Treatment of unknown primary head and neck squamous cell carcinoma: primary surgery versus primary radiotherapy

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Table of Contents

Tables

Figures

Abbreviations

AAOHNS: American Academy of Otolaryngology–Head and Neck Surgery

AJCC: American Joint Committee on Cancer

AMSTAR: assessment of multiple systematic reviews

BOT: base of tongue

CI: confidence interval

CPG: clinical practice guidelines

CSS: cancer-specific survival

CT: computed tomography

DFS: disease free survival

DSS: disease-specific survival

EBV: Epstein Barr virus

EORTC: European Organisation for Research and Treatment of Cancer

FACT-H&N: functional assessment of cancer therapy head and neck cancer questionnaire

FDG-PET: fluorodeoxyglucose positron emission tomography

FOIS: function oral intake scale

GRADE: grades of recommendation, assessment, development and evaluation

HNCUP: head and neck carcinoma of unknown primary site

HNSCC: head and neck squamous cell carcinoma

HPV: human papilloma virus

HR: hazard ratio

HR: hazard ratio

HRQoL: health-related quality of life outcomes

IMRT: intensity-modulated radiation therapy

MDADI: MD Anderson dysphagia inventory

MRI: magnetic resonance imaging

MRND: modified radical neck dissection

OS: overall survival

PARSPORT: parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer

PCR: polymerase chain reaction

PE: primary emergence

PET: positron emission tomography

PFS: progression free survival

PND: planned neck dissection

PROSPERO: prospective register of ongoing systematic reviews

QLQ-C30: Quality of life questionnaire

QoL: quality of life

Rb: retinoblastoma

RCT: randomised controlled trial

RFS: relapse free survival

RR: relative rate

RRFS: regional relapse free survival

SCC: squamous cell carcinoma

SND: selective neck dissection

TAME: toxicity, adverse long-term effects, mortality risk and end result

TLM: transoral laser microsurgery

TNM: tumour, nodes and metastasis

TORS: transoral robotic surgery

TTR: time to recurrence

TTTF: time to treatment failure

UICC: International Union Against Cancer

UQWOL: University of Washington quality of life questionnaire

VHI: voice handicap index

VMAT: volumetric-modulated arc therapy

V-RQOL: voice related quality of life measure

WHO: World Health Organisation

Abstract

Unknown primary head and neck squamous cell carcinoma is a rare condition with poor prognosis compared to tumours with a known primary site. There are no consistent guidelines or strong evidence to guide the management of these tumours. Surgery or radiotherapy are equally common primary treatment modalities for these patients. A systematic review was therefore conducted to assess the effectiveness of primary surgery compared to primary radiotherapy.

A pre-defined search strategy was used to search PubMed, Embase and ProQuest databases. Titles and abstracts were screened against inclusion criteria and full texts of potentially relevant studies retrieved to assess final eligibility. These studies underwent critical appraisal by two independent reviewers for assessment of their methodological quality. Five of these studies were included in pooled meta-analysis. Primary outcome measures of interest were overall survival and regional and relapse free survival. Primary emergence, neck recurrence and distant metastasis rates were extracted and analysed to substantiate the primary outcome measures.

Following screening of 9376 unique records identified by the search, ten retrospective cohort studies, including a total of 655 participants that analysed data from patient registries, were included in the review. Across the included studies, quality of data synthesis and reporting was poor, especially the stratification of end point survival data, summary statistics, reporting of treatment related toxicities and quality of life measures. Meta-analysis (n=5) revealed no statistically significant difference in overall survival based on the primary treatment modality (HR:0.86, p=0.60) but favoured primary surgery for regional and relapse free survival (HR:0.57, p=0.07). Early stage disease at

the time of treatment initiation had improved overall survival, regardless of the treatment modality (HR:0.27, p=0.008). Rate of primary emergence (median = 5%) after five years did not increase when the mucosa was not irradiated in suspected cutaneous cancer patients. However, treatment with neck dissection alone without patient risk stratification increased primary emergence rates as well as neck failure rates.

In conclusion, there is no treatment modality dependent difference in overall survival or regional and relapse free survival. Cutaneous origin of unknown primary head and neck cancers need to be considered and treated differently to cancers of occult mucosal origin.

Declaration

I, Nuwan Shyanaka Dharmawardana, certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of The University of Adelaide and, where applicable, any partner institution responsible for the joint-award of this degree.

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CHAPTER 1: INTRODUCTION

1.1 Review question

What is the effectiveness of primary surgery compared to primary radiotherapy in the treatment of unknown primary head and neck squamous cell carcinoma?

1.2 Significance of the research question

Head and neck squamous cell carcinoma (HNSCC) of unknown primary site (HNCUP) is described as the presence of cervical lymph node metastasis without an identifiable primary tumour site.[1] A truly unknown primary HNSCC is relatively rare, accounting for approximately 3% of newly diagnosed HNSCC.[2] In the absence of advanced imaging techniques such as fluorodeoxyglucose positron emission tomography (FDG-PET) currently available for detection of small tumours hidden from plain site, confirmed rates are historically as high as 10%.[3] In HNCUP, the primary tumour is thought to arise from the upper aero-digestive tract or the skin, based on the patterns of lymphatic drainage mapped in previous studies.[4] Treatment paradigms for HNCUP are heterogeneous; treatment options include a primary neck dissection with adjuvant radiotherapy or primary radiotherapy with concurrent chemotherapy. Recently, however, diagnostic transoral robotic surgery (TORS) assisted endoscopic procedures have begun to be adopted as a component of primary surgical treatment. The advantages of the TORS tongue base mucosectomy include exclusion of one possible site for an occult primary lesion, eliminating the need to irradiate the tongue base.[5] The non-surgical approach to HNCUP includes primary radiotherapy to the neck nodal site and suspected mucosal sites, with or without chemotherapy.[6] A planned neck dissection (PND) may also be included

in the treatment protocol following chemoradiation,[7] although controversy exists regarding the role of a PND, as no clear survival benefit has been shown after primary chemoradiation, except as a salvage procedure following treatment failure.[8]

The objective of the systematic review presented in this thesis is to assess the effectiveness of common treatment modalities for HNCUP. Mainstream modalities are primary surgery, followed by adjuvant radiotherapy, with or without the addition of chemotherapy, or primary radiation with chemotherapy. An existing meta-analysis by Liu *et al.*[9] that evaluated the optimum radiotherapy options for HNCUP included multiple comparisons: surgical versus radiotherapy, unilateral versus bilateral neck irradiation and neck only versus neck and possible primary site irradiation. They found that surgery followed by adjuvant radiotherapy had a five-year overall survival advantage (RR = 0.74, 95% CI 0.59 – 0.92, $p < 0.001$). However, the usefulness of this analysis to elucidate which treatment modality is superior and better inform clinical practice is questionable due to the inclusion of various radiation techniques that are no longer used in HNCUP in the pooled analysis and the inclusion studies without direct comparison to other treatment modalities. Another comprehensive outcomes review of HNCUP, appraising studies from 1998 to 2010, reported no statistically significant five-year survival difference between primary surgery and primary radiotherapy.[10] The authors also reported a neck stage dependent reduction in overall survival where smaller neck nodes had improved survival.[10] However, in this study, the analysis was not stratified based on type of radiotherapy used nor morbidity associated with the treatment.

1.3 Epidemiology of head and neck squamous cell carcinoma

Squamous cell carcinoma (SCC) is the predominant histopathological diagnosis of head and neck cancers.[11] It is the sixth most common cancer worldwide, with an incidence of up to 600,000 cases per year with a predilection to the male gender.[12] Prior to the 2000s, tobacco and alcohol use were the predominant identifiable causative agents for HNSCC.[13] However, in recent times, the human papilloma virus (HPV) has been identified to play a more dominant role as a causative agent.[14] Interestingly, HPV positive cancers are affecting younger patients of higher socio-economic status compared to the patients with HPV negative HNSCCs with no clear reasons identified to date.[15]

1.4 Mucosal, cutaneous and lymphatic anatomy of the head and neck region

Lymph nodes in the head and neck region are divided into multiple segments (also known as lymph node levels), based on generally consistent anatomical landmarks and consistent with biologically significant pathways of regional tumour metastasis (Figure 1).[16] This classification is used to describe various forms of lymph node dissections in head and neck surgery. Classically, regions of the neck are divided into cervical triangles based on prominent musculature, namely, anterior, carotid and posterior triangles. Each of these compartments can be further divided. The anterior triangle is subdivided into the submandibular and submental triangles by the anterior belly of the digastric muscle. The carotid triangle is subdivided into superior and inferior triangles by the superior belly of the omohyoid muscle. The posterior triangle is further divided into occipital and supraclavicular triangles by the inferior belly of the omohyoid muscle.[17]

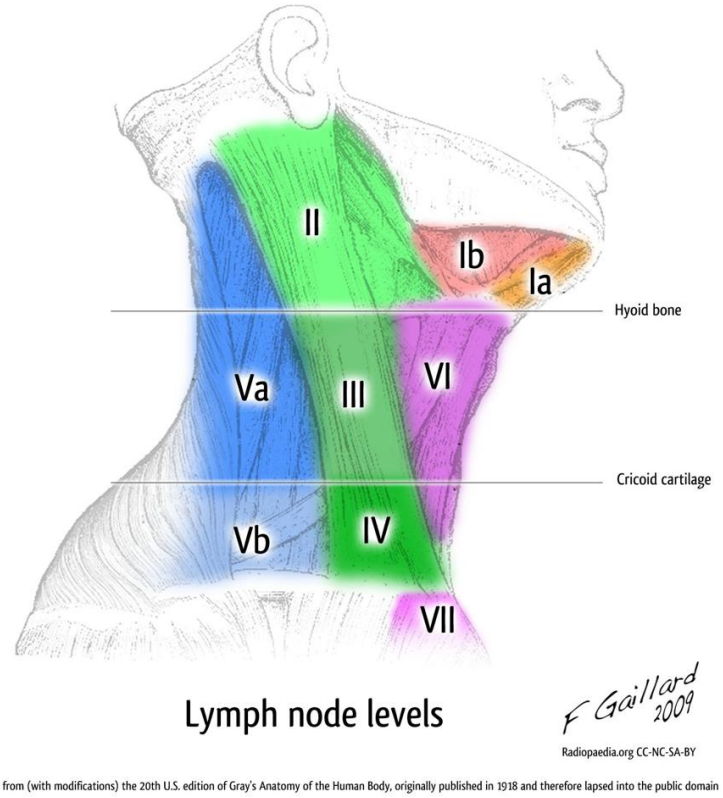

Figure 1. Neck lymph node levels, as described by the American Joint Committee on Cancer, showing relevant anatomical landmarks and a schematic view of described nodal levels. Image courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 9618, creative commons license.[18]

Classification of neck lymph nodes have evolved since the first anatomical description by Henri Rouviere in 1938.[19] It has been revised by Shah et al. in 1981,[20],Som et al. in 2000[21,22] and most recently by the American Academy of Otolaryngology–Head and Neck Surgery (AAOHNS).[23] The improvement in the classification system has been driven by the clinical applicability and ability for radiological discrimination of node levels. In the most recent iteration, neck lymph nodes are divided into six main levels and six sublevels (Table 1, Figure 1). The boundary separating level 1b from 2a is formally defined as the border of the stylohyoid muscle; however, the stylohyoid muscle is not palpable or easily identifiable on radiology.[24]

Table 1. Surgically distinct lymph node areas divided into "levels" with specific anatomical boundaries

Lymph node level	Anatomical boundaries
Level 1a	Mandibular symphysis
	Anterior belly of contralateral and ipsilateral digastric muscle
	Body of hyoid bone
Level 1b	Body of mandible
	Anterior belly of digastric muscle
	Stylohyoid muscle
	Body of hyoid bone
Level 2a	Skull base
	Inferior border of the hyoid bone
	Stylohyoid muscle
	Spinal accessory nerve
Level 2b	Skull base
	Horizontal plane defined by the inferior border of the hyoid bone
	Spinal accessory nerve
	Lateral border of sternocleidomastoid muscle
Level 3	Horizontal plane defined by the inferior border of the hyoid bone
	Horizontal plane defined by the inferior border of the cricoid cartilage
	Lateral border of the sternohyoid muscle
	Lateral border of the sternocleidomastoid muscle
Level 4	Inferior border of the cricoid cartilage
	Clavicle
	Lateral border of the sternohyoid muscle
	Lateral border of the sternocleidomastoid muscle
Level 5a	Apex of the sternocleidomastoid and trapezius muscle
	Horizontal plane defined by the inferior border of cricoid cartilage
	Lateral border of the sternocleidomastoid muscle
	Medial border of the trapezius muscle
Level 5b	Horizontal plane defined by the inferior border of the cricoid cartilage
	Clavicle
	Lateral border of the sternocleidomastoid muscle
	Medial border of the trapezius muscle
Level 6	Hyoid bone
	Suprasternal notch
	Common carotid artery either side

All mucosal sites of the head and neck region could be a potential target for an occult tumour. These sites can be separated to nasal cavity (including paranasal sinuses), oral cavity, nasopharynx, oropharynx, laryngopharynx (or hypopharynx) and the larynx.[25] However, the nasopharynx, oropharynx and hypopharynx is considered the most at risk for occult primary tumours giving rise to an HNCUP. In countries such as Australia, where smoking rates are significantly lower, the rates of hypopharyngeal cancers have become rare. Similarly, nasopharyngeal cancers appear largely limited to high risk East Asian populations.

Regular exposure to ultraviolet light from the sun increases the incidence of cutaneous SCC in countries such as Australia.[26] Head and neck cutaneous sites are especially at risk. These cancers could also present as a HNCUP. Head and neck cutaneous sites at risk include skin covering the scalp, face, ears and neck. Cutaneous SCC from a head and neck source has a regional metastatic rate of approximately 5%[27] and metastasis to intra-parotid lymph nodes is also common in contrast to mucosal SCC.[28] The parotid gland is the largest salivary gland in the head and neck region, present bilaterally, antero-inferior to the external auditory canal, lateral to the ramus of mandible, and overlying the masseteric muscle. It is closely associated to facial skin, only separated by the superficial musculo-aponeurotic system and the parotid fascia that overlies this gland, that may also allow direct invasion of cutaneous malignancies. This salivary gland is unique, with intra-glandular lymph nodes due to embryologically late development of its capsule following the development of the surrounding lymphatic pathways.[29] These lymph nodes located within the parotid gland are often the first-echelon nodes draining the skin covering the face and scalp.[30] Therefore, in patients prone to cutaneous SCC presenting with a HNCUP, involvement of the ipsilateral parotid gland should be considered and included in the treatment decision, even in the absence of gross parotid disease.

1.5 Pathophysiology of head and neck squamous cell carcinoma

HNSCC arise as a result of clonal transformation of pre-cancerous lesions, progressing from dysplasia to carcinoma in situ and subsequently to an invasive tumour. Risk factors mentioned earlier lead to molecular insults that accumulate in order to facilitate the development of these highly aggressive malignancies. Various molecular pathways are described in current literature and these are reviewed in this section.

1.5.1 Molecular basis of squamous cell carcinomas

HNSCCs occur due to a combination of molecular events, including numerous gene mutations. Numerous genes have been implicated in the pathogenesis of HNSCCs; these include *NOTCH1, NOTCH2, NOTCH3, IRF6, TP53, CDKN2A, HRAS, PTEN, SYNE1*, *SYNE2, RIMS2, PCLO, Rb/INK4/ARF* and *PIK3CA*.[31] The *TP53* (*p53*) gene pathway is the most common mutation identified in more than half of all HNSCC.[32] *p53* is a tumour suppressor gene that is identified in malignant as well as pre-malignant lesions such as leukoplakia.[33] This has led to the "patch-field" progression theory of HNSCC, where a field of genetically abnormal mucosal tissue gaining growth advantage and further mutations lead to a carcinoma.[34] Further research suggests that *p53* mutations in adjacent tissue can be different from the primary neoplasm, indicating the potential for metachronous tumours in the same patient after accumulation of further mutations in adjacent tissues.[35] There is also an independent association with poor survival in patients with a truncating or function disrupting *p53* mutation compared to patients without.[36]

Another key tumour suppressor gene pathway of importance is *Rb/INK4/ARF*.[34] Inactivation of *CDKN2A* via the retinoblastoma (Rb) pathway is found in up to 30% of tumours.[37] *CDKN2A* under normal physiological conditions encode for cell cycle regulators. These regulators include *p16/INK4A* and *p14/ARF/INK4B*. The *p16/INK4A* pathway is particularly important in HPV positive HNSCC that is further explored in Section 1.5.2.

NOTCH is an evolutionarily highly conserved signalling pathway that is also implicated in HNSCC differentiation.[38] In benign tissue, *TP63* (*p63*) and *NOTCH1* controls the squamous morphogenesis of mucosa.[39] The transcription factor *p63* is

expressed in keratinocytes of the basal layer and maintains their potential for proliferation, and the expression of *NOTCH1* causes terminal differentiation into spinous and granular layers of the mucosa. Loss of *NOTCH1* and mutated expression of p63 remove further barriers to neoplastic proliferation and survival of malignant cells.[39]

PI3K pathway is negatively regulated by *PTEN* and positively regulated by *PIK3CA*. Up to 40% of HNSCC has a *PTEN* mutation, causing the activation of the *PI3K* signalling pathway. This is important in HPV positive HNSCCs as the combination of HPV E6 and E7 proteins with *PIK3CA* can lead to more invasive oropharyngeal carcinomas.[40] The loss of *p53*, *CDKN2A*, *TGFBR2*/*SMAD4* and amplification of *CCND1* promotes progression and stops apoptosis of neoplasms.[34] Invasive features of HNSCC are promoted by the loss of cell adhesion molecules such as FAT1, SMAD3 and TFGB1.[34] This summary of genetics in HNSCC implicates various molecular steps of cell differentiation, tumour genesis, tumour progression and tumour suppression, giving rise to a largely heterogeneous group of neoplasms despite a common and contiguous anatomical location.

1.5.2 Role of human papilloma virus

Human papilloma viruses are DNA viruses with more than 100 subtypes identified in humans.[41] They are known to infect mucosal and cutaneous sites causing benign and malignant lesions. High risk HPV genotypes have demonstrated a strong causal relationship to SCC.[42] The oncogenic potential of HPV is due to viral oncogenes E6 and E7, blocking the function of *p53* and *Rb*, respectively (*p53* and *Rb* are tumour suppressor genes; see Section 1.5.1).[43] The HPV subtypes 16 and 18 are considered high risk for malignant potential. These are associated with up to 30% of head and neck cancers.[44]

However, a positive HPV status in oropharyngeal HNSCC gives an independent prognostic advantage compared to HPV negative mucosal carcinomas.[45] HPV status may also determine the treatment response, as HPV positive patients are more responsive to radiotherapy compared to HPV negative patients.[42] A recent prospective trial have identified a clear therapeutic response and a survival advantage for HPV positive oropharyngeal HNSCC patients.[46] In some treatment centres, an HPV positive tumour neck node is considered an occult mucosal primary tumour likely originating from the oropharynx.[47] However, up to 30% of cutaneous SCC are also p16 positive without the survival advantage described in mucosal primaries.[48,49] A recent review and meta-analysis confirms the presence of high-risk HPV in cutaneous SCCs more so compared to normal skin, although, no causative or prognostic relationship was inferred.[50] Therefore, cutaneous primary sites for HNCUP must also be considered when a neck node is positive for HPV. There is no clear evidence to indicate if the survival advantage demonstrated in patients with known primary sites can be extrapolated to HNCUP.[47]

To compound the issue, the way in which HPV is detected varies according to resource availability and there is no international standard for this. p16 is a surrogate marker that is commonly reported in the literature and p16 protein expression can be detected in aspirated biopsy (through generation of a cell block) and resected samples using cytological techniques and immunohistochemistry, respectively.[51] A positive p16 stain provides indirect evidence of transcriptionally active HPV.[52] A recent systematic review exploring this topic indicated that p16 expression is better at predicting HPV presence when more than 70% of tumour cells are stained positive.[53] However, the percentage quantification of staining is subjective. Direct evidence of HPV infection (HPV DNA) can also be detected via polymerase chain reaction (PCR) or in-situ

hybridization techniques.[51] While the specificity of HPV hybridization is reported to be high, the sensitivity is low.[54] Studies using a combined approach to detect HPV have positive patients, intermediate benefits for HPV negative but p16 positive patients, and limited benefits for patients with p16 negative with or without HPV positivity.[55] Recently, the College of American Pathologists recommended the first-line use of p16 as an immunohistochemical marker and only to use the HPV DNA testing on a case by case basis for extra information or in ambiguous cases.[56] The recommendation to use HPV DNA testing is largely based on access to technology and associated cost. The American Joint Committee on Cancer (AJCC) recommends a combined approach for reporting HPV status.[57] Prior to the availability of HPV testing, tumour morphology was used to differentiate tumour prognosis and the Basaloid histological variant is often associated with HPV positivity. Recent research however, suggests a poor congruence between histological types and HPV positivity and does not recommend this as a primary method of inferring HPV positivity.[58]

1.6 Classification of head and neck squamous cell carcinoma

Appropriate clinical and pathological staging of cancer is crucial for clinical decision making. Staging involves the grouping of patients based on similarities concerning anatomy and other relevant factors. This categorisation becomes useful for future research and standardised survival analysis to predict best practise for patients. The AJCC regularly reviews staging systems to appropriately revise the staging based on current evidence. Until 2017, HNSCC was staged using the seventh edition of AJCC staging manual.[59] Staging of HNSCC is currently based on the International Union Against Cancer (UICC) TNM (tumour, nodes and metastasis) classification of malignant tumours, and the 8th Edition or the AJCC staging manual.[57] The eighth edition was

released in mid-2016 for utilisation from 1 January 2017. Both systems identified T-category based on local tumour growth, N-category (Table 2) based on regional nodal spread of tumour and M-category based on distant metastasis, beyond the head and neck region. Combination of the TNM categories allows for an overall four-tier overall staging system, with stages 1-2 considered early and stages 3-4 considered advanced stage malignancy with minor adjustments based on viral mediated of malignancy (Tables 3, 4 and 5).[57] This tiered organisation of staging allows for treatment decision making processes to choose between curative verses palliative, and single-modality versus multi-modality treatment regimens. The most important change from the 7th to the 8th edition of AJCC TNM staging system is the inclusion of prognostic advantage of HPV positive malignancies and the prognostic disadvantage of extra nodal extension of tumour.[57,60] The clinical component of staging relies on physical examination of the patient with the aid of radiological findings (Table 6), while pathological staging is based on the analysis of the histopathological specimen after surgical resection of the tumour (Table 3). At present, p16 status is based on tissue immunohistochemistry from an initial biopsy of the suspected tumour or following surgical resection of the neoplasm.

Table 2. HNCUP pathological staging of lymph nodes AJCC/UICC 2017[60]

Node category	Pathological criteria
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node 3cm or smaller in greatest dimension No extra-nodal extension
N2	
N2a	Metastasis in a single ipsilateral node 3cm or smaller With extra-nodal extension **OR** Metastasis in a single ipsilateral lymph node Larger than 3cm but smaller than 6cm No extra-nodal extension
N2b	Metastasis in multiple ipsilateral lymph nodes All smaller than 6cm No extra-nodal extension

Node category	Pathological criteria
N2c	Metastasis in bilateral or contralateral lymph nodes All smaller than 6cm No extra-nodal extension
N3	
N3a	Metastasis in a lymph node larger than 6cm No extra-nodal extension
N3b	Metastasis in a single ipsilateral lymph node larger than 3cm With extra-nodal extension **OR** Multiple ipsilateral, contralateral, or bilateral nodes of any size With extra-nodal extension **OR** A single contralateral node smaller than 3cm With extra-nodal extension

HNCUP – head and neck carcinoma of unknown primary site, AJCC – American Joint Committee on Cancer, UICC – International Union Against Cancer, N – neck

Table 3. Non-virally mediated HNCUP prognostic staging AJCC/UICC 2017[60]

T – stage	N – stage	M – stage	Overall stage
T0	N1	M0	III
T0	N2	M0	IV-A
T0	N3	M0	IV-B
T0	N – Any	M1	IV-C

HNCUP – head and neck carcinoma of unknown primary site, AJCC – American Joint Committee on Cancer, UICC – International Union Against Cancer, N – neck

Table 4. EBV mediated HNCUP prognostic staging AJCC/UICC 2017[60]

T – stage	N – stage	M – stage	Overall stage
T0	N1	M0	II
T0	N2	M0	III
T0	N3	M0	IV-A
T0	N – Any	M1	IV-B

EBV – Epstein Barr virus, HNCUP – head and neck carcinoma of unknown primary site, AJCC – American Joint Committee on Cancer, UICC – International Union Against Cancer, T – primary tumour, N – neck, M – distant metastasis, EBV – Epstein Barr virus

Table 5. Human papilloma virus (HPV) mediated HNCUP prognostic staging AJCC/UICC 2017[60]

T – stage	N – stage	M – stage	Overall stage
T0	N1	M0	I
T0	N2	M0	II
T0	N3	M0	III
T0	N – Any	M1	IV

HPV – human papilloma virus, HNCUP – head and neck carcinoma of unknown primary, AJCC – American Joint Committee on Cancer, UICC – International Union Against Cancer, T – primary tumour, N – neck, M – distant metastasis, HPV – human papilloma virus

Table 6. HNCUP clinical staging of lymph nodes AJCC/UICC 2017[60]

Node Category	Clinical criteria
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node

Node Category	Clinical criteria
	3cm or smaller in greatest dimension No extra-nodal extension
N2	
N2a	Metastasis in a single ipsilateral lymph node Larger than 3cm but smaller than 6cm No extra-nodal extension
N2b	Metastasis in multiple ipsilateral lymph nodes All smaller than 6cm No extra-nodal extension
N2c	Metastasis in bilateral or contralateral lymph nodes All smaller than 6cm No extra-nodal extension
N3	
N3a	Metastasis in a lymph node larger than 6cm No extra-nodal extension
N3b	Metastasis in any lymph node with clinically overt extra-nodal extension or invasion of skin overlying the lymph node

HNCUP – head and neck carcinoma of unknown primary, AJCC – American Joint Committee on Cancer, UICC – International Union Against Cancer, N – neck

1.7 Current diagnostic modalities for identification of unknown primary head and neck carcinoma

In current practice, the diagnostic approach to locating the primary site includes clinical examination including flexible nasendoscopic examination, radiological studies, rigid endoscopic biopsies and biomarker identification of fine needle aspirates or core biopsies of the cervical nodal disease.[61] Radiologically, whole body positron emission tomography (PET) scans,[62] high resolution contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are all commonly utilised.[63] Surgically, unilateral or bilateral tonsillectomies,[64] targeted biopsies of the tongue base and more recently mucosectomy by either TORS[5,65] or other means can be used. Surrogate and direct biomarkers of causative agents such as HPV and the Epstein Barr virus (EBV) can also be utilised for identifying a possible primary site.[66] Whilst a broad range of modalities are described above, the approach chosen is largely dependent on the local availability of resources and clinical expertise. Due to the lack of high level evidence, some modalities are overlooked and others over-represented.[67] A recent study by Dale *et*

al.[67] highlighted the poor diagnostic value of over-utilised modalities in the identification of the primary site, with PET scanning only having a detection rate of 7%. Hatten *et al.* reported an 80% primary site detection rate using TORS-assisted endoscopy procedures.[5] While the difference in point estimate (7% detection rate compared to 80%) between these studies appears to be very large, the lack of studies with direct comparison and widely distributed baseline characteristics does not allow for ready or valid comparison of published data.

1.8 Current treatment modalities for unknown primary head and neck carcinoma

Surgical and non-surgical treatment options are described for the management of HNCUP.[68] However, the choice of optimum treatment modality remains controversial.

1.8.1 Surgical options

Comprehensive dissection of lymph nodes from the affected side of the neck is the current surgical option for HNCUP. The type or extent of neck dissection is modified based on the involved nodal levels and invasion into adjacent structures. The need for adjuvant radiotherapy following neck dissection is mandatory in HNCUP due to poor survival without adjuvant radiotherapy.[68,69] Comprehensive lymph node dissection to treat HNCUP as a primary modality has shown improved locoregional control and survival benefit.[68,70]

Lymph node dissection is based on the levels described earlier (Section 1.4, Table 1, Figure 1) and can be in the form of a modified radical neck dissection (MRND) or a selective neck dissection (SND). The comprehensive clearance of lymph nodes from a complete ipsilateral compartment of the neck (level 1 to level 5), with some disease

dependent and practitioner dependent variability, is termed a MRND. In this surgical procedure, the lymph nodes in described level 1, 2, 3, 4 and 5 are dissected out while frequently preserving the sternocleidomastoid muscle, internal jugular vein and spinal accessory nerve. SND refers to a neck dissection where the affected and surrounding nodal levels are dissected without comprehensively dissecting all ipsilateral neck lymph node levels. For example, a SND would include levels 2 to 4, provided the malignant node is not in level 1 or 5 of the ipsilateral neck. There are no randomised datasets to definitively inform the best type of neck dissection to conduct for an HNCUP. However, a recent study has found that SND including levels 2 to 4 should be considered in patients with no clinical or radiological evidence of nodal involvement in levels 1 or 5 of the ipsilateral neck. This recommendation was based on a small study (n=25) with a median follow-up of 33 months, where occult disease in levels 1 and 5 following MRND was 0% and 6%, respectively.[71]

Tonsillectomy is considered a standard component of the contemporary diagnostic process for a HNCUP,[2] nonetheless, this is a surgical procedure and forms part of the overall surgical-interventions for these patients. Various tonsillectomy techniques are described.[72,73] These include but are not limited to cold-steel dissection techniques, bipolar or monopolar electrocautery techniques, Coblation™ tonsillectomy, Bizact™ tonsillectomy or microdebrider assisted tonsillectomy. Regardless of the technique, the principle includes the dissection of lymphoid tissue with or without their capsule while leaving behind the superior constrictor muscle fibres. The mucosa and musculature of the palatopharyngeus muscle and palatoglossus muscle is usually left behind. When considering a potential tonsil malignancy, it is important to consider significant diathermy artefact that may hinder the histological evaluation. While there are no recommendations

available in the literature as to which tonsillectomy technique is superior in the presence of potential tonsil malignancy, certain techniques would be unsuitable in this setting, based on first principles. For example, using microdebrider assisted techniques or Coblation™ techniques, more specifically intra capsular dissection, would not provide an adequately intact histological sample for further evaluation.

Tongue base mucosectomy is another recognised procedure in the diagnostic process of HNCUP.[74] Since the mid-2000s, the use of TORS technique to access the tongue base has gained popularity. Small case series studies from the United Kingdom and Australia using TORS have reported tumour identification rates of 53% (n = 17) and 71% (n = 7), respectively.[74,75] Earlier studies using TORS from the United States of America (USA) have reported up to a 90% detection rate.[65,76,77] A recent systematic review reported an improved primary detection rate (80%) using TORS or transoral laser microsurgery (TLM) if the whole examination process including palatine and lingual tonsillectomy was conducted with TORS/TLM compared to TORS tongue base mucosectomy alone (72%).[78] Another meta-analysis reported a TORS/TLM primary detection rate of 70.8% (range: 53.1% – 90%) with 64% of primary tumours identified in base of tongue (BOT).[79] However, they also reported a high positive margin rate of 22.8% (range: 15.4% to 48.6%) that negates some of the benefits of conducting a BOT mucosectomy as re-resection or irradiation of that mucosa would be necessary, adding to the morbidity of treatment.

The mucosectomy technique involves dissecting away the mucosa and lymphoid layer (lingual tonsils) from the BOT; this can be done unilaterally or bilaterally. However, bilateral mucosectomy puts the patient at risk of circumferential cicatrisation that may cause significant oropharyngeal stenosis. Therefore, carefully considered surgical steps

are described, where tonsillectomy and mucosectomy are well clear of the tonsil-lingual sulcus, at least on a single side, preventing circumferential cicatrisation.[74] The laterality of HNCUP is important to consider because contralateral primary tumour rates are reported to be approximately 6% and 15% for tongue base and palatine tonsil, respectively.[78]

1.8.2 Non-surgical options

Intensity-modulated radiation therapy (IMRT) and its variations, including volumetric-modulated arc therapy (VMAT), have become the preferred technique in radiation oncology approach to the treatment of HNSCC since the mid-2000s.[80] Its popularity is primarily due to the advanced three-dimensional control of radiation intensity, which maintains the appropriate dosage at the tumour site while limiting toxicity to the surrounding tissue.[80] The PARSPORT trial (parotid sparing intensity modulated versus conventional radiotherapy in head and neck cancer – multicentre randomised controlled trial)[80,81] highlighted the superiority of IMRT in reducing radiation dosage to normal tissues and reducing the evidence of severe xerostomia.[81] Irradiation of the potential primary tumour sites in addition to the neck however was associated with significantly more adverse events.[9] A significant issue impacting the practical utility of this meta-analysis[9] was the inclusion and combination of all studies published up to 2015; this included studies that used both IMRT and conventional radiotherapy, where the survival rates and adverse event profiles are notably significantly different with these techniques.[81,82] Given the superior adverse events profile of IMRT and the relatively common use in head and neck setting today, the systematic review presented in this thesis will only include studies using IMRT (or an acceptable form of IMRT) to obtain a more homogeneous study population with comparable treatments. More recently, neoadjuvant

radiotherapy techniques have also been described more specifically for advanced stage oral cavity SCC.[83] However, no neoadjuvant treatment paradigms are published relevant to the treatment of HNCUP.

Systemic therapy is used in two clinical scenarios in relation to HNCUP: first, in the setting of improving locoregional control by addition of chemotherapy to primary or adjuvant radiotherapy;[84] second, in the palliative care setting, where other modes of treatment have failed, or the presenting disease is locally advanced with distant metastasis.[84] Use of chemotherapy in HNCUP was first described by de Braud et al.[85] in 1989, where the addition of concurrent chemotherapy during radiotherapy treatment significantly improved survival rates in advanced stages of disease (stage N3). While some recent non-randomised studies indicate a survival benefit[82,84] with an acceptable toxicity profile, others do not.[86] Data is not available to show a definite advantage of systemic therapy, especially when the toxicity profile is considered.

1.9 Endpoint measures in cancer research

There are numerous cancer specific endpoints described in the literature. However, the nomenclature used in various publications is inconsistent and at times misleading. Punt *et al.* [87] described consensus agreement of nine different endpoints in cancer research (Table 7). Overall survival is commonly used as the gold standard endpoint for reporting treatment effectiveness in cancer research. However, when considering head and neck cancers and comparing treatments, differences have been shown in other clinical endpoints despite there being no differences in overall survival. This is also true for other cancer subsites such as colorectal and breast cancer studies.[87] The consensus statement from Punt *et al.* [87] suggests the following definitions for cancer related outcome measures:

- Disease-free survival (DFS), defined as the time to any event (except loss to follow-up), regardless of the causative agent. This includes recurrence of disease or death.
- Relapse-free survival (RFS), defined as events such as recurrence or death from the same cancer, and death from treatment related to other causes. However, it excludes events from the same type of second primary cancer or another type of primary cancer. Failure to follow-up is censored in this metric.
    - In the context of head and neck cancer, regional relapse-free survival (RRFS) is defined as the time to disease recurrence at the site of tumour presentation or regional lymph nodes.
- Progression free survival (PFS) is another endpoint measure in head and neck cancer research, where it is the interval from treatment completion recurrence in local, locoregional or distant organs.[88]
- Cancer-specific survival (CSS) or disease-specific survival (DSS), defined as the time to death caused by the same cancer. This includes the original tumour as well as any second primary tumours of the same type. However, it excludes death from other types of cancers or treatment related events. It also excludes recurrences or any other tumour related events. Loss to follow-up is censored.
- Overall survival (OS), defined as the time to death, regardless of the cause. Any other tumour related event is excluded, with loss to follow-up censored like other end points.
- Time to recurrence (TTR), defined as any event related to the cancer of interest. The emergence of recurrence or death related to the cancer of interest is considered an event. Deaths related to other malignancies, comorbidities or treatment are censored.

- Time to treatment failure (TTTF), defined as the time to recurrence or death from any cancer or treatment. Only non-cancer related deaths and loss to follow-up are excluded.

An outcome measure specifically related to HNCUP is:

- Primary emergence (PE), defined as the percentage of patients with a tumour appearing in a subsite known to have lymphatic drainage to the affected metastatic lymph node. This is normally reported as a percentage event at five years following treatment.

Table 7. Cancer specific time-to-event outcome measures and composition of each measure for determining effectiveness of treatment[87]

Event	DFS	RFS	TTR	TTF	CSS	OS
Locoregional recurrence	E	E	E	E	I	I
Distant metastasis	E	E	E	E	I	I
Second primary, same cancer	E	I	I	E	I	I
Second primary, other cancer	E	I	I	E	I	I
Death from same cancer	E	E	E	E	E	E
Death from other cancer	E	E	C	E	C	E
Non-cancer related death	E	E	C	C	C	E
Treatment related death	E	E	C	E	C	E
Loss to follow-up	C	C	C	C	C	C

DFS = disease-free survival, RFS = relapse-free survival, TTR = time to recurrence, TTF = time to treatment failure, CSS = cancer specific survival, OS = overall survival, E = event, I = ignore, C = censor

1.10 Toxicities and quality of life with treatment of HNSCC and their measurement

Despite advances in the delivery of surgery, radiation oncology and medical oncology, patients continue to suffer from significant adverse events and long term toxicity.[89] Therefore, it is important to consider quality of life (QoL) for these patients. The World Health Organization (WHO) defines QoL as the person's perception of their

own position in life, within the context of their culture and value systems, related to their goals, expectations, standards and concerns.[90] As the definition suggests, the concept of QoL is complex, where the general wellbeing of a person is quantitatively or qualitatively assessed from multiple perspectives, relevant to a particular context in the patient's life.[91] In the context of head and neck cancer, adverse events are directly related to the modality of treatment received and the stage of their cancer.

For patients treated with primary surgery, adverse events or toxicities can be categorised into peri-operative, intra-operative, immediate post-operative and late complications. General anaesthesia is a requirement for head and neck surgery and patient comorbidities can result in adverse events, including death. However, anaesthetic complications are beyond the scope of this review and therefore are not further discussed. Intra-operatively, various vital structures within the neck are exposed and there is potential for injury. One of the most common symptoms reported following a neck dissection is limited shoulder abduction or pain secondary to injury of spinal accessory nerve. In modern day neck dissections, this nerve is preserved.[92] Other named neural structures with potential injury include the vagus nerve, lingual nerve, hypoglossal nerve and the marginal mandibular nerve. In very rare cases where the tumour is invading deep into the root of the neck, there is potential to injure the brachial plexus (innervate the upper limb) as well as the phrenic nerve that innervates the diaphragm. Other intra-operative complications include vascular injury (venous or arterial and related air emboli), pneumothorax and chyle leak (due to thoracic duct injury). Potential post-operative complications range from wound infections,[93] wound dehiscence, hypertrophic or poorly aesthetic scar, haematoma, seroma and lastly carotid blow out injury secondary to tumour invasion to the carotid artery or adventitial injury during neck dissection.[94] Most post-

operative complications are minor and managed conservatively.[95] However, in rare cases, return to theatre is necessary.

For patients treated with radiation alone or combined chemoradiation, the most prevalent acute toxicity is high-grade mucositis.[96] According to Givens *et al.,*[96] other common complications related to chemoradiation include, haematological toxicity, desquamation, neurotoxicity, ototoxicity, dehydration, malnutrition, pneumonia, trismus, osteoradionecrosis and febrile episodes.

Trotti *et al.,*[97] describes TAME (Toxicity, Adverse long-term effects, Mortality risk and End result) as a validated method of reporting adverse events to allow for useful clinical decision making. Adverse events described above directly contribute to health-related quality of life outcomes (HRQoL). In the context of head and neck cancer, the domains of interest for HRQoL include speech, eating, aesthetics, physical health, mental health and social disruption.[96] However, dysphagia, xerostomia and voice outcomes dominate the literature as long-term complications of both surgical and radiotherapy treatment modalities.[98-101]

Various reporting tools are described in the literature to quantify HRQoL.[102,103] The most recent systematic review of literature by Klein *et al.*[103] identified 18 high quality studies describing four validated HRQoL measurement tools. The most commonly utilised tools were the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30 and HN-35 module), the University of Washington Quality of Life Questionnaire (UWQOL), and the Functional Assessment of Cancer Therapy Head and Neck Cancer questionnaire (FACT-H&N).[103] More specifically for assessment of dysphagia, the MD Anderson Dysphagia Inventory

(MDADI)[104] and the Functional Oral Intake Scale (FOIS) were widely used.[105] In the current literature, voice related outcomes for adult patients are reported using the Voice Handicap Index (VHI),[106] the abbreviated VHI-10[107] and the Voice-Related Quality of Life Measure (V-RQOL).[108] All three tools are validated patient reported outcome measure tools to specifically assess voice-specific functional status.[108-110].

1.11 Overview of systematic review methodology and evidence synthesis

There are multiple retrospective case series and cohort studies investigating the effectiveness of one treatment modality over others for HNCUP, however, no randomised datasets are available. A preliminary search of the Cochrane Library, PubMed, Embase and the *JBI Database of Systematic Reviews and Implementation Reports* found no published systematic reviews or protocols that directly investigate the effectiveness of primary surgery versus primary radiotherapy for the treatment of HNCUP. A systematic review by Liu *et al.*[9] was identified during the formal search process, hence the decision to systematically review available literature.

In 1979 a method of documenting levels of evidence was described by a Canadian Task Force. A three-tier rating scale of evidence was implemented to determine the effectiveness of periodic health examination for specific medical conditions.[111] Since then, multiple modifications have been made to the method of documenting evidence in health care settings. For example, Sackett *et al.*[112] added two further tiers to rate evidence in a scale of 1 to 5. They also defined evidence-based health care as decisions made regarding the care of individual patients based on the best available evidence.[112] Appropriate evidence synthesis of multiple studies allows for the estimation of true effect

compared to a single study.[113] Herein lies the importance of a well conducted systematic review.

Reproducibility and a rigorous approach to identifying primary research and subsequent critical appraisal of the quality of research allows for synthesis of evidence to form a systematic review with or without the meta-analysis of data. Systematic reviews and synthesis of multiple, well-designed, double-blind randomised controlled trials (RCTs) provide ideal datasets for guiding evidence based clinical practice to evaluate the effectiveness of an intervention or therapy. While randomised datasets minimise bias and confounding, the conduct of RCTs is not always clinically safe or logistically possible or feasible. However, evidence synthesis is required to promote evidence-based clinical practice and the development of clinical practice guidelines, regardless of presence of RCTs. A systematic review achieves a high-quality data synthesis by first having an *a priori* protocol detailing the search methodology and selection criteria.[114] This pre-defined, peer reviewed publication of the *a priori* protocol allows for bias minimisation and effective guidance of the conduct of the review.[113,115] Interestingly, a recent study found that systematic reviews with a published protocol had superior reporting of methodology and findings while taking longer from search to result submission.[115] Registration of ongoing systematic reviews similar to the registration of ongoing clinical trials is another method of bias minimisation, allowing for *a priori* publication and public scrutiny of the methodology. The Prospective Register of Ongoing Systematic Reviews (PROSPERO) an international advisory group in collaboration with UK National Institutes of Health Research, allows for free registration of ongoing systematic reviews online. Sideri *et al.*[116] reported a superior quality of reviews registered in PROSPERO compared to non-registered reviews using the Assessment of Multiple Systematic

Reviews (AMSTAR) tool. The protocol for this review was published[117] on a peer reviewed journal as well as registered on PROSPERO (CRD42018089182)

Quality evidence synthesis that can inform clinicians and patients about diagnostic or treatment options based on available best evidence is an important step prior to the development of clinical practice guidelines (CPG). A CPG should make strong recommendations to influence clinical decision making and is based on the quality of available evidence. The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) working group has developed a system for grading the certainty of the evidence and strength of recommendations.[118] A comprehensive list of already established evidence based healthcare organisations have adopted and endorsed the use the GRADE system, including Cochrane and the WHO.[118] The main advantages of using the GRADE system is the clear separation between quality of evidence and strength of recommendation, explicit criteria for downgrading or upgrading quality of evidence, consideration of various outcomes to patients, explicit advice to make recommendations (even when very little evidence is available), clear pragmatic interpretation of strong or weak recommendations, and having a balance between methodological comprehensiveness and simplicity of reporting.[118]

In the setting of HNCUP, the low incidence of disease occurrence does not permit for practical and timely prospective trials. Hence, the majority of studies are based on retrospective review of patient databases. In light of this, a well conducted systematic review using the GRADE approach to determine the certainty of the evidence would increase the likelihood of informing and influencing current clinical practice.

CHAPTER 2: METHODS

2.1 Types of participants

Participants included adults (aged 18 years or older) who had undergone treatment with curative intent for an HNCUP. All stages of tumours were included.

2.2 Types of interventions

This review included studies comparing surgery to radiotherapy as the primary intervention with curative intent. Surgery included any form of a neck dissection conducted as the primary treatment. Types of neck dissections considered included MRND or SND. Excisional node biopsy was not considered as a primary surgical treatment as this is only recommended for diagnostic purposes in non-SCC head and neck pathologies. In addition to the neck dissection, tongue base mucosectomy with TORS with bilateral or unilateral tonsillectomy was also included as a primary surgical treatment. Patients with planned adjuvant radiotherapy (radiotherapy alone or concurrent chemoradiation) following primary surgery were also included. Only studies that specifically utilised IMRT (see Section 1.8.2) or related techniques were included.

Patients who had salvage surgery following primary radiotherapy were included if there was adequate description of survival and QoL prior to salvage surgery as salvage surgery would be considered the point of primary treatment failure. When a study specified a planned neck dissection within a specified period following primary radiotherapy, this data was included. Studies with concurrent or induction chemotherapy as an addition to primary radiotherapy or adjuvant radiotherapy were also included.

2.3 Outcomes

This review considered studies that included the following outcomes:

2.3.1 Primary outcomes:

This review examined OS and RRFS as primary outcome measures. These outcome measures were further categorised according to the relationship between rates of primary neck dissection, diagnostic paradigm and staging. In order to substantiate the survival outcomes, the primary tumour emergence, neck failure (residual or recurrent disease in the neck) and distant metastasis percentages were also extracted. Descriptions of these outcome measures are detailed in Section 1.9.

2.3.2 Secondary outcomes:

- QoL following treatment: measured with validated tools for QoL (e.g. TAME, HRQoL, QLQ-C30, UWQOL, FACT-H&N, MDADI, FOIS, V-RQOL and VHI), mainly related to xerostomia, swallowing and voice outcomes. See section 1.10 for descriptions of these tools.
- Toxicities commonly reported following cancer treatment: dysphagia, xerostomia, mucositis and other end organ complications

2.4 Types of studies

This review considered both experimental and quasi-experimental study designs including RCTs and non-RCTs. In addition, analytical observational studies including prospective and retrospective cohort studies and case series were considered for inclusion.

Studies published from 2005 were included as the technology used in radiation oncology has significantly changed since then, causing less toxicity.[9] Also, the use of the TORS has become more common since 2005.

2.5 Search strategy

The search strategy aimed to locate both published and unpublished studies. An initial, limited search of PubMed was undertaken (on 6th May 2017), followed by an analysis of the text words contained in the titles and abstracts, and of the index terms used to describe the article. This informed the development of a search strategy which was tailored for each information source (PubMed, Embase, ProQuest (Dissertations and Theses), ClinicalTrials.gov, International Clinical Trials Registry Platform, Canadian Cancer Trials, Australian New Zealand Clinical Trials Registry, European Union Clinical Trials Register, Chinese Clinical Trial Register, Clinical Research Information Service – Korea, Clinical Trials Registry India, Cuban Public Registry of Clinical Trials, Iranian Registry of Clinical Trials, Japan Primary Registries Network and Pan African Clinical Trial Registry). This search strategy was submitted for peer review as part of the *a priori* protocol.[117] A full search strategy for PubMed, Embase and ProQuest databases is detailed in Appendix I. Search of trial registries and journal databases (PubMed, Embase and ProQuest) were conducted on 4th December 2017. The reference lists of studies selected for full text review were screened for additional studies; no further studies were identified.

2.6 Study selection

Following the search, all identified records were collated and uploaded into EndNote Version x9.1 (Clarivate Analytics, PA, USA) and duplicates were removed. Titles and abstracts were screened by a single reviewer (ND) for assessment against the inclusion criteria for the review. Full text of studies that met the inclusion criteria were retrieved, their details were imported into Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI),[119] and assessed in detail against the inclusion criteria of the review (Sections 2.1-2.4). Full-text studies that did not meet the inclusion criteria were excluded and reasons for exclusion are provided in Appendix I.

2.7 Critical appraisal

Selected studies were critically appraised by two independent reviewers (ND and MM) at the study level for methodological quality in the review using the standardised critical appraisal instrument for cohort studies from the Joanna Briggs Institute.[119] Minor disagreements were resolved with discussion and a third reviewer was not required for further independent appraisal. None of the studies were excluded based on critical appraisal.

2.8 Data extraction

Data of interest were extracted from articles by a single reviewer (ND) using Microsoft Excel®. The extracted data included specific details about the interventions, participants, study methods and outcomes of significance (see Sections 2.1-2.4) to the review question and specific objectives. Authors of these studies were contacted to

request missing or additional data (see Appendix II). However, none of the corresponding authors contacted provided additional data and only one corresponding author for Kamal *et al.*[120] responded.

2.9 Data synthesis

Meta-analysis was conducted using Review Manager (RevMan®) version 5.3.[121] Effect sizes are expressed as hazard ratios (HR) and their respective 95% confidence intervals. Heterogeneity was assessed and reported using the standard chi-squared (χ^2) test and I squared (I^2) statistic. I^2 value of less than 40% was considered an acceptable level of heterogeneity for further interpretation of pooled data, where as an I^2 of more than 75% was consistent with considerable heterogeneity.[122] The I^2 statistic was interpreted along with the associated confidence intervals, magnitude and direction of effects and the significance testing based on χ^2. A low p-value from the χ^2 test as well as poorly overlapping confidence intervals would indicate the presence of heterogeneity. A p-value less than 0.10 was used for consideration of statistical significance because the studies included in this review had relatively low sample sizes.[122] Therefore, a non-significant result in isolation was not considered to have no heterogeneity. A random effects model was used for meta-analysis as we were not able to confidently assume that each study was estimating an equal number of effects and that at least minor heterogeneity was observed.[123] Subgroup analysis could not be performed as intended *a priori* [117] based on TORS mucosectomy or HPV status due to lack of stratified reporting of data. Hazard ratio (HR) was calculated as the summary statistic for five studies included in the meta-analysis. The five studies included for meta-analysis did not provide summary statistics for direct comparison. Therefore, the HR was calculated using the method described and worksheet provided by Tierney *et al.*[124] that calculated the HR for each comparison (see

Appendix III). In brief, HRs were calculated based on published Kaplan-Meier plots (see Appendix III for an example) and the number of at risk patients provided for time intervals between year 1 and 5 after treatment using the method described by Tierney *et al*.[124] The accuracy of estimation using this method is increased when the number of patients at risk for the time period of interest is provided as part of the Kaplan-Meier plot (see Appendix III).

Where statistical pooling was not possible, non-parametric Spearman rank-order correlation and linear regression analysis were conducted to identify interdependent relationships using GraphPad Prism Version 8.0 (GraphPad Software, CA, USA). Data not suitable for statistical analysis are presented in narrative form including tables and figures to aid in data presentation, where appropriate. Funnel plots were not generated as less than ten studies were included in the meta-analysis.[122]

2.10 Assessing certainty

A 'Summary of Findings' table was created using GRADEPro GDT Version 3.0 (McMaster University, ON , Canada).[125] The 'Summary of Findings' table presents the HR for OS and RRFS, for the comparison between primary treatment modalities, and a ranking of the quality of the evidence based on study limitations (risk of bias), indirectness, inconsistency, imprecision and publication bias.

CHAPTER 3: RESULTS

3.1 Study identification and inclusion

Following database searching and removal of duplicates, 9376 unique records were available for screening (Figure 2). Title and abstract review (see Section 2.6) identified 83 studies for full text retrieval and review. Following full text review, a further 68 studies that did not meet the inclusion criteria were excluded. Specific reasons for these exclusions are listed in Appendix I (see Section 6.1). Ultimately, 10 studies were included in this systematic review.

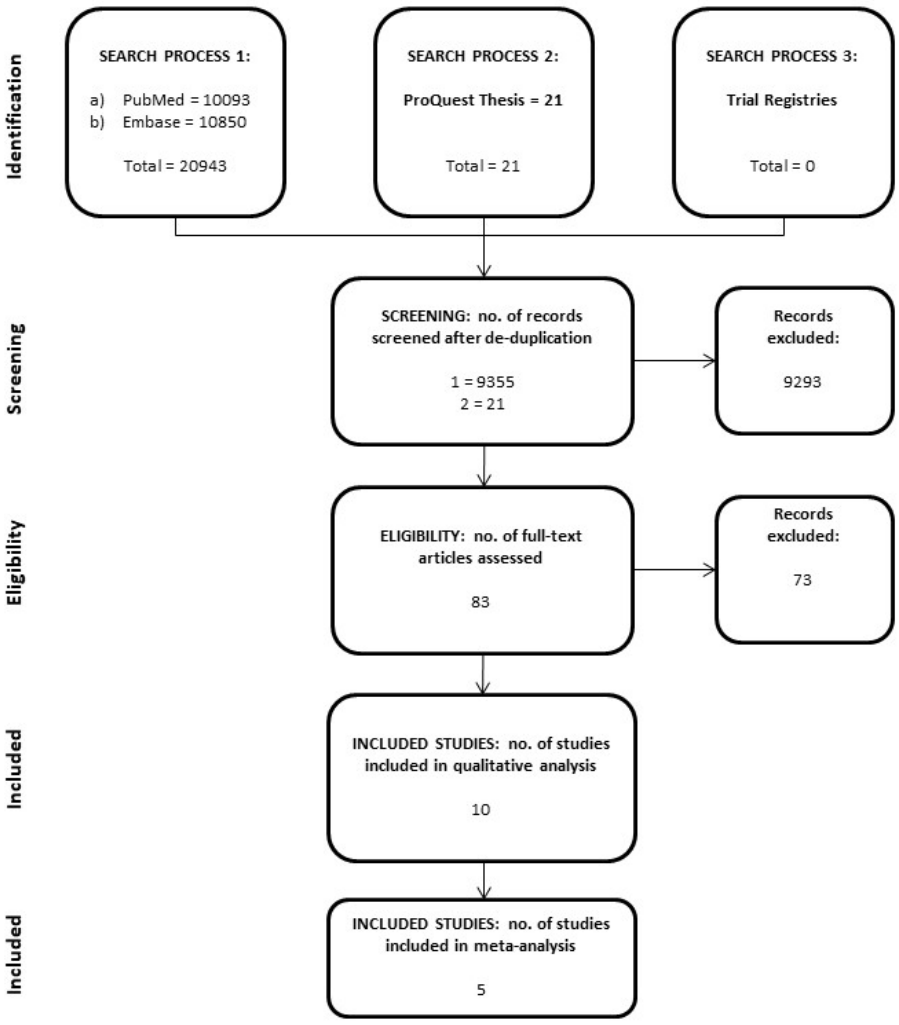

Figure 2. Flow diagram illustrating the process of study inclusion in this systematic review.

3.2 Critical appraisal of included studies

Ten retrospective cohort studies underwent independent critical appraisal by two independent reviewers (Table 8). Overall, the quality of the included studies was poor. Patients in all studies had a neck metastasis from an unknown primary tumour prior to commencing treatment, therefore, the comparison groups were recruited, albeit retrospectively, from the same disease population (Question 1). Interventions were administered similarly and in a valid and reliable way in all included studies (Questions 2 and 3). Only three studies[98,99,102] identified and reported confounding factors in detail; the majority of studies had unclear descriptions of identifying or including confounding factors in their analyses (Question 4).[126-128] Therefore, strategies for dealing with confounding factors were not clearly stated or identifiable in any of the included studies (Question 5). Outcomes were measured in a valid and reliable manner, with adequate follow-up time for the outcome to occur in all studies (Questions 6, 7 and 8). However, these studies failed to consistently report on five-year survival outcomes that affected the ability to comment on long-term survival outcomes and led to the inability to conduct a pooled data analysis. However, the reported time intervals were acceptable from a clinical point of view, given the retrospective nature of studies included. Outcomes were analysed with appropriate statistical analysis (Question 11). However, only five articles reported survival and toxicity outcomes, stratified according to primary treatment modality.[88,120,126,129,130] Due to the retrospective nature of all included studies, follow-up was not complete and further strategies to address incomplete follow-up were not described (Questions 9 and 10).

Table 8. Critical appraisal of included studies using JBI Critical Appraisal Checklist for Cohort Studies (Appendix I)

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Amsbaugh[88]	Y	Y	Y	N	N	Y	Y	Y	U	U	Y
Chen[131]	Y	Y	Y	U	U	Y	Y	Y	U	U	Y
Demiroz[126]	Y	Y	Y	Y	U	Y	Y	Y	U	U	Y
Frank[127]	Y	Y	Y	Y	N	Y	Y	Y	U	U	Y
Huo[129]	Y	Y	Y	U	U	Y	Y	Y	Y	U	Y
Kamal[120]	Y	Y	Y	N	N	Y	Y	Y	Y	U	Y
Klem[80]	Y	Y	Y	U	U	Y	Y	Y	U	U	Y
Lu[6]	Y	Y	Y	U	U	Y	Y	Y	U	U	Y
Madani[128]	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y
Mizuta[130]	Y	Y	Y	U	U	Y	Y	Y	Y	U	Y
Yes %	100	100	100	27.3	0.0	100	100	100	36.4	0.0	100

Q = Question, Y = Yes, N = No, U = Unclear

3.3 Characteristics of included studies

3.3.1 Geographical location

Geographical location is likely to influence the rate of occult skin malignancies presenting as HNCUP because in Caucasian populations, the level of ultraviolet light exposure via sunlight is directly proportional to the incidence of skin HNSCC. Australia is geographically a high-risk nation for skin malignancies.[132] However, only one study included in this review was conducted in Australia[129] Figure 3 shows the geographical distribution of the studies included in this review. Seven studies were from the USA, where parts of this country are at high-risk of non-melanoma cutaneous malignancies. They included patients from the following states: Texas,[120,127] Michigan,[126] Iowa,[6] New York,[80] California[131] and Kentucky.[88] The remaining studies were from Japan,[130] Germany[133] and Belgium.[128]

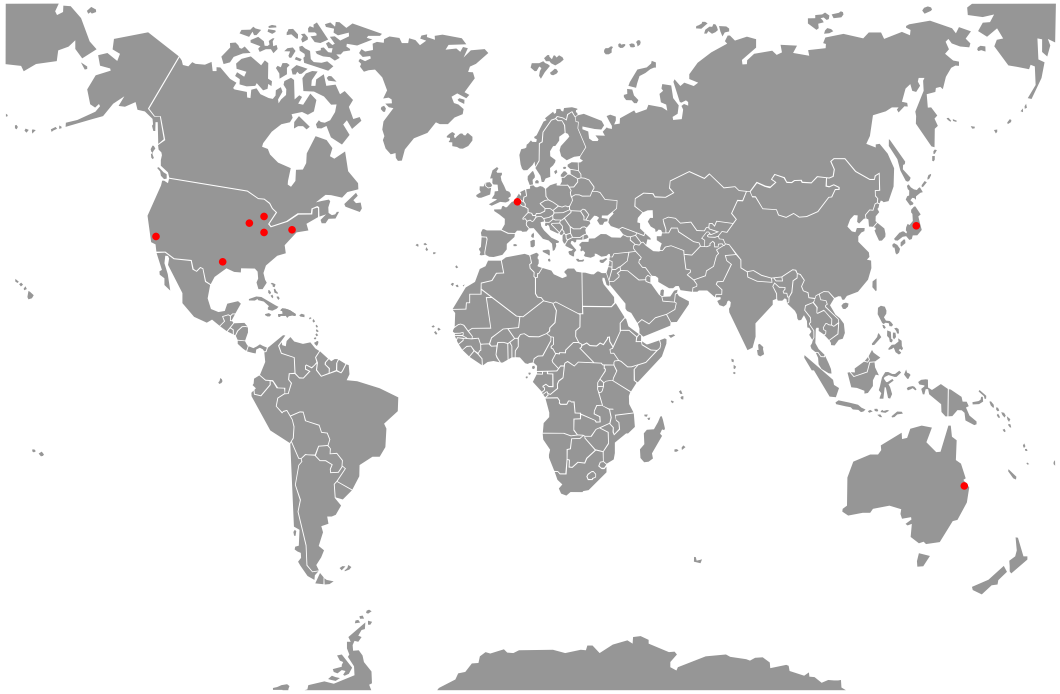

Figure 3. Geographical location of patients recruited for studies included in this review. Each red dot represents an individual study, except for Houston and Texas, USA, where two of the study populations were recruited.

3.3.2 Study participants

The combined sample size was 655 participants from 10 studies (Table 9). These studies included patients diagnosed with a HNCUP between the years 1991 to 2015. The overall median age of patients was 58 years, ranging from 19 to 89 years, with a skewed Gaussian distribution towards the older age group. There was a large male predominance, with five to one male to female representation.

Table 9. Population characteristics of included studies

Author	Year	n	pND (%)		pRT (%)		Age (range)	Gender (%F)	
Chen[131]	2018	31	10	(32%)	21	(68%)	60 (45 – 71)	7	(24%)
Huo[129]	2018	63	37	(59%)	26	(41%)	64 (35 – 88)	8	(13%)
Kamal[120]	2018	260	79	(30%)	181	(70%)	58 (19 – 84)	39	(15%)
Mizuta[130]	2018	80	41	(51%)	12	(15%)	65 (39 – 83)	18	(23%)
Amsbaugh[88]	2017	66	37	(56%)	29	(44%)	56 (21 – 83)	13	(20%)
Demiroz[126]	2014	41	22	(54%)	19	(46%)	53 (38 – 72)	4	(10%)
Frank[127]	2010	52	13	(25%)	39	(75%)	56 (NR)	6	(12%)
Lu[6]	2009	18	12	(67%)	6	(33%)	55 (37 – 89)	2	(11%)
Klem[80]	2008	21	16	(76%)	5	(24%)	57 (39 – 80)	4	(19%)
Madani[128]	2008	23	19	(83%)	4	(17%)	61 (47 – 85)	6	(26%)
Overall		655	286	(44%)	342	(52%)	58 (19 – 89)	109	(17%)

Median age is reported; Year = year of publication; n = total number of participants; pND = primary neck dissection; pRT = primary radiotherapy; NR = not reported; F = female

These patients had neck nodal SCC that ranged from stages 1 to 3, based on the seventh edition of AJCC cancer staging manual (Section 1.6). The predominant nodal stage was N2b (294 patients, 46%), followed by N2a (131 patients, 20%), N1 (97 patients, 15%), N3 (66 patients, 10%) and N2c (55 patients, 9%), respectively (Table 10). Three studies reported the nodal stage distribution between treatment paradigms.[88,126,129] Four studies reported the p16 status for their respective cohorts.[120,126,129,131] However, only one study tested all their patients for p16 status as well as cross validating these patients with *in situ* hybridisation technique for HPV DNA positivity.[131]

Table 10. Neck nodal staging distribution based on primary treatment modality and p16 status

Author	Tx	N1	N2a	N2b	N2c	N3	p16+
Chen[131]	pND						
	pRT						
	All	5	11	9	0	0	10
Huo[129]	pND	11	8	18	0	0	*0
	pRT	1	7	15	0	3	*14
	All	12	15	33	0	3	*14
Kamal[120]	pND						
	pRT						
	All	26	40	141	31	22	*90
Mizuta[130]	pND						
	pRT						
	All	15	16	34	5	10	NR
Amsbaugh[88]	pND	10	6	12	5	4	
	pRT	5	9	6	3	6	
	All	15	15	18	8	10	NR
Demiroz[126]	pND	2	6	8	0	6	*10
	pRT	2	4	10	0	3	NR
	All	4	10	18	0	9	*10
Frank[127]	pND						
	pRT						
	All	8	10	18	6	4	NR
Lu[6]	pND						
	pRT						
	All	0	8	7	2	1	NR
Klem[80]	pND						
	pRT						
	All	9	0	8	1	3	NR
Madani[128]	pND						
	pRT						
	All	3	6	8	2	4	NR
Overall (%)		97 (15%)	131 (20%)	294 (46%)	55 (9%)	66 (10%)	*124 (19%)

Tx = primary treatment, pND = primary neck dissection, pRT = primary radiotherapy, N = neck staging, NR = not reported, p16+ = presumed human papilloma virus (HPV) positive disease, * = not all patients were tested for HPV status

Two studies[120,129] considered and analysed separately the cutaneous origin of nodal SCC. Kamal *et al*. [120] identified patients with high risk of cutaneous origin of SCC and excluded these patients from further analysis. Huo *et al.*[129] identified patients with high risk of a cutaneous primary SCC and the treatment paradigm was stratified according to their risk and outcomes presented accordingly. The remaining studies in this review did not specifically report any consideration of HNCUP with potential cutaneous origin.

3.3.3 Study design and interventions

All ten studies included in this systematic review were retrospective cohort studies, with samples largely taken from retrospective interrogation of cancer databases. All, except for Kamal *et al*.[120] Frank *et al*.[127] and Lu *et al.,*[6] treated the majority of their patients with a primary neck dissection (Table 11), followed by adjuvant radiotherapy alone or adjuvant concurrent chemo-radiotherapy. The remaining three studies[6,120,127] principally treated their patients with primary radiotherapy (pRT) as per local guidelines, with only a small group of patients receiving a planned neck dissection. Other treatment options included pRT alone, primary concurrent chemo-radiotherapy, neck dissection alone, or primary radiotherapy followed by pND.

The two studies from MD Anderson Cancer Center,- Kamal *et al.*[120] and Frank *et al.,*[127] treated the majority of their patients with primary IMRT 84% and 58%, respectively. Lu *et al.*[6] similarly treated the majority of their patients with primary IMRT (56%). In Australia, Huo *et al.*[129] treated all suspected cutaneous primary patients with a pND (100%) and suspected mucosal primary patients with mainly primary IMRT (88%). Neck dissection alone was performed in 27 patients reported by Mizuta *et al*.[130] None of the other studies provided neck dissection only as a treatment option to their patients.

Demiroz *et al.*[126] and Kamal *et al.*[120] treated patients with a pND after pRT in 5% and 1% of their respective patient cohorts. Only four studies[88,126,129,130] described the treatment modality based on nodal staging with the majority of these cases being treated with primary neck dissections. Overall, N1, N2a, N2b, N2c and N3 were treated with primary surgery 80%, 64%, 67%, 84% and 59% of the time, respectively.

Tonsillectomy was described as part of the diagnostic pathway in four studies [88,120,127,131] and tongue base mucosectomy (with or without TORS) in only one study.[131] Bilateral tonsillectomy was described in most cases. However, Chen *et al.* treated all patients with an ipsilateral tonsillectomy and Frank *et al.* treated 10% of patients with an ipsilateral tonsillectomy. Base of tongue mucosectomy was only done in three patients (overall only 0.4%) in the study by Chen *et al*.[131] While two other studies mentioned tongue base biopsies, they did not describe a tongue base mucosectomy.[88,120]

3.3.4 Length of follow-up

Due to the retrospective nature of the studies included, the median follow-up time varied significantly between the studies of interest, ranging from 17 to 73 months (Table 11). Demiroz *et al.*[126] did not report an overall follow-up time, instead providing a stratified follow-up time based on treatment modality. The median follow-up time for Amsbaugh *et al.*,[88] Chen *et al.*,[131] Klem *et al.*[80] and Madani *et al.*[128] was less than 24 months. While these studies had some patients followed up for longer than five years, the data from patients followed up for less than 24 months is likely to add bias to Kaplan-Meier estimates of survival reported in these studies (see Section 2.9). This is an inherent limitation of retrospective studies with small sample sizes.

Table 11. Median follow-up time for included studies

Author	Follow-up - median months (range)
Amsbaugh[88]	22 (0.2 – 125.2)
Chen[131]	21 (6 – 61)
*Demiroz[126]	39 (11 – 98) RT 73 (18 – 126) ND+RT
Frank[127]	44 (12 – 91.2)
Huo[129]	47 (IQR 24.8 – 61.7)
Kamal[120]	61 (0 – 176)
Klem[80]	20 (5 – 21)
Lu[6]	26 (6.5 – 86.3)
Madani[128]	17 (2 – 39)
Mizuta[130]	34 (2 – 132)

*Demiroz *et al*. did not provide an overall median follow-up value, RT = radiotherapy, ND = neck dissection, IQR= interquartile range

3.4 Primary outcomes

3.4.1 Overall survival

OS was reported in all studies for the whole cohort except Demiroz *et al.*[126] Furthermore, only five studies[83,112,118,121,122] reported OS based on primary treatment modality (Table 12). The maximum reported five-year OS was 92% for the pND group in Kamal *et al.*[120] (Table 12). The maximum reported two-year OS was 93% for the pRT group in Demiroz *et al*.[126] As mentioned earlier, due to the retrospective nature of these studies, the follow-up period was variable and therefore the reporting year of survival was not readily comparable. Two studies that provided a five-year OS between primary treatment modalities had a 10%- 13% difference in five-year overall survival that was not statistically significant ($p > 0.05$). Meta-analysis of five studies that provided stratified survival data based on primary treatment modality did not show a statistically significant result ($p = 0.60$) towards a particular treatment modality. Analysis of heterogeneity in this analysis was surprisingly low (Figure 4, I^2 of 32%, $p = 0.21$). There was a poor linear correlation between two-year OS and the percentage of pND (Figure 5, $R^2 = 0.1737$, $p = 0.442$).

Table 12. Overall survival based on primary treatment modality

Author	HR (95% CI)	Primary Tx	1 year	2 years	3 years	4 years	5 years
Amsbaugh[88]	0.77 (0.26-2.30)	ND+RT±C	-	-	63.9%	-	-
		RT±C	-	-	59.8%	-	-
Demiroz[126]	1.6 (0.22-11.41)	ND+RT±C	-	90.7%	-	85.3%	-
		RT±C	-	93.3%	-	85.6%	-
Huo[129]	1.68 (0.58-4.90)	ND+RT±C	-	-	-	-	66.0%
		RT±C	-	-	-	-	79.6%
Kamal[120]	0.43 (0.21-0.87)	ND+RT±C	-	-	-	-	92%
		RT±C	-	-	-	-	82%
Mizuta[130]	1.05 (0.37-3.00)	ND+RT±C	-	-	71.9%	-	-
		RT±C	-	-	83.3%	-	-

ND = neck dissection; RT = radiotherapy; C = chemotherapy; Tx = treatment; HR = hazard ratio; CI = confidence interval

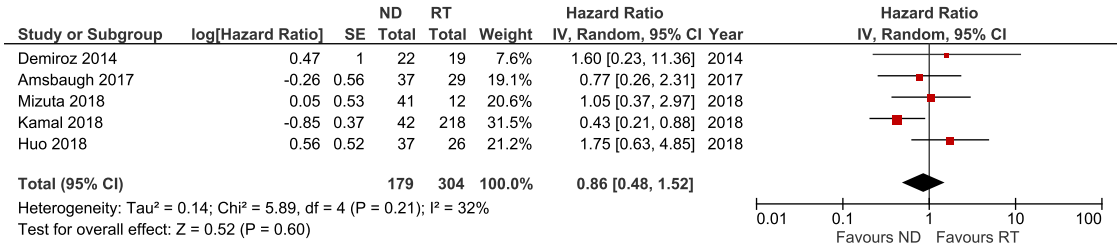

Figure 4. Meta-analysis of overall survival from five studies directly comparing and reporting overall survival outcomes based on primary treatment modality. Calculated two-year overall survival data from Table 10 used for this analysis. ND = Primary neck dissection, RT = Primary radiotherapy.

Table 13. Overall survival of participants having a primary neck dissection

Author	ND	1 year	2 years	3 years	4 years	5 years
Kamal[112]	16%		92%			84%
Frank[119]	25%		***81%			81%
Chen[123]	32%		92%			
Lu[6]	44%		74.2%			*64%
Mizuta[122]	51%		***72.5%	72.5%		
Demiroz[118]	54%		**92%		**85%	
Amsbaugh[84]	56%		***69.4%	69.4%		
Klem[76]	62%	*85%	85%	*85%	*85%	*85%
Huo[121]	63%	96.6%	85.5%	*75%	*75%	71.2%
Madani[120]	83%		74.8%	*50%		
Overall	51±21%		78±14%			

*Estimated based on published Kaplan-Meier Graphs (Appendix III), **Estimated based on average survival rates, ***Estimated based on worst case scenario based on published data

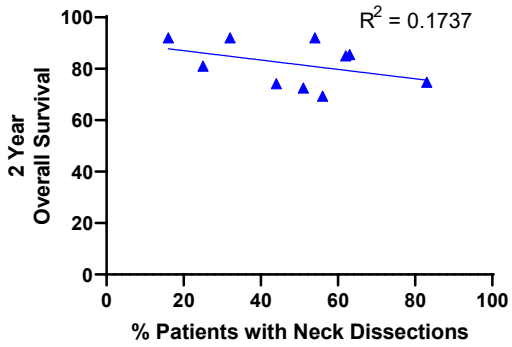

Figure 5. The relationship between two-year overall survival and percentage of patients who received a primary neck dissection in each study.

Table 14 indicates the percentage of patients who received a tonsillectomy, tongue base mucosectomy or an fluorodeoxyglucose positron emission tomography (FDG-PET) scan as a part of their diagnostic paradigm, compared to their two-year OS. Only three studies[88,129,131] reported on whether or not a tongue base mucosectomy was conducted, ranging from 0%-100%. Amsbaugh *et al.*[88] was the only study reporting a 100% adherence to tonsillectomy and tongue base mucosectomy during the diagnostic phase. Six studies[6,88,120,126,129,131] reported whether a tonsillectomy was conducted, and seven studies[6,80,88,128-131] reported whether an FDG-PET scan was conducted during their diagnostic phase. The percentage of patients who had an FDG-PET scan (Figure 6A, $R^2 = 0.086$, $p = 0.5208$) or a tonsillectomy (Figure 6B, $R^2 = 0.3321$, $p = 0.2313$) during the diagnostic phase did not have a statistically significant linear relationship to OS (Figure 7).

Table 14. Overall survival of participants and diagnostic criteria

Author	Tonsillectomy	Mucosectomy	FDG-PET	2-year overall survival
Amsbaugh[84]	100%	100%	57.6%	***69.4%
Chen[123]	100%	10%	100%	92%
Demiroz[118]	49%	NR	NR	**92%
Frank[119]	NR	NR	NR	***81%
Huo[121]	41%	0%	41%	85.5%
Kamal[112]	55%	NR	NR	92%
Klem[76]	NR	NR	95%	85%
Lu[6]	100%	NR	86%	74.2%
Madani[120]	NR	NR	57%	74.8%
Mizuta[122]	NR	NR	87%	***72.5%

*Estimated based on published Kaplan-Meier Graphs, **Estimated based on average survival rates, ***Estimated on worst case scenario based on published data, FDG-PET: fluorodeoxyglucose positron emission tomography

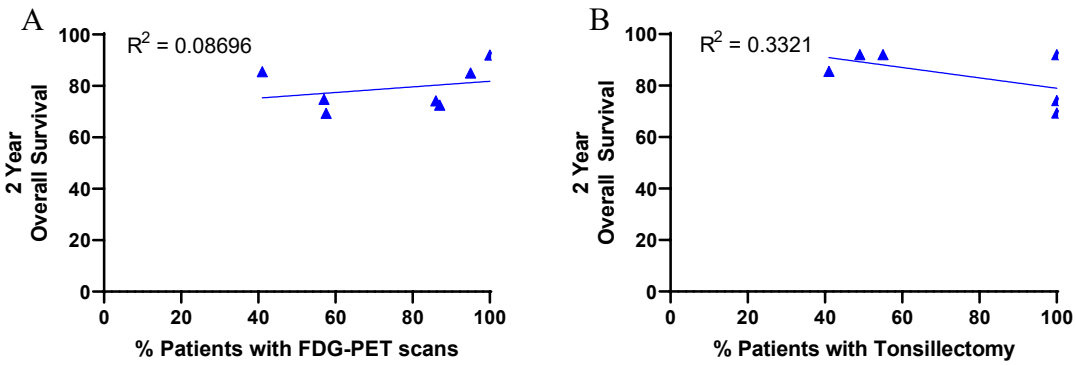

Figure 6. The relationship between two-year overall survival and percentage of patients who had a fluorodeoxyglucose positron emission tomography (FDG-PET) scan (graph A) or tonsillectomy (graph B) prior to treatment.

3.4.2 Regional relapse free survival

RRFS was reported by all studies except Huo *et al.*[129] and Madani *et al.*[128] for their respective cohorts. However, only three studies[88,126,130] reported RRFS stratified based on primary treatment modality (Table 15). The maximum reported four-year RRFS was 76%[126] for pND and the maximum reported three-year RRFS was 82%[88] also for pND. Meta-analysis of RRFS for the studies that provided stratified values was not statistically significant ($p = 0.07$), with no significant heterogeneity amongst these studies (Figure 8, $I^2 = 0\%$, $p = 0.78$).

Table 15. Reported regional relapse free survival based on primary treatment modality

Author	HR (95% CI)	Primary Tx	1 year	2 years	3 years	4 years	5 years
Amsbaugh[88]	0.44 (0.18-1.12)	ND+RT±C	-	-	82.2%	-	-
		RT+C	-	-	46.4%	-	-
Demiroz[126]	0.73 (0.20-2.60)	ND+RT±C	-	-	-	76.1%	-
		RT±C	-	-	-	75.0%	-
Mizuta[130]	0.66 (.25-1.77)	ND+RT±C	-	-	77.9%	-	-
		RT±C	-	-	66.7%	-	-

ND = neck dissection, RT = radiotherapy, C = chemotherapy, Tx = treatment, HR = hazard ratio, CI = confidence interval

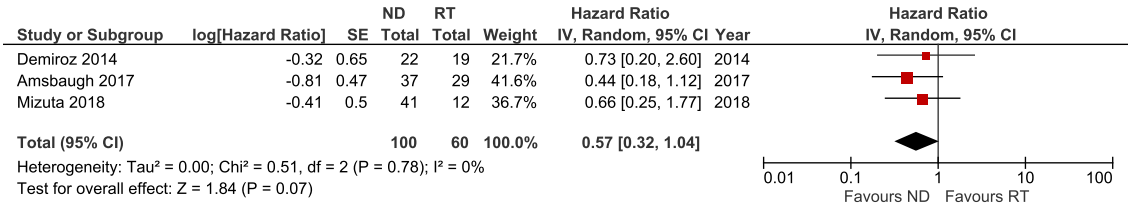

Figure 7. Meta-analysis of regional relapse free survival for three studies directly comparing and reporting regional relapse free survival outcomes based on primary treatment modality. ND = primary neck dissection, RT = primary radiotherapy, CI = confidence interval.

The maximum reported two- and five-year RRFS for all study cohorts was 92%[120] and 94.2%,[127] respectively (Table 16). There was no statistically significant linear relationship between percentage of patients who underwent a pND and two-year RRFS (Figure 8, $R^2 = 0.02479$, $p = 0.664$).

Table 16. Whole cohort regional relapse free survival and percentage of participants having a primary neck dissection

Author	ND	1 year	2 years	3 years	4 years	5 years
Amsbaugh[84]	56%	*90%	*82%	*78.6%	*78.6%	78.6%
Chen[123]	32%	*96	91%	*91%	*91%	*91%
Demiroz[118]	54%	*100%	*76%	*76%	*76%	*76%
Frank[119]	25%	*100%	*94.2%	*94.2%	*94.2%	94.2%
Huo[121]	63%	NR	NR	NR	NR	NR
Kamal[112]	16%	***92%	92%	***91%	***91%	91%
Klem[76]	62%	*85%	85%	*85%		
Lu[6]	44%	*88.5%	88.5%	*88.5%	*88.5%	*88.5%
Madani	83%	NR	NR	NR	NR	NR
Mizuta[122]	51%	***74.0%	***74.0%	74.0%		

*Estimated based on published Kaplan-Meier Graphs, **Estimated based on average survival rates, ***Estimated on worst case scenario based on published data; ND = neck dissection; NR = not reported.

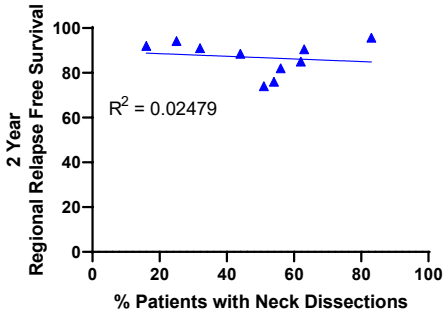

Figure 8. Relationship between two-year regional relapse free survival and percentage of patients treated with a primary neck dissection.

Table 17 displays the percentage of patients who had a tonsillectomy, tongue base mucosectomy or FDG-PET scan during the diagnostic phase, compared to two-year RRFS. Similar to OS results above, there were no statistically significant linear relationships between FDG-PET scan (Figure 9A, R2 = 0.1264, p = 0.5571) or tonsillectomy (Figure 9B, R2 = 0.0073, p = 0.5964) and two-year RRFS.

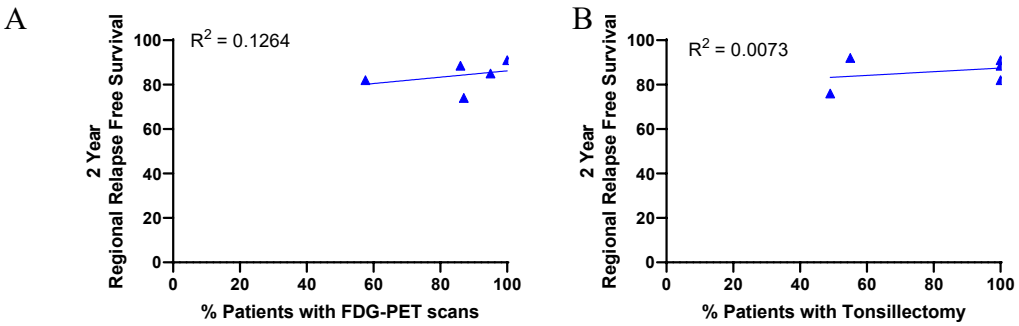

Figure 9. Relationship between two-year regional relapse free survival and percentage of patients who had an fluorodeoxyglucose positron emission tomography (FDG-PET) (graph A) or tonsillectomy (graph B) scan prior to treatment.

Table 17. Two-year regional relapse free survival in participants who had a tonsillectomy, mucosectomy or fluorodeoxyglucose positron emission tomography as a diagnostic test prior to treatment initiation

Author	Tonsillectomy	Mucosectomy	FDG-PET	2-year RRFS
Amsbaugh[84]	100%	100%	57.6%	*82%
Chen[123]	100%	10%	100%	91%
Demiroz[118]	49%	NR	NR	*76%
Frank[119]	NR	NR	NR	*94.2%
Huo[121]	41%	0%	41%	NR
Kamal[112]	55%	NR	NR	92%
Klem[76]	NR	NR	95%	85%
Lu[6]	100%	NR	86%	88.5%
Madani[120]	NR	NR	57%	NR
Mizuta[122]	NR	NR	87%	***74.0%

Percentages represent the rate specific for each study that reported a tonsillectomy, mucosectomy or FDG-PET scan, *Estimated based on published Kaplan-Meier Graphs, ***Estimated on worst case scenario based on published data. NR = not reported; FDG-PET = fluorodeoxyglucose positron emission tomography; RRFS = regional relapse free survival

Two studies[120,130] reported regional and relapse free survival based on the neck nodal staging. Both of these studies considered low neck stages to be inclusive of N1 to N2a and high neck stages to be inclusive of N2b and N3 stages. Meta-analysis of these two studies indicated a clear benefit (p = 0.0002) of having lower neck stage for regional and relapse free survival regardless of the primary treatment modality. There was minimal heterogeneity in this comparison (I^2 = 0%, p = 0.82) (6). Indicating improved survival based on early detection and treatment regardless of the treatment modality.

Table 18. Hazard ratios comparing regional and relapse free survival based on neck nodal staging

Study	Neck stage	Hazard ratio, p-value
Kamal[112]	N1-N2a vs N2b-N3	HR = 0.32, p = 0.015
Mizuta[122]	N1-N2a vs N2b-N3	HR = 0.28, p = 0.008

HR = hazard ratio, HR < 1 survival favours lower neck stage, HR calculated as per Tierney *et al.*[124] (Appendix III)

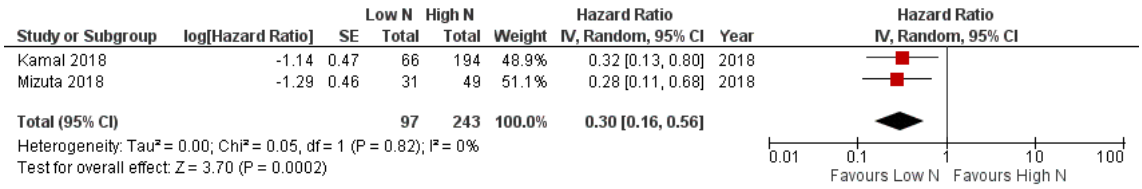

Figure 10. Meta-analysis of regional and relapse free survival for two studies directly comparing low (N1 to N2a) and high (N2b to N3) neck (N) stage indicating survival benefit for lower neck stage at the beginning of treatment.

3.4.3 Primary emergence

Delayed emergence of a primary tumour (primary emergence [PE]) in a mucosal site is likely to be influenced by the primary or adjuvant radiation applied at the time of treatment. All of the included studies except Mizuta *et al.*[130] reported specific mucosal sites subjected to radiotherapy to cover potential occult tumour sites. Mizuta *et al.*[130] also

included a group with only neck dissection without any mucosal irradiation. The remainder of the studies included nasopharynx and oropharynx in their radiation fields as potential occult primary sites. Two studies[126,131] only included ipsilateral oropharynx (Table 19) while the other eight studies reported bilateral mucosal site irradiation. However, there was no radiation laterality dependent relationship with PE, neck failure (NF) or distant metastasis (DM) (Figure 11). Hypopharynx and laryngeal irradiation were patient dependent and based on whether the radiation oncologist had a strong suspicion of involvement of such mucosal sites based on risk factors such as smoking. Most studies did not irradiate the larynx and the hypopharynx as routine practice. Retropharyngeal nodes were also irradiated in almost all studies, with the exception of two studies[88,126] that did not explicitly describe this region in their radiation fields.[88,126]

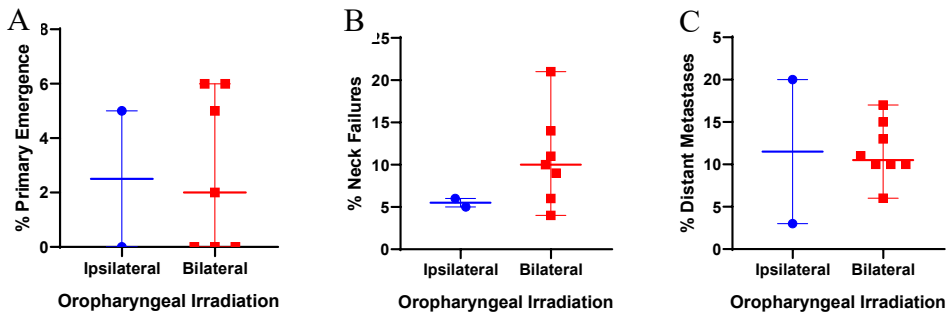

Figure 11. Oropharyngeal irradiation laterality dependent changes to primary emergence (graph A), neck failure (graph B) and distant metastasis (graph C). Median and range for each group displayed.

Table 19. Mucosal irradiation sites for potential occult primary tumours

Author	N	BOT	T	IO	BO	IL	BL	IH	BH	RPL
Amsbaugh[84]	X	X	X		X		X		X	NR
Chen[123]	X	X	X	X		NR	NR	X		X
Demiroz[118]	X	X	X	X		X		X		NR
Frank[119]	X	X	X		X		X		X	X
Huo[121]	X	X	X		X			X		X
Kamal[112]	X	X	X		X	X		NR	NR	X
Klem[76]	X	X	X		X		X		X	X
Lu[6]	X	X	X		X	NR	NR	NR	NR	X
Madani[120]	X	X	X		X	NR	NR	X		X
Mizuta[122]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

N = nasopharynx, BOT = base of tongue, T = tonsil, IO = ipsilateral oropharynx, BO = bilateral oropharynx, IL = ipsilateral larynx, BL = bilateral larynx, IH = ipsilateral hypopharynx, BH = bilateral hypopharynx, RPL = retropharyngeal lymph nodes, NR = not reported, X = radiation field

The overall PE following a minimum five-year follow-up period ranged from 0% to 11% (Table 20, Figure 12). Mizuta *et al.*[130] reported the highest rate (11%) of patients with a primary tumour emergence within a five-year period. This result is likely due to the group in this study that was treated with pND alone, with no adjuvant radiotherapy. Four out of the ten studies reviewed here observed 0% PE.[80,128,129,131] Those studies with no PE had variable treatment paradigms despite having achieved similar primary site control. Huo *et al.*[129] irradiated bilateral mucosal sites of patients that were deemed at risk of occult mucosal SCC and did not irradiate the mucosal sites of patients deemed to be at risk of cutaneous SCC. Chen *et al.* treated all their patients with ipsilateral mucosal irradiation, while Klem *et al.*[80] and Madani *et al.*[128] treated bilateral mucosal sites with irradiation. A clear relationship cannot be made between PE and treatment paradigms. Practically, a pND usually delays radiotherapy treatment to potential occult mucosal sites by approximately six to eight weeks. However, this does not appear to have a clear relationship with PE reported in the studies reviewed (Figure 12A).

Table 20. Treatment failures based on primary emergence, neck failure or distant metastasis

Author	5-year PE (%)		5-year NF (%)		5-year DM (%)	
Amsbaugh[84]	4	(6%)	14	(21%)	10	(15%)
Chen[123]	0	(0%)	2	(6%)	1	(3%)
Demiroz[118]	2	(5%)	2	(5%)	8	(20%)
Frank[119]	1	(2%)	3	(6%)	5	(10%)
Huo[121]	0	(0%)	6	(10%)	6	(10%)
Kamal[112]	14	(5%)	24	(9%)	16	(6%)
Klem[76]	0	(0%)	3	(14%)	2	(10%)
Lu[6]	1	(6%)	2	(11%)	2	(11%)
Madani[120]	0	(0%)	1	(4%)	4	(17%)
Mizuta[122]	9	(11%)	20	(25%)	10	(13%)
Overall	**31**	**(5%)**	**77**	**(12%)**	**64**	**(10%)**

PE = primary emergence, NF = neck failure, DM = distant metastasis

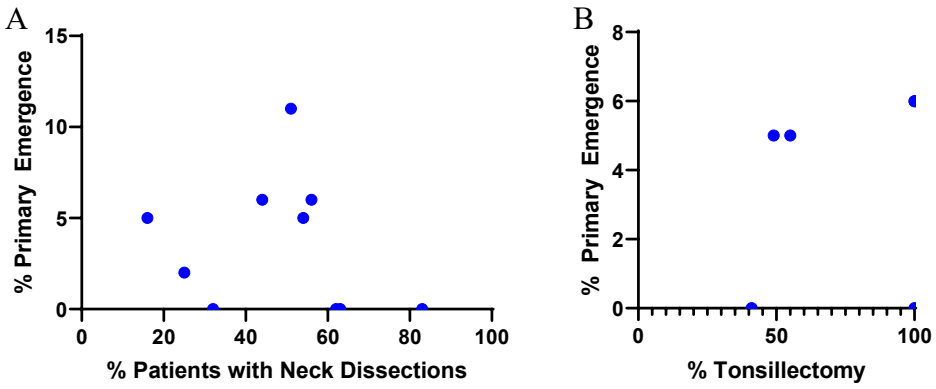

Figure 12. Percentage of primary tumour emergence after five-year follow-up as a function of percentage of patients who had a primary neck dissection (graph A) and rate of patients who had a tonsillectomy (graph B) in each study.

The rate of patients receiving a tongue base mucosectomy as part of the diagnostic process was reported as 0%, 10% and 100% for Huo *et al.*,[129] Chen *et al.*[131] and Amsbaugh *et al.*,[88] respectively. Their respective PE rates were 0%, 0% and 4%. Therefore, a logical relationship cannot be made between tongue base mucosectomy alone and prevention of PE, whereby a patient selection paradigm based on risk factors such as in Huo *et al.*[129] may play a larger role influencing PE and determining who needs a tongue base mucosectomy. The rate of tonsillectomies performed was reported in six studies[6,88,120,126,129,131] and ranged from 41% to 100% (see

Table 18). However, there was no clear relationship between the percentage of patients who had a tonsillectomy and PE (Figure 12B).

3.4.4 Neck failure

Neck failure is defined as a recurrence or residual disease in the neck occurring more than three months following the end of primary treatment (see Section 1.9). Neck failure rates are likely related to: disease stage at the time of treatment, occult primary site and treatment modality utilised. The overall neck failure rate after a minimum five-year follow-up was 12% (range 4%-25%) (Table 20). Again, the highest rate of patients with neck failure was noted in Mizuta *et al.*[130] (25%), likely related to inadequate primary treatment, as mentioned earlier. However, Amsbaugh *et al.*[88] also reported a neck failure rate (21%) similar to Mizuta *et al.*,[130] with vastly different treatment paradigms. Mizuta *et al.*[130] had a cohort of patients who were only treated with neck dissection of the affected side but did not have detailed reporting of irradiation sites for comparison, whereas the patients in Amsbaugh *et al.*[88] had bilateral mucosa irradiation as well as primary or adjuvant radiotherapy to the affected neck as well as contralateral neck. Both of these studies did not report on clinical target volumes or specific irradiation intensities for sites of interest. The lowest rate of neck failures (4%) was observed by Madani *et al.*[128] where the treatment paradigm included a bilateral mucosal irradiation as well as primary or adjuvant radiotherapy to bilateral necks. The rate of neck dissections in each study is the only clear difference between Amsbaugh *et al.*[88] (ND = 56%) and Madani *et al.*[128] (ND = 83%), both of which otherwise had similar radiation oncology treatment plans. However, in contrast, Demiroz *et al.*[126] reported a neck failure rate of 5% similar to Madani *et al.*[128] but only had 54% of their patients with primary neck dissections. Therefore, a clear

relationship cannot be made between the rate of primary neck dissections performed and that of neck failure (Figure 13).

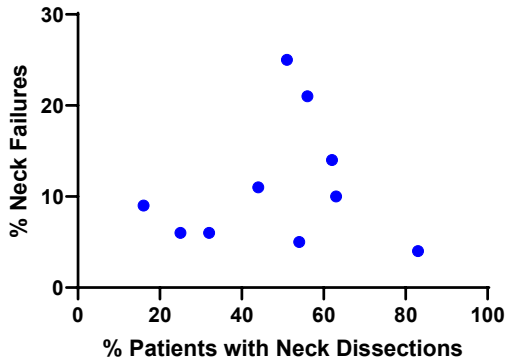

Figure 13. Rate of neck failure after five-year follow-up as a function of rate of patients who had a primary neck dissection in each study.

3.4.5 Distant metastasis

The rate of patients with distant metastasis ranged from 3% to 20% (Table 20). The study with the lowest reported rate of distant metastasis was Chen *et al.*[131] and the study with the highest reported rate of distant metastasis was Demiroz *et al*[126] Interestingly, both these studies only irradiated potential occult mucosal sites of the ipsilateral side with similar radiation intensities (Table 21); with the main interventional differences that 100% of patients in Chen *et al.*[131] had a tonsillectomy compared to 41% in Demiroz *et al.*[126] Furthermore, 32% patients in Chen *et al.*[131] had a primary neck dissection compared to 54% in Demiroz *et al.*[126] Since the rates of primary neck dissections in these two studies are similar, tonsillectomies may contribute to reducing distant metastasis. However, the available data does not allow for the establishment of a causative relationship. Statistically, the percentage of patients with distant metastasis did not correlate well with rate of primary emergence, neck failure or neck dissections performed ($p > 0.05$).

Table 21. Clinical target volumes and respective radiation dosage

Author		CTV1 (dose range)	CTV2 (dose range)	CTV3 (dose range)
Amsbaugh[84]		NR	NR	NR
Chen[123]	P	66-70Gy	60Gy (54-60)	60-66Gy
	A	60-66Gy		
Demiroz[118]	P	70Gy	54Gy	56-59Gy
	A	60Gy		54Gy
Frank[119]	P	66Gy (60 – 72)	54Gy	54Gy
	A	60Gy (60 – 70)		
Huo[121]		NR	NR	NR
Kamal[112]	P	66Gy (63 – 72)		54Gy (50 – 66)
	A	60Gy (60 – 66)		
Klem[76]	P	70Gy	54-60Gy	70Gy
	A	60Gy (60- 70)		60Gy (60-70)
Lu[6]	P	64-66Gy	60-64Gy	50-54Gy
	A	60Gy	50-54Gy	60Gy
Madani[120]	P	69Gy	56Gy	66Gy
	A	62-66Gy		
Mizuta[122]		NR	NR	NR
Overall (range)	**P**	**64 - 72Gy**	**50 - 64Gy**	**54 - 70Gy**
	A	**60 - 70Gy**		

CTV = clinical target volumes, CTV1 = involved nodal basin, CTV2 = contralateral nodal basin, CTV3 = mucosa of potential occult primary sites, P = primary treatment, A = adjuvant treatment, Gy = gray, NR: = not reported

3.5 Secondary outcomes

3.5.1 Quality of life and treatment related toxicity

The reporting of QoL markers and treatment related toxicities was poor overall (Table 22). While most studies reported some aspects of treatment related toxicities, only Chen *et al.*[131] used a validated instrument to assess QoL (Table 23). Only Amsbaugh *et al.*[88] reported treatment related toxicities stratified according to primary treatment modality (Table 23). Surgery related toxicities or complications were not clearly reported by any of the studies included in this review.

Table 22. Reporting of quality of life or treatment related toxicity

Author	Year	Toxicity and/or QoL reported	Toxicity ≥ Grade III	Validated QoL tool used	Comparative reporting
Amsbaugh[84]	2017	Yes	Yes	No	No
Chen[123]	2017	Yes	No	Yes	Yes
Demiroz[118]	2014	No	N/A	N/A	No
Frank[119]	2010	Yes	Yes	No	No
Huo[121]	2018	No		N/A	No

Author	Year	Toxicity and/or QoL reported	Toxicity ≥ Grade III	Validated QoL tool used	Comparative reporting
Kamal[112]	2018	Yes		No	No
Klem[76]	2008	Yes		No	No
Lu[6]	2009	Yes		No	No
Madani[120]	2008	Yes		No	No
Mizuta[122]	2018	No		N/A	No

QoL = quality of life

Based on Amsbaugh *et al.,*[83] the overall toxicity of Grade III or higher in the pRT group was greater than that in the pND group (Table 23). The largest contributor to this overall toxicity was dysphagia, that was higher (16.2%) in the pND group compared to the pRT group (13.8%). Mucositis, a common toxicity related to radiotherapy, appears to be similar, irrespective of primary or adjuvant therapy dosage (13.8% compared to 13.5% respectively). Xerostomia that is normally considered a common toxicity following radiotherapy. However, rates of xerostomia in these studies were reported at very low rates and interestingly had a 0% reported rate following primary radiotherapy.

Table 23: Comparative treatment related toxicity reporting

Author	Year	Reported toxicity	pND + aRT	pRT
Amsbaugh[84]	2017	Any toxicity	35.1%	41.4%
		Xerostomia	2.7%	0%
		Dermatitis	2.7%	10.3%
		Dehydration	2.7%	10.3%
		G-tube	8.1%	10.3%
		Fibrosis	13.5%	3.4%
		Mucositis	13.5%	13.8%
		Dysphagia	16.2%	13.8%

pND = primary neck dissection, aRT = adjuvant radiotherapy, pRT = primary radiotherapy, G-tube = gastrostomy tube dependence for more than six months post treatment

In contrast to Amsbaugh *et al.,*[83] studies with a higher rate of pND appeared to have a significantly higher percentage of patients with toxicity of Grade III or higher (Figure 15, $R^2 = 0.9152$, $p = 0.0108$), as this group of patients would also be treated with adjuvant radiotherapy with or without concurrent chemotherapy. A cohort of these patients would receive a triple modality treatment, hence the likelihood of having worse toxicities. The most common Grade III or higher toxicities and their rates are summarised in Table 24.

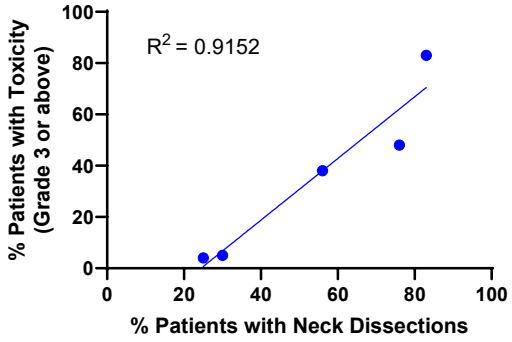

Figure 14. Percentage of patients with Grade III or higher toxicities as a function of percentage of patients who had a primary neck dissection in each study.

Table 24. Number of patients with Grade III or higher acute or chronic toxicities

Author	Year	Patients	Grade III or higher toxicity	Patients with toxicity (%)
Amsbaugh[88]	2017	66	Xerostomia, dermatitis, dehydration, G-tube, fibrosis, mucositis, dysphagia	25 (38%)
Frank[127]	2010	52	Dysphagia, G-tube	2 (4%)
Kamal[120]	2018	260	G-tube, dysphagia, osteoradionecrosis	14 (5%)
Klem[80]	2008	21	Haematologic, skin toxicity, mucositis, dehydration, renal toxicity, pulmonary toxicity, infection, pain, constipation	10 (48%)
Lu[6]	2009	18	Mucositis, G-tube	NR
Madani[128]	2008	23	Mucositis, dysphagia, dermatitis, hoarse voice	19 (83%)

Year = publication year; NR = not reported

Table 25. GRADE Summary of Findings

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Primary Radiotherapy	**Risk with Primary Surgery**				
OS assessed with: Kaplan-Meier Survival Estimate follow up: range 2 weeks to 176 months	**2-year OS**		**HR 0.86** (0.48 to 1.52) [No Death]	483 (5 non-randomised studies)	⨁⨁◯◯ LOW [a,b,c]	Surgery may result in little or no difference to OS
	93 per 100	94 per 100 (90 – 97)				
	5-year OS					
	81 per 100	83 per 100 (72 to 90)				
RRFS assessed with: Kaplan-Meier Survival Estimate follow up: range 2 weeks to 132 months	**2-year RRFS**		**HR 0.57** (0.32 to 1.04) [No Death and No Locoregional Recurrence of Disease]	160 (3 non-randomised studies)	⨁⨁◯◯ LOW [a,c]	Surgery may result in substantial difference to RRFS
	57 per 100	72 per 100 (55 to 83)				
	4-year RRFS					
	75 per 100	85 per 100 (74 to 91)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **HR:** Hazard Ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: Wehave very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a = non-randomised study designs, retrospective data, no consistent diagnostic paradigm; b = patient demographics were similar; no significant statistical heterogeneity; c = wide confidence intervals; OS = overall survival, RRFS = regional and relapse free survival

CHAPTER 4: DISCUSSION

4.1 Overview of findings

The systematic analysis of ten studies comparing pND to pRT for the treatment of HNCUP found that the primary modality of treatment had no clinically relevant or statistically significant difference to OS (Section 3.4.1). However, pND provided a better RRFS compared to pRT, although this is not statistically significant (Section 3.4.2). The variations in regional failure is likely multifactorial. However, the studies reviewed here did not provide adequate data to investigate causative relationships. Local practices such as how often and thoroughly these patients are followed up after their treatment is likely to affect regional failure pick up rate. The majority of studies reported a clinically acceptable PE under 6% after a five-year follow-up. The one study reporting more than 10% PE[130] treated their patients with only neck dissection (Section 3.4.3); this is not the recommended treatment modality in current guidelines.[134] The number of neck failures had no clear relationship with primary treatment modality or radiation treatment protocols (Section 3.4.4). The number of distant metastases had a clear linear relationship with the pND conducted in each study, where the study with the highest rate of pND had the highest incidence of distant metastasis (Section 3.4.5). Treatment related toxicities and patient reported QoL were poorly described in the literature analysed. This may be in part due to lack of validated tools to evaluate surgical complications and the toxicities related to radiotherapy do not occur following surgery to allow for direct comparison. Therefore, meaningful inferences from toxicity or QoL in relation to treatment decision making is difficult. Analysis of diagnostic criteria in each study indicated a large variation in treatment paradigms from study to study, generating largely inconsistent survival

outcome measures. Overall, there is no clear evidence to favour pND or pRT for the treatment of HNCUP. However, the certainty of these results is rated low (Table 25).

Advanced surgical techniques with improved access to parts of the anatomy that are difficult to locate, with reduced treatment related morbidity, provide an attractive treatment option for patients. However, the reduced toxicity of novel radiotherapy techniques has also improved patient QoL while maintaining treatment efficacy. In HNCUP, the optimum treatment modality to pursue continues to be a dilemma due to the poor evidence available to inform decision making. While non-invasive techniques such as FDG-PET scanning has markedly improved the detection of primary cancers, the patients left with true unknown primary diseases appear to receive more toxic treatments and, ultimately, poorer outcomes.[135] Due to the complex anatomy and myriad of potential primary sites within the head and neck region, risk stratification and the subsequent applied treatment modality has not always been the best choice for the individual patient. The relatively low incidence of true unknown primary HNSCC (three per 100,000 cases per year)[9] is also problematic for evidence gathering, as any high quality study would require a significant duration to recruit an adequate number of patients for statistical power, hence the lack of randomised prospective studies.

The previous meta-analysis by Liu *et al.*[9] on a similar topic had reported greater five-year OS and DFS when surgery was combined with RT compared to RT alone. This is in contrast to our findings of no difference between treatment modality and OS. Our study did not include any of the individual studies pooled by Liu *et al.*[9] as they pre-dated the search window for this systematic review. Also Liu *et al.*[9] included studies pre-dating the use of FDG-PET scanning as a routine in the diagnostic process of HNCUP. Therefore, it is likely that some of the included studies would contain 'non-true' HNCUP participants

(poorly sensitive diagnostic paradigm). Due to high smoking rates in the past, older studies are more likely to have patients with HNSCC that are not virally (HPV) mediated, therefore, the observed response to pRT is likely to be less effective than more recent studies. Current review included up to 20% (Table 10) HPV positive patients with good response to pRT.[136] This is not implying pRT is superior to pND in HPV positive HNSCC patients. They also reported less primary tumour emergence in patients treated with RT to both the affected neck and occult mucosal sites. However, we did not see such a clear relationship between RT protocol and PE, mainly because we did not have studies directly comparing neck only RT to neck and mucosal RT as compared by Liu *et al.*[9]

Another systematic review by Balaker *et al.*[10] analysing studies from 1998 to 2010 reported that survival outcomes were largely dependent on the disease stage at the time of diagnosis and treatment modality had no influence on OS. These authors did not conduct a pooled meta-analysis as a part of their review. Balaker *et al.*[10] included one study[6] that was in common with our review but the rest of the studies pre-dated our search window. Interestingly, there was a large difference between minimum and maximum five-year OS noted in their review: 25% (study from 2006[137]) and 79% (study from 2007[138]), respectively, compared to our review where minimum and maximum five-year OS was 64% (study from 2009[6]) and 85% (study from 2008[120]), respectively. There appears to be a publication year dependent improvement in five-year OS, likely related to improved prognosis from higher prevalence of HPV related HNSCC as well as improved identification of small tumours with FDG-PET[139] and robotic techniques.[74,79] While the results of this review echo our findings, the study participants were included when FDG-PET was not routinely used to identify an occult primary site and at a time when HPV rates were not a significant factor affecting overall prognosis. These

confounding factors reduce the confidence in the overall result of their review. As mentioned, FDG-PET scan is paramount for the identification of 'true' HNCUP. This is recommended by USA[134] and United Kingdom[140] HNCUP treatment guidelines.

There appears to be a conflict between protocolised, institution-based treatment paradigms and the novel approach of individualised patient care. The lack of standardised treatment protocols in the past decade appears to have hindered the development of individualised care plans. Utilisation of patient risk profiles and a patient dependent diagnostic paradigm may yield improved identification of an occult primary and better treatment outcomes for this group of patients.

4.2 Limitations of the review

Despite rigorous searching, we were unable to identify prospective randomised studies that directly compared the two primary modalities of treatment. Hence, there are significant confounding factors considered in this analysis that are inherent to retrospective datasets. The study selection and data extraction were performed by only one reviewer that adds to the risk of error. Furthermore, meta-analysis conducted here is based on estimated data interpolated from published material.

4.3 Implications for clinical practice

The results of this systematic review do not favour either primary surgery or primary radiotherapy as the superior treatment modality and neither offers a clear OS benefit. Therefore, both treatment options should be put forward for shared decision making with the patient. However, due to the nature of studies included in this review, the certainty of the above result is low.

However, it appears that individualised treatment plans based on risk factors could maintain treatment effectiveness while reducing morbidity, as demonstrated in the study by Huo *et al*.[129] Using patient history and examination to determine if the unknown primary SCC is from a skin or a mucosal source could determine which primary treatment modality is offered, hence, avoiding mucosal irradiation to patients presumed to have a occult cutaneous malignancy.

4.4 Consideration for future clinical practice

If a patient is presumed to have an occult mucosal primary cancer (due to heavy smoking history, heavy alcohol intake, previous oral/oropharyngeal lesions with dysplasia, lack of cutaneous SCC risk factors) that has metastasised to the neck, then pRT to the potential mucosal sites as well as the affected neck should be considered their primary treatment option. However, there is no clear evidence to guide when this group of patients should have a neck dissection. It could be argued that higher nodal disease (N2b and above) would benefit from surgical disease clearance followed by adjuvant radiotherapy. However, a pND would delay radiotherapy treatment to occult mucosal sites, potentially increasing the risk of PE and DM. However, the data analysed in this systematic review, regardless of the primary treatment modality, suggests that the PE rate was fairly constant at 5%. This patient group should receive a FDG-PET scan, bilateral tonsillectomy and a tongue base mucosectomy (or at least directed biopsies) during the diagnostic phase.

On the contrary, if a patient is presumed to have an occult skin malignancy (previous skin SCC, Fitzpatrick skin type 1, actinic skin, parotid involvement) that has metastasised to the neck, they should be treated with a pND and adjuvant radiotherapy.

Also, these patients should be spared from radiotherapy to occult mucosal sites, thus reducing radiotherapy related morbidity. A superficial parotidectomy in the absence of gross parotid disease should also be considered in a presumed cutaneous primary tumour due to the first echelon nodes from the head and facial skin draining to intra-parotid lymph nodes. This group of patients should not have a diagnostic tonsillectomy or a tongue base mucosectomy.

However, the dilemma still exists for patients with no clear history favouring either primary site or the p16 status of nodal tissue. Given the p16 marker is positive in approximately 30% of cutaneous SCCs, this marker cannot be used as a method of determining the likely occult primary site. This patient group should be offered primary surgery with adjuvant radiotherapy as well as irradiation to occult mucosal sites. These patients should also receive a diagnostic bilateral tonsillectomy and tongue base mucosectomy (or equivalent). If p16 status is negative, primary surgery followed by adjuvant radiotherapy should be recommended.

Concurrent chemotherapy in combination with radiotherapy should be determined by histological or radiological identification of extra-capsular spread as detailed in known primary guidelines.[134] However, primary radiotherapy patients should receive a combined form of chemotherapy as this has shown to increase survival in known primary HNSCCs.[141]

4.5 Implications for research

This review provides the foundation for future clinical research for a direct comparison of primary modality of treatment for HNCUP. As we did not identify a

significant difference in survival outcomes, ethically, it would be appropriate to randomise patients to either primary treatment modality in a trial setting. However, due to the relatively similar survival rates between treatment modalities, a large sample size would be required to adequately power a clinical trial. Also, HNCUP with a very low incidence, recruitment of large number of patients would be impractical. Therefore, large, well designed retrospective studies are likely to provide valuable data for clinical decision making. Clinical registries with appropriate data collection to calculate overall as well disease specific outcomes becomes an important component of such research.

Overall, there was a lack of high-quality evidence to confidently inform clinical decision making. There were no published or unpublished RCTs on the topic. Future studies should report on clinically relevant survival end points that are consistent to allow for appropriate data synthesis. Kaplan-Meier plots should always report the at-risk number of participants at each time interval to allow for accurate pooling of data for meaningful clinical decision making.

The risk factors associated with HNSCC are many and variable amongst patients. Therefore, stratified data reporting based on patient risk factors could also guide clinical decision making in the future. p16 status should be stratified in future HNCUP data reporting as this continues to be a dilemma in decision making. Further high-quality data is required to identify the best treatment modality or a combination of modalities for the treatment of patients with p16 positive neck nodal metastasis with presumed mucosal or cutaneous origin. We propose stratification of patient survival data according to p16 status, HPV DNA status (if available), smoking status, alcohol intake status and skin type (Fitzpatrick grade).

4.6 Conclusion

There were no clinically or statistically significant survival difference between primary surgery or primary radiotherapy for the treatment of unknown primary head and neck squamous cell carcinoma. While primary neck dissection appears to benefit locoregional control of disease, this was not statistically significant. Higher stage of neck disease results in poorer overall survival, regardless of the primary treatment modality. Certainty of these results is low due to overall poor quality of studies reviewed.

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APPENDICES

Appendix I

Search strategy – PubMed

(Carcinoma, squamous cell of head and neck[supplementary concept] OR Carcinoma, Squamous Cell[mh] OR human papillomavirus[tw] OR squamous cell carcinoma*[tw] OR squamous cell cancer*[tw] OR head and neck cancer*[tw] OR p16[tw] OR p-16[tw] OR unknown primary head and neck cancer[tw] OR head and neck cancer of unknown primary site[tw] OR head and neck carcinoma[tw] OR head and neck neoplasms[mh] OR unknown primary[tw] OR occult mucosal primary[tw] OR occult primary[tw]) AND (neck dissection[mh] OR tonsillectomy[tw] OR robotic surgical procedures[mh] OR lymph node excision[mh] OR surgery[tw] OR neck dissect*[tw] OR lymph node excisi*[tw] OR neck surgery[tw] OR surgical procedures, operative[mh]) AND (Radiotherapy[mh] OR radiotherapy, intensity-Modulated[mh] OR radiotherapy, conformal[mh] OR radiotherapy Dosage[mh] OR dose fractionation[mh] OR chemoradiotherapy[mh] OR chemoradiotherapy[tw] OR radiation therapy[tw] OR radiation oncology[tw] OR radiotherapy[tw] OR IMRT[tw] OR intensity modulated radiotherapy[tw])

Search strategy – Embase

(('head and neck squamous cell carcinoma':de,ti,ab OR 'squamous cell carcinoma':de,ti,ab OR 'wart virus':de OR 'squamous cell carcinoma*' OR 'squamous cell cancer*' OR 'head and neck cancer*' OR 'p16' OR 'p-16' OR 'cancer of unknown primary site':de,ti,ab OR 'head and neck cancer of unknown primary site' OR 'head and neck

carcinoma':de,ti,ab OR 'head and neck tumor':de,ti,ab OR 'head and neck squamous cell carcinoma'/exp OR 'head and neck squamous cell carcinoma' OR 'squamous cell carcinoma'/exp OR 'squamous cell carcinoma' OR 'head and neck carcinoma'/exp OR 'head and neck carcinoma' OR 'head and neck tumor'/exp OR 'head and neck tumor' OR 'cancer of unknown primary site'/exp OR 'cancer of unknown primary site') AND ('unknown primary'/exp OR 'unknown primary')) AND ('neck dissection':de,ti,ab OR 'tonsillectomy':de,ti,ab OR 'robotic surgical procedure':de,ti,ab OR 'lymph node dissection':de,ti,ab OR 'surgery':de,ti,ab OR 'neck dissect*' OR 'lymph node excisi*' OR 'neck surgery' OR 'neck dissection' OR 'tonsillectomy' OR 'robotic surgical procedure' OR 'lymph node dissection' OR 'surgery') AND ('radiotherapy':de,ti,ab OR 'radiotherapy, intensity-modulated':de,ti,ab OR 'conformal radiotherapy':de,ti,ab OR 'radiation dose escalation':de,ti,ab OR 'radiation dose fractionation':de,ti,ab OR 'chemoradiotherapy':de,ti,ab OR 'adjuvant chemoradiotherapy':de,ti,ab OR 'radiation therapy' OR 'radiation oncology' OR 'radiotherapy' OR 'imrt' OR 'intensity modulated radiotherapy' OR 'radiation dose' OR 'chemotherapy':de,ti,ab OR 'chemotherapy')

Search strategy – ProQuest Theses and Dissertations

AB(Carcinoma, squamous cell of head and neck OR Carcinoma, Squamous Cell OR human papillomavirus OR squamous cell carcinoma* OR squamous cell cancer* OR head and neck cancer* OR p16 OR p-16 OR unknown primary head and neck cancer OR head and neck cancer of unknown primary site OR head and neck carcinoma OR head and neck neoplasms OR unknown primary OR occult mucosal primary OR occult primary) AND AB(neck dissection OR tonsillectomy OR robotic surgical procedures OR lymph node excision OR surgery OR neck dissect* OR lymph node excisi* OR neck surgery OR surgical procedures, operative) AND AB(Radiotherapy OR radiotherapy,

intensity-Modulated OR radiotherapy, conformal OR radiotherapy Dosage OR dose fractionation OR chemoradiotherapy OR chemoradiotherapy OR radiation therapy OR radiation oncology OR radiotherapy OR IMRT OR intensity modulated radiotherapy)

Studies excluded on full text review and reasons for their exclusion

Foreign language

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Absence of comparator

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No original data (Review only)

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JBI Critical Appraisal Checklist for Cohort Studies

Reviewer_____Date_____

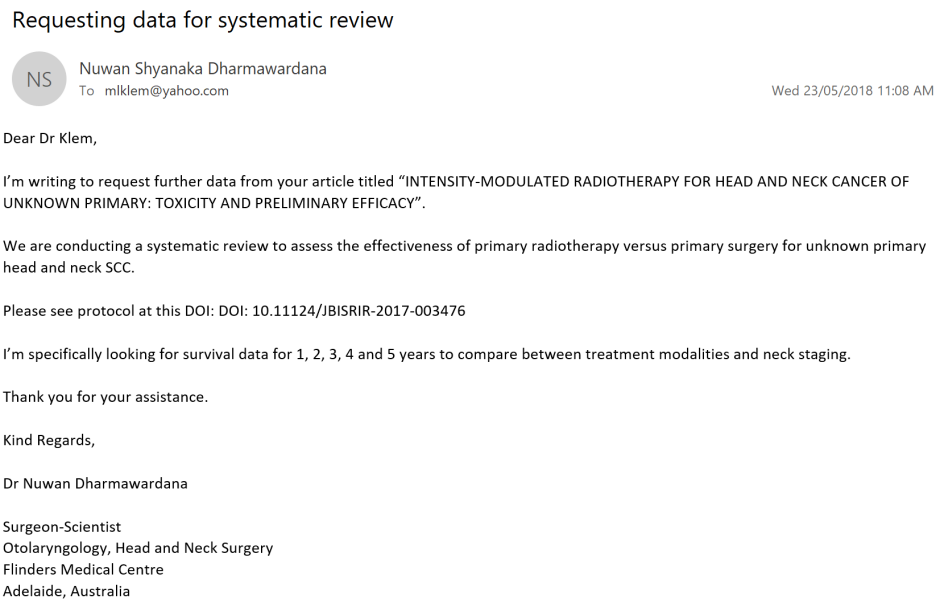
Author _____Year_____Record Number _____

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	□	□	□	□
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	□	□	□	□
3. Was the exposure measured in a valid and reliable way?	□	□	□	□
4. Were confounding factors identified?	□	□	□	□
5. Were strategies to deal with confounding factors stated?	□	□	□	□
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	□	□	□	□
7. Were the outcomes measured in a valid and reliable way?	□	□	□	□
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	□	□	□	□
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	□	□	□	□
10. Were strategies to address incomplete follow up utilized?	□	□	□	□
11. Was appropriate statistical analysis used?	□	□	□	□

Appendix II

Email correspondence for data request

Following is a record of email correspondences requesting further data for this systematic review. We did not receive any additional data from any source.



Requesting data for systematic review

NS Nuwan Shyanaka Dharmawardana
To mlklem@yahoo.com Wed 23/05/2018 11:08 AM

Dear Dr Klem,

I'm writing to request further data from your article titled "INTENSITY-MODULATED RADIOTHERAPY FOR HEAD AND NECK CANCER OF UNKNOWN PRIMARY: TOXICITY AND PRELIMINARY EFFICACY".

We are conducting a systematic review to assess the effectiveness of primary radiotherapy versus primary surgery for unknown primary head and neck SCC.

Please see protocol at this DOI: DOI: 10.11124/JBISRIR-2017-003476

I'm specifically looking for survival data for 1, 2, 3, 4 and 5 years to compare between treatment modalities and neck staging.

Thank you for your assistance.

Kind Regards,

Dr Nuwan Dharmawardana

Surgeon-Scientist
Otolaryngology, Head and Neck Surgery
Flinders Medical Centre
Adelaide, Australia

Requesting data for systematic review

NS Nuwan Shyanaka Dharmawardana
To indira@krtkg1.ugent.be Wed 23/05/2018 11:06 AM

Dear Dr Madani,

I'm writing to request further data from your article titled "INTENSITY-MODULATED RADIOTHERAPY FOR CERVICAL LYMPH NODE METASTASES FROM UNKNOWN PRIMARY CANCER".

We are conducting a systematic review to assess the effectiveness of primary radiotherapy versus primary surgery for unknown primary head and neck SCC.

Please see protocol at this DOI: DOI: 10.11124/JBISRIR-2017-003476

I'm specifically looking for survival data for 1, 2, 3, 4 and 5 years to compare between treatment modalities and neck staging.

Thank you for your assistance.

Kind Regards,

Dr Nuwan Dharmawardana

Surgeon-Scientist
Otolaryngology, Head and Neck Surgery
Flinders Medical Centre
Adelaide, Australia

Requesting data for systematic review

NS Nuwan Shyanaka Dharmawardana
To sjfrank@mdanderson.org Wed 23/05/2018 11:03 AM

Dear Dr Frank,

I'm writing to request further data from your article titled "INTENSITY-MODULATED RADIOTHERAPY FOR CERVICAL NODE SQUAMOUS CELL CARCINOMA METASTASES FROM UNKNOWN HEAD-AND-NECK PRIMARY SITE: M. D. ANDERSON CANCER CENTER OUTCOMES AND PATTERNS OF FAILURE".

We are conducting a systematic review to assess the effectiveness of primary radiotherapy versus primary surgery for unknown primary head and neck SCC.

Please see protocol at this DOI: DOI: 10.11124/JBISRIR-2017-003476

I'm specifically looking for survival data for 1, 2, 3, 4 and 5 years to compare between treatment modalities and neck staging.

Thank you for your assistance.

Kind Regards,

Dr Nuwan Dharmawardana

Surgeon-Scientist
Otolaryngology, Head and Neck Surgery
Flinders Medical Centre
Adelaide, Australia

Requesting data for systematic review

NS Nuwan Shyanaka Dharmawardana
To jvainsh@med.umich.edu Wed 23/05/2018 10:59 AM

Dear Dr Vainshtein,

I'm writing to request further data from your article titled "Head and neck squamous cell carcinoma of unknown primary: Neck dissection and radiotherapy or definitive radiotherapy".

We are conducting a systematic review to assess the effectiveness of primary radiotherapy versus primary surgery for unknown primary head and neck SCC.

Please see protocol at this DOI: DOI: 10.11124/JBISRIR-2017-003476

I'm specifically looking for survival data for 1, 2, 3, 4 and 5 years to compare between treatment modalities and neck staging.

Thank you for your assistance.

Kind Regards,

Dr Nuwan Dharmawardana

Surgeon-Scientist
Otolaryngology, Head and Neck Surgery
Flinders Medical Centre
Adelaide, Australia

Requesting data for systematic review

NS Nuwan Shyanaka Dharmawardana
To achen5@kumc.edu Wed 23/05/2018 10:52 AM

Dear Dr Chen,

I'm writing to request further data from your article titled "Oropharynx-directed ipsilateral irradiation for p16-positive squamous cell carcinoma involving the cervical lymph nodes of unknown primary origin".

We are conducting a systematic review to assess the effectiveness of primary radiotherapy versus primary surgery for unknown primary head and neck SCC.

Please see protocol at this DOI: DOI: 10.11124/JBISRIR-2017-003476

I'm specifically looking for survival data for 1, 2, 3, 4 and 5 years to compare between treatment modalities and neck staging.

Thank you for your assistance.

Kind Regards,

Dr Nuwan Dharmawardana

Surgeon-Scientist
Otolaryngology, Head and Neck Surgery
Flinders Medical Centre
Adelaide, Australia

Requesting data for systematic review

NS Nuwan Shyanaka Dharmawardana
To mark.amsbaugh@louisville.edu
Wed 23/05/2018 10:54 AM

Dear Dr Amsbaugh,

I'm writing to request further data from your article titled "Neck dissection for unknown cancer of the head and neck in the era of chemoradiation".

We are conducting a systematic review to assess the effectiveness of primary radiotherapy versus primary surgery for unknown primary head and neck SCC.

Please see protocol at this DOI: DOI: 10.11124/JBISRIR-2017-003476

I'm specifically looking for survival data for 1, 2, 3, 4 and 5 years to compare between treatment modalities and neck staging.

Thank you for your assistance.

Kind Regards,

Dr Nuwan Dharmawardana

Surgeon-Scientist
Otolaryngology, Head and Neck Surgery
Flinders Medical Centre
Adelaide, Australia

Requesting data for systematic review

NS Nuwan Shyanaka Dharmawardana
To achen5@kumc.edu
Wed 23/05/2018 10:50 AM

You replied to this message on 23/05/2018 10:51 AM.

Dear Dr Huo,

I'm writing to request further data from your article titled "Oropharynx-directed ipsilateral irradiation for p16-positive squamous cell carcinoma involving the cervical lymph nodes of unknown primary origin".

We are conducting a systematic review to assess the effectiveness of primary radiotherapy versus primary surgery for unknown primary head and neck SCC.

Please see protocol at this DOI: DOI: 10.11124/JBISRIR-2017-003476

I'm specifically looking for survival data for 1, 2, 3, 4 and 5 years to compare between treatment modalities and neck staging.

Thank you for your assistance.

Kind Regards,

Dr Nuwan Dharmawardana

Surgeon-Scientist
Otolaryngology, Head and Neck Surgery
Flinders Medical Centre
Adelaide, Australia

Requesting data for systematic review

NS Nuwan Shyanaka Dharmawardana
To michael.huo@health.qld.gov.au
Wed 23/05/2018 10:49 AM

Dear Dr Huo,

I'm writing to request further data from your article titled "Head and neck squamous cell carcinoma of unknown primary: Outcomes of a pre-defined institutional treatment policy in a region with a high prevalence of skin cancer".

We are conducting a systematic review to assess the effectiveness of primary radiotherapy versus primary surgery for unknown primary head and neck SCC.

Please see protocol at this DOI: DOI: 10.11124/JBISRIR-2017-003476

I'm specifically looking for survival data for 1, 2, 3, 4 and 5 years to compare between treatment modalities and neck staging.

Thank you for your assistance.

Kind Regards,

Dr Nuwan Dharmawardana

Surgeon-Scientist
Otolaryngology, Head and Neck Surgery
Flinders Medical Centre
Adelaide, Australia

Requesting Data for Systematic Review

NS Nuwan Shyanaka Dharmawardana
To agarden@mdanderson.org
Wed 23/05/2018 10:44 AM

Dear Dr Garden,

I'm writing to request further data from your article titled "Outcomes of Patients Diagnosed With Carcinoma Metastatic to the Neck From an Unknown Primary Source and Treated With Intensity-Modulated Radiation Therapy".

We are conducting a systematic review to assess the effectiveness of primary radiotherapy versus primary surgery for unknown primary head and neck SCC.

Please see protocol at this DOI: DOI: 10.11124/JBISRIR-2017-003476

I'm specifically looking for survival data for 1, 2, 3, 4 and 5 years to compare between treatment modalities and neck staging.

Thank you for your assistance.

Kind Regards,

Dr Nuwan Dharmawardana

Surgeon-Scientist
Otolaryngology, Head and Neck Surgery
Flinders Medical Centre
Adelaide, Australia

Requesting Access to Data for Systematic Review

NS Nuwan Shyanaka Dharmawardana
To m_mizuta@ent.kuhp.kyoto-u.ac.jp Wed 23/05/2018 10:42 AM

Dear Dr Mizuta,

I'm writing to request further data from your article titled "Unknown primary squamous cell carcinoma of the head and neck: retrospective analysis of 80 cases".
We are conducting a systematic review to assess the effectiveness of primary radiotherapy versus primary surgery for unknown primary head and neck SCC.
Please see protocol at this DOI: DOI: 10.11124/JBISRIR-2017-003476

I'm specifically looking for survival data for 1, 2, 3, 4 and 5 years to compare between treatment modalities and neck staging.

Thank you for your assistance.

Kind Regards,

Dr Nuwan Dharmawardana

Surgeon-Scientist
Otolaryngology, Head and Neck Surgery
Flinders Medical Centre
Adelaide, Australia

Appendix III

Estimation of survival data from Kaplan-Meier plot

As mentioned in Section 2.9 of this thesis, studies included in this review did not report comparable time to event data intervals. Therefore, Kaplan-Meier estimate curves were used to manually estimate survival rates for each time interval. As illustrated in Figure A-1, lines were drawn manually at each time interval and the corresponding survival rate was documented at the intercept point. These values were then entered into the worksheet provided by Tierney *et a.l*[116] to complete the calculation of hazard ratios. When patient 'number at risk' (highlighted in yellow in Figure A-1) were provided in the Kaplan-Meier plots, this data was included to also allow for more accurate calculation of summary statistics; 'number at risk' values indicate patients lost to follow-up, a value difficult to ascertain from isolated plots. The survival values estimated here were also used for correlation and regression analysis for the two-year overall survival mark (see

Section 2.9). The two-year survival rates were chosen as these represented the minimum from those reported across two-, three-, four- or five-year intervals from the included studies.

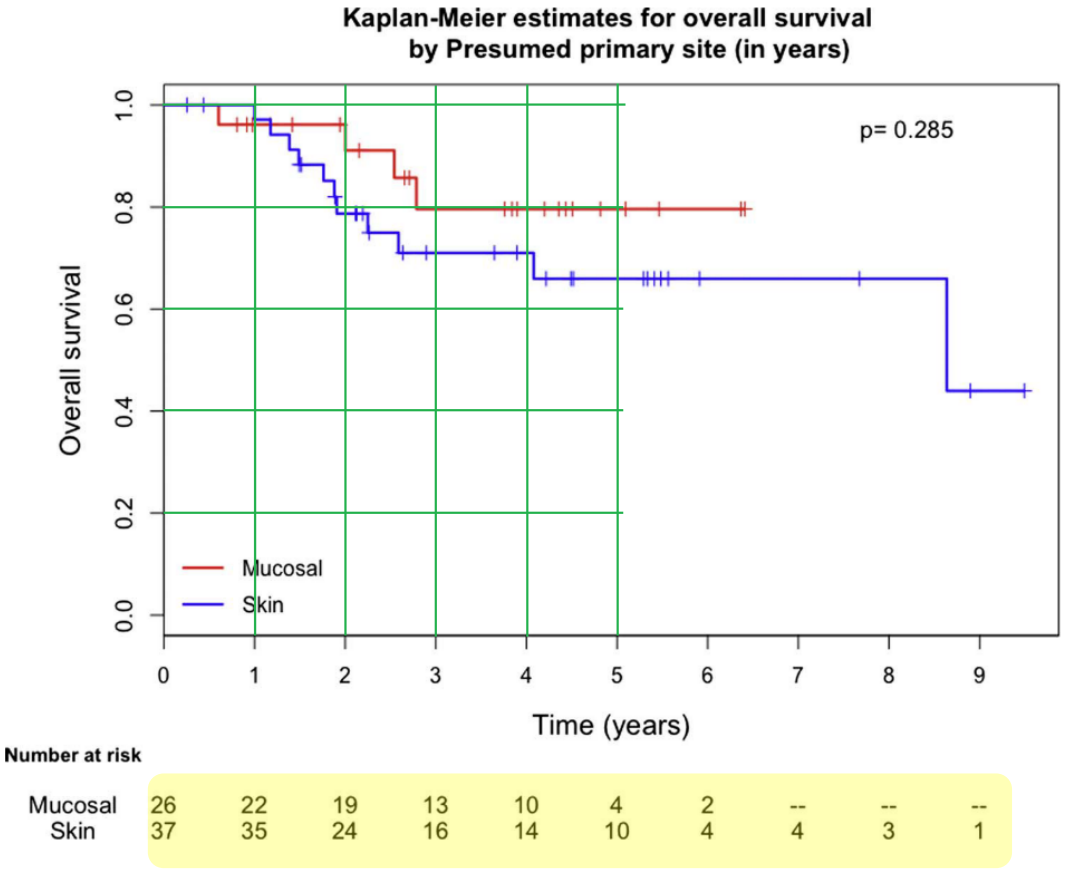
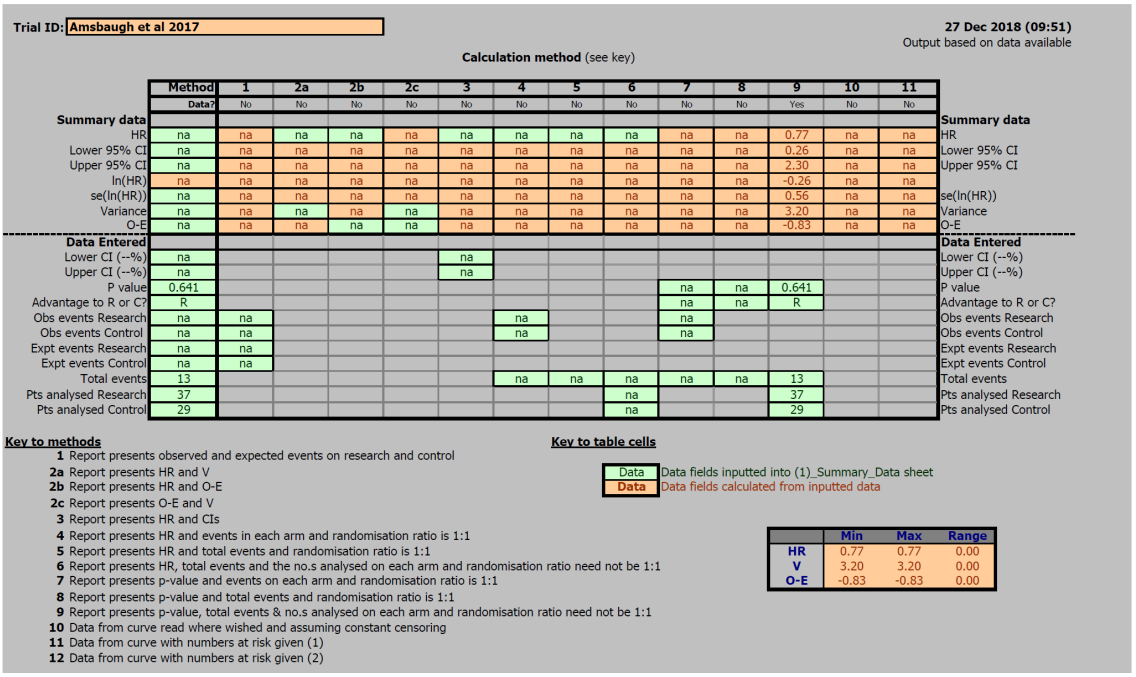


Figure A - 1. Example of a manual drawing of 'green' lines to estimate overall survival for each time interval. This graph was modified from Huo et al.[129]

Calculation of hazard ratios

The list of figures below (Figures A-2 to A-9) record the HR calculations based on a worksheet provided by Tierney *et al*.[124] Calculations for each study was based on the data available and each figure below indicates which set of data was used to calculated the summary statistic.



Trial ID: Amsbaugh et al 2017

27 Dec 2018 (09:51)
Output based on data available

Calculation method (see key)

	Method	1	2a	2b	2c	3	4	5	6	7	8	9	10	11	
	Data?	No	No	No	No	No	No	No	No	No	No	Yes	No	No	
Summary data															**Summary data**
HR	na	na	na	na	na	na	na	na	na	na	na	0.77	na	na	HR
Lower 95% CI	na	na	na	na	na	na	na	na	na	na	na	0.26	na	na	Lower 95% CI
Upper 95% CI	na	na	na	na	na	na	na	na	na	na	na	2.30	na	na	Upper 95% CI
ln(HR)	na	na	na	na	na	na	na	na	na	na	na	-0.26	na	na	
se(ln(HR))	na	na	na	na	na	na	na	na	na	na	na	0.56	na	na	se(ln(HR))
Variance	na	na	na	na	na	na	na	na	na	na	na	3.20	na	na	Variance
O-E	na	na	na	na	na	na	na	na	na	na	na	-0.83	na	na	O-E
Data Entered															**Data Entered**
Lower CI (--%)	na					na									Lower CI (--%)
Upper CI (--%)	na					na									Upper CI (--%)
P value	0.641									na	na	0.641			P value
Advantage to R or C?	R									na	na	R			Advantage to R or C?
Obs events Research	na	na					na			na					Obs events Research
Obs events Control	na	na					na			na					Obs events Control
Expt events Research	na	na													Expt events Research
Expt events Control	na	na													Expt events Control
Total events	13						na	na	na	na	na	13			Total events
Pts analysed Research	37								na			37			Pts analysed Research
Pts analysed Control	29								na			29			Pts analysed Control

Key to methods

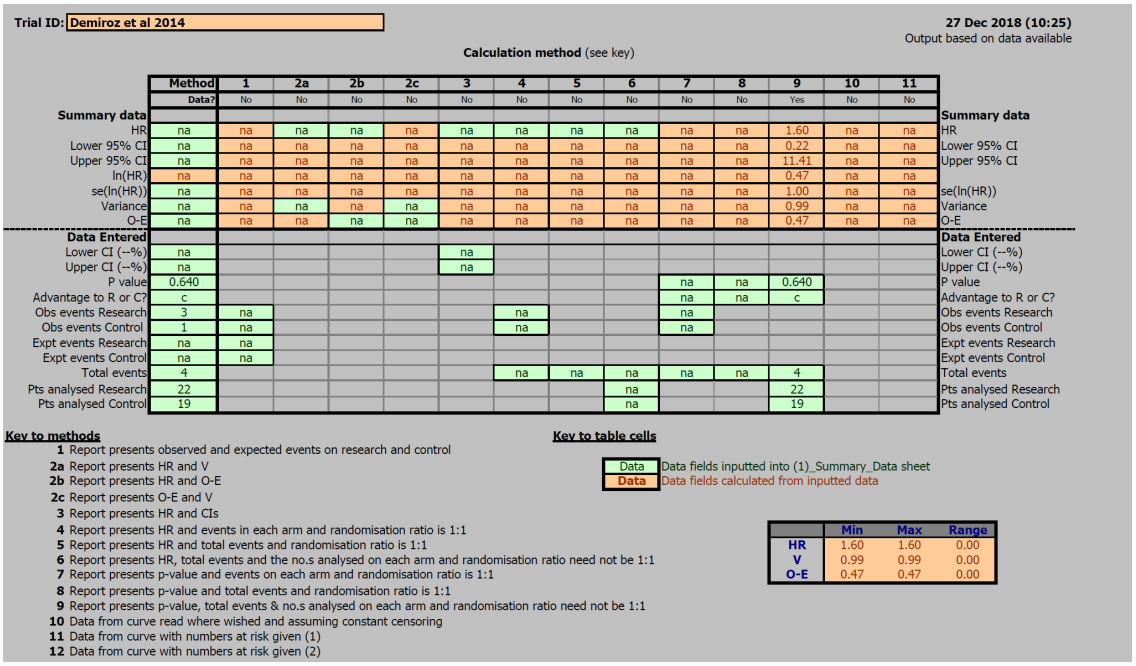
1 Report presents observed and expected events on research and control
2a Report presents HR and V
2b Report presents HR and O-E
2c Report presents O-E and V
3 Report presents HR and CIs
4 Report presents HR and events in each arm and randomisation ratio is 1:1
5 Report presents HR and total events and randomisation ratio is 1:1
6 Report presents HR, total events and the no.s analysed on each arm and randomisation ratio need not be 1:1
7 Report presents p-value and events on each arm and randomisation ratio is 1:1
8 Report presents p-value and total events and randomisation ratio is 1:1
9 Report presents p-value, total events & no.s analysed on each arm and randomisation ratio need not be 1:1
10 Data from curve read where wished and assuming constant censoring
11 Data from curve with numbers at risk given (1)
12 Data from curve with numbers at risk given (2)

Key to table cells

Data — Data fields inputted into (1)_Summary_Data sheet
Data — Data fields calculated from inputted data

	Min	Max	Range
HR	0.77	0.77	0.00
V	3.20	3.20	0.00
O-E	-0.83	-0.83	0.00

Figure A - 2. Worksheet for overall survival summary statistic calculation for Amsbaugh et al.[88]



Trial ID: Demiroz et al 2014

27 Dec 2018 (10:25)
Output based on data available

Calculation method (see key)

	Method	1	2a	2b	2c	3	4	5	6	7	8	9	10	11	
	Data?	No	No	No	No	No	No	No	No	No	No	Yes	No	No	
Summary data															**Summary data**
HR	na	na	na	na	na	na	na	na	na	na	na	1.60	na	na	HR
Lower 95% CI	na	na	na	na	na	na	na	na	na	na	na	0.22	na	na	Lower 95% CI
Upper 95% CI	na	na	na	na	na	na	na	na	na	na	na	11.41	na	na	Upper 95% CI
ln(HR)	na	na	na	na	na	na	na	na	na	na	na	0.47	na	na	
se(ln(HR))	na	na	na	na	na	na	na	na	na	na	na	1.00	na	na	se(ln(HR))
Variance	na	na	na	na	na	na	na	na	na	na	na	0.99	na	na	Variance
O-E	na	na	na	na	na	na	na	na	na	na	na	0.47	na	na	O-E
Data Entered															**Data Entered**
Lower CI (--%)	na					na									Lower CI (--%)
Upper CI (--%)	na					na									Upper CI (--%)
P value	0.640									na	na	0.640			P value
Advantage to R or C?	c									na	na	c			Advantage to R or C?
Obs events Research	3	na					na			na					Obs events Research
Obs events Control	1	na					na			na					Obs events Control
Expt events Research	na	na													Expt events Research
Expt events Control	na	na													Expt events Control
Total events	4						na	na	na	na	na	4			Total events
Pts analysed Research	22								na			22			Pts analysed Research
Pts analysed Control	19								na			19			Pts analysed Control

Key to methods

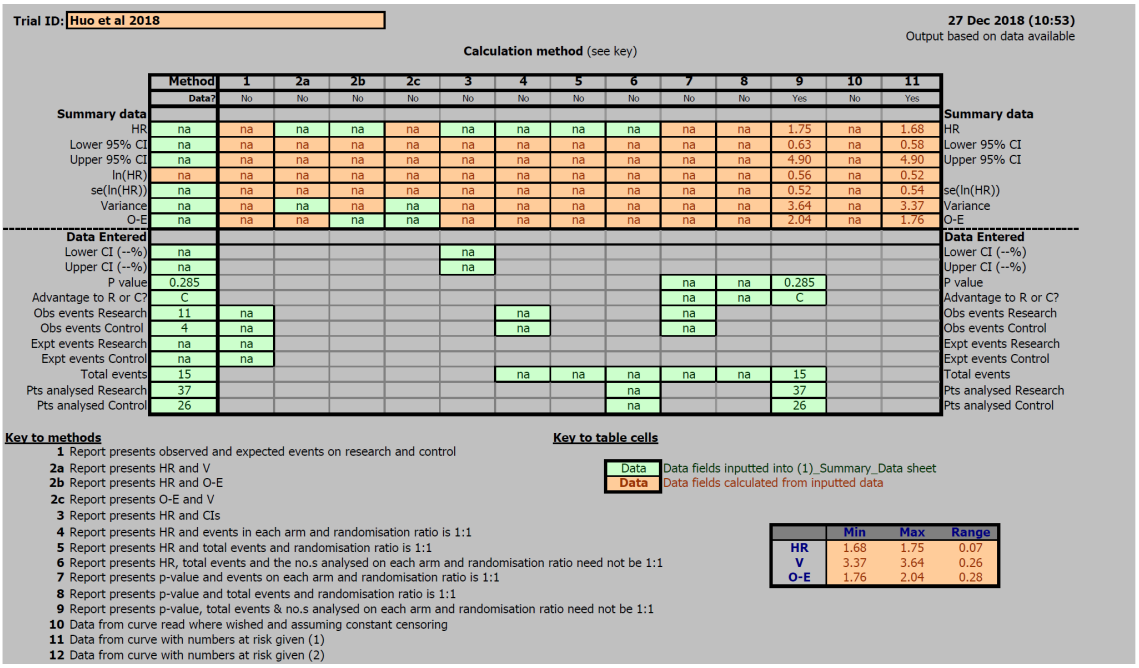
1 Report presents observed and expected events on research and control
2a Report presents HR and V
2b Report presents HR and O-E
2c Report presents O-E and V
3 Report presents HR and CIs
4 Report presents HR and events in each arm and randomisation ratio is 1:1
5 Report presents HR and total events and randomisation ratio is 1:1
6 Report presents HR, total events and the no.s analysed on each arm and randomisation ratio need not be 1:1
7 Report presents p-value and events on each arm and randomisation ratio is 1:1
8 Report presents p-value and total events and randomisation ratio is 1:1
9 Report presents p-value, total events & no.s analysed on each arm and randomisation ratio need not be 1:1
10 Data from curve read where wished and assuming constant censoring
11 Data from curve with numbers at risk given (1)
12 Data from curve with numbers at risk given (2)

Key to table cells

Data — Data fields inputted into (1)_Summary_Data sheet
Data — Data fields calculated from inputted data

	Min	Max	Range
HR	1.60	1.60	0.00
V	0.99	0.99	0.00
O-E	0.47	0.47	0.00

Figure A - 3. Worksheet for overall survival summary statistic calculation for Demiroz et al.[126]



Trial ID: Huo et al 2018

27 Dec 2018 (10:53)
Output based on data available

Calculation method (see key)

	Method	1	2a	2b	2c	3	4	5	6	7	8	9	10	11	
	Data?	No	No	No	No	No	No	No	No	No	No	Yes	No	Yes	
Summary data															**Summary data**
HR	na	na	na	na	na	na	na	na	na	na	na	1.75	na	1.68	HR
Lower 95% CI	na	na	na	na	na	na	na	na	na	na	na	0.63	na	0.58	Lower 95% CI
Upper 95% CI	na	na	na	na	na	na	na	na	na	na	na	4.90	na	4.90	Upper 95% CI
ln(HR)	na	na	na	na	na	na	na	na	na	na	na	0.56	na	0.52	
se(ln(HR))	na	na	na	na	na	na	na	na	na	na	na	0.52	na	0.54	se(ln(HR))
Variance	na	na	na	na	na	na	na	na	na	na	na	3.64	na	3.37	Variance
O-E	na	na	na	na	na	na	na	na	na	na	na	2.04	na	1.76	O-E
Data Entered															**Data Entered**
Lower CI (--%)	na					na									Lower CI (--%)
Upper CI (--%)	na					na									Upper CI (--%)
P value	0.285									na	na	0.285			P value
Advantage to R or C?	C									na	na	C			Advantage to R or C?
Obs events Research	11	na					na			na					Obs events Research
Obs events Control	4	na					na			na					Obs events Control
Expt events Research	na	na													Expt events Research
Expt events Control	na	na													Expt events Control
Total events	15						na	na	na	na	na	15			Total events
Pts analysed Research	37								na			37			Pts analysed Research
Pts analysed Control	26								na			26			Pts analysed Control

Key to methods

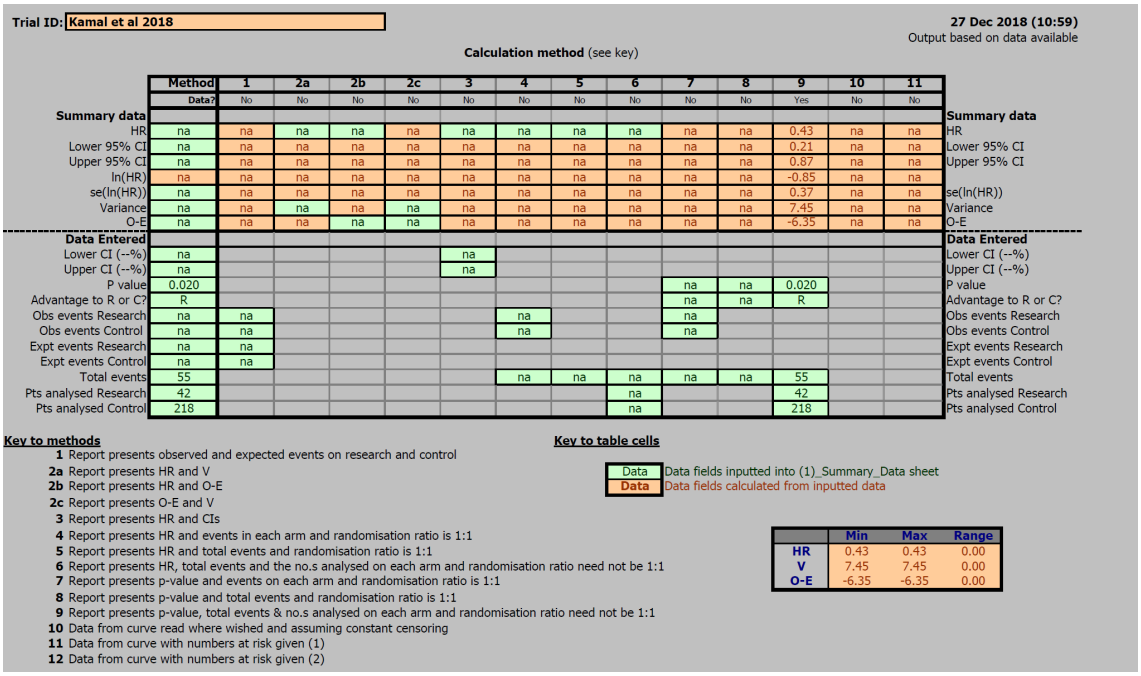
1 Report presents observed and expected events on research and control
2a Report presents HR and V
2b Report presents HR and O-E
2c Report presents O-E and V
3 Report presents HR and CIs
4 Report presents HR and events in each arm and randomisation ratio is 1:1
5 Report presents HR and total events and randomisation ratio is 1:1
6 Report presents HR, total events and the no.s analysed on each arm and randomisation ratio need not be 1:1
7 Report presents p-value and events on each arm and randomisation ratio is 1:1
8 Report presents p-value and total events and randomisation ratio is 1:1
9 Report presents p-value, total events & no.s analysed on each arm and randomisation ratio need not be 1:1
10 Data from curve read where wished and assuming constant censoring
11 Data from curve with numbers at risk given (1)
12 Data from curve with numbers at risk given (2)

Key to table cells

Data — Data fields inputted into (1)_Summary_Data sheet
Data — Data fields calculated from inputted data

	Min	Max	Range
HR	1.68	1.75	0.07
V	3.37	3.64	0.26
O-E	1.76	2.04	0.28

Figure A - 4. Worksheet for overall survival summary statistic calculation for Huo et al.[129]



Trial ID: Kamal et al 2018

27 Dec 2018 (10:59)
Output based on data available

Calculation method (see key)

	Method	1	2a	2b	2c	3	4	5	6	7	8	9	10	11	
	Data?	No	No	No	No	No	No	No	No	No	No	Yes	No	No	
Summary data															**Summary data**
HR	na	na	na	na	na	na	na	na	na	na	na	0.43	na	na	HR
Lower 95% CI	na	na	na	na	na	na	na	na	na	na	na	0.21	na	na	Lower 95% CI
Upper 95% CI	na	na	na	na	na	na	na	na	na	na	na	0.87	na	na	Upper 95% CI
ln(HR)	na	na	na	na	na	na	na	na	na	na	na	-0.85	na	na	
se(ln(HR))	na	na	na	na	na	na	na	na	na	na	na	0.37	na	na	se(ln(HR))
Variance	na	na	na	na	na	na	na	na	na	na	na	7.45	na	na	Variance
O-E	na	na	na	na	na	na	na	na	na	na	na	-6.35	na	na	O-E
Data Entered															**Data Entered**
Lower CI (--%)	na					na									Lower CI (--%)
Upper CI (--%)	na					na									Upper CI (--%)
P value	0.020									na	na	0.020			P value
Advantage to R or C?	R									na	na	R			Advantage to R or C?
Obs events Research	na	na					na			na					Obs events Research
Obs events Control	na	na					na			na					Obs events Control
Expt events Research	na	na													Expt events Research
Expt events Control	na	na													Expt events Control
Total events	55						na	na	na	na	na	55			Total events
Pts analysed Research	42								na			42			Pts analysed Research
Pts analysed Control	218								na			218			Pts analysed Control

Key to methods

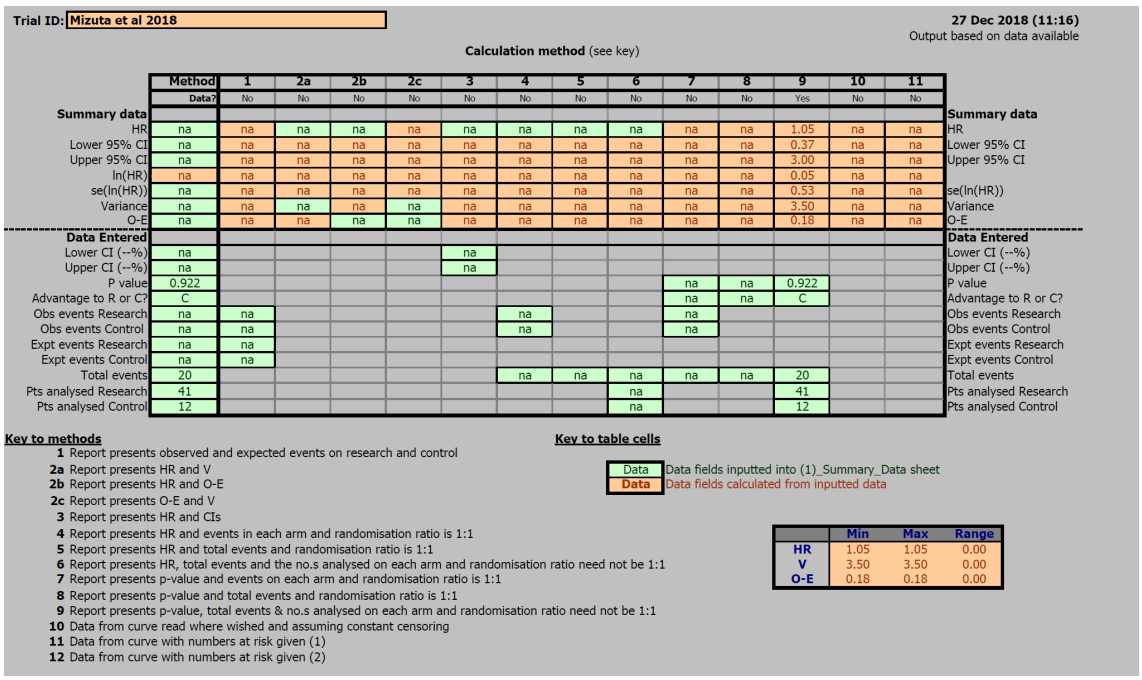
1 Report presents observed and expected events on research and control
2a Report presents HR and V
2b Report presents HR and O-E
2c Report presents O-E and V
3 Report presents HR and CIs
4 Report presents HR and events in each arm and randomisation ratio is 1:1
5 Report presents HR and total events and randomisation ratio is 1:1
6 Report presents HR, total events and the no.s analysed on each arm and randomisation ratio need not be 1:1
7 Report presents p-value and events on each arm and randomisation ratio is 1:1
8 Report presents p-value and total events and randomisation ratio is 1:1
9 Report presents p-value, total events & no.s analysed on each arm and randomisation ratio need not be 1:1
10 Data from curve read where wished and assuming constant censoring
11 Data from curve with numbers at risk given (1)
12 Data from curve with numbers at risk given (2)

Key to table cells

Data — Data fields inputted into (1)_Summary_Data sheet
Data — Data fields calculated from inputted data

	Min	Max	Range
HR	0.43	0.43	0.00
V	7.45	7.45	0.00
O-E	-6.35	-6.35	0.00

Figure A - 5. Worksheet for overall survival summary statistic calculation for Kamal et al.[120]



Trial ID: Mizuta et al 2018

27 Dec 2018 (11:16)
Output based on data available

Calculation method (see key)

	Method	1	2a	2b	2c	3	4	5	6	7	8	9	10	11	
	Data?	No	No	No	No	No	No	No	No	No	No	Yes	No	No	
Summary data															**Summary data**
HR	na	na	na	na	na	na	na	na	na	na	na	1.05	na	na	HR
Lower 95% CI	na	na	na	na	na	na	na	na	na	na	na	0.37	na	na	Lower 95% CI
Upper 95% CI	na	na	na	na	na	na	na	na	na	na	na	3.00	na	na	Upper 95% CI
ln(HR)	na	na	na	na	na	na	na	na	na	na	na	0.05	na	na	
se(ln(HR))	na	na	na	na	na	na	na	na	na	na	na	0.53	na	na	se(ln(HR))
Variance	na	na	na	na	na	na	na	na	na	na	na	3.50	na	na	Variance
O-E	na	na	na	na	na	na	na	na	na	na	na	0.18	na	na	O-E
Data Entered															**Data Entered**
Lower CI (--%)	na					na									Lower CI (--%)
Upper CI (--%)	na					na									Upper CI (--%)
P value	0.922									na	na	0.922			P value
Advantage to R or C?	C									na	na	C			Advantage to R or C?
Obs events Research	na	na					na			na					Obs events Research
Obs events Control	na	na					na			na					Obs events Control
Expt events Research	na	na													Expt events Research
Expt events Control	na	na													Expt events Control
Total events	20						na	na	na	na	na	20			Total events
Pts analysed Research	41								na			41			Pts analysed Research
Pts analysed Control	12								na			12			Pts analysed Control

Key to methods

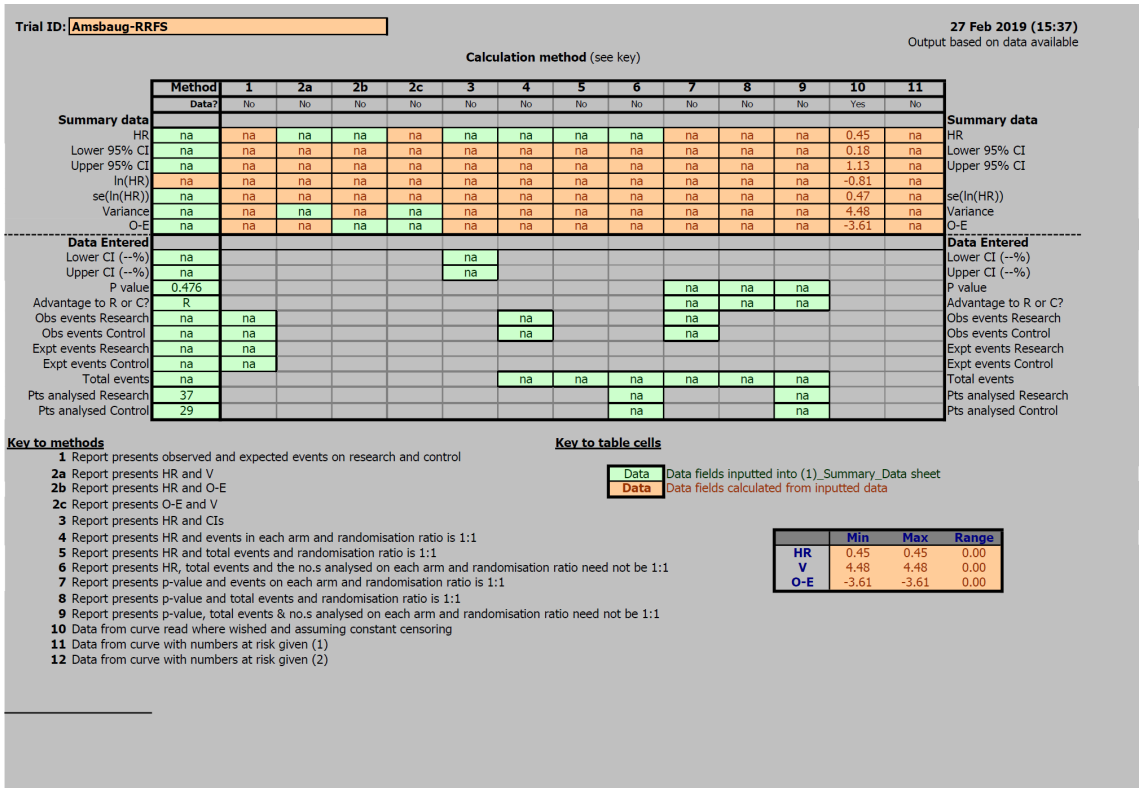
1 Report presents observed and expected events on research and control
2a Report presents HR and V
2b Report presents HR and O-E
2c Report presents O-E and V
3 Report presents HR and CIs
4 Report presents HR and events in each arm and randomisation ratio is 1:1
5 Report presents HR and total events and randomisation ratio is 1:1
6 Report presents HR, total events and the no.s analysed on each arm and randomisation ratio need not be 1:1
7 Report presents p-value and events on each arm and randomisation ratio is 1:1
8 Report presents p-value and total events and randomisation ratio is 1:1
9 Report presents p-value, total events & no.s analysed on each arm and randomisation ratio need not be 1:1
10 Data from curve read where wished and assuming constant censoring
11 Data from curve with numbers at risk given (1)
12 Data from curve with numbers at risk given (2)

Key to table cells

Data — Data fields inputted into (1)_Summary_Data sheet
Data — Data fields calculated from inputted data

	Min	Max	Range
HR	1.05	1.05	0.00
V	3.50	3.50	0.00
O-E	0.18	0.18	0.00

Figure A - 6. Worksheet for overall survival summary statistic calculation for Mizuta et al.[130]



Trial ID: Amsbaug-RRFS

27 Feb 2019 (15:37)
Output based on data available

Calculation method (see key)

	Method	1	2a	2b	2c	3	4	5	6	7	8	9	10	11	
	Data?	No	No	No	No	No	No	No	No	No	No	No	Yes	No	
Summary data															**Summary data**
HR	na	na	na	na	na	na	na	na	na	na	na	na	0.45	na	HR
Lower 95% CI	na	na	na	na	na	na	na	na	na	na	na	na	0.18	na	Lower 95% CI
Upper 95% CI	na	na	na	na	na	na	na	na	na	na	na	na	1.13	na	Upper 95% CI
ln(HR)	na	na	na	na	na	na	na	na	na	na	na	na	-0.81	na	
se(ln(HR))	na	na	na	na	na	na	na	na	na	na	na	na	0.47	na	se(ln(HR))
Variance	na	na	na	na	na	na	na	na	na	na	na	na	4.48	na	Variance
O-E	na	na	na	na	na	na	na	na	na	na	na	na	-3.61	na	O-E
Data Entered															**Data Entered**
Lower CI (--%)	na					na									Lower CI (--%)
Upper CI (--%)	na					na									Upper CI (--%)
P value	0.476									na	na	na			P value
Advantage to R or C?	R									na	na	na			Advantage to R or C?
Obs events Research	na	na					na			na					Obs events Research
Obs events Control	na	na					na			na					Obs events Control
Expt events Research	na	na													Expt events Research
Expt events Control	na	na													Expt events Control
Total events	na						na	na	na	na	na	na			Total events
Pts analysed Research	37								na			na			Pts analysed Research
Pts analysed Control	29								na			na			Pts analysed Control

Key to methods

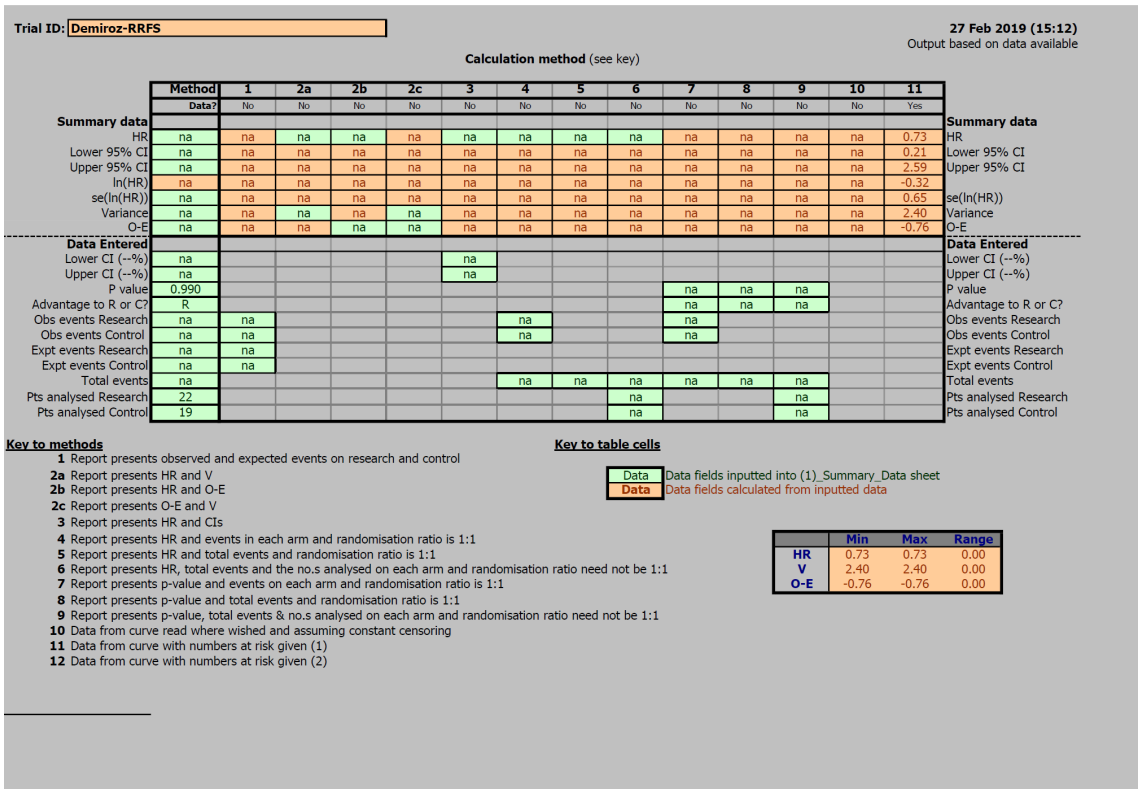
1 Report presents observed and expected events on research and control
2a Report presents HR and V
2b Report presents HR and O-E
2c Report presents O-E and V
3 Report presents HR and CIs
4 Report presents HR and events in each arm and randomisation ratio is 1:1
5 Report presents HR and total events and randomisation ratio is 1:1
6 Report presents HR, total events and the no.s analysed on each arm and randomisation ratio need not be 1:1
7 Report presents p-value and events on each arm and randomisation ratio is 1:1
8 Report presents p-value and total events and randomisation ratio is 1:1
9 Report presents p-value, total events & no.s analysed on each arm and randomisation ratio need not be 1:1
10 Data from curve read where wished and assuming constant censoring
11 Data from curve with numbers at risk given (1)
12 Data from curve with numbers at risk given (2)

Key to table cells

Data — Data fields inputted into (1)_Summary_Data sheet
Data — Data fields calculated from inputted data

	Min	Max	Range
HR	0.45	0.45	0.00
V	4.48	4.48	0.00
O-E	-3.61	-3.61	0.00

Figure A - 7. Worksheet for regional relapse free survival summary statistic calculation for Amsbaugh et al.[88]



Trial ID: Demiroz-RRFS

27 Feb 2019 (15:12)
Output based on data available

Calculation method (see key)

	Method	1	2a	2b	2c	3	4	5	6	7	8	9	10	11	
	Data?	No	No	No	No	No	No	No	No	No	No	No	No	Yes	
Summary data															**Summary data**
HR	na	na	na	na	na	na	na	na	na	na	na	na	na	0.73	HR
Lower 95% CI	na	na	na	na	na	na	na	na	na	na	na	na	na	0.21	Lower 95% CI
Upper 95% CI	na	na	na	na	na	na	na	na	na	na	na	na	na	2.59	Upper 95% CI
ln(HR)	na	na	na	na	na	na	na	na	na	na	na	na	na	-0.32	
se(ln(HR))	na	na	na	na	na	na	na	na	na	na	na	na	na	0.65	se(ln(HR))
Variance	na	na	na	na	na	na	na	na	na	na	na	na	na	2.40	Variance
O-E	na	na	na	na	na	na	na	na	na	na	na	na	na	-0.76	O-E
Data Entered															**Data Entered**
Lower CI (--%)	na					na									Lower CI (--%)
Upper CI (--%)	na					na									Upper CI (--%)
P value	0.990									na	na	na			P value
Advantage to R or C?	R									na	na	na			Advantage to R or C?
Obs events Research	na	na					na			na					Obs events Research
Obs events Control	na	na					na			na					Obs events Control
Expt events Research	na	na													Expt events Research
Expt events Control	na	na													Expt events Control
Total events	na						na	na	na	na	na	na			Total events
Pts analysed Research	22								na			na			Pts analysed Research
Pts analysed Control	19								na			na			Pts analysed Control

Key to methods

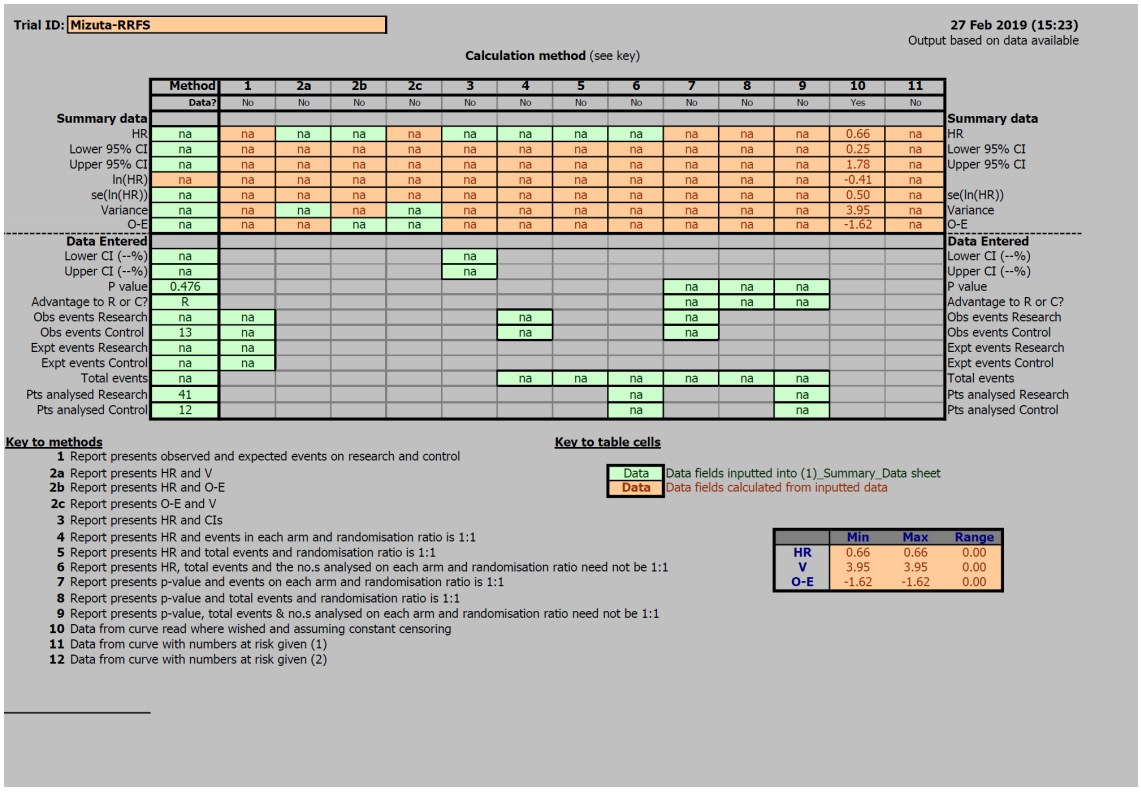
1 Report presents observed and expected events on research and control
2a Report presents HR and V
2b Report presents HR and O-E
2c Report presents O-E and V
3 Report presents HR and CIs
4 Report presents HR and events in each arm and randomisation ratio is 1:1
5 Report presents HR and total events and randomisation ratio is 1:1
6 Report presents HR, total events and the no.s analysed on each arm and randomisation ratio need not be 1:1
7 Report presents p-value and events on each arm and randomisation ratio is 1:1
8 Report presents p-value and total events and randomisation ratio is 1:1
9 Report presents p-value, total events & no.s analysed on each arm and randomisation ratio need not be 1:1
10 Data from curve read where wished and assuming constant censoring
11 Data from curve with numbers at risk given (1)
12 Data from curve with numbers at risk given (2)

Key to table cells

Data — Data fields inputted into (1)_Summary_Data sheet
Data — Data fields calculated from inputted data

	Min	Max	Range
HR	0.73	0.73	0.00
V	2.40	2.40	0.00
O-E	-0.76	-0.76	0.00

Figure A - 8. Worksheet for regional relapse free survival summary statistic calculation for Demiroz et al.[126]



Trial ID: Mizuta-RRFS

27 Feb 2019 (15:23)
Output based on data available

Calculation method (see key)

	Method	1	2a	2b	2c	3	4	5	6	7	8	9	10	11	
	Data?	No	No	No	No	No	No	No	No	No	No	No	Yes	No	
Summary data															**Summary data**
HR	na	na	na	na	na	na	na	na	na	na	na	na	0.66	na	HR
Lower 95% CI	na	na	na	na	na	na	na	na	na	na	na	na	0.25	na	Lower 95% CI
Upper 95% CI	na	na	na	na	na	na	na	na	na	na	na	na	1.78	na	Upper 95% CI
ln(HR)	na	na	na	na	na	na	na	na	na	na	na	na	-0.41	na	
se(ln(HR))	na	na	na	na	na	na	na	na	na	na	na	na	0.50	na	se(ln(HR))
Variance	na	na	na	na	na	na	na	na	na	na	na	na	3.95	na	Variance
O-E	na	na	na	na	na	na	na	na	na	na	na	na	-1.62	na	O-E
Data Entered															**Data Entered**
Lower CI (--%)	na					na									Lower CI (--%)
Upper CI (--%)	na					na									Upper CI (--%)
P value	0.476									na	na	na			P value
Advantage to R or C?	R									na	na	na			Advantage to R or C?
Obs events Research	na	na					na			na					Obs events Research
Obs events Control	13	na					na			na					Obs events Control
Expt events Research	na	na													Expt events Research
Expt events Control	na	na													Expt events Control
Total events	na						na	na	na	na	na	na			Total events
Pts analysed Research	41								na			na			Pts analysed Research
Pts analysed Control	12								na			na			Pts analysed Control

Key to methods

1 Report presents observed and expected events on research and control
2a Report presents HR and V
2b Report presents HR and O-E
2c Report presents O-E and V
3 Report presents HR and CIs
4 Report presents HR and events in each arm and randomisation ratio is 1:1
5 Report presents HR and total events and randomisation ratio is 1:1
6 Report presents HR, total events and the no.s analysed on each arm and randomisation ratio need not be 1:1
7 Report presents p-value and events on each arm and randomisation ratio is 1:1
8 Report presents p-value and total events and randomisation ratio is 1:1
9 Report presents p-value, total events & no.s analysed on each arm and randomisation ratio need not be 1:1
10 Data from curve read where wished and assuming constant censoring
11 Data from curve with numbers at risk given (1)
12 Data from curve with numbers at risk given (2)

Key to table cells

Data — Data fields inputted into (1)_Summary_Data sheet
Data — Data fields calculated from inputted data

	Min	Max	Range
HR	0.66	0.66	0.00
V	3.95	3.95	0.00
O-E	-1.62	-1.62	0.00

Figure A - 9. Worksheet for regional relapse free survival summary statistic calculation for Mizuta et al.[130]