systematic approach to assessment of the HNSCCUP allows a higher number of occult primary sites to be identified. Random biopsies do not add significantly to the yield. As a minimum, ipsilateral tonsillectomy is warranted. In patients with a negative ipsilateral tonsil cancer, tongue base mucosectomy (unilateral or bilateral) has the best chance of identifying a primary site.

Suggested areas for future research

- High quality prospective studies regarding benefits and risks of staged versus combined tonsillectomy and TBM
- Defining the efficacy of TBM in P16 negative
- Detection rate and morbidity of bilateral vs unilateral TBM

Conflicts of Interest: None Declared

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