1 Project Details			
Protocol/Research Project Title:	**Outcomes in patients with high risk intramucosal cancer and superficial submucosal oesophageal adenocarcinoma managed initially with endoscopic local resection – a multi-centre retrospective study**		
Protocol Number (Version and Date):	1.1 – 29.11.2022		
Project Start Date:	02.01.2023	**Project Finish Date:**	29.12.2023
Coordinating Principal Investigator Name:	Dr Spiro Raftopoulos		
Coordinating Principal Investigator Contact Details:	Spiro.raftopoulos@health.wa.gov.au		

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1.1 Project Summary

Contemporary treatment of early oesophageal (food pipe) cancer, involves minimally invasive endoscopic procedures; while surgery is reserved only for cases with the highest-risk of the cancer spreading into the surrounding tissues.

The risk of cancer spread is determined by samples removed at endoscopy, in which a pathologist is looking to see the depth of cancer spread into the wall of the oesophagus or for abnormal characteristics of the cancer. Conventionally, higher risk of cancer spreading is linked to whether the cancer has reached the deeper layers of the oesophagus containing (lymphatic) draining vessels or if the cancer has very abnormal characteristics. However, many patients who are considered high-risk of cancer spreading and then go on to have surgery were later found to have no left-over cancer making the surgery unnecessary.

Thus, the prognostication of cancer spread, disease recurrence, morbidity and cancer-related mortality based histopathological findings after endoscopic resection of these oesophageal cancers requires further study.

Therefore, the purpose of this study is to try and identify patients who are considered higher risk by conventional practice, who are actually at low risk for cancer spread; and, thus can forgo the need for a major operation with poor post-operative outcomes with respect to quality of life, morbidity and mortality. This study will detail patients who have been prospectively followed up after they underwent endoscopic resection of high-risk oesophageal cancer to determine rates of cancer recurrence both locally, nodally or metastatic; mortality and causes of death; surgical mortality and morbidity in surgical candidates; use of adjuvant chemotherapy/radiotherapy post ELR/surgery; method of ELR (EMR, ESD); and cancer-free survival. These findings will then be used to determine which patients, with lower risk of cancer spread would be considered candidates for non-surgical management, to avoid an unnecessary (major) oesophageal operation.

2 Rationale / Background

In recent decades, endoscopic local resection (ELR) has become the treatment of choice for early oesophageal adenocarcinoma (EAC) with surgery reserved for high-risk cases where risk of nodal metastasis is high and therefore justifies the mortality and morbidity associated with oesophagectomy.

The potential of ELR to be a curative organ preserving treatment depends on the adequacy of the resection and the risk of lymph node metastasis. In general, early cancers confined to the mucosal layer (T1a) without high-risk features (absent lymphovascular invasion, clear deep margins, absent poor differentiation) carry a low risk of lymph node involvement of 1.3-2.5 % (1, 2, 3).

In contrast, patients with submucosal invasion (T1b) or T1a cancer with other high-risk features (presence of LVI, poor differentiation) carry an increased risk of nodal metastasis of 12-31% (2, 3). Whilst commonly performed CT, PET and EUS have a low sensitivity in locoregional lymph node staging with very early metastatic disease and therefore many of these patients proceed to oesophagectomy for definitive surgical nodal staging. Recent studies have suggested a lower risk of lymph node metastasis of 4% with very early SM1 invasion (4) however no Australian data exists, and case numbers are small.

3 Project Aims / Objectives / Hypotheses

The aim of this study is to investigate the clinical implications and long-term outcomes of patients with high risk T1a and all T1b oesophageal cancers managed in Australia and New Zealand via ELR over the last 12 years.

Primary Endpoints:
1. To assess the rates of cancer recurrence both locally, nodally or metastatic.

Secondary Endpoints:
1. To determine patient survival and describe the cause(s) of death
2. To describe surgical mortality and morbidity in surgical candidates
3. To describe the use of adjuvant chemotherapy/radiotherapy post ELR/surgery
4. To describe the method of ELR, including EMR, ESD
5. To determine cancer-free survival

4 Project Design

The scientific integrity of the project and the credibility of the project data depend substantially on the project design and methodology.

4.1 Project Design

This study is a retrospective multi-centred cohort study of patients undergoing ELR for early oesophageal cancer.

4.2 Source and Selection of Participants

Eligible patients include all those with histopathological evidence of high-risk T1a (LVI positive or poor differentiation) and T1b oesophageal cancers treated across Australia and New Zealand from 1Jan 2010 to 31 Dec 2022. Data will be sourced from gastroenterologists, endoscopy databases, treatment databases, and chart review (including paper-based and electronic medical records). Demographic, clinical, and histopathological findings will be collected by investigators of each study site on a predefined data collection tool. The sample size will be approximately 200 cases (each site will be approximately 20 cases).

4.2.1 Participant inclusion criteria

All patients ≥18 years-old, with a diagnosis of high risk T1a (HR-IMC) and T1b EAC on ELR specimens.

4.3 Participant exclusion criteria

- Age < 18 years;
- Prior surgery for oesophageal cancer
- Known Lymph node or distant metastasis seen on baseline staging EUS, CT or PET

4.4 Participant withdrawal criteria

Not applicable as study is utilising a Waiver of Consent

4.5 Bias

Not applicable: we are looking at outcomes related to histopathological findings within a cohort of patients with oesophageal cancer.

4.6 Blinding and Randomisation

Not applicable to this study.

4.7 Methods

Patients will be identified through query of pathology, endoscopy and treatment databases at each participating centre. Patient demographics (age, gender), details of staging investigations including EUS, CT or PET scans over study period, surgical outcomes including any associated morbidity and mortality, outcome at last clinical review (disease free, recurrence, death).

All pathology slides from each study centre will be reviewed by their own institutional pathologist and record histopathology findings as per the RCPA standardised reporting guidelines. All slides will undergo central review by the lead site (Investigator Prof. Priyanthi Kumarasinghe, a well-recognised

expert in this area) to ensure concordant histology findings. In the event there is a discrepancy between the central review and peripheral site, a third pathologist from one of the other study sites will be asked to review for a consensus opinion.

4.8 Project Duration/Schedule

The study duration will be 1 year. Our plan is as follows;

It is planned to have ethics approval completed by January 2023 with data collection commencing February ’23 and completed by April ’23. Review of pathology slides will commence once data collection has completed and concluded by June ’23. Preliminary data will be presented at the Australian New Zealand Endoscopic Leaders Forum (ANZELF) in August ’23 and at the Australian Gastroenterology Week (AGW) in September '23. Manuscript submission for publication will be completed by December ‘23

4.9 Project Termination

This project will terminate upon the successful collection and analysis.

5 Treatment of Participants

5.1 Description and justification for treatments, interventions or methods to be utilised

Not applicable as only data will be collected under a Waiver of Consent.

6 Assessment of Safety

6.1 Risks and Benefits

As this is a retrospective review of outcome in patients who have already undergone ELR or surgical treatment for EAC, there is no immediate or late risks to the study participants. Given the lack of evidence about cancer recurrence, the risk of cancer-spread, morbidity and mortality in individuals with oesophageal cancer, this study will produce real-world findings which will significantly benefit future patients and better inform clinicians as to the need for further surgical intervention or whether surgery can be avoided entirely.

7 Data Management, Statistical Analysis and Record Keeping

7.1 Statistics and Interim Analysis

A sample of 200 participants’ data (approximately 20 at each site) will be reviewed for this descriptive study.

Patients will be stratified according to histopathological grading (T1a/T1b disease or AJCC staging) and treatment (ELR vs surgical) status. Descriptive summaries of patient cohort demographic and clinical data will consist of frequency distributions (n, %) for categorical data and means and standard deviations or medians and interquartile ranges for continuous data, depending on data distribution. Incidences of cancer recurrence (local, nodal or metastatic) and mortality outcomes (overall and disease-free survival) over the study period will be described using frequency distributions. Time to event survival outcomes (recurrence and mortality) will be examined using Kaplan-Meier survival probabilities and summarised using medians and 95% confidence intervals (CIs).

Stata version 17.0 (StataCorp, College Station, TX) will be used for data analysis and significance (alpha) will be set at 0.05.

7.2 Sample Size

This cohort of patients with T1b and HR-IMC represent only a small percentage of patients resected via ELR. It is therefore expected that each treatment site will likely only have between 10-20 patients over the study period. There are 16 study centres involved and therefore it is expected to have a sample size of approximately 200 patients.

7.3 Study Power and Significance

Poisson regression rates and rate ratios with 95%CIs will be used to describe and assess outcomes with few events.

7.4 Statistical plan deviations

Any deviations from the original statistical analysis plan will be described in protocol amendments and in the manuscript of the final paper.

7.5 Selection of participants for analyses

All consecutive patients who have undergo ELR for EAC and have been identified to have T1b and HR-IMC cancer in the resection specimen where complete data collection is available.

7.6 Data Management

Each study centre will maintain a separate password protected electronic file that will link the patient study number to the medical record number for data collection purposes. This log will be stored in each respective study centres hospital network and will not leave each study centre. Each included patient data will be collected on a data sheet with no identifiers (name, date of birth) apart from the unique study ID in the event further information is required. All completed data sheets will be sent via secure file transfer to the primary study centre for entry into a secured electronic database which will be hosted on the Sir Charles Gairdner Hospital Intranet. This network is not available from outside the hospital and requires a valid Novel Password to access. Once accessed a second password will be required to access the electronic study database. Only the Chief Investigator (Dr Spiro Raftopoulus), and Associate Investigator (Ms Warren Raymond) will have access to the de-identified study data.

All investigators/researchers involved with this project will adhere to and follow the WA Health Information Retention and Disposal Policy.

Regarding transfer of slides to the central pathology review site at PathWest Laboratory at Sir Charles Gairdner Hospital and in the event a third opinion is required by a third site pathologist for consensus opinion, all slides will be de-identified and only contain the patients unique study ID. Were available, slides will be scanned using the pathology laboratories slide scanner and then sent via secure file transfer to the review centre. Where a slide scanner is not available, these slides with be sent via registered courier services to the review centre.

7.7 Procedure for accounting for missing, unused, and spurious (*false*) data.

As this is a nation-wide, multi-centred study, each site will be responsible for the provision and integrity of the data provided to the study team.

8 Monitoring / Audit

8.1 Monitoring, Audit and Regulatory Inspections Statement

All project investigators/institutions will adhere to the conditions of approval and project-related monitoring, audits, and regulatory inspections, providing direct access to source data/documents. This may include, but not limited to, review by Human Research Ethics Committees and institutional governance review bodies. At a minimum annual progress reports and a final report will be provided.

8.2 Procedures for Monitoring and auditing

All sites will maintain a study log with enrolled patients. This log will be stored in a locked research office that is restricted to study research staff and will be available for review if required for any monitoring and audit reviews.

9 Quality Control And Quality Assurance

9.1 Compliance statement

This project will be conducted according to the approved protocol and its amendments, Good Clinical Practice and in accordance with relevant national guidelines and regulatory requirements. The investigator will ensure that this study is conducted in agreement with the Declaration of Helsinki and the NHMRC National Statement on Ethical Conduct in Human Research. Any protocol deviations and/or violations will be recorded and reported to the relevant regulatory bodies. The investigators will not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s). Changes and amendments to the protocol will only be implemented after approval by the Institutional HREC and associated regulatory committees.

9.2 Quality control

The validity of collected data will be confirmed by expert pathologists review at the primary site (central review) with any discrepancy in the original pathology report resolved through a third opinion for consensus outcome.

The statistician (AI: Warren Raymond – UWA/SCGH) will analyse the data provided by each site relative to the data of all other centres, deviations of site-specific demographic, clinical, comorbidity data of more than >15% will be asked to review their database for missing or incomplete data.

10 Ethics

10.1 Consent

As this is a retrospective review of outcomes in patients who have already undergone treatment, we are seeing a waiver of consent, as per Section 2.3.10 of the National Statement. Specifically:

a) Involvement in the research carries no more than low risk (see paragraphs 2.1.6 and 2.1.7, page 20) to participants

This study involves the use of existing data sets recorded in the patient medical records of each participating site including data that has been prospective collected in specific treatment databases as part of routine clinical care. As such, we consider it to be of negligible risk to participants or their communities. There is no foreseeable risk of harm or discomfort (as per the NHMRC National Statement on Ethical Conduct in Human Research, 2007) other than the risk of a *breach of privacy and confidentiality*. We consider the steps outlined below (criteria e & f) to provide sufficient protection against these risks.

b) The benefits from the research justify any risks of harm associated with not seeking consent

The potential benefits of the study include *identification of future patients with T1b and HR-IMC oesophageal cancer resected via ELR be considered lower risk based on our data and thereby avoid the need for highly morbid (40%) surgeries which carry a risk of death in up to 10% even in expert centres.* We therefore consider these benefits to outweigh the manageable risks associated with breach of confidentiality.

c) It is impracticable to obtain consent (for example, due to the quantity, age or accessibility of records)

We consider it to be impracticable to seek the consent of the patients for the use of their data because the data to be included in this project has been collected over 11 years (2012 – 2023) in ≥160 patients with EAC. Given the nature of the disease and that many patients who did not undergo surgery following identification of T1b/HR-IMC cancers due to age and co-morbidities, it is estimated that 20% may already be deceased from the primary disease or other co-existing co-morbidities. Given the low numbers of patients in each study centre, it is critically that all patients are included in the analysis to provide meaningful clinical outcomes

d) There is no known or likely reason for thinking that participants would not have consented if they had been asked

Given the negligible risk, lack of impact or burden on individual patients and provisions to ensure privacy and confidentiality, there is no known or likely reason that patients would not have consented could they be asked.

e) There is sufficient protection of their privacy?

In order to protect patient privacy, the CPI at each site will assign each patient a unique study number against which data from all sources will be entered into the study datasheet. During the data collection and checking phases, the CPI will maintain a separate password protected electronic file that will link the patient study number to the medical record number with no other identifiable data collected (e.g. name, date of birth), making the study dataset re-identifiable (coded) during these phases. Once the dataset is finalised and the data has been checked for errors or missing data, the file containing the link codes will be deleted, rendering the study dataset non-identifiable. With all pathology slides sent electronically or via registered post, these slides will be de-identified prior to sending and will only include the unique study identifier to enable entry into the database.

f) There is an adequate plan to protect the confidentiality of data

Patient privacy and confidentiality will be protected as far as the law allows. The re-identifiable (coded) electronic data file and the separate link file will be password protected and held on secure Department of Health Server at each study site. No identifiable data will leave each study site

g) **In case the results have significance for the participants' welfare there is, where practicable, a plan for making information arising from the research available to them (for example, via a disease-specific website or regional news media)**
The study will involve only the use of existing, routinely-obtained, data and will not impact on participant welfare. The results of the study will be made publicly available in aggregate form (individuals not identifiable) via presentation at conferences and publication.

h) **The possibility of commercial exploitation of derivatives of the data or tissue will not deprive the participants of any financial benefits to which they would be entitled**
The study is not funded by a commercial organisation and there is no opportunity for commercial exploitation of the data.

i) **The waiver is not prohibited by State, federal, or international law**
To the best of our knowledge, a waiver of consent is not prohibited by state, federal or international law.

11 Budget, Financing, Indemnity And Insurance

Each study site investigator will provide their time in-kind with no financial remuneration paid towards data collection. The only anticipate costs would relate to costs of scanning and / or sending slides for central pathology review and the costs associated with facilitating ethics and governance together with statistical analysis. This study has received a start-up research grant of $10,000 as a selected protocol which was presented at the Australian New Zealand Endoscopic Leaders Forum (ANZELF) in August '22 and a grant application has been made to the WA Cancer and Palliative Care Network to assist with the remainder of the study costs.

12 Publication

The results will be presented at the next ANZELF meeting scheduled for August '23 and then later at both national and international meetings. It is then planned for later submission to a high impact peer reviewed journal for publication.

13 References

1. Kumarasinghe MP, Brown I, Raftopoulos S, Bourke MJ, Charlton A, de Boer WB, et al. Standardised reporting protocol for endoscopic resection for Barrett oesophagus associated neoplasia: expert consensus recommendations. Pathology. 2014;46(6):473-80.
2. Pech O, May A, Gunter E, Gossner L, Ell C. The impact of endoscopic ultrasound and computed tomography on the TNM staging of early cancer in Barrett's esophagus. The American journal of gastroenterology. 2006;101(10):2223-9.
3. Dunbar KB, Spechler SJ. The risk of lymph-node metastases in patients with high-grade dysplasia or intramucosal carcinoma in Barrett's esophagus: a systematic review. The American journal of gastroenterology. 2012;107(6):850-62; quiz 63.
4. Graham D, Sever N, Magee C, Waddingham W, Banks M, Sweis R, et al. Risk of lymph node metastases in patients with T1b oesophageal adenocarcinoma: A retrospective single centre experience. World journal of gastroenterology : WJG. 2018;24(41):4698-707.

14 Appendices

Form 1 – Data Collection Form

Patient Study ID: INSCODE-xxx
Unique study ID, centre specific
Date of Study Entry: dd/mm/yyyy

This is the date of diagnosis (i.e. index procedure when diagnosis established)

DEMOGRAPHICS
Gender: M/F
Patient gender
Age: yy
Age of patient in years at date of study entry
Comorbidity Score: Charlson Comorbidity index

HISTOLOGY
Depth of Invasion: STOLTE (M1-4, SM), AJCC (M1-3, SM)
This is the depth of tumour invasion reported as both STOLTE and AJCC
Depth of Invasion in SM: xx microns
Grade of Tumour: Well Differentiated / Moderately Differentiated / Poorly Differentiated
LVI Status: Present / Absent
Reported presence or absence of lymphatic and capillary space invasion
Vein/Artery Invasion: Present / Absent
Reported presence or absence of vein and/or artery space invasion
Perineural Invasion: Present / Absent
Reported presence or absence of perineural invasion
Size/Volume of Tumour (mm):

OUTCOME POST MDT
Referred for Surgery: No (Co-morbidities), No (patients' preference), Yes
Referred for Adjuvant Chemo/Radiotherapy: No, Yes (Chemo), Yes (Radio), Yes (chemo/radio)
Date of Surgery: dd/mm/yyyy
Residual Tumour: No, Local, Nodal, Both
Number of LN Resected: xx
Number of +ve LN: xx
Referred for Neo-adjuvant Chemo/Radiotherapy: No, Yes (Chemo), Yes (Radio), Yes (chemo/radio)

FINAL OUTCOME
Study exit date: 31/12/2022
Date last reviewed: dd/mm/yyyy
*This is the **date of death** or **date of last chart/patient review** or date of lost-to-follow-up (emigration)*

Death status: Alive (0) or Died (1)
Cause of Death: OAC, Non-OAC, Non-malignant, Surgical Complication, chemotherapy Complication
Cancer status: Remission, Recurrence (Nodal/Local/Metastatic)
PET Date: dd/mm/yyyy
PET Results: Normal / Abnormal
CT Date: dd/mm/yyyy
CT Result: Normal / Abnormal
Endoscopy Date: dd/mm/yyyy
Endoscopy Result: Dysplasia Absent, New Dysplasia (low risk), New Dysplasia (high risk), Recurrent Dysplasia
Referred for Salvage Surgery: No (remission), No (Co-morbidities), No (patients' preference), Yes
Referred for Adjuvant Chemo/Radiotherapy: No, Yes (Chemo), Yes (Radio), Yes (chemo/radio)
Date of Surgery: dd/mm/yyyy
Residual Tumour: No, Local, Nodal, Metastatic
Number of LN Resected: xx
Number of +ve LN: xx
Referred for Neo-adjuvant Chemo/Radiotherapy: No, Yes (Chemo), Yes (Radio), Yes (chemo/radio)