HNSCCUP Audit 2021:
National audit of the management of head & neck squamous cell carcinoma of unknown primary

Audit standards

The National Audit Standards relating to management of head and neck squamous cell carcinoma of unknown primary (HNSCCUP) are derived here from the the United Kingdom Multidisciplinary guidelines (2016)[1], the National Institute for health and Care Excellence guideline 36 (2018)[2], American Society of Clinical Oncology guideline (2020)[3], and the British Association of Head and Neck Oncologists standards (2020)[4].

Summary of abbreviations

Abbreviation	Definition
CT	Computed tomography
EBV	Epstein Barr Virus
FNAC	Fine needle aspiration cytology
HPV	Human Papilloma Virus
HNSCCUP	Head and neck squamous cell carcinoma of unknown primary
MDT	Multi-disciplinary team
MRI	Magnetic resonance imaging
NBI	Narrow band imaging
PET-CT	Positive emissions tomography- computed tomography
SCC	Squamous cell carcinoma
UADT	Upper aerodigestive tract
US	Ultrasound

US guided biopsy

Standard: all patients with suspected unknown primary should undergo an ultrasound guided FNAC or core biopsy to confirm presence of SCC as part of the initial neck lump assessment.

Guideline	**Recommendation**
UK 5th ed. (2016)	As part of assessment initial assessment in neck lump clinic the lymph node should be sampled by US guided FNAC or core biopsy
NICE 36 (2018)	N/A
ASCO (2020)	FNAC or core biopsy of a clinically suspicious neck mass should be performed
	HPV testing should be done routinely on level II and III HNSCCUP nodes.
	EBV testing should be considered on HPV-negative metastases
BAHNO (2020)	Provide FNA/core biopsy for all neck lumps suspected of being cancer of the UADT. This should be performed by a specialist radiologist, pathologist or clinician.

CT & MRI

Standard: all patients with confirmed cervical lymph node SCC should undergo CT and/ or MRI imaging as part of their initial diagnostic investigations.

Guideline	**Recommendation**
UK 5th ed. (2016)	All patients should have CT from skull base to diaphragm as part of the assessment of a newly diagnosed SCC of the head and neck.
	If the disease presents in a level II/III lymph node MRI of the oropharynx, in particular the tongue base, tonsil and tonsil lingual angle, should be carried out.
	May be supplanted by PET-CT as first line investigation.
NICE 36 (2018)	Consider an MRI or CT scan before diagnostic surgery to help with radiotherapy treatment planning.
ASCO (2020)	CT neck should be the initial test for workup of metastatic cervical lymphadenopathy
	No recommendations for MRI
BAHNO (2020)	N/A

Whole Body PET-CT

Standard: All patients with confirmed cervical lymph node SCC and no apparent primary site on examination or cross sectional imaging should undergo whole body PET-CT.

Guideline	**Recommendation**
UK 5th ed. (2016)	All patients with confirmed cervical lymph node and metastatic SCC and no apparent primary site should undergo whole body PET-CT. May be carried out as a first line investigation.
NICE 36 (2018)	Consider a PET-CT as the first investigation to detect the primary site in people with metastatic nodal squamous cell carcinoma of unknown origin that is thought to arise from the upper aerodigestive tract
ASCO (2020)	If a primary is not evident on clinical examination and CT, PET should be the next diagnostic step
BAHNO (2020)	All units treating individuals with HNSCCUP should have access to PET-CT scanning facilities

Panendoscopy & biopsy

Standards:

1. All patients with biopsy confirmed cervical lymph node SCC and no apparent primary site on examination, cross-sectional imaging, or PET CT should undergo a panendoscopy and directed biopsies of suspected primary sites after initial diagnostic imaging.

2. Directed biopsies of suspected primary sites on examination and diagnostic imaging may be performed.

Guideline	**Recommendation**
UK 5th ed. (2016)	All patients with confirmed cervical lymph node and metastatic SCC and no apparent primary site should undergo panendoscopy + palpation of the oral cavity/ tongue base.
	Should occur after completion of all imaging as instrumentation and biopsy prior to scanning would compromise the accuracy of the subsequent radiological assessments
NICE 36 (2018)	Offer surgical diagnostic assessment if PET does not identify a primary site. This may include guided biopsies, tonsillectomy, and TBM.
	Consider using narrow-band imaging endoscopy to identify a possible primary site when it has not been possible to do so using PET.
ASCO (2020)	Patients should undergo a complete operative upper aerodigestive tract evaluation of mucosal sites at risk including directed biopsy of any suspicious areas.
	Intraoperative advanced visualization techniques (e.g., NBI) may be used to investigate potential primary sites for targeted biopsy
BAHNO (2020)	There should be an agreed protocol for the surgical assessment of the primary site when PET-CT does not identify a possible primary site.

Tonsillectomy

Standard: All patients with biopsy confirmed cervical lymph node SCC and no apparent primary site on examination or cross-sectional imaging should undergo bilateral tonsillectomy.

Guideline	**Recommendation**
UK 5th ed. (2016)	All patients with confirmed cervical lymph node and metastatic SCC and no apparent primary site should undergo bilateral tonsillectomy
NICE 36 (2018)	See panendoscopy
ASCO (2020)	Unilateral lymphadenopathy: if a primary site is not confirmed, the surgeon should perform ipsilateral tonsillectomy. Bilateral palatine tonsillectomy may be considered according to clinical suspicion.
	Bilateral palatine tonsillectomy after bilateral lingual tonsillectomy should be avoided (see mucosectomy)
BAHNO (2020)	N/A

Mucosectomy

Standard: Where the expertise is available, all patients with biopsy confirmed cervical lymph node SCC and no apparent primary site on examination or cross-sectional imaging should undergo TBM.

Guideline	**Recommendation**
UK 5th ed. (2016)	All patients with confirmed cervical lymph node and metastatic SCC and no apparent primary site can be offered TBM if facilities and expertise exist
NICE 36 (2018)	See “panendoscopy”
ASCO (2020)	Unilateral lymphadenopathy: if ipsilateral tonsillectomy fails to identify a primary, ipsilateral lingual tonsillectomy may be performed.
	Bilateral lymphadenopathy: if a primary site is not confirmed, the surgeon may perform unilateral lingual tonsillectomy on the side with the greater nodal burden and may perform contralateral lingual tonsillectomy if the ipsilateral procedure fails to identify a primary.
	In patients in whom the primary tumour is identified and definitive surgical management is intended, clinicians should make every effort to resect the identified primary using transoral techniques to a negative surgical margin
	Intraoperative frozen section evaluation of palatine or lingual tonsillectomy specimens should be performed when the primary tumor remains undetected.
BAHNO (2020)	There should be an agreed pathway for a tongue base mucosectomy where indicated.

Excisional biopsy

Standard: patients with suspected or confirmed cervical lymph node SCC and no apparent primary site on examination or cross-sectional imaging should not undergo excisional biopsy without prior MDT discussion

Guideline	**Recommendation**
UK 5th ed. (2016)	N/A
NICE 36 (2018)	N/A
ASCO (2020)	N/A
BAHNO (2020)	Excisional biopsy of the malignant neck mass must not be undertaken without prior discussion in the H&N MDT.

Surgical intervention

Standards:

1. Patients with early nodal disease (N1) and no ENE can be managed with surgery or radiotherapy alone.
2. Patients with early nodal disease (N1) and obvious ENE can be managed with surgery and post-operative radiotherapy
3. Patients with moderate nodal disease (N2a-c) and those with advanced (N3) disease who are being treated with curative intent can be managed with surgery and post-operative radiotherapy +/- chemotherapy

Guideline	Recommendation
UK 5th ed. (2016)	Small nodal disease with no ENE (T0 N1) can be treated with surgery alone. Patients with ENE should also receive post-operative radiotherapy to the involved nodal level or the entire ipsilateral nodal chain.
	Moderate nodal disease (T0 N2a-N2c) can be treated with selective or modified radical neck dissection, with post-operative radiotherapy to one or both sides of the neck.
	Advanced (N3) disease treated with curative intent can be managed with a radical or Type I modified radical neck dissection with postoperative chemoradiotherapy. There is a potential role for surgery as palliation.
NICE 36 (2018)	Offer patients the choice of: neck dissection and adjuvant radiation +/- chemotherapy OR primary radiation +/- chemotherapy, with surgery for persistent disease
ASCO (2020)	For unilateral, small-volume neck disease, either definitive surgery or radiotherapy may be offered after MDT discussion
	For small-volume bilateral neck disease with no clinical ENE, either definitive surgery (+/- adjuvant therapy) or radiotherapy (+/- concurrent chemotherapy) may be offered after MDT discussion
	When primary surgery is planned, levels IIA, III, and IV should be routinely dissected when an oropharyngeal primary is suspected or confirmed.
BAHNO (2020)	N/A

See appendix I for table of proposed treatment recommendations according to UK 5th ed guidelines

Radiotherapy

Standards:

1. Radiotherapy with or without concomitant chemotherapy can be considered as a primary treatment modality in patients with N2-3 nodal disease and/or evidence of ENE, with planned neck dissection reserved for those who do not achieve a complete metabolic response.
2. Adjuvant radiotherapy with or without chemotherapy should be considered in patients with N2/3 nodal disease and/or pathologic evidence of ENE.

Guideline	Recommendation
UK 5th ed. (2016)	Patients with N1 disease with ENE, N2/ N3 disease can be treated with primary chemoradiation with a planned neck dissection in those without a complete metabolic response on post-treatment PET-CT
	Post-operative patients with N1 disease and evidence of ENE should receive adjuvant ipsilateral neck treatment
	Post-operative patients with N1 disease and evidence of ENE should receive adjuvant ipsilateral or bilateral neck treatment
	TMI remains a controversial issue & there is no conclusive evidence to support its use.
NICE 36 (2018)	See “surgical interventions” recommendations
ASCO (2020)	Large-volume bilateral neck disease and/or gross macroscopic ENE favour definitive chemoradiotherapy
	Patients with unilateral HPV positive and negative nodal disease should receive treatment to the gross node(s) and with consideration of coverage of putative primary sites in the ipsilateral tonsil, ipsilateral soft palate, and the mucosa of the entire base of tongue.
	Patients presenting with bilateral (N2c) nodal disease should receive bilateral treatment of the oropharyngeal mucosa
	Patients with unilateral involvement of multiple nodes and no evidence of ENE should routinely receive bilateral treatment
	Patients with N3 and/or bilateral nodal involvement and/or evidence of ENE require bilateral neck treatment

	Patients receiving radiotherapy or concurrent chemoradiotherapy adjuvant to surgical management should receive treatment to regions of the neck and mucosa at risk of containing microscopic disease.
	Adjuvant radiotherapy should be administered to patients with multiple pathologically involved nodes and/or pathologic evidence of ENE
BAHNO (2020)	All centres should have written protocols for different tumour sites and intents using local or national guidelines. These should be reviewed and updated at least every two years.

Chemotherapy

Standard: Concomitant chemotherapy should be considered alongside radiotherapy in patients with N2-3 nodal disease or evidence of ENE and in select post-operative patients.

Guideline	Recommendation
UK 5th ed. (2016)	Concomitant chemotherapy with radiation should be considered in patients with an unknown primary
	Concomitant chemotherapy with radiation should be considered in suitable patients in the post-operative setting
	Neo-adjuvant chemotherapy can be used in gross ‘unresectable’ disease
NICE 36 (2018)	See “surgical interventions” recommendations
ASCO (2020)	Concurrent administration of cisplatin with definitive radiotherapy should be offered to patients with a suspected mucosal primary HPV/p16-negative SCC in the presence of unresected N2-N3 nodal disease OR unresected multiple ipsilateral, or bilateral, lymph nodes OR unresected nodes >3cm OR pathologic evidence of ENE OR an EBV encoding region–positive stage II-IVA carcinoma of unknown primary
BAHNO (2020)	N/A

Follow-up

Standard: patients treated for unknown primary SCC of the H&N should be followed up for a minimum of five years, with a PET-CT performed at 3-4 months in those treated with chemoradiation.

Guideline	**Recommendation**
UK 5th ed. (2016)	Patients should be followed up at least two months in the first two years and three to six months in the subsequent years
	Patients should be followed up to a minimum of five years with a prolonged follow up for selected patients.
	PET-CT at three to four months after treatment is a useful follow-up strategy for patients treated by chemoradiation therapy
NICE 36 (2018)	N/A
ASCO (2020)	N/A
BAHNO (2020)	N/A

References

1. Mackenzie K, Watson M, Jankowska P, Bhide S, Simo R. Investigation and management of the unknown primary with metastatic neck disease: United Kingdom National Multidisciplinary Guidelines. The Journal of Laryngology & Otology. 2016 May 12;130(S2).

2. National Institute for health and care excellence. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over. NICE guideline [NG36]. 2018.

3. Maghami E, Ismaila N, Alvarez A, Chernock R, Duvvuri U, Geiger J, et al. Diagnosis and Management of Squamous Cell Carcinoma of Unknown Primary in the Head and Neck: ASCO Guideline. Journal of Clinical Oncology. 2020 Aug 1;38(22).

4. Schache A et al. BAHNO standards. British Association of Head and Neck Oncologists. 2020.

Appendix I

Table of treatment recommendations according to the UK 5th edition guidelines for the Investigation and management of the unknown primary with metastatic neck disease (2016).

Stage	**Surgery**	**Radiotherapy**	**Chemotherapy**
N1 no ECS	Selective or modified radical neck dissection	No, unless for mucosal sites	No
N1 with ECS	Selective or modified radical neck dissection	Yes- either to involved nodes or ipsilateral nodes with boost to involved lymph nodes	Should be considered
N2a-N2c	Selective or modified radical neck dissection +/- contralateral	Yes- ipsilateral but bilateral should be considered	Should be considered
N3	Radical or type 1 neck dissection	Yes- ipsilateral but bilateral should be considered	Should be considered