Head and neck squamous cell carcinoma of unknown primary - Who can be offered surgery as the sole treatment modality? A systematic review

Arunjit Takhar[1], Mark Wilkie[2], Devraj Srinivasan[3], and Emma King[4]

[1]St George's University Hospitals NHS Foundation Trust Department of ENT Surgery
[2]Royal Adelaide Hospital
[3]NHS Lothian
[4]University Hospitals Dorset NHS Foundation Trust

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Abstract

Objective Evaluate the role of neck dissection (ND) as the sole treatment modality for patients with cervical head and neck squamous cell carcinoma of unknown primary (HNSCCUP). **Design** Systematic review of observational cohort studies with qualitative synthesis. **Setting** PubMed, Ovid EMBASE, and Cochrane Controlled register of Trials (CENTRAL) were screened from January 2000 up to October 2021. **Participants** HNSCCUP patients undergoing ND. **Main Outcome Measures** The primary outcome was 3-year overall survival (OS). Secondary outcomes included disease-free survival (DFS), primary emergence, regional recurrence, and distant metastasis. **Results** Fourteen eligible studies were identified, including 1,780 patients, of whom 294 received ND as their sole treatment (seven studies) with 3-year OS ranging from 43.9% to 100%. 3-year DFS was reported in four studies (n=62) ranging from 42.8% to 67.0%. 5-year OS and DFS were available in three studies (n=31), ranging from 36.6% to 75.0%, and 43.6% to 67.0%, respectively. The rate of primary emergence ranged from 11.1% to 33.3% (seven studies, n=157), regional relapse from 0.0% to 50.0% (five studies, n=60), and distant metastasis from 0.0% to 3.3% (three studies, n=45). Patients undergoing ND as a sole treatment had predominantly p16 positive N1 (TNM7) disease without ECS. **Conclusion** Outcomes for HNSCCUP patients undergoing ND alone range widely in the literature but appear reasonable in a subset of patients with early stage p16 positive disease. Data is lacking for p16 negative disease where the potential primary site is more varied and primary emergence appears more common.

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Outcomes for HNSCCUP patients undergoing ND alone range widely in the literature but appear reasonable in a subset of patients with early stage p16 positive disease. Data is lacking for p16 negative disease where the potential primary site is more varied and primary emergence appears more common.

KEY WORDS

Cancer of unknown primary, head and neck cancer, human papillomavirus, squamous cervical carcinoma, treatment of cancers of unknown primary

KEY POINTS

- True unknown primary head and neck squamous cell carcinoma is increasingly rare with the evolution in diagnostic paradigms. In addition, changes in oncogenesis (Human papillomavirus related) have improved prognosis and led to a trend towards treatment de-escalation.
- Due to these issues, there is a paucity of relevant data on treatment outcomes, which is currently limited to historic observational studies only.
- Lower survival figures along with higher primary emergence and regional recurrence rates were observed in patients with p16- (or undefined p16 status) disease.
- Where populations of studies had higher rates of p16 positivity; outcomes from early-stage nodal disease (N1 without ECS) were favourable and there were lower primary emergence and regional recurrence rates. Primary emergences were often successfully treated with further curative intent.
- ND alone may be a reasonable treatment in a subset of HNSCCUP, namely p16+ N1 (TNM7) disease without ECS. For p16- disease it appears multi-modality treatment is required for optimal survival outcomes.

INTRODUCTION

As alluded to throughout this special issue, diagnostic and treatment paradigms for head and neck squamous cell carcinoma of unknown primary (HNSCCUP) are vexed issues, reflecting a dearth of robust contemporary evidence on the topic. This is largely because true unknown primary disease is relatively uncommon (1-5 % of all HNSCC cases (1)), resulting in small study cohorts, particularly in single-centre settings, compounded by a lack of uniformity between studies on the definition of what constitutes an 'unknown primary', making inter-study comparisons or pooled-analyses challenging or indeed unfeasible. Furthermore, the relatively recent realisation of the importance of human papillomavirus (HPV) in HNSCC oncogenesis (2), the particular

pertinence this has to HNSCCUP given the typical clinical presentation (that p16 positive HNSCCUP is considered oropharyngeal in the most recent edition of TNM/AJCC Classification for Head and Neck Cancer attests to this) (3), together with the dramatic upsurge HPV-related HNSCC (4), casts aspersion on the relevance of many historic studies to modern day practice.

An issue of contemporary interest in the management of HNSCCUP is in which specific circumstances can patients be managed by surgery as a single modality, thus avoiding adjuvant treatment and associated toxicity. The increased traction of this notion in recent years is underpinned, firstly, by advances in diagnostic surgical work-up resulting in more comprehensive oropharyngeal sampling, with tongue base mucosectomy becoming a standard of care in many centres internationally, and secondly, by a shift towards treatment de-escalation in HPV-related oropharyngeal SCC, something which is the subject of several international clinical trials currently recruiting (5,6)

Current guidelines internationally recommend that in HNSCCUP single-modality treatment can be considered in the presence of N1 or "small-volume" disease in the absence of extra-nodal extension (7–9). However, such recommendations are relatively tentative, suggesting multi-disciplinary discussion on an individual case basis; and are largely derived from consensus and expert opinion and/or extrapolation from contemporary oropharyngeal SCC data. To this end, to the best of our knowledge there have been no prior attempts to formally synthesise data on this topic to inform such decision-making.

Cognisant of these issues, the purpose of this systematic review was to collate and interrogate in detail the evidence for HNSCCUP patients treated with neck dissection (ND) alone with respect to oncological outcomes.

METHODS

This systematic review was conducted in accordance with preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement (10). As this study was a systematic review there was no requirement for local ethics approval or institutional board review.

Study Characteristics

Type of studies to be included

All types of observational and experimental study designs will be eligible for inclusion.

Setting

All countries and health systems will be considered.

Report Characteristics

- Publications from 1st January 2000 up until the date search conducted.
- English Language.
- Any publications status, including grey literature.
- Conference abstracts were excluded.
- Minimum 5 patients per report undergoing ND as sole treatment modality.

Participants

Inclusion criteria

- Patients with squamous cell carcinoma of unknown primary in cervical lymph nodes after clinical examination, radiological investigations +/- diagnostic surgery (biopsies, tonsillectomy, tongue base mucosectomy)
- Aged over 18
- Both sexes
- Treated with curative intent ND as their primary and sole therapeutic intervention

Exclusion criteria

Other tumour types of unknown primary in cervical lymph nodes (e.g., adenocarcinoma, melanoma, thyroid, salivary)

Intervention

Neck dissection (selective, modified radical, radical, extended)

Comparator

None selected

Outcome Measures

Primary Outcome

3- year survival (overall (OS), disease-free (DFS))

Secondary Outcomes

- Any other reported survival data (2- and 5- year survival, regional control rates)
- Primary emergence rates and sites of emergence
- Regional recurrence and distant metastasis

Information Sources

Sources to be searched: Databases PubMed, Ovid EMBASE, and Cochrane Controlled register of Trials (CENTRAL). References from previous review articles were also citation checked against the search results.

Search Strategy

Searches were limited to English Language entries reported from 1st January 2000 onwards and were last conducted on 7th October 2021. Searches were based around 3 broad search terms with expansions and synonyms for each database summarised in appendix 1:

- Squamous cell carcinoma of head and neck
- Neoplasms, unknown primary
- Neck dissection

Data Extraction

Selection of studies

The titles and abstracts of all studies were screened independently by two authors (AT/MDW) against the inclusion and exclusion criteria. Where there was uncertainty regarding eligibility, or there was disagreement between authors, the full texts of articles were obtained and reviewed. There were no differences of opinion that were not resolved through discussion. Where title and abstracts were identified in English language, but the main report was in a foreign language, they were subsequently excluded from analysis.

Data collection and items

Both authors independently extracted data using a standardised proforma with data entered to a Microsoft excel spreadsheet and final approval ratified by consensus of the first two authors.

Data items included: patient demographics, smoking history, diagnostic interventions performed prior to therapeutic ND, pathological nodal and p16 status. Further data items to reflect the primary and secondary outcomes were collected and are detailed in the table 1 and 2 below.

Risk of Bias

A study level risk of bias assessment was performed for all studies using the MINORS tool (11) as all studies eligible for inclusion were observational. Scores are summarised in table 1 and risk of bias cumulatively is commented upon.

Data Synthesis

Summary data are presented in table format from the studies. Given the heterogeneity in presentation and reporting of data in the studies, a statistical meta-analysis of these results was not possible, and the results were presented descriptively, with findings grouped according to outcome measures set out above.

RESULTS

Study Selection

A total of 390 potentially relevant records were identified, reducing to 290 after duplicates were removed. A PRISMA flowchart is demonstrated in figure 1. On review of full text articles 17 were removed as the series contained less than five patients that were treated with ND alone (12–28). A further 15 were removed as they comprised conference abstracts only (29–43) while six were non-English language (44–49). A total of 14 studies have met the eligibility criteria and are presented herein. (50–63).

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Figure 1. Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flowchart with results for searches, screening, and application of eligibility criteria.

Study Characteristics

The characteristics of the studies included in this systematic review are summarised in table 1. The studies were published between 2002 and 2021 and originate from centres in the USA (51,53,55,57), Europe (50,52,56,64), Asia (58,59,61–63) and Australia (54). There were no eligible studies from the UK. One of the studies was based on extraction of data from a national cancer database (51), while the remainder were single institution or multi-centre studies from a single geographical region. Three studies were based on prospective databases (53–55) that were retrospectively analysed, and the remainder were all retrospective studies. All the studies identified patients based on diagnosis and reported outcomes with respect to treatments given, and as such, were observational cohort studies. None of the studies directly compared ND alone to radiotherapy alone in a prospective or matched cohort manner, although some retrospectively commented on outcomes for both groups.

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The 14 eligible studies included a total of 1780 patients, of which 294 underwent ND as their single primary treatment for HNSCCUP. There were on average 17.5 (5-63) (median(range)) cases per study. Although all studies met the initial eligibility criteria and presented outcome data relevant to the primary and / or secondary aims, there was significant heterogeneity in reporting parameters, precluding any meta-analysis. There was a male preponderance, ranging from 76-88% across the studies, with an average age of 55-65

years. Four (28.6%) of the studies reported on p16 status, with one (7.1%) also reporting on high-risk HPV status by in situ hybridisation. In these studies, data were incomplete, with anywhere between 19.1% and 86.7% of included patients having status recorded.

The studies were evaluated for quality of diagnostic investigations compared to perceived 'gold standards' (FDG PET-CT, MRI, panendoscopy, tonsillectomy, tongue base mucosectomy). No single study included all investigations prior to treatment. PET-CT was performed on all patients in two studies (53,58) and on a proportion (20.0-58.6%) of patients in a further eight studies (50,54,56,57,59–62). Three studies (51,55,63) made no mention of cross-sectional imaging being performed, with the remainder confirming all patients underwent either CT or MRI scan prior to treatment. One study (51) didn't state if panendoscopy was performed and in two further studies only a proportion (45.1-64.0%) underwent panendoscopy (56,63). Tonsillectomy was undertaken for all patients in nine of the studies; a proportion of patients (5.8-41.7%) in three of the studies (50,56,63), and was not stated in two studies (51,55). Only one study reported on tongue base mucosectomy, stating that all patients had this procedure (52).

All the studies reported data on the nodal status (AJCC/UICC TNM7) of patients treated; however only half provided discernible data on nodal status for patients undergoing ND alone, totalling 132 of the 294 patients (44.9%). Of these, the breakdown of nodal status was: N1 (n= 35,26.5%), N2a (n= 28, 21.2%), N2b (n =58, 43.9%), N2c (n=4, 3.0%), and N3 (n=7, 5.3%).

Follow up duration was reported in 10 studies (n=800), but none specified follow up timeframes for ND only patients, median follow up duration ranged from 31.1 to 83.5 months, 6 studies reported a lower end range of follow up <12 months post treatment, which may impact interpretation of this data. Data for survival, primary emergence, recurrence, or metastasis was not stratified by p16 status in any of the studies.

Risk of bias in studies

MINORS scores are presented in table 1. The median MINORS score was 9 (range 6-13) out of a maximal score of 16. In general studies presented clearly stated aims, however lack of clarity on whether consecutive patients were included was a frequent issue. Endpoints were typically well defined, and reporting was unbiased. None of the studies prospectively calculated a study size and there was variable reporting on minimal follow-up periods and attrition rates, thus impacting reliability of extracted survival data.

Survival

A summary of survival data is presented in table 2. 3-year OS was reported on patients undergoing ND only in five studies (n=89) and ranged from 43.9% to 100%. 3-year DFS was available in four studies (n=62) for the same and ranged from 42.8-67.0%. 5-year OS and DFS was available in three studies (n=31) and ranged from 36.6-75.0% and 43.6-67.0% respectively.

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Table 2: Survival outcomes

Primary emergence, regional recurrence, and distant metastasis

A summary of primary emergence, recurrence and distant metastasis is presented in table 3. Twelve of the studies reported on primary emergence with reported rates between 1.5% and 21.8%. These studies included a total of 117 emergences in 1007 patients (11.6%). Primary emergence rates in patients having ND only were reported in seven studies (n=157) and ranged from 11.1-33.3%. Sites of primary emergence were reported on in 10 studies; but only three studies discerned sites of primary emergence in patients receiving ND only from the whole cohort. There were 95 primary site emergences reported in 823 patients, sites were as follows: 32 oropharynx (3.9%), 19 hypopharynx (2.3%), 18 nasopharynx (2.2%), 7 larynx (0.9%), 5 oesophagus (0.6%),

4 supraglottic (0.5%), 4 oral cavity (0.5%), 3 sino-nasal (0.4%), 3 lung (0.4%). Amongst those reporting on site of primary emergence for ND alone (n=82) there were: 8 hypopharynx (7.2%), 6 nasopharynx (7.3%), 6 oropharynx (7.3%), 3 larynx (3.7%), and 1 oral cavity (1.2%).

Eleven studies reported on nodal relapse rates overall, with rates varying from 8.7% to 42.0%. These studies included a total of 184 regional recurrences in 932 patients (19.7%). Five studies (n=60) reported on nodal relapse rates for ND alone and rates varied from 0.0% to 50.0%. 11 studies reported on distant metastasis with overall rates ranging from 1.5% to 36.2%, amongst the ND only patients, only three studies (n=45) reported, with rates of 0-3.3%.

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Table 3: Primary emergence and recurrence data

DISCUSSION

In this systematic review we sought to identify if there is a subset of HNSCCUP patients that can be treated with ND as single modality therapy and provide acceptable oncological safety. Despite broad search criteria, only 294 patients were identified as eligible for inclusion across 14 studies, none of which reported exclusively on patients treated with ND alone. Patients in these studies were recruited over a protracted time frame (1969-2018) during which the oncogenesis, risk factors and diagnostic approaches have evolved considerably. In addition, the nodal status of those receiving ND alone was only reported for 44.9% patients, of which 52.2% had N2b disease or above (table 1). As such, the results need to be approached with caution, as they do not reflect treatment within the framework of current international guidelines (7–9). The lack of granularity regarding p16 status and limited diagnostic work-up compared to contemporary practice further confounds the interpretation of this review.

Survival

In general, studies with a greater proportion of early N-stage patients treated with ND only tended to have improved survival. In Miller*et al.* (53) 88.9% of ND only patients had N1 or N2a disease, with a 3-yr DFS and OS of 66.7% and 100%, respectively. Furthermore, they report that in the 7 patients that were treated for N1 disease without evidence of extracapsular spread (ECS) progression-free survival (PFS) was 100%. In Mizuta *et al* . (58) 55.5% of ND only patients had N1 or N2a disease with 3-year disease specific survival (DSS) of 81.8% and 3-yr distant metastasis free survival (DMFS) of 88.6%. Whilst Iganej *et al.* (55) and Patel *et al* . (54) do not provide as detailed data the authors summarised that there was a '5-yr tumour control rate of 81% for N1 and N2a disease without ECS' and a '100% ipsilateral regional control for pN1' respectively. In contrast to this, Dou *et al* . (61) and Wongsritrang *et al* . (63) report only 10.4% and 17.3% of their whole cohort had N1 disease respectively, whilst the authors do not report on the N-stage for surgery only, we surmise that the lower 3-yr DFS & OS observed for ND only is reflective of this (42.8%, 87.5% and 54.5%, 43.9% respectively). Furthermore, these studies were conducted in China and Thailand, respectively, where a putative primary site is more likely to be nasopharyngeal (65), further limiting the interpretation of these findings in Western practice.

None of the studies included in this review could identify a survival benefit for primary radiotherapy over primary surgery, and some could not find a survival benefit for any particular combination of treatment modalities (51,58). However, four of the studies demonstrated improved survival when ND formed part of initial multi-modality treatment (50,59,60,62).

Primary site emergence, recurrence, and distant metastasis

Despite the heterogeneity in data reporting between studies, it appears that primary emergence was consistently higher amongst patients treated with ND only. For the whole cohort of patients 66.3% of primary

emergences were from non-oropharyngeal sites, and where data was available for ND only emergences, 75.0% were non-oropharyngeal. For the three studies that report on both p16 status and primary emergence (50,57,60), rates of p16 positive disease were 43.5%, 69.5% and 76.3%, with emergence rates of 7%, 1.5% and 5.3% respectively. This suggests that primary emergence rates may be lower in p16 positive disease compared to p16 negative disease where the primary site is more likely to be non-oropharyngeal and less prognostically favourable.

The 3-yr mucosal control rate for ND only was observed to be 67% in one study compared to 100% with the addition of adjuvant radiotherapy (to neck and putative primary site based on nodal basin)(61). However, this did not translate into a difference in 3-yr OS between groups (83.5% vs. 84.7%, p=0.591). Several studies additionally reported on outcomes after primary emergence. In Mizuta *et al* . (58) where there were six emergences after ND only (3 hypopharynx, 2 oropharynx, 1 oral cavity), three were treated with chemoradiotherapy, one with surgery and radiotherapy, and two with surgery alone. Four of the six remained disease free at the time of reporting with two of the hypopharynx cancers being alive with recurrent disease (distant metastasis). In Miller *et al* . (53), the sole primary emergence ND only (N2b) patient (oropharynx) was successfully treated with chemoradiotherapy 16 months after initial treatment.

The data with respect to primary emergence highlights three pertinent points. Firstly, the patterns and rates of emergence likely reflect the heterogeneity of patients included in these studies, and thus the variability in applicability and reliability of the data to contemporary practice. Secondly, the sites of emergence reported in these studies indicate a likely high incidence of p16 negative disease, conferring a poorer prognosis than p16 positive disease. Finally, consideration should be given to 'salvageability' when considering ND only as primary treatment, from the limited data presented, outcomes appear to be acceptable when considering the OS of ND only to the whole cohorts in these studies.

Due to the limited reporting and sample size for regional recurrence and distant metastasis it is difficult to draw any more meaningful conclusions from the data beyond what has been discussed with regards to survival and primary emergence.

Limitations

Several limitations must be considered in addition to those already discussed. Firstly, diagnostic and treatment protocols varied considerably both within and between studies. In some, treatment approaches varied upon likely putative primary site (61), and others reported a change in practice during the study period (60). Whilst some studies identified which patients were not treated 'per protocol' (53,54) (usually due to patient refusal of adjuvant treatment), the majority gave no explanation for decision making regarding treatments given, leading to potential selection bias. The lack of clarity regarding patients excluded, small sample sizes, and attrition rates in several studies leads to potential concerns for reporting bias within the studies. The geographical differences in incidence of disease (65) and prognostic impact of p16 (66) mean that the tumour biology both within and between these studies is likely to be variable, impacting on the results and interpretability.

Summary

This review has highlighted the paucity of evidence relevant to contemporary practice for HNSCCUP. The studies identified are heterogenous and span a timeframe from 1969-2018 during which oncogenesis and diagnostic strategies have evolved considerably, limiting interpretability of the findings. Crude interpretation of the data may suggest ND alone is a reasonable treatment consideration for select patients with p16 positive N1 (TNM7) disease without ECS. For patients with p16 negative disease the potential primary site is more varied, and outcomes were inferior with ND alone, given the high rates of primary emergence. For p16 negative patients it is likely that multi-modality treatment is nearly always indicated for optimal survival outcomes.

Whilst a prospective randomised control trial would prove highly valuable in further defining optimal management strategies, given the rarity and heterogeneity of this disease entity, patient accrual is likely to be

a significant barrier. Multi centre studies examining treatment outcomes in a contemporary era of practice may be more informative. Given the recent updates to AJCC/UICC TNM8 guidelines where p16 positive HNSCCUP is to be treated along oropharynx paradigms; extrapolation from relevant studies may be appropriate. For example, recent randomised control trial data from ECOG 3311(6) report a 2-yr PFS of 96.9% for a group of patients with T1-2, N0-1 (TNM 7) oropharynx cancer treated with surgery alone (27/38 patients N1 disease, no ECS)

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Appendix 1: Search Terms

PUBMED

Squamous Cell Carcinoma of head and neck [mh] OR	**Neoplasms, unknown primary [mh] OR**	**Neck Disse**
Squamous cell carcinoma of head and neck OR Head and Neck Cancer OR Head and Neck SCC OR Squamous cell carcinoma	Neoplasms, unknown primary OR Unknown primary OR Carcinoma of unknown primary	Neck dissect Cervical lyn

EMBASE

"Squamous Cell Carcinoma of head and neck"/syn OR	**"Neoplasms, unknown primary"/syn OR**	**"Neck**
"Squamous cell carcinoma of head and neck"/exp OR "Head and Neck Cancer":ti,ab OR "Head and Neck SCC":ti,ab OR "Squamous cell carcinoma":ti,ab	"Neoplasms, unknown primary"/exp OR "Unknown primary" :ti,ab OR "Carcinoma of unknown primary" :ti,ab	"Neck d "Cervica

CENTRAL

"Squamous Cell Carcinoma of head and neck"ti,ab,kw OR	**"Neoplasms, unknown primary" ti,ab,kw OR**
Squamous Cell Caricinoma" ti,ab,kw "Head and Neck Cancer":ti,ab,kw OR "Head and Neck SCC":ti,ab'kw OR	"Unknown primary" :ti,ab, kwOR "Carcinoma of unknown primary" :ti,ab, kw

Study	Country	Centre	Summary	Study timeframe	n total	n surgery only	Mean age (range)	Sex (% male)	N classification (%) All patients	N classification (%) surgery only	Pathology	Follow-up duration (months)	HPV/P16 + rate	MINORS Score
Dou 2016	China	Fudan University Shanghai Cancer Center	Presentation of data relating two-step decision making tailoring treatment for HNSCCUP	2007-2013	77	30	57** (31-75)	83.1	N1 = 8 (10.4) N2a = 16 (20.8) N2b = 38 (49.4) N2c = 13 (16.9) N3 = 3 (2.6)	Not stated	46/77 (59.7 %) SCC 31/77 (40.3 %) Poorly / undifferentiated carcinoma	34 (9-51)	Not stated	8
Lou 2015	China	Zhejiang Cancer Hospital	Impact on survival of adding neck dissection to treatment of HNSCCUP	2001-2012	133	46	55** (19-77)	81.9	N1 = 14 (10.5) N2a = 21 (15.8) N2b = 78 (58.6) N2c = 7 (5.3) N3 = 13 (9.8)	N1 = 7 (15.2) N2a = 5 (10.9) N2b = 30 (65.2) N2c = 3 (6.5) N3 = 1 (1.7)	SCC	39 (6-120)	Not stated	11
Wongsritrang 2012	Thailand	Prince of Songkla University	Clinical outcomes of HNSCCUP from single centre	2000-2010	139	17	63.6 (33-95)	87.0	N1 = 24 (17.3) N2 = 61 (43.9) N3 = 48 (38.5) Unknown = 6 (4.3)	Not stated	104/139 (74.8%) SCC 35/139 (25.2%) undifferentiated / Other carcinoma	Not stated	Not stated	6
Rodel 2009	Germany	University of Gottingen	Oncological outcomes of CUP based on treatments	1986-2006	58	8	55**(37-77)	82.8	N1 = 9 (15.5) N2a = 8 (13.8) N2b = 15 (25.9) N2c = 3 (5.2) N3 = 23 (39.7)	N1 = 2 (25.0) N2a = 2 (25.0) N2b = 1 (12.5) N3 = 3 (37.5)	48/58 (82.3%) SCC 10/58 (17.7%) Other carcinoma	83.5 (24-162)	Not stated	9
Miller 2008	USA	University of Texas Health Science Center, San Antonio	Prospective evaluation of diagnostic protocol and long-term follow up	Not stated	17	9	60.5 (39-81)	87.1	N1 = 7 (41.2) N2a = 4 (23.5) N2b = 2 (11.8) N3 = 4 (23.5)	N1 = 7 (77.8) N2a = 1 (11.1) N2b = 1 (11.1)	SCC	31.1 (21-60)	Not stated	12
Patel 2007	Australia	Sydney Head and Neck Cancer Institute	Retrospective analysis of prospective entry into surgery +/- PORT protocol	1987-2006	70	10	62** (38-86)	81.4	N1 = 5 (7.1) N2a = 13 (18.6) N2b = 30 (42.9) N2c = 4 (5.7) N3 = 18 (25.7)	Not stated	SCC	45 (2-158)	Not stated	12
Iganej 2002	USA	Southern California Permanente Medical Group	Management and patterns of relapse for HNSCCUP	1969-1994	106	29	57.3 (no range provided)	77.4	N1 = 14 (13.2) N2a = 27 (25.4) N2b = 39 (36.8) N2c = 2 (1.9) N3 = 24 (22.6)	N1 = 5 (17.2) N2a = 8 (27.6) N2b = 13 (44.8) N3 = 3 (10.3)	SCC	56 (no range provided)	Not stated	13

Table 1. Study Characteristics (Study 8-14)

Abbreviations: HNSCCUP – head and neck squamous cell carcinoma of unknown primary. Notes: AJCC TNM7 is used for nodal staging.
**=Median

Study	Country	Centre	Summary	Study timeframe	n total	n surgery only	Mean age (range)	Sex (% male)	N classification (%) All patients	N classification (%) surgery only	Pathology	Follow-up duration (months)	HPV/P16 + rate	MINORS Score
Cummings 2021	USA	Rochester, New York	National cancer database retrospective review	2004-2015	540	63	57 (22-90)	78.1	N1 = 145 (26.9) N2/2a = 143 (26.5) N2b = 172 (31.9) N2c = 33 (6.1) N3 = 47 (8.7)	Not stated	SCC	Not stated	82.4%	9
Wichmann 2021	Germany	University Hospital Leipzig	Diagnostic and therapeutic differences 1988-2006 vs. 2007-2018	1988-2018	115	19	Not stated	87.0	N1 = 17 (14.8) N2a = 31 (27.0) N2b = 35 (30.4) N2c = 6 (5.2) N3 = 26 (22.6)	Not stated	SCC	37.4 (median)	43.5% P16+ 45.5% HR HPV+	8
Dorobisz 2019	Poland	Wroclaw Medical University	How clinical assessment and treatments affect survival	Not stated	233	18	Not stated	76.0	N1 = 33 (14.2) N2 = 100 (42.9) N3 = 100 (42.9)	Not stated	202/233 (86.7%) SCC	Not stated	Not stated	7
Zhou 2018	USA	University of California, San Francisco	Comparison of treatment strategies and prognostic factors	1993-2015	75	6	58.3 (31-80)	88.0	N1 = 10 (26.3) N2a = 8 (21.1) N2b = 9 (23.7) N2c = 4 (10.5) N3 = 7 (18.4)	N1 = 3 (50.0) N2a = 2 (33.3) N2b = 1 (16.7)	SCC	82.8 (4-265) (median (range))	76.3%	10
Hung 2018	Taiwan	Taiching Veterans General Hospital	Treatment outcomes of HNSCCUP	1995-2013	69	5	55.7 (37-48)	82.6	N1 = 1 (1.4) N2a = 12 (17.4) N2b = 32 (46.4) N2c = 4 (5.8) N3 = 20 (29.0)	Not stated	SCC	55.5 (6-234) (median (range))	Not stated	9
Mizuta 2018	Japan	Kyoto University	Multi-centre retrospective analysis (12 institutions)	2006-2015	80	27	65** (39-83)	77.5	N1 = 15 (18.8) N2a = 16 (20.0) N2b = 34 (42.5) N2c = 5 (6.3) N3 = 10 (12.5)	N1 = 9 (33.3) N2a = 6 (22.2) N2b = 11 (40.7) N2c = 1 (3.7)	SCC	34 (2-132) (median (range))	Not stated	12
Axelsson 2017	Sweden	University of Gothenburg	Prognostic factors for HNSCCUP and impact of HPV	1992-2009	68	7	59 (36-87)	81.0	N1 = 13 (19.1) N2a = 24 (35.3) N2b = 13 (19.1) N2c = 6 (8.8) N3 = 12 (17.6)	N1 = 2 (28.6) N2a = 4 (57.1) N2b = 1 (14.3)	SCC	Not stated	69.5%	10

Table 1. Study Characteristics (Study 1-7)

Abbreviations: HNSCCUP – head and neck squamous cell carcinoma of unknown primary. Notes: AJCC TNM7 is used for nodal staging. **=Median

	Neck Dissection Only						Entire Study						
Study	n	Nodal staging	3-yr DFS	3-yr OS	5-yr DFS	5-yr OS	n	Nodal Staging	3-yr DFS	3-yr OS	5-yr DFS	5-yr OS	Other reported survival data
USA													
Cummings 2021	63	-	-	-	-	-	540	N1 = 145 (26.9) N2/2a = 143 (26.5) N2b = 172 (31.9) N2c = 33 (6.1) N3 = 47 (8.7)	-	-	-	**79.0%**	**5-yr OS 81% for chemoradiation** **5-yr OS 74% for radiotherapy alone** **5-yr OS 70% if 'received neither'*** *National database data so lack of granularity in reporting – 'received neither' could mean had surgery only or even no treatment
Zhou 2018	6	N1 = 3 (50.0) N2a = 2 (33.3) N2b = 1 (16.7)	-	-	**60.0%**	**68.0%**	75	N1 = 10 (26.3) N2a = 8 (21.1) N2b = 9 (23.7) N2c = 4 (10.5) N3 = 7 (18.4)	-	-	**64.0%**	**72.0%**	
Miller 2008	9	N1 = 7 (77.8) N2a = 1 (11.1) N2b = 1 (11.1)	**66.7%**	**100.0 %**	-	-	17	N1 = 7 (41.2) N2a = 4 (23.5) N2b = 2 (11.8) N3 = 4 (23.5)	**70.6%**	**88.2%**	-	-	**Surgery only: 6/7 (85.7%) were N1 without ECS – 100% PFS**
Iganej 2002	29	N1 = 5 (17.2) N2a = 8 (27.6) N2b = 13 (44.8) N3 = 3 (10.3)	-	-	-	-	106	N1 = 14 (13.2) N2a = 27 (25.4) N2b = 39 (36.8) N2c = 2 (1.9) N3 = 24 (22.6)	-	-	**53.0%**	-	**Surgery only: 81% 5-year tumour control for N1 & N2a disease without ECS**
Europe													
Wichmann 2021	19	-	-	-	-	-	115	N1 = 17 (14.8) N2a = 31 (27.0) N2b = 35 (30.4) N2c = 6 (5.2) N3 = 26 (22.6)	-	-	**66.1%**	**56.5%**	**Entire study: 5-yr DSS = 74.8%**
Dorobisz 2019	18	-	-	-	-	-	233	N1 = 33 (14.2) N2 = 100 (42.9) N3 = 100 (42.9)	-	-	-	-	**Surgery only: 9 (50%) survived <12 months, 4 (22.2%) survived 12-24 months, 5 (27.8%) survived >24 months** **Entire study: 93 (39.9%) survived <12 months, 46 (11.2%) survived 12-24 months, 82 (35.2%) survived >24 months**
Axelsson 2017	7	N1 = 2 (28.6) N2a = 4 (57.1) N2b = 1 (14.3)	-	-	-	-	68	N1 = 13 (19.1) N2a = 24 (35.3) N2b = 13 (19.1) N2c = 6 (8.8) N3 = 12 (17.6)	-	-	**74.0%**	**87.0%**	**Entire study: 2-yr DFS 81%, 2-yr OS 87%**
Rodel 2009	8	N1 = 2 (25.0) N2a = 2 (25.0) N2b = 1 (12.5) N3 = 3 (37.5)	**67.0%**	**88.0%**	**67.0%**	**75.0%**	58	N1 = 9 (15.5) N2a = 8 (13.8) N2b = 15 (25.9) N2c = 3 (5.2) N3 = 23 (39.7)	**50.9%**	**52.9%**	**39.7%**	**40.9%**	
Australia													
Patel 2007	10	NA	-	-	-	-	70	N1 = 5 (7.1) N2a = 13 (18.6) N2b = 30 (42.9) N2c = 4 (5.7) N3 = 18 (25.7)	-	-	**62.0%**	**56.0%**	
Asia													
Hung 2018	5	-	-	-	-	-	69	N1 = 1 (1.4) N2a = 12 (17.4) N2b = 32 (46.4) N2c = 4 (5.8) N3 = 20 (29.0)	-	-	-	-	**Surgery only: 5-yr DSS 80%** **Entire study: 5-yr DSS 60.3%**
Mizuta 2018	27	N1 = 9 (33.3) N2a = 6 (22.2) N2b = 11 (40.7) N2c = 1 (3.7)	-	**71.0%**	-	-	80	N1 = 15 (18.8) N2a = 16 (20.0) N2b = 34 (42.5) N2c = 5 (6.3) N3 = 10 (12.5)	-	**72.5%**	-	-	**Surgery only: 3-yr DSS 81.8%, 3-yr DMFS 88.6%** **Entire study: 3-yr DSS 80.3%, 3-yr DMFS 86.9%**
Dou 2016	30	-	**42.8%**	**87.5%**	-	-	77	N1 = 8 (10.4) N2a = 16 (20.8) N2b = 38 (49.4) N2c = 13 (16.9) N3 = 3 (2.6)	**59.4%**	**84.5%**	-	-	
Lou 2015	46	N1 = 7 (15.2) N2a = 5 (10.9) N2b = 30 (65.2) N2c = 3 (6.5) N3 = 1 (1.7)	-	-	-	-	133	N1 = 14 (10.5) N2a = 21 (15.8) N2b = 76 (56.6) N2c = 7 (5.3) N3 = 13 (9.8)	-	-	-	**67.1%**	**5-yr OS with Neck Dissection +/- adjuvant treatment 71.3%** **5-yr OS with non-surgical primary treatment 53.2%** **(p=0.061)**
Wongsritrang 2012	17	NA	**54.5%**	**43.9%**	**43.6%**	**36.6%**	139	N1 = 24 (17.3) N2 = 61 (43.9) N3 = 48 (38.5) Unknown = 6 (4.3)	**55.5%**	**33.9%**	**48.6%**	**27.8%**	

Study	n total	n Surgery only	HPV/P16+ rate	Primary emergence (%)		Sites of emergence	Regional recurrence (%)		Distant metastasis (%)	
				ND only	Entire study		ND only	Entire study	ND only	Entire study
Cummings 2021	540	63	82.4%	-	-	-	-	-	-	-
Wichmann 2021	115	19	43.5% P16+ 45.5% HR HPV+	-	**7.0%**	-	-	**8.7%**	-	**9.6%**
Dorobisz 2019	233	18	Not stated	-	-	-	-	-	-	-
Zhou 2018	75	6	76.3%	**16.7%**	**5.3%**	4 total (1 in surgery only group but site not stated): Oral cavity - 2 Oropharynx - 1 Supraglottis - 1	**50.0%**	-	**0.0%**	-
Hung 2018	69	5	Not stated	-	**11.6%**	-	**40.0%**	**42.0%**	-	**27.5%**
Mizuta 2018	80	27	Not stated	**22.2%**	**11.0%**	Surgery only (6): Oropharynx - 2 Hypopharynx - 3 Oral cavity – 1 Multi-modality treatment (3): Nasopharynx - 1 Oropharynx – 1 Hypopharynx - 1	-	**20.0%**	-	**12.5%**
Axelsson 2017	68	7	69.5%	-	**1.5%**	Oropharynx – 1 (initial treatment not specified)	-	**8.8%**	-	**1.5%**
Dou 2016	77	30	Not stated	**33.3%**	**18.1%**	14 total (10 in surgery group but site not stated): Nasopharynx - 3 Oropharynx - 3 Oral cavity - 3 Hypopharynx - 3 Sinonasal - 1 Oesophagus – 1	**33.3%**	**20.8%**	**3.3%**	**7.8%**
Lou 2015	133	46	Not stated	**37.0%**	**21.8%**	Surgery only (17): Nasopharynx - 6 Oropharynx – 3 Hypopharynx – 5 Larynx – 3 Multi-modality (12): Nasopharynx – 4 Oropharynx – 3 Hypopharynx – 1 Oesophagus – 2 Lung – 2	-	**13.5%**	-	**3.8%**
Wongsritrang 2012	139	17	Not stated	-	**8.6%**	12 total (initial treatment not specified): Nasopharynx – 2 Sinonasal – 2 Oropharynx – 3 Oral Cavity – 2 Larynx – 1 Oesophagus – 2	-	**13.7%**	-	**7.9%**
Rodel 2009	58	8	Not stated	-	**7.0%**	4 total (initial treatment not specified): Larynx – 1 Hypopharynx - 2 Lung - 1	-	**22.4%**	-	**36.2%**
Miller 2008	17	9	Not stated	**11.1%**	**5.9%**	Surgery only (1): Oropharynx – 1	**22.2%**	**17.6%**	**0.0%**	**5.9%**
Patel 2007	70	10	Not stated	**20.0%**	**11.4%**	8 total (2 in surgery group but site not specified): Oropharynx – 4 Oral Cavity – 2 Larynx – 2	**0.0%**	**20.0%**	-	**7.1%**
Iganej 2002	106	29	Not stated	**27.6%**	**17.9%**	19 total (initial treatment not specified): Nasopharynx - 2 Oropharynx – 10 Supraglottis – 3 Hypopharynx – 4	-	**34.0%**		**9.4%**

Table 3: Primary emergence and recurrence data.