Factors affecting surgical mortality of oral squamous cell carcinoma resection

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Australian Safety and Efficacy Register of New Interventional Procedures-Surgical

ABSTRACT

Survival rates for oral cancer showed minimal improvement in six decades, improving surgical outcomes could be an avenue to reduce mortality. This thesis seeks to identify the causes of surgical mortalities, evaluate the factors involved and determine if there are any modifiable risks that could be targeted to reduce the mortality in the post-operative period.

The systematic review found that there is a paucity of existing knowledge on the factors affecting surgical mortality of oral squamous cell carcinoma. While there were two studies included, only one had detailed characteristics on the patients who died after the operation. A population level study illustrated that factors such as advanced age, an increased Charlson Comorbidity Index score, T classification had statistical significance in increasing the risk of surgical mortality, and the risk increases if these factors were combined.

Analysis of data from the Australian and New Zealand Audit of Surgical Mortality (ANZASM) found that many of the preventable deaths were related to poor patient selection. The surgeons and assessors felt that these patients had very high pre-operative risk due to various factors such as advanced age, co-existing systemic illnesses such are cardiac and respiratory conditions and advanced malignancy.

Changes could be made to ANZASM to improve the results for analysis. Further population analysis and establishment of an externally validated model to assess risk stratification will allow surgeons to make better decisions around patient selection and reduce avoidable surgical mortalities.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, 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 in my name, 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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I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Yi Long Roy Ong

December 2020

Publications

Work presented in this thesis includes the contributions of persons involved in the following multi-authored publications included in the thesis:

1. Factors affecting surgical mortality of oral squamous cell carcinoma resection: a systematic review

   65%: Yi Long Roy Ong – Formulation of research question

   20%: David Tivey – formulation of research question, manuscript revision

   5% Guy Maddern – manuscript revision

   5%: Paul Sambrook – manuscript revision

   2.5%: Lucy Huang – second reviewer

   2.5%: Ning Ma – Analysis of statistical process

   Ong YLR, Tivey D, Huang L, Sambrook P, Maddern G. Factors affecting surgical mortality of oral squamous cell carcinoma resection. International Journal of Oral and Maxillofacial Surgery. 2020 Aug 7.

2. Oral squamous cell carcinoma resection and neck dissection: a 10 year national audit study

   80%: Yi Long Roy Ong – Formulation of research question

   10% Guy Maddern – manuscript revision

   7.5%: Paul Sambrook – manuscript revision

   2.5%: Ryan Maloney – Data extraction

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STATEMENTS OF AUTHORSHIP

INTERNATIONAL JOURNAL OF ORAL & MAXILLOFACIAL SURGERY

CONFIRMATION OF AUTHORSHIP FORM

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"I warrant that all the authors listed above have made a significant contribution to this manuscript and have agreed to its submission to the IJOMS".

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Contribution to the Paper	Conceptualisation (equal); formal analysis (lead); funding acquisition (lead); investigation (lead); methodology (equal); visualisation (lead); writing – original draft preparation (lead); writing – review & editing (lead)		
Overall percentage (%)	80		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	1 December 2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Paul Sambrook		
Contribution to the Paper	Conceptualisation (equal); Supervision (support); writing – review & editing (support)		
Signature		Date	1st December 2020

Name of Co-Author	Guy Maddern
Contribution to the Paper	Conceptualisation (equal); data curation (lead); methodology (equal); project administration (lead); resources (lead); supervision (lead); writing – review & editing (support)
Signature	

Please cut and paste additional co-author pa

Dedication

This thesis is dedicated to my wife, Margaret, my parents and sister for their unconditional love and support in my academic endeavours.

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First and foremost, I would like to express my greatest appreciation to Professor Guy Maddern for giving me the opportunity to undertake an incredible journey at the Department of Surgery, The Queen Elizabeth Hospital, The University of Adelaide. Your charisma, wisdom, and leadership continue to inspire me. Thank you for always keeping your doors open for me.

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Staff members from Australia and New Zealand Audit of Surgical Mortality (ANZASM) including Dr Helena Kopunic and Dr Ryan Maloney, thank you for your hard work in assisting me in my requests for processing and extracting the data to make this research possible.

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CHAPTER 1 – INTRODUCTION

Head and neck cancer is the seventh most frequent type of cancer by incidence and ninth most common cause of cancer death according to the World Health Organization (WHO). [1] These related cancers involve the oral cavity, pharynx (which includes the oropharynx, nasopharynx, hypopharynx), and larynx. Most tumours, especially the ones involving the oral cavity, are squamous cell carcinomas (OSCC). [2]

The five-year survival rate for cancers of the tongue, oral cavity and oropharynx were reported to be around 50% or less, and this showed minimal improvement since studies from the 1960s. [2, 3] Can reducing surgical mortality be an avenue to improve the overall survival? The worst outcome of surgical intervention is the death of the patient during the post-operative rehabilitation. Indeed, the 30-day post-operative mortality rates are variable and range from 2.6% in Brazil for oral and oropharyngeal surgery [4] to 8% for all post head and neck cancer surgeries in the USA. [5] These values may not accurately reflect the true mortality of oral squamous cell carcinoma resections as it includes other head and neck cancer procedures.

There are multiple factors that may contribute to these deaths. This thesis seeks to identify the causes of mortalities, evaluate the factors involved and determine if there are any modifiable risks that could be targeted to reduce the mortality in the post-operative period. This was approached by using a systematic review to identify existing knowledge in the international literature, and a review of all the related deaths that occurred in Australia over the past ten years. Analysis of the combined data will determine whether the factors identified in Australia are similar to those reported in other parts of the world.

CHAPTER 2 – FACTORS AFFECTING SURGICAL MORTALITY OF ORAL SQUAMOUS CELL CARCINOMA RESECTION: PROTOCOL FOR A SYSTEMATIC REVIEW

Based on the preliminary literature review, surgical mortalities were often reported in groups comprising different head and neck cancer procedures. [4, 5] This is not an accurate representation of the surgical mortality of oral squamous cell carcinoma as the surgical approach and complications for other head and neck cancer sites varies due to their anatomical differences and pathological processes. For example, in oropharyngeal cancer, unlike oral cancer resection, has an increasing use of transoral robotic surgery, [6] and human papilloma virus was found to be involved in certain groups. [7] Further, lip cancer, while categorised by the World Health Organisation in the same group as oral cavity cancer, [8] has different risk factors comparted to oral cavity, especially in the context of ultraviolet exposure. [9] The approach for resection is also different as it is conducted extra-orally, sometimes with a V or W type resection, with minimal airway risk. [10] Hence, to limit cofounders, it was decided to focus the Systematic Review on surgical resection for oral cavity squamous cell carcinoma, defined anatomically as posterior to the lip and anterior to the tonsils.

This protocol was written in accordance Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, the current gold standard of systematic review design at the time of writing. [11] And registered in The International Prospective Register of Systematic Reviews (PROSPERO). [12] The aim of this protocol is to guide the systematic review as part of an in-depth literature search of the existing knowledge on surgical mortality from oral squamous cell carcinoma resection and the factors surrounding the deaths.

Below was the protocol used for conducting the systematic review on the topic.

Factors affecting surgical mortality of oral squamous cell carcinoma resection: Protocol for a systematic review

Administrative Information

Registration

In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO). Registration number CRD42020150310.

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Contributions

Ong is the primary researcher. Tivey advised on the search strategy and systematic review process. Maddern and Sambrook acted as the supervisor for Ong and contributed in the development of the research question, selection criteria, risk of bias assessment strategy, and data extraction criteria. Sambrook provided expertise on oral squamous cell carcinoma. All authors read, provided feedback and approved the final manuscript.

Amendments

Nil

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Abstract

Background

Head and neck cancers are a related group of cancers that involve the oral cavity, pharynx (which includes oropharynx, nasopharynx, hypopharynx), and larynx. Most tumours, especially the ones involving the oral cavity, are squamous cell carcinomas.

Oral squamous cell carcinoma is a significant public health issue, but literature review had revealed scarce information on the factors surrounding deaths after operative intervention. The quoted mortality rate is low at approximately 2-3%, and there were few existing studies that explore and draw conclusions on the factors surrounding these deaths. This systematic review aims to identify these factors and explore changes that can be put in place to reduce the mortality.

Methods/Design

Electronic databases will be systematically searched for publications in English that examine the factors affecting in-hospital and 30-day mortality of patients after surgery for oral squamous cell carcinoma. Screening of both titles and abstracts will be done by two independent reviewers. All disagreements will be resolved by an independent third reviewer. Data analysis will be completed and reported in a narrative review.

Discussion

A scoping search identied studies that explored factors contributing to surgical mortality confirming the viability of this systematic review. This systematic review will allow identification and prevention of factors that may improve the 30-day post surgery survival of OSCC patients.

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1. Introduction

1.1. Rationale

Head and neck cancers are a related group of cancers that involve the oral cavity, pharynx (which includes oropharynx, nasopharynx, hypopharynx), and larynx. Most tumours, especially the ones involving the oral cavity, are squamous cell carcinomas.

Head and neck cancer is the seventh most frequent type of cancer by incidence and ninth most common cause of cancer death according to the World Health Organization (WHO).[1] Further the WHO in 2012 estimated that 529,000 new cases occurred worldwide, with 292,000 deaths.

Many patients treated for oral cancer have to cope with devastating consequences for their treatment, including difficulties with eating, drinking, swallowing and speaking. Despite advances in reconstructive techniques, many patients suffer from poor aesthetic outcomes post-surgery. These issues lead to mental health problems such as depression and nutritional deficiencies from poor oral intake.[2-4]

The five-year survival rate for cancers of the tongue, oral cavity and oropharynx are around 50%, and the survival rates for oral cancer in the UK have not shown any improvement over three decades from 2009.[5] Complications from their surgery account for a proportion of these cancer-related deaths. A study from Brazil which looked at oral and oropharyngeal surgery found the surgical mortality rate to be 2.6%.[6] Further a study conducted in the United States reported a higher estimated of 5 to 8% for the 30-day mortality for all post head and neck cancer surgeries.[7] There are multiple factors that may contribute to these deaths, review of current literature may assist in identifying the preventable causes and reduce the mortality rate.

A literature search on multiple databases including PubMed, EMBASE, Cochrane Library and PROSPERO revealed that while many studies report the mortality rates, few examined the factors contributing to surgical death. Further, the initial search did not identify recent systematic reviews on the topic.

This systematic review explores the factors affecting surgical mortality in oral squamous cell carcinoma (OSCC) patients, to identify features to improve survival of this population of patients.

1.2. Objectives

This systematic review aims to evaluate the factors affecting surgical mortality of patients who underwent OSCC resection. To this end the systematic review will answer the following questions:

1. What are the causes of mortality?
2. What are the factors that increase the risk of mortality?
3. Which are the modifiable and non-modifiable risk factors?
4. Are there recommendations that can be put in place to reduce the mortality rate?

2. Assessment Methodology

2.1. Eligibility criteria

The following criteria define the selection criteria for the inclusion of studies.

Study Designs

Eligible study designs include systematic reviews, meta-analyses, randomised control trials, prospective and retrospective cohort studies, case-control studies, cross-sectional studies, observation studies, case series and case studies.

Participants

The general adult human population is the participant of interest. Studies that include both adults and children will be considered if data provided for adults are reported separately.

Interventions

Of interest are patients who have received surgical resection of squamous cell carcinoma from the oral cavity. The oral cavity includes structures posterior to the lip and anterior to the tonsils. Surgical procedures include simple tissue excisions, glossectomies, partial glossectomies, maxillectomies, partial maxillectomies, mandibulectomies and hemi-mandibulectomies. Studies that include lymph node excision and neck dissections will be considered if oral resections were performed in the same surgery.

Outcomes

The outcome is surgical mortality, where death is recorded as a direct result of the surgery or a surgical related complication.

Timing

To ensure that review focuses on surgical related deaths, only deaths that occurred in hospital or within 30 days of the surgery will be included.

Setting

There will be no restrictions by type of setting.

Language

Only articles in English will be included.

2.2. Information sources

The primary information sources are the PubMed, EMBASE and Cochrane Library databases

2.3. Search Strategy

Quantitative studies will be sought. No study design limits will be imposed. Results will be limited by English language, human subjects and published in the last 10 years.

The specific search strategies will be created in discussion with a Health Science Librarian and a research manager with expertise in systematic review searching. Literature search strategies will be developed using medical subject headings (MeSH), Emtree terms and text words related to factors affecting surgical mortality of OSCC.

The search strategy will then be evaluated using the PRESS (Peer Review of Electronic Search Strategies) standard. A sample search strategy for PubMed is included in appendix 1.

To ensure literature saturation, we will scan the reference lists of the included studies or relevant reviews identified through the search.

2.4. Study Records

2.4.1. Data Management

Duplicates originating from different databases will be removed using both EndNote before exporting citation to Rayyan QCRI (Qatar Computing Research Institute).[8] Rayyan QCRI is a web-based software programme that facilitates collaboration among reviewers during the study selection process. Before the formal screening process, a calibration exercise will be undertaken to pilot and refine the screening questions.

2.4.2. Selection process

The two review authors will independently screen the titles and abstracts yielded by the search against the inclusion criteria. The screening process will be blinded; then the results will be revealed and compared. Full reports will be obtained for all the titles that appear to meet the inclusion criteria or where there is any uncertainty. Review authors will then screen the full text reports to discuss and decide again whether these meet the inclusion criteria. Additional information from study authors will be sought where necessary to resolve questions about eligibility. A discussion will be made to settle any disagreements. Reasons for excluding trials will be recorded. Neither of the review authors will be blind to the journal titles or to the study authors or institutions.

2.4.3. Data collection process

To ensure consistency across reviewers, calibration exercises will be conducted before starting the review. Quantitative data will be included. The Microsoft Excel programme will be used to collate the data. Reviewers will resolve disagreements by discussion, and one arbitrator who may be the supervisor of the review will decide unresolved disputes. Study authors will be contacted to resolve any uncertainties.

2.5. Data Items

Data abstractions will include demographic information including age, gender, risk factors including smoking, alcohol intake, co-morbidities including existing cardiorespiratory conditions and diabetes, diagnosis including area and extent of OSCC and lymph node involvement, intervention including the surgery performed, post-operative conditions including infection, bleeding and cause of mortality.

2.6. Outcomes and prioritisations

This systematic review is not aimed to compare outcomes. The outcome of interest is surgical mortality. Which may be explicitly defined in the report, or maybe in-hospital or 30-day mortality post-surgery.

2.7. Risk of bias in individual studies

To assess the risk of bias for each study, critical appraisal tools appropriate for the study design will be used.

A measurement tool to assess systematic reviews (AMSTAR 2) will be used for systematic review.[9] The instrument is included in the appendix 2 for reference. This updated tool is based on a widely used AMSTAR from 2007.[10] This tool consists of 10 domains and 16 questions.

Cochrane risk of bias tool will be used for randomised control trials.[11] This tool assesses 6 souces of bias. The instrument is included in the appendix 3 for reference.

Methodological index for non-randomized studies (MINORS) will be used to assess observational or non-randomised studies.[12] This contains 12 items, first eight being specifically for non-comparative studes. The instrument is included in appendix 4 for reference.

A case series studies quality appraisal checklist using a modified Delphi techinique developed by the Institute of Health Economics (IHE) will be used to assess case reports and case series.[13, 14] The checklist is included in appendix 5 for reference.

Apprasials will be made independently by two review authors. Disagreements will be resolved first by discussion and then by consulting a third author for arbitration.

2.8. Data Synthesis

2.8.1. Criteria

If studies are sufficiently homogenous in terms of design and comparator, we will conduct meta-analysis using either a random-effects model, fixed-effects model or mixed-effects model.

2.8.2. Planned summary measures

Dichotomous data (e.g. occurrence of cardiorespiratory event leading to mortality) will be determined by using risk ratio (RR) with 95% confidence interval (CI).

Continuous data will be summarised using standardised mean difference with associated distribution or error (SD or SEM).

2.8.3. Dealing with missing data

When there are missing data, we will attempt to contact the original authors of the study to obtain the relevant missing data.

2.8.4. Assessment of heterogenicity

If meta analysis is possible, statistical heterogeneity will be performed. The clinical heterogeneity will be tested by considering the variability in study design, patient population, surgical intervention and outcome definition (e.g. in-hospital mortality, 30-day mortality). Statistical heterogeneity will be testing using the I^2 statistic. Percentages of around 25% (I^2 = 25), 50% (I^2 = 50), and 75% (I^2 = 75) would mean low, medium, and high heterogeneity, respectively.[15] If high levels of heterogeneity among the trails exist (I^2>=50%) Explanation of the source of heterogeneity by subgroup analysis or sensitivity analysis will be made.

2.8.5. Data synthesis

Values will be combined and calculated using Microsoft Excel and/or the statistical software R.

2.8.6. Additional analyses

Subgroup analysis will be used to explore possible sources of heterogeneity, based on the following:

- Patient demographics
  - Age
  - Gender
- Types of treatment/surgery

- Types of complications/cause of death

Sensitivity analysis will be performed in order to explore the source of heterogeneity as follows:

- Quality components, including full-text publications versus abstracts, preliminary results versus mature results, published versus unpublished data
- Risk of bias (by omitting studies that are judged to be at high risk of bias).

2.8.7. Type of summary planned if meta-analysis is not possible.

A text and tables format will be adopted to summarise and explain the characteristics and findings of the included studies. The narrative synthesis will explore the relationship and findings both within and between the included studies.

2.9. Meta-bias

The ROBIS tool[16] will be used to assess bias in the systematic review process. This involves 3 phases: Assessing relevance, identifying concerns about bias in the review process and judge risk of bias in the review. The second phase, identifying concerns about bias in the review process consists of 4 domains to cover key review processes: study eligibility criteria; identification and selection of studies; data collection and study appraisal; and synthesis and findings.

2.10. Confidence in cumulative evidence

The quality of evidence for all outcomes will be judged using the Grading of Recommendations Assessment, Development and Evaluations (GRADE) working group methodology.[17] The quality of evidence will be assessed across the domains of risk of bias, consistency, directness, precision and publication bias. Additional domains may be considered where appropriate. Quality will be adjudicated as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or very low (very uncertain about the estimate of effect).

3. Discussion

Oral squamous cell carcinoma is a significant public health issue with high prevalence, incidence and mortality worldwide. With poor 5-year survival rates[5], and 30 day mortality ranging from 2.6% to 8%[6, 7], there is a need to review the literature to determine whether all preventable causes had been identified and actions were taken to control them.

As surgical resection is one of the first line treatment option, improvement of surgical mortality is an avenue to improve survival rates.

A scoping search identied studies that explored factors contributing to surgical mortality confirming the viability of this systematic review. This systematic review will allow identification and prevention of factors that may improve the 30-day post surgery survival of OSCC patients.

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Appendix 1 – Search Strategy

Search strategy

5 main concepts in logic grid using PICO question

1. Problem
    a. Diagnosis
    b. Location/anatomy
2. Intervention
    a. Surgery
3. Comparison, control or comparator
    a. none
4. Outcome
    a. Surgical mortality
5. Others
    a. 10 year limit
    b. English language
    c. Human studies

Problem – diagnosis	Problem – Anatomy	Intervention	Outcome	Others
Squamous-Cell-Carcinoma and other associated Mesh terms for Pubmed and Emtee terms for Embase and synonyms	**Oral cavity** and associated Mesh terms for Pubmed and Emtee terms for Embase and synonyms	**Surgery** and associated Mesh terms for Pubmed and Emtee terms for Embase and synonyms	**Surgical Mortality** and associated Mesh terms for Pubmed and Emtee terms for Embase and synonyms	10 year limit AND English Language AND Human Studies

Pubmed

Search Pubmed using Medical Subject Heading (MeSH) terms. MeSH term will also be searched in text words [tw] field tag. Text words includes all words and numbers in the title, abstract, other abstract, MeSH terms, MeSH Subheadings, Publication Types, Substance Names, Personal Name as Subject, Corporate Author, Secondary Source, Comment/Correction Notes, and Other Terms.

MeSH associated entry terms to find synonyms. Look for more synonyms using Embase emtree and associated synonyms. Only relevant synonyms will be included. Synonyms will be searched with text word [tw] field tag. Pubmed only allows truncation at the end of the word or phrase and do not have proximity operators and terms will be searched according to these limitations. Procedure for performing phrase searches will be made in the following steps:

1. Truncating the final term
2. Joining terms with a hypen
3. Enclosing phrase in double quotes
4. Using a field tag

Boolean operator "OR" will be used within each search concept as described above and Boolean operator "AND" will be used between each search concept.

Problem – Diagnosis, squamous cell carcinoma - 165 265 results

("Carcinoma, Squamous Cell"[Mesh] OR "Neoplasms, Squamous Cell"[Mesh] OR carcinoma[tw] OR carcinomas[tw] OR cancer[tw] OR cancers[tw] OR tumor[tw] OR tumors[tw] OR tumour[tw] OR tumours[tw] OR neoplasm[tw] OR neoplasms[tw] OR malignant[tw] OR malignancy[tw] OR malignancies[tw] OR epithelioma[tw])

AND

(squamous-cell[tw] OR epidermoid[tw] OR prickle-cell[tw] OR planocellular[tw] OR squamous-epithelium[tw])

Problem – Anatomy, Oral Cavity - 1 129 992 results

“Mouth”[Mesh] OR mouth[tw] OR Oral[tw] OR intraoral[tw] OR

Tongue[tw] OR lingual[tw] OR

Palate[tw] OR palatal[tw] OR

Uvula[tw] OR

“Gingiva”[Mesh] OR gingiva[tw] OR gingival[tw] OR gum[tw] OR gums[tw] OR interdental-papilla[tw] OR

“Cheek”[Mesh] OR Cheek[tw] OR Buccal[tw] OR

"Maxilla"[Mesh] OR maxilla[tw] OR maxillae[tw] OR maxillary[tw] OR

“Mandible”[Mesh] OR mandible[tw] OR mandibular[tw] OR maxillomandibular[tw] OR maxillo-mandibular[tw]

Intervention – Surgery 5 052 408

“Surgical Procedures, Operative”[Mesh] OR “Surgery, Oral”[Mesh] OR surgery[tw] OR surgeries[tw] OR surgical[tw] OR operation[tw] OR operations[tw] OR operative[tw] OR procedure[tw] OR procedures[tw] OR resect[tw] OR resection[tw] OR resections[tw] OR reconstruct[tw] OR reconstruction[tw] OR reconstructions[tw] OR reconstructive[tw] OR flap[tw] OR flaps[tw] OR maxillofacial[tw] OR

Glossectom*[tw] OR maxillectom*[tw] OR maxillactom*[tw] OR maxillotom*[tw] OR mandibulectom*[tw] OR mandibulotom*[tw] OR hemi-mandibulectom*[tw] OR hemimandibulectom*[tw] OR osteotom*[tw]

Outcomes- Surgical Mortality - 95 278 results

"hospital mortality"[Mesh] OR surgical-mortality[tw] OR operation-mortality[tw] OR operative-mortality[tw] OR postoperative-mortality[tw] OR surgery-mortality[tw] OR hospital-mortality[tw] OR inhospital-mortality[tw] OR in-hospital-mortality[tw] OR inhouse-mortality[tw] OR in-house-mortality[tw] OR 30day-mortality[tw] OR 30-day-mortality[tw] OR thirty-day-mortality[tw] OR surgical-mortalities[tw] OR operation-mortalities[tw] OR operative-mortalities[tw] OR postoperative-mortalities[tw] OR surgery-mortalities[tw] OR hospital-mortalities[tw] OR inhospital-mortalities[tw] OR in-hospital-mortalities[tw] OR inhouse-mortalities[tw] OR in-house-mortalities[tw] OR 30day-mortalities[tw] OR 30-day-mortalities[tw] OR thirty-day-mortalities[tw] OR surgical-death[tw] OR operation-death[tw] OR operative-death[tw] OR postoperative-death[tw] OR surgery-death[tw] OR hospital-death[tw] OR inhospital-death[tw] OR in-hospital-death[tw] OR inhouse-death[tw] OR in-house-death[tw] OR 30day-death[tw] OR 30-day-death[tw] OR thirty-day-death[tw] OR surgical-deaths[tw] OR operation-deaths[tw] OR operative-deaths[tw] OR postoperative-deaths[tw] OR surgery-deaths[tw] OR hospital-deaths[tw] OR inhospital-deaths[tw] OR in-hospital-deaths[tw] OR inhouse-deaths[tw] OR in-house-deaths[tw] OR 30day-deaths[tw] OR 30-day-deaths[tw] OR thirty-day-deaths[tw] OR surgical-fatality[tw] OR operation-fatality[tw] OR operative-fatality[tw] OR postoperative-fatality[tw] OR surgery-fatality[tw] OR hospital-fatality[tw] OR inhospital-fatality[tw] OR in-hospital-fatality[tw] OR inhouse-fatality[tw] OR in-house-fatality[tw] OR 30day-fatality[tw] OR 30-day-fatality[tw] OR thirty-day-fatality[tw] OR surgical-fatalities[tw] OR operation-fatalities[tw] OR operative-fatalities[tw] OR postoperative-fatalities[tw] OR surgery-fatalities[tw] OR hospital-fatalities[tw] OR inhospital-fatalities[tw] OR in-hospital-fatalities[tw] OR inhouse-fatalities[tw] OR in-house-fatalities[tw] OR 30day-fatalities[tw] OR 30-day-fatalities[tw] OR thirty-day-fatalities[tw]

Other – 10 years, English, not animals or plants 8 354 007 Results

"2009/05/11"[PDat] : "2019/05/08"[PDat]
AND
English[lang]
NOT
((animals [MH] OR plants [MH]) NOT humans [MH])
NOT
((animals [tw] OR plants [tw]) NOT humans [tw])

Combined all of above – 19 results

((((("Carcinoma, Squamous-Cell"[Mesh] OR "Neoplasms, Squamous Cell"[Mesh] OR carcinoma[tw] OR carcinomas[tw] OR cancer[tw] OR cancers[tw] OR tumor[tw] OR tumors[tw] OR tumour[tw] OR tumours[tw] OR neoplasm[tw] OR neoplasms[tw] OR malignant[tw] OR malignancy[tw] OR malignancies[tw] OR epithelioma[tw]) AND (squamous-cell[tw] OR epidermoid[tw] OR prickle-cell[tw] OR planocellular[tw] OR squamous-epithelium[tw]))) AND ("Mouth"[Mesh] OR mouth[tw] OR Oral[tw] OR intraoral[tw] OR "Tongue"[Mesh] OR Tongue[tw] OR lingual[tw] OR "Palate"[Mesh] OR Palate[tw] OR palatal[tw] OR "Uvula"[Mesh] OR uvula[tw] OR "Cheek"[Mesh] OR Cheek[tw] OR Buccal[tw] OR "Gingiva"[Mesh] OR gingiva[tw] OR gingival[tw] OR gum[tw] OR gums[tw] OR interdental-papilla[tw] OR "Maxilla"[Mesh] OR maxilla[tw] OR maxillae[tw] OR maxillary[tw] OR "Mandible"[Mesh] OR mandible[tw] OR mandibular[tw] OR maxillomandibular[tw] OR maxillo-mandibular[tw])) AND ("Surgical Procedures, Operative"[Mesh] OR "Surgery, Oral"[Mesh] OR surgery[tw] OR surgeries[tw] OR surgical[tw] OR operation[tw] OR operations[tw] OR operative[tw] OR procedure[tw] OR procedures[tw] OR resect[tw] OR resection[tw] OR resections[tw] OR reconstruct[tw] OR reconstruction[tw] OR reconstructions[tw] OR reconstructive[tw] OR flap[tw] OR flaps[tw] OR maxillofacial[tw] OR Glossectom*[tw] OR maxillectom*[tw] OR maxillactom*[tw] OR maxillotom*[tw] OR mandibulectom*[tw] OR mandibulotom*[tw] OR hemi-mandibulectom*[tw] OR hemimandibulectom*[tw] OR osteotom*[tw])) AND ("hospital mortality"[Mesh] OR surgical-mortality[tw] OR operation-mortality[tw] OR operative-mortality[tw] OR postoperative-mortality[tw] OR surgery-mortality[tw] OR hospital-mortality[tw] OR inhospital-mortality[tw] OR in-hospital-mortality[tw] OR inhouse-mortality[tw] OR in-house-mortality[tw] OR 30day-mortality[tw] OR 30-day-mortality[tw] OR thirty-day-mortality[tw] OR surgical-mortalities[tw] OR operation-mortalities[tw] OR operative-mortalities[tw] OR postoperative-mortalities[tw] OR surgery-mortalities[tw] OR hospital-mortalities[tw] OR inhospital-mortalities[tw] OR in-hospital-mortalities[tw] OR inhouse-mortalities[tw] OR in-house-mortalities[tw] OR 30day-mortalities[tw] OR 30-day-mortalities[tw] OR thirty-day-mortalities[tw] OR surgical-death[tw] OR operation-death[tw] OR operative-death[tw] OR postoperative-death[tw] OR surgery-death[tw] OR hospital-death[tw] OR inhospital-death[tw] OR in-hospital-death[tw] OR inhouse-death[tw] OR in-house-death[tw] OR 30day-death[tw] OR 30-day-death[tw] OR thirty-day-death[tw] OR surgical-deaths[tw] OR operation-deaths[tw] OR operative-deaths[tw] OR postoperative-deaths[tw] OR surgery-deaths[tw] OR hospital-deaths[tw] OR inhospital-deaths[tw] OR in-hospital-deaths[tw] OR inhouse-deaths[tw] OR in-house-deaths[tw] OR 30day-deaths[tw] OR 30-day-deaths[tw] OR thirty-day-deaths[tw] OR surgical-fatality[tw] OR operation-fatality[tw] OR operative-fatality[tw] OR postoperative-fatality[tw] OR surgery-fatality[tw] OR hospital-fatality[tw] OR inhospital-fatality[tw] OR in-hospital-fatality[tw] OR inhouse-fatality[tw] OR in-house-fatality[tw] OR 30day-fatality[tw] OR 30-day-fatality[tw] OR thirty-day-fatality[tw] OR surgical-fatalities[tw] OR operation-fatalities[tw] OR operative-fatalities[tw] OR postoperative-fatalities[tw] OR surgery-fatalities[tw] OR hospital-fatalities[tw] OR inhospital-fatalities[tw] OR in-hospital-fatalities[tw] OR inhouse-fatalities[tw] OR in-house-fatalities[tw] OR 30day-fatalities[tw] OR 30-day-fatalities[tw] OR thirty-day-fatalities[tw])) AND ("2009/05/11"[PDat] : "2019/05/08"[PDat] AND English[lang] NOT ((animals[MH] OR plants[MH]) NOT humans[MH]) NOT ((animals[tw] OR plants[tw]) NOT humans[tw]))

Discussion on Pubmed search

In the first concept "Problem – Diagnosis, squamous cell carcinoma," an "AND" Boolean operator is used within the concept, which is not common practice as only "OR" is usually used. This strategy has been applied to overcome the lack of a proximity operator in Pubmed and increase the precision of the search.

There is no surgical mortality MeSH term, only hospital mortality. Due to the inability to use proximity operators in Pubmed, permutations of "synonyms of surgical and hospital" are matched with "synonyms of mortality" hence the need for multiple search termsin the surgical mortality concept.

Appendix 2 – A measurement tool to assess systematic reviews (AMSTAR 2)

AMSTAR 2

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes: ☐ Population ☐ Intervention ☐ Comparator group ☐ Outcome	Optional (recommended) ☐ Timeframe for follow-up	☐ Yes ☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☐ review question(s) ☐ a search strategy ☐ inclusion/exclusion criteria ☐ a risk of bias assessment	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan, if appropriate, *and* ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐ Yes ☐ Partial Yes ☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following: ☐ *Explanation for* including only RCTs ☐ OR *Explanation for* including only NRSI ☐ OR *Explanation for* including both RCTs and NRSI	☐ Yes ☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following): ☐ searched at least 2 databases (relevant to research question) ☐ provided key word and/or search strategy ☐ justified publication restrictions (eg, language)	For Yes, should also have (all the following): ☐ searched the reference lists/bibliographies of included studies ☐ searched trial/study registries ☐ included/consulted content experts in the field ☐ where relevant, searched for grey literature ☐ conducted search within 24 months of completion of the review	☐ Yes ☐ Partial Yes ☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following: ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies <u>and</u> achieved good agreement (at least 80 per cent), with the remainder selected by one reviewer	☐ Yes ☐ No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following: ☐ at least two reviewers achieved consensus on which data to extract	☐ Yes

from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder extracted by one reviewer		☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:	For Yes, must also have:	
☐ provided a list of all potentially relevant studies that were read in full text form but excluded from the review	☐ Justified the exclusion from the review of each potentially relevant study	☐ Yes ☐ Partial Yes ☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):	For Yes, should also have ALL the following:	
☐ described populations ☐ described interventions ☐ described comparators ☐ described outcomes ☐ described research designs	☐ described population in detail ☐ described intervention and comparator in detail (including doses where relevant) ☐ described study's setting ☐ timeframe for follow-up	☐ Yes ☐ Partial Yes ☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs For Partial Yes, must have assessed RoB from ☐ unconcealed allocation, *and* ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality)	For Yes, must also have assessed RoB from: ☐ allocation sequence that was not truly random, *and* ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ☐ from confounding, *and* ☐ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, *and* ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐ Yes ☐ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present	☐ Yes ☐ No ☐ No meta-analysis

☐ AND investigated the causes of any heterogeneity	conducted
For NRSI For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☐ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect	☐ Yes ☐ No ☐ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?

For Yes: ☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☐ Yes ☐ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes: ☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☐ Yes ☐ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No ☐ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes: ☐ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☐ Yes ☐ No

Appendix 3 - Cochrane Risk of Bias Tool

Table 8.5.a: The Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias.		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias.		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias.		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Appendix 4 – Methodological index for non-randomized studies (MINORS)

Table 2. The revised and validated version of MINORS

Methodological items for non-randomized studies	Score†
1. **A clearly stated aim:** the question addressed should be precise and relevant in the light of available literature	
2. **Inclusion of consecutive patients**: all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion)	
3. **Prospective collection of data**: data were collected according to a protocol established before the beginning of the study	
4. **Endpoints appropriate to the aim of the study**: unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis.	
5. **Unbiased assessment of the study endpoint**: blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise the reasons for not blinding should be stated	
6. **Follow-up period appropriate to the aim of the study**: the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events	
7. **Loss to follow up less than 5%**: all patients should be included in the follow up. Otherwise, the proportion lost to follow up should not exceed the proportion experiencing the major endpoint	
8. **Prospective calculation of the study size**: information of the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes	
Additional criteria in the case of comparative study	
9. **An adequate control group**: having a gold standard diagnostic test or therapeutic intervention recognized as the optimal intervention according to the available published data	
10. **Contemporary groups**: control and studied group should be managed during the same time period (no historical comparison)	
11. **Baseline equivalence of groups**: the groups should be similar regarding the criteria other than the studied endpoints. Absence of confounding factors that could bias the interpretation of the results	
12. **Adequate statistical analyses**: whether the statistics were in accordance with the type of study with calculation of confidence intervals or relative risk	

†The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies and 24 for comparative studies.

Appendix 5 – Institute of Health Economics Checklist

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Quality Appraisal Checklist for Case Series Studies*

Study objective		
1.	**Was the hypothesis/aim/objective of the study clearly stated?**	Yes ☐ Partial ☐ No ☐
Study design		
2.	**Was the study conducted prospectively?**	Yes ☐ Unclear ☐ No ☐
3.	**Were the cases collected in more than one centre?**	Yes ☐ Unclear ☐ No ☐
4.	**Were patients recruited consecutively?**	Yes ☐ Unclear ☐ No ☐
Study population		
5.	**Were the characteristics of the patients included in the study described?**	Yes ☐ Partial ☐ No ☐
6.	**Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?**	Yes ☐ Partial ☐ No ☐
7.	**Did patients enter the study at a similar point in the disease?**	Yes ☐ Unclear ☐ No ☐
Intervention and co-intervention		
8.	**Was the intervention of interest clearly described?**	Yes ☐ Partial ☐ No ☐
9.	**Were additional interventions (co-interventions) clearly described?**	Yes ☐ Partial ☐ No ☐

This checklist should be cited as: Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014. Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about

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Outcome measure		
10.	**Were relevant outcome measures established a priori?**	Yes ☐ Partial ☐ No ☐
11.	**Were outcome assessors blinded to the intervention that patients received?**	Yes ☐ Unclear ☐ No ☐
12.	**Were the relevant outcomes measured using appropriate objective/subjective methods?**	Yes ☐ Partial ☐ No ☐
13.	**Were the relevant outcome measures made before and after the intervention?**	Yes ☐ Unclear ☐ No ☐
Statistical analysis		
14.	**Were the statistical tests used to assess the relevant outcomes appropriate?**	Yes ☐ Unclear ☐ No ☐
Results and conclusions		
15.	**Was follow-up long enough for important events and outcomes to occur?**	Yes ☐ Unclear ☐ No ☐
16.	**Were losses to follow-up reported?**	Yes ☐ Unclear ☐ No ☐
17.	**Did the study provided estimates of random variability in the data analysis of relevant outcomes?**	Yes ☐ Partial ☐ No ☐
18.	**Were the adverse events reported?**	Yes ☐ Partial ☐ No ☐
19.	**Were the conclusions of the study supported by results?**	Yes ☐ Unclear ☐ No ☐
Competing interests and sources of support		
20.	**Were both competing interests and sources of support for the study reported?**	Yes ☐ Partial ☐ No ☐

*Note: Assessor(s) may decide to remove from the checklist the items that are not applicable to their project.

CHAPTER 3 – FACTORS AFFECTING SURGICAL MORTALITY OF ORAL SQUAMOUS CELL CARCINOMA RESECTION: A SYSTEMATIC REVIEW

This systematic review confirmed that there is a paucity of existing knowledge on the factors affecting surgical mortality of oral squamous cell carcinoma. While there were three studies included, only one had detailed characteristics on the patients who died after the operation. [13] The paper by Luryi et al. is a population level study which illustrated that factors such as advanced age, an increased Charlson Comorbidity Index score, T classification had statistical significance in increasing the risk of surgical mortality, and the risk increases if these factors were combined. [14]

However, a limitation of the paper by Luryi et al. was that the description of the type and approach of surgery was not included in the paper. Hence, it was not possible not able to compare the mortality rates of different approaches or techniques and reconstructive options. The unique health care system and demographics of the USA may have implication on the generalisbility of the evidence to other jurisdictions/health systems.

Below is the paper published in the International Journal of Oral and Maxillofacial surgery. [15]

Int. J. Oral Maxillofac. Surg. 2019; xxx: xxx–xxx
https://doi.org/10.1016/j.ijom.2020.07.011, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Systematic Review
Head and Neck Oncology

Factors affecting surgical mortality of oral squamous cell carcinoma resection

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Y. L. R. Ong, D. Tivey, L. Huang, P. Sambrook, G. Maddern: Factors affecting surgical mortality of oral squamous cell carcinoma resection. Int. J. Oral Maxillofac. Surg. 2019; xxx: xxx–xxx.

Abstract. Survival rates for oral squamous cell carcinoma (OSCC) has remained stagnant in recent years and improving surgical mortality could be an avenue to enhance outcomes. This systematic review aims to identify the causes of mortalities, determine both the modifiable and non-modifiable factors involved and target a reduction in postoperative 30-day mortality. In May 2019, a comprehensive search of key databases including PubMed, EMBASE, Cochrane Library was conducted. Blinded selection by two researchers identified papers that included participants who received oral squamous cell carcinoma resection and suffered an in-hospital or 30-day mortality. Selection identified two relevant papers that meet the inclusion criteria. One study had one death in its population sample but only had the cause of death described. Another study had an overall surgical mortality rate of 1% in a population of 21,681. Patients with multiple factors had the highest mortality rates; 4.6% in patients >85 years old and have a T4 diagnosis, 3.9% in patients with a Comorbidity Index ≥1 and a T4 diagnosis. These studies did not determine relationships between factors and causes of death. There are significant knowledge gaps in the literature, that can be addressed through further population analysis studies.

Key words: oral cavity; oral; squamous cell; squamous cell carcinoma; resection; surgery; surgical mortality; systematic review.

Accepted for publication 3 July 2020

Head and neck cancer is the seventh most frequent type of cancer by incidence and ninth most common cause of cancer death according to the World Health Organization (WHO)[1]. These related cancers involve the oral cavity, pharynx (which includes the oropharynx, nasopharynx, hypopharynx), and larynx. Most tumours, especially those involving the oral cavity, are squamous cell carcinomas (OSCC)[2].

The 5-year survival rate for cancers of the tongue, oral cavity and oropharynx are around 50%, and the survival rates for oral cancer in the UK as reported in 2009 showed no improvement in the preceding three decades[2]. The worst outcome of surgical intervention is the death of the patient during the peri-operative period. Indeed, the 30-day postoperative mortality rates are variable and range from 2.6% in Brazil for oral and oropharyngeal surgery[3] to 8% for all post head and neck cancer surgeries in the USA[4]. These values may not accurately reflect the true mortality of oral squamous cell carcinoma resections as they include other head and neck cancer procedures. There is limited data in the literature that specifically explores oral cavity surgical mortality.

0901-5027/000001+06

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There are multiple factors that may contribute to these deaths. This systematic review aims to identify the causes of mortalities, evaluate the factors involved and determine whether there are any modifiable risks that could be targeted to reduce the mortality in the postoperative period.

Methods

Study Designs

Eligible study designs included systematic reviews, meta-analyses, randomized control trials, prospective and retrospective cohort studies, case–control studies, cross-sectional studies, observation studies, case series and case studies.

Participants

The general adult human population was the participant of interest.

Interventions

Of interest were patients who had received surgical resection of squamous cell carcinoma from the oral cavity. The oral cavity includes structures posterior to the lip and anterior to the tonsils.

Outcomes

The outcome was surgical mortality, where death was recorded because of the surgery or a surgical related complication. To ensure that this systematic review focuses on surgical-related deaths, only deaths that occurred in hospital or within 30 days of the surgery were included.

Search Strategy

The primary information sources were the PubMed, EMBASE and Cochrane Library databases. Quantitative studies were sought. No study design limits were imposed. Results were limited by English language, human subjects and papers published in the last 10 years.

The specific search strategies were developed in discussion with a Health Sciences Librarian and a research manager with expertise in systematic review searching. Literature search strategies were developed using medical subject headings (MeSH), Emtree terms and text words related to factors affecting surgical mortality of OSCC.

The search strategies were formulated using the PRESS (Peer Review of Electronic Search Strategies) standard[5]. The search strategies for each database are included in the Supplementary Material. To ensure literature saturation, we scanned the reference lists of the included studies or relevant reviews identified through the search.

Study Records

Data Management

Duplicates originating from different databases were removed using both EndNote application before exporting citation to Rayyan QCRI (Qatar Computing Research Institute)[6]. Rayyan QCRI is a web-based software programme that facilitates collaboration among reviewers during the study selection process. A calibration exercise was undertaken before the review process to pilot and refine the screening questions.

Selection process

The two review authors independently screened the titles and abstracts yielded by the search against the inclusion criteria. The screening process was blinded; then the results were revealed and compared. Full reports were obtained for all the titles that appeared to meet the inclusion criteria or where there was any uncertainty. Review authors then screened the full text reports to finalize whether the reports met the inclusion criteria. A discussion was carried out to settle any disagreements. Reasons for excluding trials were recorded. Neither of the review authors were blinded to the journal titles or to the study authors or institutions.

Data collection process and synthesis

To ensure consistency across reviewers, calibration exercises were conducted before starting the review. Quantitative data was included. Reviewers resolved disagreements by discussion, and one arbitrator who was the supervisor of the review decided on the unresolved disputes. Data was synthesized in a narrative analysis.

Data Items

Data abstractions included demographic information including age, gender, risk factors including smoking, alcohol intake, comorbidities including existing cardiorespiratory conditions and diabetes, diagnosis including area and extent of OSCC and lymph node involvement, intervention including the surgery performed, postoperative conditions including infection, bleeding and cause of mortality.

Outcomes and prioritizations

This systematic review was not aimed to compare outcomes. The outcome of interest was surgical mortality. Investigation was focused on factors that influenced these mortalities.

Risk of bias in individual studies

To assess the risk of bias for each study, critical appraisal tools appropriate for the study design were used.

Methodological index for non-randomized studies (MINORS) was used to assess observational or non-randomized studies[7]. This contains 12 items, the first eight being specifically for non-comparative studies. For reports of individual cases or case series appraisal was performed using the validated Institute of Health Economics (IHE) critical appraisal tool[8,9]. Appraisals were made independently by two review authors. Disagreements were resolved first by discussion and then by consulting a third author for arbitration. Irrespective of quality score, appraisal was not used to eliminate studies, but to be used in interpreting results.

Results

Results of search

The search of PubMed, Embase and Cochrane Library conducted on 28 May 2019 returned a total of 62 citations. A search update was established to provide alerts on new publications after the initial search, at the time of writing this paper no additional publications were identified. The study selection process is described in Fig. 1. After adjusting for duplicates, 52 remained for title and abstract screening. Of these 52 studies, 40 studies were discarded because they did not meet the inclusion criteria. For the remaining 12 studies a full-text review was undertaken, resulting in the rejection of a further 10 studies. The reasons for exclusion are provided in the Supplementary Material. Overall, two studies met the inclusion criteria and were included.

Methods

Of the two papers included, one study was single centred[10,11] while the other was a multicentred, population-level study[12], which covered over 1500 institutions. The study populations were from America

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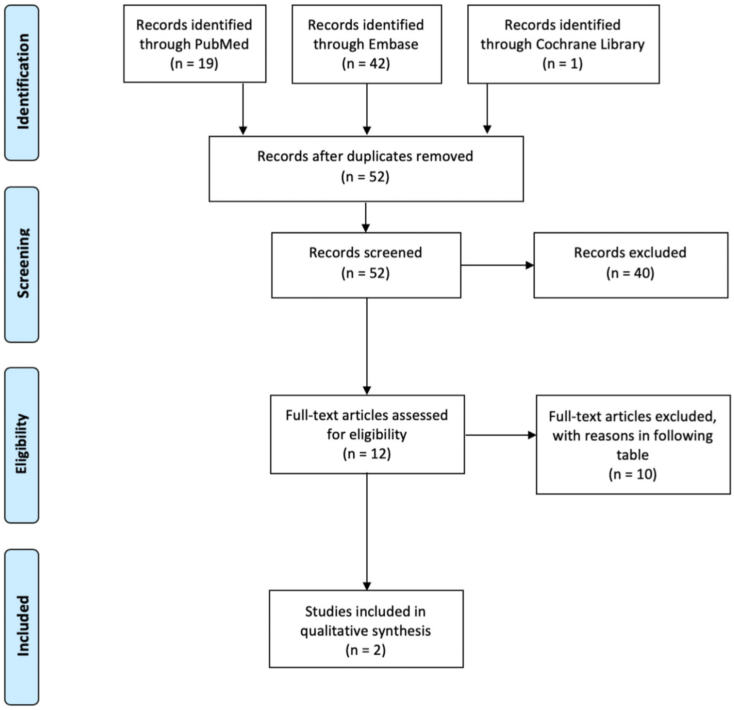

Fig. 1. Flow diagram for study selection.

and India. One study was retrospective and one was prospective. Details of included studies are provided in Table 1. The study duration ranged from 4 years to 9 years, covering 2003 to 2011.

Patients

The included studies involved a total of 22,357 patients. Of which, 676 were a population of patients who attended a hospital in South India[11], and 21,681 patients who attended multiple institutions in the USA[12].

The 676 patients included in the study report by Divya et al.[11] were 65% males with the largest age group at 31.2% belonging to 51–60 years. In that study, 52% were tobacco chewers, 43% were alcohol consumers and 42% had a history of smoking. Unfortunately, the demographic breakdown was not detailed in the patients who suffered from surgical mortality in these two studies.

The total patient sample from the study by Luryi[12] had 62% males, largest age group was 56–65 years. The racial distribution of the total sample constituted 89% Caucasian, 6% African American and 4% other racial groups. Comorbidities were defined using the Deyo-modified Charlson Comorbidity index (Comorbidity Index)[13].

Intervention

Participants in both studies had a diagnosis of oral cavity squamous cell carcinoma and received surgical treatment.

The study by Divya et al. reported on multiple surgeries including mandibulectomy (47%), segmental/hemimandibulectomy (37.7%), marginal mandibulectomy (6.5%), arch mandibulectomy (2.5%) and maxillectomy (4.6%). Reconstruction for mucosal lining was performed in 54.4% of included cases[11].

The study by Luryi et al.[12] did not specify the surgeries performed, but only had information of the site of cancer and the extent of the surgery, for example, local vs. wide vs. radical excision and whether a neck dissection was performed.

Outcomes

The outcome of interest for this systematic review is surgical mortality related to the surgical intervention. All studies had deaths within 30 days of the surgical procedure.

For this systematic review, the factors that are associated with the patient and treatment were explored. This analysis was undertaken to identify any circumstances that influence the likelihood of patient death within the 30-day postoper-

Table 1. Types of included studies.

Paper	Type of study	Location	Date range	Number of participants
Divya et al., 2018	Single centre Prospective study	India	2007–2010	676
Luryi et al., 2016	Multicentre Retrospective study	America	2003–2011	21681

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Table 2. Results of individual studies.

Paper	Number of participants	Number of deaths	Causes of death	Contains detailed patient characteristics related to death
Divya et al., 2018	676	1	Sudden cardiac death	No
Luryi et al., 2016	21681	213	Not described	Yes

ative window. As shown in Table 2, only one of two studies reported on factors that may have influenced the occurrence of surgical mortality.

Risk of bias within studies

MINORS[7], an externally validated instrument to assess quality of studies was used for Divya et al.[11] and Luryi et al.[12] and scores of 14 and 15 were, respectively, obtained. Scores for individual categories can be viewed in the Supplementary Material. In comparison to a global ideal score of 16, both studies were considered medium to high quality.

Results of individual studies

Table 2 summarizes the salient findings from each paper. The paper by Divya et al.[11] stated the causes of death but did not have patient characteristics related to their deaths. Luryi et al.[12] did not have the causes of death for the patients who died but had detailed characteristics for these patients.

One death was reported in the 676 patients included in the prospective study of postoperative complications in oral cancer surgery[11]. The death was attributed to sudden cardiac arrest on postoperative day 28. Details specific to the patient and surrounding the death were not described in the paper.

The latter of the included studies was a population level retrospective study using a National Database and reported on over 20,000 patients and surgeries in which 213 (1% of the study population) deaths occurred within the 30-day postoperative window[12]. Statistical analysis was performed using the SPSS statistical software. Association between covariates and outcomes was determined by Pearson's Chi-squared tests and Z-tests of proportions. Binary logistic regression was used to identify variables independently associated with 30-day mortality with odds ratios used to describe association magnitudes. Cases with missing or unknown covariate data were excluded from multivariate analysis. Significance in all analyses was set at $P < 0.05$.

Amongst the mortality group, after a univariate analysis, statistically significant differences were found in age groups, comorbidity index, stage, T classification, procedure extent and length of stay. Mortality rates were found to increase with increasing age of the patient. The mortality rate of patients greater than 85 years of age was 3.4%, 32 out of 929 patients in this group died as a result of the surgery. These 32 patients contributed to 15% of all reported deaths in this study. There was a similar trend for the Comorbidity Index. The score of ≥1 contributed to 45% of all deaths, 2.1% of patients who had a score of ≥1 died after the surgery, compared with 0.7% who had a score of 0. There was no increase in mortality from stage II compared to stage III at 1% to 0.9%, respectively, but stage IV had a higher mortality at 1.5%. T classification followed an upward trend from 0.4% at T1 to 1.7% at T4. Other characteristics such as procedure extent and length of stay followed a predictable increasing trend.

Combinations of factors lead to higher rates of mortality. The highest 30-day mortality rates (4.6%) were observed in patients older than 85 years who had a T4 classification. There was a similar trend when the Comorbidity Index and T classification variables were combined. Patients with a Comorbidity Index ≥1 who had an SCC classified T4 had a mortality rate of 3.9%. This was almost four times higher than the overall mortality rate.

The multivariate analyses identified factors associated with a 30-day mortality; these included age >65, comorbidity index ≥1 and stage T2, T3, and T4 disease. The highest odds ratio (OR) of 10.24 [OR 4.28—24.51 95% confidence interval (CI)] was found for patients greater than 85 years of age. Further, the odds of dying within the 30-day postoperative window were 2.31 (OR 1.69–3.15 95% CI) for patients with a comorbidity index ≥1, and 3.24 times greater (OR 1.90–5.55 95% CI) for patients with the highest T classification the disease.

Discussion

Paucity of literature

While two studies were included, only the study report by Luryi et al.[12] had analysed factors surrounding patients that may have contributed to a death with a 30-day postsurgery. The other included report by Divya et al.[11] only stated the cause of death. The studies originate from different geographic populations with different age populations and healthcare systems. At the time of publication in 2014, Luryi stated that it was the first population level description of 30-day mortality rates, we believe that this is still the first and only publication to the date of our search. The rest of the discussion section will be in relation to the study reported by Luryi and co-workers[12].

Statistical Approach

The statistical analysis section of the paper stated that Chi-squared tests, Z-tests and binary logistic regression were used. While they may be appropriate analytical methods, further details as to how they were employed specific to subsets of the dataset and resulting analytic outcomes were lacking.

For example, when univariate analyses were used for factors associated with a 30-day mortality, it was not explicitly stated what test was used. It is assumed that a Chi-squared test with the null hypothesis was employed to determine differences within each variable.

When 30-day mortality rates by age and T classification were analysed, and 30-day mortality rates by comorbidity index and T classification were analysed, there were starred values that represented statistically significantly high mortality rates compared with the average. The statistical model that achieved that result was not described. A potentially more useful analysis would be to compare these results with patients in the study sample who survived beyond 30-days.

A multivariate analysis of factors associated with a 30-day mortality was performed using binary logistic regression. Regression of interaction terms (e.g., between comorbidity index and T classification) were not explored but potentially could have proved useful to understand the combined effect among the significant factors. The combination of these factors could be additive or synergic. It was also commented that the variables without significant association with a 30-day mortality are not shown. In the absence of reporting on model selection procedures, it was not clear whether the reported model results were the final streamlined results. Further, the model diagnostic information was missing, so that it is not unknown whether the model fits the data well or not.

Analysis of salient findings

Luryi and co-workers[12] analysed a large population sample of more than 20,000 patients that resulted in an overall surgical mortality rate at 1%. This value is lower than that which was quoted at 2.6% and 8% in other studies mentioned in the introduction[3,4].

The paper by Luryi et al. illustrated several factors that influenced the mortality rate[12]. In particular, age, comorbidities and T classification, especially when these factors were combined. A patient aged greater than 85 years with a T4 classification diagnosis of oral squamous cell carcinoma has a mortality rate of 4.6%, more than four times the average. Unfortunately, age and T classification are non-modifiable factors, but increased postoperative monitoring and presurgical optimization could be performed for certain comorbidities. Particularly high-risk patients need to be consulted extensively about risk of surgery.

Conversely, in certain patient groups, surgery is relatively safe. For example, patients under 55 years old with stage 1 disease had a 30-day mortality under 0.5%.

T classification had statistical significance for surgical mortality, but N classification was not. This suggests that a T classification is more important than N classification for short-term survival. A high T classification translates to larger tumour bulk, and an increased need for a flap reconstruction. This leads to increased blood loss and duration of the operation which could be an important mechanism for higher mortality. Comorbidity index has statistical significance, but metastatic solid tumour which is a contributor to the comorbidity index is equivalent to a high N classification. This highlighted the weakness of using an index instead of a specific disease contributor to mortality rates. Different components of the index may play more important roles in contributing to the increased surgical mortality rate.

A limitation of the study was that the type of surgery and the intent of the surgery was not included in the data. An example of a useful comparison would be the mortality rates comparing a segmental versus a marginal mandibulectomy. This would be able to help guide surgeons if a palliative resection should be considered over a higher-risk curative radical resection. Causes of deaths were also not documented in the results, and specific relationships between factors and causes of deaths may not be determined. This information could have significance to clinical management, knowing that certain patients and surgeries predispose a specific cause of death may change clinical practice guidelines.

Validity and Generalizability

The population sample originated from the National Cancer Database (NCDB). According to the American College of Surgeons website, the database is a joint programme of the Commission on Cancer (COC) of the American College of Surgeons and the American Cancer Society[14]. This is a nationwide oncology outcomes database for more than 1500 commission-accredited cancer programmes in the USA and Puerto Rico, 70% of all newly diagnosed cases of cancer in the USA are captured at the institutional level and reported to the NCDB. The demographics of the 70% of coverage were not described hence it was unclear whether they originated from a specific geographical proportion of the American population or whether they contained mostly private or public hospitals.

According to the American Hospital Association website, there are a total of 6210 hospitals in the USA, 208 (3%) are federal government hospitals, 2968 (48%) are non-government not-for-profit community hospitals, 1322 (21%) are investor-owned (for-profit) community hospitals and 972 (16%) are state and local government community hospitals[15].

The USA has a unique ethnic demographic, 25% of the population consists of four main racial and ethnic minorities, African Americans, Hispanics, Asians/Pacific Islanders, and American Indians[16]. The study population included 89% Caucasian, which may suggest that the Caucasian population was over-represented in the data. Patients in the USA have to pay for their own healthcare, despite having subsidies such as Medicare for patients aged greater than 65 years old and Medicaid for lower-income patients[17]. This will differ from populations from countries with universal healthcare cover (UHC); for example, the UK where UHC is provided by the National Health Service. The cost of healthcare in the USA may lead to deviation from best practice for patients who cannot afford certain treatment modalities[18].

In conclusion, while the single population level study[12] is a good start, there are significant knowledge gaps that need to be addressed. Further population-level analysis of the NCDB or cancer databases/registries and surgical mortality audits from other jurisdictions need to be conducted, and validity and generalizability of findings should be tested using a robust statistical model. While the overall surgical mortality rate is 1%, in certain patient groups rates were as high as 5%, this is not a negligible risk and defining the factors that increase this risk can provide surgeons with the necessary knowledge to improve patient selection and make better clinical decisions to avoid these deaths.

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Competing interests

None.

Ethical approval

Not required.

Patient consent

Not applicable.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijom.2020.07.011.

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CHAPTER 4 – ORAL SQUAMOUS CELL CARCINOMA RESECTION AND NECK DISSECTION MORTALITY: A 10 YEAR NATIONAL AUDIT STUDY

This paper explored the factors affecting surgical deaths post resection of oral squamous cell carcinoma and neck dissection using a population level surgical mortality audit process from the Australia and New Zealand Audit of Surgical Mortality (ANZASM) over 10 years from 2009 to 2018. Cardiac and respiratory causes were the most common causes of death. However, reflecting on these events, the surgeons and assessors felt that many of these patients should not have proceeded to receive the surgery. The extensive resections and reconstructions require very long durations under general anaesthesia, and many of these patients had high pre-operative risk. This highlighted the importance of patient selection. Using risk stratification instruments to determine pre-operative risk and the use of a multidisciplinary team should be considered to help surgeons to make better informed decisions, to be able to have better risk vs benefit conversations with patients. Changes could be made to ANZASM to improve the results for analysis.

Below is the paper published in the Australia and New Zealand Journal of Surgery. [16]

ORIGINAL ARTICLE

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Oral squamous cell carcinoma resection and neck dissection mortality: a 10-year national audit study

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Key words
audit, Australia, cancer, carcinoma, neck dissection, oral, squamous cell, surgical mortality.

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Abstract

Background: Oral squamous cell carcinoma (OSCC) is a significant public health issue. Australia had 448 deaths from lip and oral cavity cancer in 2018, some of which could be prevented. Consideration of the factors contributing to mortality after OSCC resection can provide a greater insight into how deaths can be prevented.
Methods: This paper used data from the Australia and New Zealand Audit of Surgical Mortality from the last 10 years from 1 January 2009 to 31 December 2018 for analysis. All surgical deaths were captured as the treating surgeons were mandated to complete a surgical case form for assessment by an independent surgeon from the same specialty.
Results: This study found 25 cases of death after OSCC resection. In 44% of cases, death was related to cardiac causes and 40% was related to respiratory causes. Fourteen cases were found to have issues with management, and 25 issues were raised. In 36% of issues, it was found to be related to decision to operate. There were no obvious differences between the patients who had neck dissections and those who did not.
Conclusion: The decision to operate on high-risk patients, cardiovascular and respiratory causes were the major contributors to surgical mortality. The small number of deaths and the limitation of using existing data limited statistical analysis and conclusions. Changes could be made to the Australia and New Zealand Audit of Surgical Mortality to improve the results for analysis.

Introduction

Oral squamous cell carcinoma (OSCC) is a significant public health issue. The World Health Organization found 354 900 new lip and oral cavity cancer in 2018, with 177 400 deaths globally.[1] While the incidence of oral cancer was lower than other cancers, the mortality to incidence ratio was higher than some cancers more popular in the media, at 0.5 compared to 0.3 for breast cancer and 0.28 for prostate cancer.[1] One reason was because 50% of patients with oral cancer presented with advanced disease,[2] this required very wide margins and was relatively radioresistant compared to other head and neck cancers. The 5-year survival rates for cancers of the tongue, oral cavity and oropharynx were around 50%.[2]

Australia had 2917 new cases, 448 deaths and a prevalence rate of 39.9 per 100 000 of lip and oral cavity cancer in 2018 according to the World Health Organization.[3] Limited data from the last decade according to the World Health Organization reported 13 397 cases from 2009 to 2012.[4] Surgical mortality is defined as post-operative death in hospital or within 30 days of surgery. However, there was scarce literature on surgical mortality, with many studies focusing on 5-year survival rates instead. In particular, at the time of writing this paper, there was no publication on the surgical mortality rate of OSCC resection in Australia.

More than 90% of oral malignancies in the upper aerodigestive tract are squamous cell carcinomas.[2] Complete resection of the cancer including a margin of surrounding tissue is the surgical goal. The surgical procedures may include wide local excisions, glossectomies, mandibulectomies, maxillectomies, selective or radical neck dissections and reconstructions using local, regional or vascularized soft or hard tissue flaps.

The spread of tumour to the cervical lymph nodes within the neck is an early and common event in the natural history of head and neck cancer.[5] Neck dissection is a procedure performed by a head and neck surgeon to control regional metastatic disease. Due to the high risk of regional disease, even in a clinically node-negative neck, a neck dissection is regularly indicated for OSCC, as recommended in a Cochrane review.[6]

Surgical mortality of neck dissection is difficult to examine because there are many types of neck dissections and they are often performed with other major resections of the head and neck, each operation posing different risks. Post-operative mortality after neck dissection is dependent on many factors including extent of disease, type of neck dissection (radical versus selective) and patient factors such as history of radiotherapy and operator factors.[7] The risk of mortality for non-irradiated patients undergoing radical neck dissection only was 1.5% compared to 8.5% when radical neck dissection was combined with other major procedures in irradiated patients.[8] Another study found the post-operative mortality rate to be 2.7% for bilateral radical neck dissection.[9]

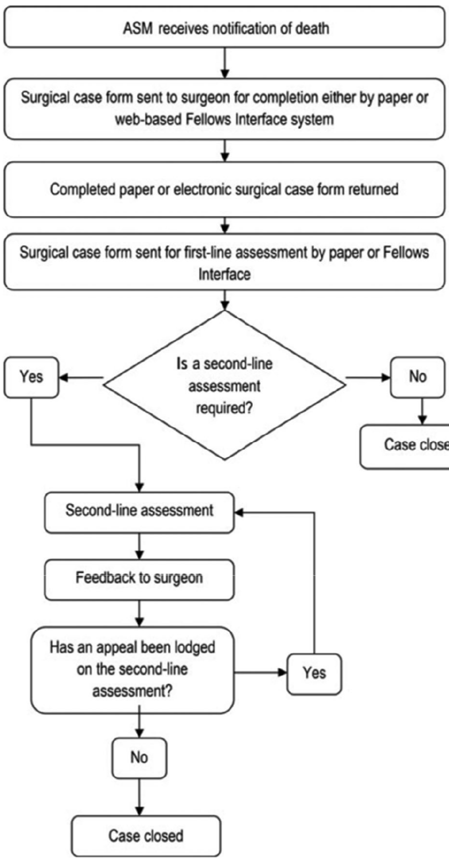

Fig 1. Process of the Australia and New Zealand Audit of Surgical Mortality.

Existing studies described factors that affect surgical mortality from OSCC. Using the TNM classification, patients with T2 to T4 disease who were also >85 years old or had documented co-morbid conditions were at highest risk of death, with 30-day mortality rates ranging from 2% to 4.7%.[10] Pulmonary, gastrointestinal, hepatological and renal diseases particularly increased the chances of death, but a higher American Society of Anesthesiologists (ASA) score, cardiovascular, neurological diseases, other cancers and type 2 diabetes were not significantly associated with deaths.[11]

This study aimed to investigate the factors surrounding mortality of patients following resection of OSCC. The factors would be compared with those who had concurrently undergone a neck dissection procedure to determine if there were neck dissection-specific complications that might increase the risk of mortality. Data would be obtained from a national audit process over a 10-year period. Discussions would be made from the salient learning points that the treating surgeon and assessors had identified that could have prevented these deaths.

Methods

The Australia and New Zealand Audit of Surgical Mortality (ANZASM) collected data from all Australian states but the New South Wales data were not assessable due to state-specific laws. This represented approximately 68% of the Australian population, reflective of a 15 million population over a 10-year period.[12,13]

Ethics approval was not required in this research project as ANZASM was a quality improvement programme and was covered under qualified privilege and state-level gazettes.

The ANZASM was conducted by the Royal Australasian College of Surgeons (RACS) to provide a snapshot of the causes behind mortality associated with surgical patients. The principal objectives are to inform, educate and facilitate change and improve quality of practice in a surgical setting.[14] In January 2010, the RACS mandated the participation in the ANZASM and made it a component of continuing professional development.[14]

Individual state-based regional audits were notified of in-hospital deaths by medical record departments. The clinical details were entered by all surgeons in a standardised surgical case form that had 25 questions, with sub-questions. The deidentified surgical case form was then sent for first-line assessment to a surgeon from the same specialty but from a different hospital or different state. If the first-line assessment was unsatisfactory due to:

- inadequate information,
- patient management issues (e.g. inappropriate post-operative care) and
- unexpected death (e.g. young fit patient with benign disease),

a further in-depth second-line assessment would be triggered. The assessor would then be provided with medical case notes. Twelve percent of all cases required a second-line assessment.[14] The confidential comments and suggestions of the assessors were then sent back to the treating surgeon. A summary is presented in Fig. 1 below.

Each type of procedure had a specific Read code and corresponding identification number. All OSCC and neck dissection-related procedures were identified from the full list of Read codes. They include, but were not limited to, excision of lesion of mouth, mandible, palate and tongue; hemi and segmental mandibulectomy; maxillectomy and glossectomy; radical block neck dissection; radical neck dissection of cervical lymph nodes; block dissection of cervical lymph nodes; and functional block dissection of cervical lymph nodes. Search criteria were consulted with a head and neck surgeon and research specialist from the ANZASM to ensure complete coverage of cases. Initial results included procedures for other indications such as odontogenic tumours and other non-OSCC lesions but a secondary filter was applied to only include OSCC-related cases. All the cases from January 2009 to December 2018 (i.e. 10-year period) were extracted from the database. Information with all the data points from the surgical case form, and first- and second-line assessments were presented in a spreadsheet format.

A spreadsheet was used to collate, count and calculate data. Narrative data were analysed and coded by the author individually.

The causes of death were reported as a narrative but were classified into seven groups:

(1) Cardiac, including cardiac arrest
(2) Respiratory, including pneumonia, pulmonary embolism and airway obstruction
(3) Bleeding and haemorrhage
(4) Sepsis
(5) Renal failure
(6) Others, including multiorgan failure and palliation due to advanced dementia
(7) Ischaemia

Multiple causes of death may be quoted in each patient.

Issues with management might be raised by either the treating surgeon completing the surgical case form or assessor in the first- or second-line assessment. There could be multiple issues raised for each patient. The issues were explored in five aspects:

(1) Nature of the issue: for example, operative decision and aspiration pneumonia
(2) Severity: if the issue was an area for:
    - Consideration – care could have been improved or different, but recognizes that it may be an area of debate
    - Concern – care should have been better
    - Adverse event – unintended injury caused by medical management rather than by disease process
(3) Outcome: if the issue made a difference to outcome
(4) Preventable: if the event was preventable
(5) Association: who the event was associated with
    - Treating surgical team
    - Another clinical team
    - Hospital
    - Others

Results

In the 10-year period from January 2009 to December 2018, there were 25 cases of surgical mortality from OSCC resection. Among the 25 patients, data were compared between the cases with and without neck dissections.

The demographics of the patients are summarized in Table 1, with male and female patients of 72% and 28%, respectively. The average age was 77 years and median age was 78 years (57–94 years). In the neck dissection group, the median age was higher at 84 compared to 77 in the no neck dissection group. Cardiac, respiratory and advanced malignancies were the predominant co-factors at 64%, 64% and 68%, respectively.

The ASA classification of Physical Status is a widely used and commonly accepted risk stratification system.[15] In our sample, majority (64%) had an ASA score of 3.

Factors surrounding the patient deaths are summarized in Table 2. The pre-surgical risk of death was categorized from minimal to expected. Twenty-eight percent of the patients had their risk of death considered minimal and small.

Cardiac causes contributed to 44% and respiratory causes contributed to 40% of all deaths. Sixteen percent of surgeons reported that the post-operative care could be improved. Forty-four percent of all deaths had an unplanned return to theatre and 48% had an unplanned return to an intensive care unit.

As per the ANZASM guidelines, all 25 cases had undergone a first-line assessment, with four cases proceeding to a second-line assessment. There were 14 patients (56% of all cases) who were identified by either the treating surgeon or assessor to have issues with the management. From these 14 patients, 25 issues were raised. The findings and differences between the cases with and without neck dissection are summarized in Table 3.

Regarding the nature of the issues, 36% of the issues were due to operative decision, it was identified as the most common issue in both neck dissection and no neck dissection groups. Other issues identified included: aspiration pneumonia, delay in transferring patient to intensive care unit, delay in recognizing complications, unsatisfactory fluid balance, inadequate preoperative optimization and inadequate post-operative cardiac monitoring.

Definitions were described previously in the Methods section. In terms of severity, none of the issues were considered an adverse event. Both groups had 80% of the issues thought to be an area for consideration.

With regards to whether the issues affected the outcome, 44% may have contributed to the death of the patient while a similar percentage (48%) made no difference. There were a slightly higher percentage of issues that were probably preventable in the neck dissection group at 33% compared to 10% in the no neck dissection group.

Taking into account that 40% of the associations were not recorded, 32% were related to the surgical treating team and 36% were related to another clinical team.

Discussion

Decision to operate

A theme that the operating surgeons and assessors brought up most commonly was operative decision, contributing to 36% of all issues

Table 1 Demographics

	All OSCC resections	OSCC resections AND neck dissections	OSCC resections NOT neck dissections
	Number of patients (%)		
Total	25	11	14
Gender			
Male	18 (72)	6 (55)	12 (86)
Female	7 (28)	5 (45)	2 (14)
Age			
Median	78	84	77
Interquartile range	75–84	77–86	73–79
ASA score			
ASA 1	0 (0)	0 (0)	0 (0)
ASA 2	3 (12)	0 (0)	3 (21)
ASA 3	16 (64)	8 (73)	8 (57)
ASA 4	5 (20)	3 (27)	2 (14)
ASA 5	0 (0)	0 (0)	0 (0)
ASA 6	0 (0)	0 (0)	0 (0)
Not recorded	1 (4)	0 (0)	1 (7)
Urgency of admission			
Elective	24 (96)	11 (100)	13 (93)
Emergency	1 (4)	0 (0)	1 (7)
Length of stay			
Median	15	15	18
Interquartile range	5–30	9–28	3–45
Co-factors present			
Cardiovascular	16 (64)	8 (73)	8 (57)
Respiratory	16 (64)	6 (55)	10 (71)
Renal	4 (16)	3 (27)	1 (7)
Hepatic	0 (0)	0 (0)	0 (0)
Neurological	5 (20)	3 (27)	2 (14)
Advanced malignancy	17 (68)	8 (73)	9 (64)
Diabetes	1 (4)	0 (0)	1 (7)
Obesity	0 (0)	0 (0)	0 (0)

ASA, American Society of Anesthesiologists; OSCC, oral squamous cell carcinoma.

raised. Assessment of these cases suggested that extensive and complex surgeries should be limited or not had been performed on these patients with high preoperative risk.

The long duration of a complex surgical resection, neck dissection, flap harvest and reconstruction had led to acute cardiorespiratory arrest or bowel ischaemia in patients. Feedback from the assessors suggested consideration of limited non-curative surgery with radiotherapy and/or medical management.

As one assessor wrote in the feedback, ‘there is the philosophical question of how best to manage a patient who has a diabolical surgical pathology, that is also at very high risk of surgical mortality’. The decision to operate is a dilemma that all head and neck surgeons face. The surgeon is caught between a rock and a hard place; to offer surgery in a patient with multiple comorbidities and high risk of mortality or decline an operation with the morbidity of a potentially disfiguring facial pathology with significant functional impairment with the danger of catastrophic death from bleeding or asphyxiation.

A long and complex surgery in a patient who was unlikely to survive due to their existing comorbidities was found to be the most common reason for surgical mortality. Assessor feedback commented that some of these patients will not have proceeded for the surgery leading to their deaths if a multidisciplinary team (MDT) discussion was made. Unfortunately, whether an MDT was used in each of the cases was not included in the data set. We believe that a routine involvement of an MDT will reduce such deaths. An MDT was shown to change 60% of diagnostic or management plans.[16] Involvement of an MDT showed increased survival, reduced use of surgery as monotherapy and increased use of multimodality therapy treatment in head and neck cancer patients.[17]

Out of the scope from the data set from the ANZASM, a study with similarly matched patient groups will be required to compare factors between survivors and mortality to draw conclusions and make recommendations on patient selection.

Neck dissection compared to no neck dissection

The preoperative risk of death in the neck dissection group was higher with 36% compared to 14% at ‘considerable’ risk. These patients were inferred to have more advanced disease requiring the neck dissections.

One would expect that there will be more cases of respiratory or haemorrhage leading to death in the neck dissection group, but this was not obvious in our sample population. Respiratory causes led to five out of 11 (45%) of deaths in the neck dissection group compared to five out of 14 (36%) of the no neck dissection group. And haemorrhage led to 9% of deaths in the neck dissection group compared to 7% in the no neck dissection group, each only having only one patient who died. Hence, neck dissection should not be omitted when indicated in a patient with increased comorbidities. However,

Table 2 Factors affecting patient deaths

	All OSCC resections	OSCC resections AND neck dissections	OSCC resections NOT neck dissections
	Number of patients (%)		
Risk of death			
Minimal	1 (4)	0 (0)	1 (7)
Small	6 (24)	3 (27)	3 (21)
Moderate	11 (44)	4 (36)	7 (50)
Considerable	6 (24)	4 (36)	2 (14)
Expected	1 (4)	0 (0)	1 (7)
Cause of death			
Cardiac	11 (44)	5 (45)	6 (43)
Respiratory	10 (40)	5 (45)	5 (36)
Haemorrhage	2 (8)	1 (9)	1 (7)
Cerebral vascular accident	1 (4)	1 (9)	0 (0)
Sepsis	2 (8)	2 (18)	0 (0)
Renal failure	2 (8)	1 (9)	1 (7)
Others	8 (32)	3 (27)	5 (36)
Management could be improved			
Preoperative preparation	2 (8)	1 (9)	1 (7)
Decision to operate	2 (8)	1 (9)	1 (7)
Choice of operation	1 (4)	1 (9)	0 (0)
Timing of operation	2 (8)	1 (9)	1 (7)
Technical management during surgery	2 (8)	1 (9)	1 (7)
Experience of surgeon making decision	0 (0)	0 (0)	0 (0)
Experience of surgeon operating	0 (0)	0 (0)	0 (0)
Post-operative care	4 (16)	2 (18)	2 (14)
Anaesthetic-associated deaths			
Yes	1 (4)	0 (0)	1 (7)
No	22 (88)	10 (91)	12 (86)
Possibly	2 (8)	1 (9)	1 (7)
DVT prophylaxis			
Yes	24 (96)	11 (100)	13 (93)
No	1 (4)	0 (0)	1 (7)
Complications			
Unplanned return to theatre	11 (44)	6 (55)	5 (36)
Unplanned admission to intensive care unit	12 (48)	7 (64)	5 (36)
Unplanned readmission within 30 days of surgery	1 (4)	1 (9)	0 (0)
Fluid balance issue	4 (16)	3 (27)	1 (7)
Communication issue	1 (4)	0 (0)	1 (7)

DVT, venous thrombo embolism; OSCC, oral squamous cell carcinoma.

we acknowledge that the number of deaths were too small to make a meaningful statistical interpretation.

Cardiac-related deaths

Cardiac causes contributed to the highest proportion of deaths in our sample at 44%. The widely used ASA score had shown to not have a significant relationship with perioperative cardiovascular complications in head and neck surgery.[11,18] The Lee Cardiac Risk Index that showed a statistically significant relationship could be used instead.[18,19]

This instrument consists of six items that define an overall Lee Index score: Lee I: 0 risk variables; Lee II: 1 risk variable; Lee III: 2 risk variables; and Lee IV: >2 risk variables. Five risk factors are co-morbid conditions: a history of ischaemic heart disease (angina pectoris and/or myocardial infarction), heart failure, history of cerebrovascular disease, insulin-dependent diabetes and kidney failure (preoperative serum creatinine >2 mg/dL). The sixth risk factor is a high-risk type of surgery.[19] A patient with a Lee Index score of II had a 1.7-fold higher risk for major cardiovascular complications compared to Lee Index score 1, and Lee Index score >2 was associated with at least 11-fold higher risk.[18]

The ANZASM did not provide data on pre-surgical optimization provided by the perioperative or anaesthetic team. Apart from risk stratification, preoperative optimization such as starting a patient on beta blockers could be considered. A large 1000+ patient randomized control trial that used beta-blocker bisoprolol commenced prior to surgery showed a 67% relative risk reduction in the perioperative incidence of cardiac death or myocardial infarction.[20] Head and neck cancer needs to be operated within a month of diagnosis and this gives the treating team time to optimize the patient.

Respiratory-related deaths

This study showed 64% of patients with respiratory disease as a co-factor, and 40% of deaths related to respiratory problems. Preoperative lung function tests might be considered to assess a patient's risk for post-surgical pulmonary complications to avoid operating on patient with a high risk of mortality. A study that looked at post head and neck cancer patients suggested that preoperative forced

Table 3 Issues with management

	All OSCC resections	OSCC resections AND neck dissections	OSCC resections NOT neck dissections
	Number of patients (%)		
Total	14	8	6
	Number of issues (%)		
Total	25	15	10
Issue			
Operative decision	9 (36)	6 (40)	3 (30)
Premature discharge from ICU	2 (8)	2 (13)	0 (0)
Others	14 (56)	7 (47)	7 (70)
Severity			
Consideration	20 (80)	12 (80)	8 (80)
Concern	3 (12)	3 (20)	0 (0)
Adverse event	0 (0)	0 (0)	0 (0)
Not recorded	2 (8)	0 (0)	2 (20)
Did it affect outcome?			
Made no difference	12 (48)	7 (47)	5 (50)
May have contributed to death	11 (44)	8 (53)	3 (30)
Caused death	0 (0)	0 (0)	0 (0)
Not recorded	2 (8)	0 (0)	2 (20)
Was it preventable?			
Definitely	0 (0)	0 (0)	0 (0)
Probably	6 (24)	5 (33)	1 (10)
Probably not	11 (44)	7 (47)	4 (4)
Definitely not	1 (4)	1 (7)	0 (0)
Not recorded	7 (28)	2 (13)	5 (50)
Associated with			
Surgical team	8 (32)	5 (33)	3 (30)
Another clinical team	9 (36)	5 (33)	4 (40)
Hospital	1 (4)	1 (7)	0 (0)
Other	0 (0)	0 (0)	0 (0)
Not recorded	10 (40)	5 (33)	5 (50)

ICU, intensive care unit; OSCC, oral squamous cell carcinoma.

expiratory volume in 1 s (FEV1) and peak flow (PF) to be significant in determining post-operative pulmonary complications.[21] It was found that patients with an FEV1 average of 70.16%, and PF average 63% of predicted suffered from pulmonary complications while those without had an FEV1 average of 84.14% and PF average of 79.9% predicted.

While the majority of deaths were related to systemic cardiorespiratory causes, there was a significant 44% of patients who had unplanned return to theatre. This suggests that almost half of all deaths had surgical-related complications. These complications coupled with the stressors of having to undergo repeated general anaesthesia and surgery may have reduced the patient's cardiorespiratory reserve.

While poor preoperative status may have put patients at a lower baseline reserve, cumulative adverse events are important in tipping patients over the edge to their demise. It is difficult to draw conclusions regarding the extent of comorbidities compared to adverse post-operative events that contribute to mortality.

Limitations

This was a population-based study that looked at overall mortality and concerns identified, not a detailed operative and pathology study. The results presented the concerns, but it could not answer the detailed questions. Information was gathered from a predetermined set of questions present in a surgical case form that was designed for the audit process, then adapted and analysed for this study.

Data points such as advanced malignancy were answered in a binary yes or no. In-depth diagnosis such as details of the TNM classification were not available in the data set and this had limited the ability to correlate what other studies had suggested, that advanced malignancy predicted a much higher risk of death.[10]

With only 25 patients identified in the sample, there was limited meaningful statistical analysis. Further research with access to data from New South Wales may provide more numbers and also paint a more complete picture having the entire Australian population. Denominator data were not obtainable, hence statistical values of mortality rates were not calculated.

Suggestions for the ANZASM

OSCC resection is unique and additional data points specifically relevant to head and neck cancer can be included in the ANZASM to improve the analysability and usefulness of the data.

Mandatory inclusion of the TNM classification of all reported cases would ensure robustness of the data collected and enable more in-depth analysis. Comparison of mortality causes and rates between different disease stages would then be possible to produce more meaningful conclusions.

More information into the type of reconstruction methods could be collected. The Read codes in the data set stated if flap reconstruction was performed, critical information such as free versus pedicled flap or the type of donor flap was not included. With this information, we could determine if free flaps had higher rates of complications or if a specific type of donor flap had higher mortality rates.

Detailed indications and type of neck dissections performed could be included in the surgical case form during data collection. Elective versus therapeutic and selective versus radial neck dissections can have different complication and mortality rates. In addition, preoperative radiographic nodal level involvement and intraoperative nodal level involvement can be a useful metric to compare as this may influence the extent of the neck dissection and staging. Nodal level involvement can also act as a criterion to compare for mortality.

The availability and use of an MDT is another parameter that could be included in the ANZASM data collection. This is especially relevant as this study had several cases where the assessors felt the surgery should not have proceeded. An MDT could have prevented these mortalities but whether an MDT was involved was unknown.

Conclusion

This was the first Australian population-level study that explored the factors surrounding surgical mortality of OSCC. The decision to operate on high-risk patients, cardiovascular and respiratory causes were the major contributors to surgical mortality.

The small number of deaths and the limitation of using existing data limited statistical analysis and conclusions. Changes could be made to the ANZASM to enrich the results for analysis. Further research exploring factors by using similarly matched groups between survivors and non-survivors, then ultimately the establishment of an externally validated model to assess risk stratification especially in the context of cardiorespiratory risk, coupled with a multidisciplinary approach, will allow surgeons to make better decisions around patient selection and reduce avoidable surgical mortalities.

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Author Contributions

Yi Long Roy Ong: Conceptualization; formal analysis; funding acquisition; investigation; methodology; visualization; writing-original draft; writing-review and editing. **Paul Sambrook:** Conceptualization; supervision; writing-review and editing. **Guy Maddern:** Conceptualization; data curation; methodology; project administration; resources; supervision; writing-review and editing.

Conflicts of interest

None declared.

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CHAPTER 5 – DISCUSSION

Patient selection

The research used the national surgical audit data and found that many of the preventable deaths were related to poor patient selection. The surgeons and assessors felt that these patients had very high pre-operative risk due to various factors such as advanced age, co-existing systemic illnesses such are cardiac and respiratory conditions and advanced malignancy. Subjecting these patients to long periods of general anaesthesia and embarking on complex resections and reconstructions had led to their deaths.

Literature described the unique ethical considerations in the treatment of head and neck cancer. [17, 18] Disfigurement, dysfunction, and the threat to personal identity are possible consequences of disease management. In contrast, other cancer surgeries such as pneumonectomy, bowel resection, and prostatectomy while being life-altering surgeries, do not change the physical appearance or alter social functioning to the degree that mandibulectomy and maxillectomy can. Assessors who investigated the OSCC deaths in the audit iterated these ethical issues that surgeons had to tackle; being compelled to operate on a patient with a functionally and aesthetically debilitating surgical pathology yet at a very high risk of surgical mortality.

A suggestion could be involvement of a multidisciplinary team. This is well supported by evidence to offer more treatment options, alter clinical decisions, allow for a more comprehensive pre-operative assessment of the patient. [19] Risk stratification instruments validated specifically for head and neck cancer surgery could be used to assess patient's preoperative risk. [20, 21] Non-curative surgical resections should be considered for high risk patients, allowing for shorter and less risky surgeries to achieve functional improvement to improve their quality of life, while not subjecting them to excessive risk of surgical mortality.

Strengths and Limitations of using data from ANZASM

The audit data came from a nation-wide surgical mortality audit of which the process is covered in detail in chapter four. The strength of such a dataset is that the registration and governing body mandates full participation of the audit. [22] Which contributed to a comprehensive coverage of a large patient population. Because one of the principle objectives is to educate, [22] assessor feedback provided valuable insights on what could have been done differently to prevent those deaths.

This was a population based study that looked at overall mortality and concerns identified, not a detailed operative and pathology study. The results presented the concerns, but it could not answer the detailed questions. Information was gathered from a predetermined set of questions contained in a surgical case form that was designed for the audit process, then adapted and analysed for this study.

As we found in the systematic review, advanced T classification was associated with high risk of death. While the surgical diagnosis such as squamous cell carcinoma was included in the dataset, detailed characteristics such as the TNM staging that will give valuable information such as the size and extent of the cancer was not available in the data.

Detailed indications and type of neck dissections performed could be included in the surgical case form during data collection. Elective versus therapeutic and selective versus radial neck dissections can have different complication and mortality rates. In addition, pre-operative radiographic nodal level involvement and intraoperative nodal level involvement can be a useful metric to compare as this may influence the extent of the neck dissection and staging. Nodal level involvement can also act as a criterion to compare for mortality.

Comparison between Systematic Review findings and Australian surgical mortality data

The salient factors that increase the risk of surgical mortality of oral squamous cell carcinoma identified in the Systematic Review whose data came primarily from a North American source were advanced age, had a T4 classification and a positive comorbidity index. In contrast, deaths identified in the ANZASM data were related majority to cardiorespiratory causes and poor patient selection.

The cardiorespiratory deaths were associated with pre-existing related comorbidities, which would have contributed to a positive comorbidity index score. This paralleled the suggestion from the Systematic Review that higher comorbidity index scores corelates to a higher risk of death. However, the comorbidity index also consists of many other factors, which included N (nodal spread) classification, which was shown not to be associated with increased risk of death. This highlights the perils of using an index score, which can include factors that may not contribute to increased risk of mortality.

Due to the lack of denominator data, the ANZASM data could not provide analysis between the patients who died and survived, hence the calculation of risk for the Australian population was not possible. This limited the opportunity to directly compare the factors from the ANZASM studies to the those of the Systematic Review. The ANZASM data, had an average and median age of patients who died 77 and 78 respectively, which echoes the Systematic Review on advanced age as a risk for mortality.

One of the salient findings from the ANZASM study was patient selection, this was not discussed in the systematic review.

CHAPTER 6 – CONCLUSION

This thesis found factors that contribute to surgical mortality of oral squamous cell carcinoma resection such as advanced age, T classification, comorbidities, and poor patient selection. But there is more work that needs to be done to address the knowledge gaps surrounding this issue. While the overall surgical mortality rate is 1%, in certain patient groups this rate could be as high as 5%, [13] this is not a negligible risk.

Further population analysis of cancer or surgical mortality databases from other countries need to be done. While databases and audits are often designed to be concise and have a “one size fits all” approach for a wide diversity of conditions or surgeries, they are a potentially important tool to answer specific questions to learn about factors affecting surgical mortality. To extend usability of audit data, detailed diagnoses needed to be included, such as the cell type and TNM staging classification. As palliative surgery was suggested in the ANZASM study to reduce surgical mortality, surgical intent is another important data point to collect. This is to identify deaths surrounding curative versus palliative surgery. A comprehensive pre-operative assessment of comorbidities and clear cause of death will also be needed to compare between factors.

Ultimately the establishment of an externally validated model to assess risk stratification will allow surgeons to make better decisions around patient selection and reduce avoidable surgical mortalities.

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