Study Protocol

Survival and Patterns of Care in the Era of FLOT-based Chemotherapy for Gastric and Gastroesophageal Adenocarcinoma (SPACE-FLOT): An international multicentre cohort study

SPACE-FLOT

Version Number: 2.0

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Confidentiality Statement

The confidential information in this document is provided to you as an Investigator for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the chief investigator.

Statement of Compliance

This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

Study administrative structure

Study co-ordinating centres

Austin Health 145 Studley Rd, Heidelberg VIC 3084, Australia	**Peter MacCallum Cancer Centre** 305 Grattan St, Melbourne, VIC 3000, Australia
Box Hill Hospital 8 Arnold St, Box Hill VIC 3128, Australia	**Flinders Medical Centre** Flinders Dr, Bedford Park SA 5042, Australia

Chief Principle Investigators and affiliations

Dr. David Liu
Upper GI Surgery Unit. Austin Health, 145 Studley Rd, Heidelberg VIC 3084, Australia
Email: liuzdx@austin.org.au

A/Prof. Cuong Duong
Division of Cancer Surgery, Peter MacCallum Cancer Centre, 305 Grattan St, Melbourne, VIC 3000, Australia
Email: cuong.duong@petermac.org

Steering Committee, Principle Investigators and affiliations

Dr. Margaret Lee
Department of Medical Oncology, Box Hill Hospital, 8 Arnold St, Box Hill VIC 3128, Australia
Email: margaret.mwlee@gmail.com

A/Prof. Ahmad Aly
Upper GI Surgery Unit, Austin Health, 145 Studley Rd, Heidelberg VIC 3084, Australia
Email: aaly@outlook.com.au

Dr. Tim Bright
Oesophago-Gastric Surgery Unit, Flinders Medical Centre, Flinders Dr, Bedford Park SA 5042, Australia
Email: tim.bright@sa.gov.au

Prof. David Watson
Oesophago-Gastric Surgery Unit, Flinders Medical Centre, Flinders Dr, Bedford Park SA 5042, Australia
Email: david.watson@flinders.edu.au

Project Management Group and affiliations

Dr. David Liu
Coordinating medical officer
Austin Health, 145 Studley Rd, Heidelberg VIC 3084, Australia
Email: liuzdx@austin.org.au

Dr. Geraldine Ooi
Australian lead
Monash Health, 246 Clayton Rd, Clayton, VIC 3168
Email: geraldineooi@gmail.com

Dr. Enoch Wong
Australian lead
Eastern Health, 8 Arnold St, Box Hill VIC 3128, Australia
Email: enochwong07@yahoo.com.au

Dr. Sean Stevens
Australian lead
Austin Health, 145 Studley Rd, Heidelberg VIC 3084, Australia
Email: enochwong07@yahoo.com.au

Dr. James Tan
New Zealand Lead
Northshore Hospital, 124 Shakespeare Rd, Takapuna, Auckland 0620, New Zealand
Email: james.tan@icloud.com

Dr. Tim Bright
United Kingdom, France, Sweden Lead
Flinders Medical Centre, Flinders Dr, Bedford Park SA 5042, Australia
Email: tim.bright@sa.gov.au

Dr. Matthew Read
The Netherlands Lead
St Vincent's Health, 41 Victoria Parade, Fitzroy VIC 3065, Australia
Email: mattread80@gmail.com

A/Prof. Cuong Duong
Asia and Pacific Lead
Peter MacCallum Cancer Centre, 305 Grattan St, Melbourne, VIC 3000, Australia
Email: cuong.duong@petermac.org

Prof. David Watson
North America Lead
Flinders Medical Centre, Flinders Dr, Bedford Park SA 5042, Australia
Email: david.watson@flinders.edu.au

Dr. Su Kah Goh
Database design
Austin Health, 145 Studley Rd, Heidelberg VIC 3084, Australia
Email: sukah84@hotmail.com

Dr. Sonia Gill
Web-media design
Austin Health, 145 Studley Rd, Heidelberg VIC 3084, Australia
Email: soniagill24@gmail.com

Dr. Candyce Cheng
Communications
Austin Health, 145 Studley Rd, Heidelberg VIC 3084, Australia
Email: candy.chaocheng@gmail.com

Dr. Darren Wong
Biostatistician
Austin Health, 145 Studley Rd, Heidelberg VIC 3084, Australia
Email: darren.wong@austin.org.au

Ms. Kat Hall
Clinical Research Coordinator
Austin Health, 145 Studley Rd, Heidelberg VIC 3084, Australia
Email: Kat.PENNA@austin.org.au

Protocol Synopsis

Background and Rationale	Gastric and gastroesophageal cancers are common and carry exceedingly high mortality rates. Of those patients treated with curative intent, the majority have locally advanced disease, and require chemotherapy before and after radical surgery. Since 2017, 5-fluorouracil, leucovorin, oxaliplatin and paclitaxel (FLOT) based chemotherapy has become the most commonly used perioperative regimen. Prognostic biomarkers are disease indicators which can predict survival outcomes. These biomarkers may facilitate patient counselling, inform treatment decision-making, and reflect tumour biology. Tumour regression grade (TRG) is a histological method of assessing and classifying a tumour's response to preoperative chemotherapy. However, whether TRG correlates with patient survival remains controversial. This is particularly so in the era of FLOT-based chemotherapy, where there is currently a paucity of data to guide clinical practice. Therapeutic biomarkers predict a tumour's response to treatment, enabling the identification of patient subpopulations that are more or less likely to benefit from a specific therapy. In this way, anti-cancer therapies can be personalised to maximise efficacy and minimise harm. This is particularly important in gastric and gastroesophageal cancers, as 40% of patients do not complete postoperative chemotherapy due to treatment-related toxicities and poor performance status. To date, the role of TRG as a therapeutic biomarker for FLOT-based chemotherapy has not been evaluated. Based on our institutional data, 40% of resected gastric and gastroesophageal cancers demonstrate minimal or no response to preoperative FLOT-based chemotherapy. In contrast, 20% of tumours exhibit complete pathological regression. Whether these two cohort of patients derive further benefit (or harm) from postoperative FLOT-based chemotherapy requires clarification. It stands to reason that in cancers which do not respond to one specific treatment, administering more of the same in the postoperative period is potentially futile and harmful. Conversely, in patients with no residual disease, additional postoperative chemotherapy may be unnecessary, and again, potentially harmful. Anecdotally, a lack of evidence to guide decision-making in this area has resulted in variation in practice. This includes continuing with more FLOT-based chemotherapy, withholding additional treatments, changing therapeutic regimens, or prescribing (chemo)radiation. To date, the pattern of care in the postoperative setting for patients with complete pathological response, and those with minimal or no response to preoperative FLOT-based chemotherapy is yet to be described.

Research Questions	In patients with gastric and gastroesophageal cancers who have undergone preoperative FLOT-based chemotherapy and radical surgery: 1. Does pathological response in the resection specimen predict patient survival? 2. What are the international patterns of care for patients with complete pathological response (pCR) and minimal/no pathological response to preoperative chemotherapy in the postoperative setting? 3. What are the clinicopathological predictors of tumour regression? 4. Does the cohort with pCR benefit from further postoperative FLOT-based chemotherapy? 5. Does the cohort with minimal/no response benefit from further postoperative FLOT-based chemotherapy?
Study Objectives	To audit the patterns of care and survival outcomes of patients with gastric and gastroesophageal adenocarcinoma who have undergone preoperative FLOT-based chemotherapy and radical surgical resection stratified by pathological response in the resected specimen.
Study Design	This study is an international (Australia, New Zealand, Singapore, Malaysia, Hong Kong, Vietnam, India, England, Ireland, Sweden, The Netherlands, France, and Canada) retrospective analysis of practice and outcomes between January 1 2017 to Dec 31 2022. Follow-up data collection is out to Dec 31, 2022 as we need a minimum one-year survival data. Using a trainee-driven collaborative research model, de-identified data from at least 1500 patients across >25 centres (based on power calculations) with gastric and gastroesophageal cancers who have received preoperative FLOT-based chemotherapy will be collated into a centralised database and analysed. **Primary endpoint**: Two-year disease-free survival. **Secondary endpoints**: • One-year overall survival • Two-year overall survival • One-year disease-free survival.
Eligibility Criteria	Inclusion Criteria • Any patient with gastric and gastroesophageal cancer • Received preoperative FLOT-based chemotherapy and surgical resection between 01/01/2017 to 01/01/2022 • Age ≥18 years-of-age
Statistical Considerations	Univariate, multivariate, Kaplan Meier and cox regression analysis will be used in this study
Study Duration	6 years
Study sponsor	Peter MacCallum Cancer Centre 305 Grattan St, Melbourne, VIC 3000, Australia

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1. Background and Rationale

1.1 Incidence and impact of gastric and gastroesophageal cancers

Gastric and gastroesophageal adenocarcinomas represent the seventh most prevalent malignancy world-wide.[1] This disease carries a disproportionally high mortality rate, evidenced by its ranking as the third most common cause of cancer-related deaths.[1]

1.2 Current treatments for curable gastric and gastroesophageal cancers

Approximately 30-40% of patients diagnosed with gastric and gastroesophageal cancers are treated with curative intent.[2] Of these only the minority present with early stage disease which is curable by surgery alone. The remainder of patients have locally advanced disease at diagnosis, and are typically treated with multimodality therapy. In this context, the management algorithms for locally advanced gastric/gastroesophageal cancers differ considerably between Eastern and Western countries.[3, 4] In the East, surgery is typically performed upfront, followed by chemotherapy or chemoradiotherapy. Of note, these chemotherapeutic regimens commonly contain tegafur/gimeracil/oteracil (S-1), which is poorly metabolised and toxic amongst the Caucasian population. Therefore, S-1 containing regimens are not routinely used in the West. By comparison, the standard-of-care across many Australian and European centres is perioperative chemotherapy. Traditionally, as per the MAGIC protocol, this consisted of three cycles of epirubicin, cisplatin and 5-fluorouracil (ECF) or capecitabine (ECX) pre- and post-surgical resection.[5] More recently, these regimens have been superseded by the combination of 5-fluorouracil, leucovorin, oxaliplatin and paclitaxel (FLOT) based on superior oncological outcomes over ECF and ECX.[6]

1.3 Prognostic biomarkers for gastric and gastroesophageal cancers

Prognostic biomarkers are clinical and molecular indicators of disease which can predict survival outcomes.[7] In general, these biomarkers facilitate patient counselling, inform decision-making around treatment intent, reflect tumour biology, and potentially shed light into the underlying drivers of carcinogenesis. In gastric and gastroesophageal cancers, the most commonly used prognostic biomarker is tumour staging. This is based on the American Joint Committee on Cancer (AJCC) T, N and M classification.[8] Other validated prognostic biomarkers include patient age, tumour grade, histological resection margin, lymphovascular invasion, perineural infiltration, mismatch repair status, *her*2 overexpression, *TP53* gene mutations and perioperative surgical complications. In population-based studies, these factors have been repeatedly correlated to disease-free (DFS) and overall survival (OS).[9]

1.4 Tumour regression grade as a prognostic biomarker

TRG is a histological method of assessing and classifying a tumour's response to treatment.[10] In practice, this assessment is usually undertaken in resection specimens following neoadjuvant chemotherapy or chemoradiotherapy, and is routinely included (for most centres) within the pathology synoptic report. Intuitively, TRG should provide important insights, albeit at one point in time, into tumour biology particularly with regards to the efficacy of anti-cancer treatments. However, whether TRG correlates with DFS and OS in patients with gastroesophageal cancers remains controversial.[11] Table 1.1 highlights key studies which support TRG as a predictor of disease survival, whilst Table 1.2

summarises studies that refute this finding. Multiple reasons may contribute to these differences and limit the clinical applicability of these studies. Firstly, different laboratories apply variable criteria (e.g., Mandard, Becker, AJCC, JES etc) for grading tumour regression. Secondly, there may be inter-observer variability in the classification of TRG. Thirdly, not all scoring systems are designed to evaluate response after chemotherapy. Fourthly, there are geographical variations in the pattern of care for patients with gastroesophageal cancer, which hinders the extrapolation and merging of datasets. Finally, and of particular relevance to our study, the published reports to date are based on chemotherapeutic regimens that are no longer standard-of-care in Western countries. In order to overcome some of these limitations, an internationally agreed method of reporting TRG was established following a consensus Delphi survey (Table 1.3).[12]

Table 1.1. Studies demonstrating that TRG *IS* predictive of patient survival

Author, Year	Study type	Key findings	Limitations
Li et al, 2018 [13]	Meta-analysis, 7 trials N=1143 Period: 1988 – 2015	pCR after neoadj CTx in gastric and GOJ ca is a/w higher OS and DFS. pCR 6.7%	- Pre-FLOT - Not periop CTx
Tomasello et al, 2017 [14]	Meta-analysis, 17 studies, N=3145 Period: pre 06/2016	pCR after neoadj CTx in GOJ ca is a/w higher OS and DFS a/w poor TRG	- Pre-FLOT - Not periop CTx
Hayashi et al, 2020 [15]	Meta-analysis, 14 studies, N=1660 Period: 2011-2015	TRG post neoadj CTx is predictive of OS	- Pre-FLOT - Mixed CTx regimens
Ajani et al, 2005 [8]	Trial, GOJ and gastric AC N=41 Period: pre 2005	pCR after taxane based CRTx correlated with OS pCR: 20%	- Pre-FLOT - Not periop CTx - Uses RTx - Low power
Xu et al, 2019 [16]	Retrospective N=264 Period: 2012-2017	Gastric and GOJ ca SOX, XELOX TRG correlated with OS	- Pre-FLOT - Not periop CTx - Uses S1
Stark et al 2019 [17]	Retrospective N=77	Gastric ca Uses neoadj CRTx Residual ypN1 correlated with worse OS	- Uses RTx - Low power
McNamara et al 2016 [18]	Retrospective N=60 Period: 2008-2012	Gastric ca Uses ECF or ECX + adj CRTx Residual disease predicts OS	- Pre-FLOT - Low power
Lombardi et al, 2021 [19]	Retrospective, single centre N=100 Period: pre 2021	TRG post neoadj CTx, is predictive of DFS and DSS	- Low power - No analysis on OS
Tong et al, 2021 [20]	Retrospective, single centre N=290	Gastric ca, neoadj SOX TRG, Mandard and Becker, independently predicts OS	- Low power
Derieux et al, 2020 [21]	Retrospective, 2 centres N=109 Period: 1997-2016	Gastric ca, neoadj CTx TRG, Mandard independently predicts DFS and OS	- Pre-FLOT - Low power
Achilli et al, 2017 [22]	Retrospective, 2 centres N=67 Period: 2009-2015	Gastric ca, neoadj ECF or ECX. TRG Becker, independently predict OS, DFS	- Pre-FLOT - Low power
Bausys et al, 2021 [23]	Retrospective, single centre N=87	LN response to preop CTx a/w increase OS	- Single centre - Small numbers
Pereira et al 2020 [24]	Retrospective, single centre N=62 Period: 2009-2018	Gastric cancer, neoadj Lymph node regression correlate with DFS and OS	- single centre - Small numbers - Pre-FLOT

AC = adenocarcinoma, a/w = associated with, ca = cancer, CTx = chemotherapy, CRTx = chemoradiotherapy, DSS = disease specific survival, GOJ = gastroesophageal junction, LN = lymph node, neoadj = neoadjuvant, pCR = pathologic complete response, periop = perioperative, SOX = S1 plus oxaliplatin, XELOX = capecitabine plus oxaliplatin

Table 1.2. Studies demonstrating that TRG *IS NOT* predictive of patient survival

Author, Year	Study type	Key findings	Limitations
Petrelli et al, 2017 [25]	Meta-analysis, 22 neoadj trials for GOJ ca N=4749 Period: pre 2017	pCR after CRTx or CTx did not correlate with OS or DFS r2 for DFS = 0.27, pCR=0.17	- Pre-FLOT - Both CRTx and CTx
Ikoma et al 2020 [26]	Retrospective, N=356 Period <2020	CRTx, or CTx in gastric ca TRG not a/w OS	- Both CRTx and CTx
Tong et al 2020 [27]	Retrospective, single centre N=290	Gastric ca, neoadj SOX TRG does not independently predict OS or DFS	- Uses S1 - Single centre
Pereira et al 2020 [24]	Retrospective, single centre N=62 Period: 2009-2018	Gastric ca, neoadj Primary tumour resp does not correlate with DFS	- Single centre - Pre-FLOT
Zhu et al, 2017 [28]	Retrospective, single centre N=192 Period: pre 2017	Gastric ca, neoadj, comparison of 5 TRG. TRG does not independently predict OS or DFS. Mandard is most reliable	- Single centre - Pre-FLOT

a/w = associated with, ca = cancer, CTx = chemotherapy, CRTx = chemoradiotherapy, GOJ = gastroesophageal junction, Neoadj = neoadjuvant, pCR = pathologic complete response, r2 = correlation coefficient, SOX = S1 plus oxaliplatin

Table 1.3. TRG: international consensus for GOJ and oesophageal adenocarcinoma based on Delphi consensus survey [12]

Primary tumour		Lymph nodes	
Grade	**Description**	**Grade**	**Description**
1	No residual tumor (complete tumor regression)	A	no residual tumor (complete tumor regression)
2	<10% residual tumor (near-complete regression)	B	partial regression (tumor cells and regression)
3	10%-50% residual tumor (partial regression)	C	no regression (no sign of tumor response).
4	>50% residual tumor (minimal/no regression)		

1.5 Tumour regression grade as a therapeutic biomarker

Therapeutic biomarkers predict a tumour's response to treatment, enabling the identification of patient subpopulations that are likely to benefit or not benefit from a specific therapy.[7] In this way, anti-cancer therapies can be personalised to maximise efficacy and minimise harm. This is particularly important in gastric and gastroesophageal cancers, as 30-40% of patients do not complete adjuvant chemotherapy due to treatment-related toxicities.[5, 6] Additionally, 40% of patients in the FLOT4 trial did not receive any adjuvant chemotherapy due to poor performance status following surgical resection.[6] Although chemotherapy in general lacks companion biomarkers, recent studies using 18F-FDG PET and analysis of tumoral mismatch repair protein expression have provided proof-of-concept that chemotherapy in gastric and gastroesophageal cancers can be tailored to the individual patient.[29-31]

To date, the role of TRG as a therapeutic biomarker for FLOT-based chemotherapy has not been evaluated. Based on our institutional data, 40% of resected gastric and gastroesophageal cancers demonstrate minimal or no response to preoperative FLOT-based chemotherapy. In contrast, 20% of tumours exhibit complete pathological regression. A conundrum that is often faced by many clinicians is whether these two cohorts of patients derive any further benefit from adjuvant FLOT-based chemotherapy. It stands to reason that in cancers which do not respond to one specific treatment, administering more of the same in the adjuvant period is potentially futile and harmful. Conversely, in patients with no residual disease, additional postoperative chemotherapy may be unnecessary. As proof-of-concept, in locally advanced rectal cancers and early-stage breast cancers where a pathologic complete response (pCR) post neoadjuvant therapy has been achieved, further adjuvant chemotherapy is often not prescribed. Anecdotally, a lack of evidence to guide decision-making has resulted in variations in practice. In patients with minimal response to neoadjuvant therapy, variations in practice may include completing FLOT-based chemotherapy, withholding additional

treatments, changing therapeutic regimens, or prescribing chemoradiation. To date, the pattern of care in the adjuvant setting for patients with complete pathological response, and those with minimal or no response to preoperative FLOT-based chemotherapy is yet to be described.

2. Study Aims

To audit the patterns of care and survival outcomes of patients with gastric and gastroesophageal adenocarcinoma who have undergone preoperative FLOT-based chemotherapy and radical surgical resection stratified by pathological response in the resected specimen.

3. Research questions

This study will address the following questions to inform clinical practice. In patients with gastric and gastroesophageal cancers who have undergone preoperative FLOT-based chemotherapy and radical surgery:

1. Does pathological response in the resection specimen predict patient survival?
2. What are the international patterns of care for patients with pathologic complete response (pCR) and minimal/no pathological response to preoperative chemotherapy in the postoperative setting?
3. What are the clinicopathological predictors of tumour regression?
4. Does the cohort with pCR benefit from further postoperative FLOT-based chemotherapy?
5. Does the cohort with minimal/no response benefit from further postoperative FLOT-based chemotherapy?

4. Study Hypotheses

For patients with gastric and gastroesophageal adenocarcinomas who have undergone preoperative FLOT-based chemotherapy and radical surgical resection:

1. Pathological response in the resected specimen does predict patient survival
2. There are significant geographical variations in the use of adjuvant therapies for patients with 1) complete pathological response (pCR) and 2) minimal/no pathological response to preoperative FLOT-based chemotherapy
3. There are clinicopathological predictors of histologically determined tumour regression
4. In patients with pCR, postoperative FLOT-based chemotherapy will confer a survival advantage compared with those who do not proceed to any adjuvant therapies
5. In patients with minimal/no pathological response, postoperative FLOT-based chemotherapy will not confer a survival advantage compared with those who do not proceed to any adjuvant therapies

5. Study design

5.1 Summary

This is an international multi-centre non-interventional retrospective audit of practice and outcomes over the study period of January 1 2017 to December 31 2022. We aim to collect data for at least 1500 consecutive patients from all participating sites, including patients treated in routine clinical practice and/or clinical trials. Clinical data will be de-identified and entered into a REDCap database. Data linkage and analysis will be performed through REDCap and other statistical software.

Data collected will include (See appendix Table 16.1):

- Patient demographics, co-morbidities and characteristics
- Treatment history including pre-operative, operative, and post-operative interventions
- Post-operative complications within 30 days post-surgery
- Clinicopathological and molecular features of disease
- Disease outcomes and survival
- Follow-up data until 2 years post-surgery

The data will be stored on a secure server at Peter MacCallum Cancer Centre. Analyses will provide information relating to factors that include decision making, patterns of care, and survival outcomes in the routine clinical management of patients with gastric and gastroesophageal cancer.

5.2 Source of patients and clinical data

Patients from each participating site who fulfil study inclusion criteria (see 5.4 below) will be de-identified and entered into the REDCap database. Data will be sourced from patient case notes and/or in-house prospective registries from individual sites. This study will not collect any new or additional patient data that is not already recorded as part of routine clinical care.

5.3 Identification of patients and clinical data

Identification of patients and data collection will be performed by health professionals that are part of the clinical team who provide care for patients. Investigators external to the clinical team who provide routine care will not be involved in the identification of patients or data collection process.

5.4 Inclusion criteria

Patients must meet the following criteria to be eligible for inclusion in this protocol:

- Any patient with gastric and gastroesophageal cancer
- Received preoperative FLOT-based chemotherapy and surgical resection between 01/01/2017 to 31/12/2021
- Age ≥18 years-of-age

5.5 Exclusion criteria

Patients will be excluded from this study if they meet any of the following criteria

- Received further neoadjuvant therapy in addition to FLOT chemotherapy
- Stage 4 disease at diagnosis
- Death within 30 days post resection

5.6 Outcome measures

Primary outcome: Two-year disease-free survival (DFS)

Secondary outcomes:

- Two-year overall survival (OS)
- One-year DFS
- One-year OS

Disease free survival: Time from histological diagnosis until disease progression (identified clinically, biochemically, and/or radiologically) or death

Overall survival: Time from diagnosis of gastric or gastroesophageal cancer until death from any cause. Participants still alive or lost to follow-up at time of data collection will be censored

5.7 Project duration

Data will be collected from January 1st 2017 to December 31st 2022 (Of all patients who completed surgery by December 31 2021. Data collection to December 31st 2022 as we need at least 1-year survival data)

5.8 Standardization of tumour regression grading between study sites

To enable merging of datasets, each participating centre will need to standardise their TRG reporting to the international consensus classification described in Table 3. It is the responsibility of each site PI to complete the pre-data collection TRG survey to allow TRG calibration. Each centre's TRG will then be adjusted accordingly at the time of data entry.

5.9 Statistical considerations

Univariate, multivariate, Kaplan Meier and cox regression analysis will be used in this study. This study is powered to address the 5th hypothesis. Based on the FLOT4 trial, 40% of patients did not receive adjuvant FLOT and the two-year DFS was 55%. Adjuvant chemotherapy is estimated to confer a DFS benefit of 15% at two years (i.e., two-year DFS of 40%, based on the adjuvant chemotherapy with surgery versus surgery alone studies in gastric and gastroesophageal cancers including CLASSIC and MAGIC).[5, 32] This equates to a hazard ratio of approximately 0.73. Based on this, we will deem 15% as a clinically significant difference in DFS. Therefore, to detect a DFS difference of 15% with 80% power at an alpha level of 0.05, assuming an enrolment ratio of 1 to 0.3 (using a conservative real-world estimate of 30% of patients not receiving adjuvant FLOT), the predicted sample size will be FLOT/surgery/FLOT group: 473 patients, and FLOT/surgery/no adjuvant FLOT group: 157 patients. In total, the number of patents required with minimal/no TRG in

the resection specimen = 473 + 157 = 630. Based on local data, 40% of all resected gastric and gastroesophageal cancer show minimal/no TRG, the overall total number of patients required for this study: 630/0.4 = **1575** patients.

6. Project Management

6.1 Coordinating centres

Peter MacCallum Cancer Centre, Austin Hospital, Box Hill Hospital and the Flinders Medical Centre will jointly manage this project to oversee key aspects including defining the dataset, database management, and generating research output.

6.1.1 Peter MacCallum Cancer Centre

The Peter MacCallum Cancer Centre (PMCC) at the Victorian Comprehensive Cancer Centre is home to the largest research group in Australia. PMCC provides quality treatment and multidisciplinary care for cancer patients, and the proximity and strong collaborative links of clinicians and scientists provides unique opportunities for medical advances. Consequently, PMCC is dedicated to clinically orientated questions resulting in more effective and individualized patient care.

6.1.2 Austin Hospital

The Austin Hospital is the largest tertiary referral centre in Victoria, Australia. It is also home to one of the largest Upper Gastrointestinal Surgery Units in the state. The Austin Hospital is dedicated to improving health outcomes through discovery, translation and education. It also founded the first and largest General Surgery Trainee-led research collaborative network in Australia.

6.1.3 Flinders Medical Centre

The Flinders Medical Centre is a tertiary referral centre in Adelaide, South Australia. It delivers the state's largest Upper Gastrointestinal Cancer service, and co-convenes the South Australian State-wide multidisciplinary cancer team meetings. Flinders Medical Centre is dedicated to excellence in patient care, teaching, research, and innovation.

6.1.4 Box Hill Hospital

The Box Hill Hospital, Eastern Health is a tertiary referral centre in Victoria, Australia. It delivers a comprehensive Upper Gastrointestinal Cancer service, and actively participates in national and international clinical trials. Eastern Health is dedicated to excellence in patient care, teaching, research and innovation.

6.2 Data collection

This project will involve the formation of mini-teams of 1 – 4 collaborators/data collectors. These teams will retrospectively collect data over the proposed study duration. To ensure data is collected on all consecutive eligible patients these teams will review internal unit registries, hospital administrative databases, and theatre lists. Mini-teams

should be supervised by up to two consultants, fellows or registrars at each site. Data will be collected through patient information systems, including internal unit registries and accessing patient charts (written and electronic e.g. anaesthetic, pre-admission, operative, inpatient and oncology notes, as well as pathology reports, discharge summaries, and outpatient letters). Please refer to appendix (Table 16.1) for data dictionary and proposed sources of data.

6.3 REDCap database

All relevant data will be input into a REDCap database in a de-identified manner. The REDCap database will be held for the time period required by institutional protocol and/or local governance approvals, and subsequently destroyed. The custodian to this database will be Prof Alexander Heriot, Executive Director, Division of Cancer Surgery Peter MacCallum Cancer Centre. The REDCap application and data repository will be hosted in the Peter MacCallum Cancer Centre data centre and governed by Peter MacCallum Cancer Centre information technology and security processes. This includes appropriate best practices such as network firewalls, system and security monitoring and two-factor authentication. REDCap access privileges will be managed and maintained by the project management group alongside Peter MacCallum Cancer Centre REDCap managers to ensure that users can only access data relevant to their site. That is, each site user will only have access to their own site's data. REDCap also implements authentication to validate the identity of users that log in to the system. REDCap maintains an audit trail that logs user activity, including contextual information (e.g. the project or record being edited). Activities such as entering data, exporting data, modifying a field, running a report, or add/modifying a user, among a plethora of other activities are logged by REDCap. The logging record can be viewed by users who have appropriate privileges.

Principle investigators from each site will keep a master list linking REDCap unique study ID to patient identifiers to enable re-identification should this situation arise. Only de-identified data will be entered into the REDCap database. The master list will be retained on a password protected computer and have restricted access to only staff directly involved with the project as determined by data access groups at each site. The master list will be destroyed once the project is closed. No identifiable information from the master list will leave each site unless otherwise specified in an agreement or approved protocol. Data will be stored for at >7 years after the completion of research activity.

6.4 Quality assurance

Following data collection, only data sets with >90% data completeness will be accepted for pooled analysis. To emphasise the importance of data completeness to collaborators, patients with >10% missing data points will be excluded from the study. A snapshot audit provided through REDCap analysis tools has been widely validated across multiple datasets internationally demonstrating high levels of case ascertainment (typically 90 to 95%) and data accuracy (96 to 98%)[33-37]. The study group will reserve the right to randomly select 5% of records for ascertainment. This will be done by a collaborator at centres who were not involved in initial data collection.

6.5 Consent

As per NHMRC guidelines, *National Statement on Ethical Conduct in Human Research (2007) Updated 2018*, section 2.3.10, our study meets the following criteria for waiver of requirement for consent

A, this retrospective audit poses low risk to participants.

B, as the data collected is not above that of routine clinical care, the benefit of our project justifies the 'potential' risk of harm associated with not seeking consent.

C, it will be impractical to obtain consent due to quantity of patients, and that some of them may have died during or prior to the study period.

D, there is no known or likely reason that participants would not have consented if they had been asked.

E, we have sufficient protection of patient privacy in place.

F, we have an adequate plan to protect the confidentiality of data.

G, we would not expect that results of this study will influence management of the participants on study.

H, there will be low possibility of commercial exploitation from this study.

I, the waiver of consent is not prohibited by state, federal or international law.

6.6 Data management and security

The following steps will be undertaken to ensure data security

- All data will be de-identified prior to entry into REDCap database.
- Patient identifiers will be replaced with a unique study number. The master list of names and matching codes will be retained on a password protected computer located at each individual site. Only staff directly involved with the project will have access to this master list.
- The master list will be destroyed once the project is closed (or when approvals have expired).
- No identifiable information from the master list will leave each site unless otherwise specified in an agreement or approved protocol.
- The REDCap database will be hosted in the Peter MacCallum Cancer Centre data repository and governed by the hospital's information technology and security processes. This includes appropriate best practices such as network firewalls, system and security monitoring and two-factor authentication.
- REDCap access privileges will be managed and maintained by the project management group alongside Peter MacCallum Cancer Centre's REDCap managers to ensure that users can only access data relevant to their site.
- REDCap implements authentication to validate the identity of users that log in to the system.
- REDCap maintains an audit trail that logs user activity. The logging record can be viewed by users who have appropriate privileges.
- Data will be stored for at least 7 years after the completion of research activity.

6.7 Privacy issues

The following steps will be undertaken to maintain the confidentiality of patients and their clinical data

- All data generated from this study will remain confidential and no published work will contain patient identifiers.
- All data will be de-identified before entry into REDCap database. Patient identifiers will be replaced with a unique study number. The master list of names and matching codes will be stored on a password protected computer located at individual sites with access to them only by study personnel in that site.
- Data collectors can only view the data that they have entered from their own site.

- Site principal investigators can view the data only from their own site.
- The project management group including the chief investigator, database manager, and statistician will have access to the entire database for database monitoring and analytical purposes.
- The data will only be available for data management, audit, or monitoring personnel involved with the study.
- All the study data will be entered into a secure REDCap database protected by network firewall requiring two-factor authentication.
- REDCap access will be password protected, traceable through logging, and limited to critical study personnel only.
- Any publication or presentation that arise from this project will be presented as general cohort information with numbers and statistics. No individual data will be published or shared to ensure that identification of individual patients is not possible.
- All study-related personnel are bound by professional standards of patient information confidentiality and will work to protect patient confidentiality at all times.

6.8 Record keeping procedures, including storage of data, access and destruction

- Data will be entered into a REDCap database. This database will be hosted in the Peter MacCallum Cancer Centre data repository and governed by the hospital's information technology and security processes. This includes appropriate best practices such as network firewalls, system and security monitoring and a two-factor authentication.
- REDCap access privileges will be managed and maintained by the project management group alongside Peter MacCallum Cancer Centre's REDCap managers to ensure that users can only access data relevant to their site.
- Data collectors will have access to the data their have entered from their own site.
- Site principal investigators will have access to the data only from their own site.
- The project management group including the chief investigator, database manager, and statistician will have access to the entire database for database monitoring and analytical purposes.
- All data will be de-identified before entry into REDCap database. Patient identifiers will be replaced with a unique study number. The master list of names and matching codes will be stored on a password protected computer located at individual sites with access to them only by study personnel in that site.
- Data will be stored for at least 7 years after the completion of research activity.

7. Additional sub-studies

It is likely that through the course of the project, additional research questions may arise that require additional data to be collected via chart review, either for all of the patients or for a specific subset. Such a scenario will involve the collection of data over and above that specifically detailed in this proposal. If clinicians desire to collect additional data, funding and ethical approval for this must be obtained separately. The collection, analysis and reporting of any additional data beyond that specifically detailed in this proposal will only occur with agreement of all individual site Principal Investigators, and only with ethical approval.

8. Ethical considerations

The study will be conducted according to the NHMRC National Statement on Ethical Conduct in Human Research (2007 and updates) and the World Medical Association Declaration of Helsinki (2013 and updates).

9. Investigators' responsibilities

- **Steering committee and writing group**:

A core group of doctors & statistician who have overall responsibility for:

  - Overall scientific content and integrity
  - Project oversight and support
  - Protocol design
  - Formation of and liaison with the project management group
  - Study site identification and selection
  - Data analysis
  - Results interpretation
  - Preparation of research manuscripts
  - Journal submission and correspondence

- **Project management group**:

A core group of doctors, nurses, and research personnel who have overall responsibility for:

  - Ethics and governance application
  - Web-based design
  - REDCap database design, monitoring and management
  - Project co-ordination including liaison with hospital leads
  - Data handling
  - Dissemination of SPACE-FLOT documents and results
  - Reporting to the steering committee

- **Hospital leads/Principal Investigators**:

A lead point of contact at each site (1-3 people, at least one must be a consultant) who has overall responsibility for:

  - Providing site-specific oversight and support
  - Site governance registration
  - Facilitating standardisation of tumour regression grading with their own pathology department
  - Identification of eligible patients
  - Appointing, registering and supporting data collectors
  - Ensuring data integrity from that site
  - Local dissemination of SPACE-FLOT documents and results
  - Contributing to results interpretation
  - Reporting to the project management group

- **Local collaborators/data collectors**:

A mini-team of 1-5 people who have the overall responsibility for:

  - Reviewing and understanding study objectives and methodologies
  - Performing site-specific chart review
  - Data extraction as per REDCap for ~ 20-60 patients each
  - Integrity of data collected
  - Being available to assist with data cleaning, corrections and data review
  - Reporting to site principal investigator(s)

Please note that, mini-team size and the total number of collaborators required at each site will be at the discretion of the hospital lead according to the caseload of each hospital. Minimum requirements for authorship for local collaborators on SPACE-FLOT output include:

- Compliance with local audit approval processes and data governance policies.
- Active involvement in data collection that meets the criteria for inclusion within the SPACE-FLOT dataset.
- Collaboration with the hospital lead to ensure that data are reported back to the project management group

10. Criteria for centre inclusion within SPACE-FLOT

- Obtain all appropriate local governance approvals for the conduct of the SPACE-FLOT audit.
- Successful completion of data collection for eligible patients meeting inclusion criteria
- >90% data completeness and >90% data accuracy has been achieved.
- All data for the period has been uploaded within the specified deadlines.

Please note if these criteria are not met, then the contributing mini-team and/or the centre may be removed from the dataset and authorship list (please contact the project management group as soon as potential issues arise so that we can support as many centres to be included as possible).

11. Authorship for publications and presentations

In accordance with Research Collaborative authorship guidelines,[38] all research outputs from SPACE-FLOT will be listed under a single corporate authorship (SPACE-FLOT Collaborative). All collaborators will be listed as PubMed-citable collaborators within the SPACE-FLOT Collaborative in accordance with the roles and responsibilities defined above in section 9 (so long as the minimum requirements for authorship are met).

Corporate model:

Due to the increasing recognition of collaborative research and the large number of investigators contributing to such research, many journals have adopted a corporate authorship model. An example of this is:

Elective surgery cancellations due to the COVID-19 pandemic: global predictive modelling to inform surgical recovery plans.
COVIDSurg Collaborative.Br J Surg. 2020 May 12:10.1002/bjs.11746. doi: 10.1002/bjs.11746.

All investigators will be listed as collaborators and citable on PubMed. A supplementary file will detail the role and contribution of each investigator. The chief investigator will be the corresponding author. Specific to us, the format will be as follows: [Article title]. [SPACE-FLOT collaborative]. [Journal name]. [Year]. [Volume]. [Issue]. [Pages]. [DOI]
Academic citations and CV references will follow the following formatting: [Name]. [Role e.g. collaborator]. [SPACE-FLOT collaborative]. [Article title]. [Journal name]. [Year]. [Volume]. [Issue]. [Pages]. [DOI]

12. Exclusion from Study

This is a multi-centre study that is dependent on the input of multiple investigators in a timely fashion. We recognise that investigators participating in this study, being clinicians of varying levels of seniority, have a number of competing commitments that may affect their capacity to complete their data collection. If the investigator is unable to fully complete their task, but has completed the majority of the allocated responsibilities and has identified a replacement to complete any remaining data collection, we would expect that the investigator is credited appropriately for their work. If an investigator has not fulfilled the above criteria and is unable to complete the required duties in the time allocated, that investigator may be excluded from the study and further publications at the discretion of the steering committee. If removed from the study, investigator is responsible for returning all collected data to the committee and to securely destroy any remaining data.

13. Modes of communication

Clear lines of communication between all investigators is highly encouraged. The steering committee, project management group and hospital leads will meet on a regular basis, either in person or via video conferencing to discuss progress, expected and un-expected issues. Minutes will be kept and distributed amongst committee members and hospital leads. Formal communication should occur via secure email without any identifying confidential information, especially when research documents are sent to each other. An official webpage, Google account, email address and cloud drive will be set up for correspondence and sharing of non-clinical, research related documents. A monthly newsletter will also be circulated to all investigators.

14. Project timeline

Time period	Activity
Feb 2021 – Apr 2021	Formation of principle investigators Study proposal: conceptualisation, design, assessment of feasibility, identification of potential collaborative institutions
Apr 2021 – May 2021	Application for research funding
May 2021 – Nov 2021	Confirmation of collaborative institutions Multicentre ethics and governance application, review and revision
Nov 2021 – Feb 2022	Appointment of personnel infrastructure including: - Website designer and manager - Database designer and manager - Statistician - Research coordinator
Feb 2022 – Apr 2022	Standardisation of research instruments (e.g., tumour regression grading) across all participating sites
Apr 2022 – Jun 2022	Pilot of data collection across nominated two to three pilot sites Troubleshooting and amendment of data collection tools and databases
Jun 2022 – Feb 2023	Data collection across all participating sites
Feb 2023 – Jun 2023	Data review and cleaning Further data collection anticipated
Jun 2023 – Sep 2023	Data review, analysis, and interpretation
Sep 2023 – Feb 2024	Presentation of results Drafting, submission and reviews of manuscripts

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16. Appendix

Table 16.1 Data dictionary and definitions

Variable	Parameters/units	Source
P1. Eligibility		
P1.1. Age ≥18 years	Yes, No *(only 1 answer allowed)*	
P1.2. Has gastric and/or gastroesophageal cancer	Yes, No *(only 1 answer allowed)*	
P1.3. Had preoperative FLOT chemotherapy and surgical resection	Yes, No *(only 1 answer allowed)*	
P1.4. Inclusion into study	Yes (Yes to all above), No (No to one or more above) (Auto-calculated based on above 3 questions)	
P2. Baseline characteristics		
P2.1. Study number	Number	Self-generated, sites specific
P2.2. Centre code	Number	Auto generated in REDCAP
P2.3. Country	Drop down menu – choose from all centres	Self-reported
P2.4. Date of birth (DD/MM/YYYY)	Dd/mm/yyyy	Anaesthetic chart Pre-admission notes
P2.5. Gender	Male, Female *(only 1 answer allowed)*	
P2.6. Height (meters)	m	
P2.7. Weight (kg)	Kg	
P2.8. Body Mass Index	Auto-calculated (=kg/m^2)	Auto-calculated
P3. Co-morbidity (Charlson co-morbidity index)		
P3.1. Age at surgery (Op year – year of birth)	<50 (0), 50-59 (+1), 60-69 (+2), 70-79 (+3), 80-100 (+4) *(only 1 answer allowed)*	Anaesthetic chart Pre-admission notes
P3.2. Cerebrovascular disease (history of Strokes, TIA)	Yes (+1), No (0) *(only 1 answer allowed)*	
P3.3. Hemiplegia	Yes (+2), No (0) *(only 1 answer allowed)*	
P3.4. Ischaemic heart disease (history of MI, angina)	Yes (+1), No (0) *(only 1 answer allowed)*	
P3.5. Congestive heart failure	Yes (+1), No (0) *(only 1 answer allowed)*	
P3.6. Chronic pulmonary disease (history of emphysema, COPD)	Yes (+1), No (0) *(only 1 answer allowed)*	
P3.7. Chronic liver disease (history of chronic hepatitis, cirrhosis)	Yes (+1), No (0) *(only 1 answer allowed)*	
P3.8. Chronic renal injury (on dialysis, Cr >270 umol/L OR >3mg/dL)	Yes (+2), No (0) *(only 1 answer allowed)*	
P3.9. Connective tissue disease (history of rheumatoid arthritis, SLE, scleroderma, systemic sclerosis, polymyositis, dermatomyositis, mixed connective tissue disease)	Yes (+1), No (0) *(only 1 answer allowed)*	
P3.10. Peripheral vascular disease (history of claudication, limb gangrene, intervention for arterial insufficiency, aortic aneurysm)	Yes (+1), No (0) *(only 1 answer allowed)*	
P3.11. Dementia (Any cause of chronic cognitive deficit)	Yes (+1), No (0) *(only 1 answer allowed)*	
P3.12. Peptic ulcer disease (history of ulcer bleeding, perforation and treatment)	Yes (+1), No (0) *(only 1 answer allowed)*	
P3.13. Diabetes (on any medication)	Yes (+1), No (0) *(only 1 answer allowed)*	
P3.14. Leukaemia/lymphoma (active disease)	Yes (+2), No (0) *(only 1 answer allowed)*	
P3.15. Metastatic non-UGI solid tumour (active disease)	Yes (+6), No (0) *(only 1 answer allowed)*	
P3.16. Charlson comorbidity index	Auto-calculated (=2+sum of above)	
P3.17. Smoking status at time of surgery	Active smoker, Ex-smoker, Never smoked *(only 1 answer allowed)*	
P3.18. ASA at time of surgery	1: Normal health 2: mild systemic disease 3: severe systemic disease 4: systemic disease constant threat to life *(only 1 answer allowed)*	
P3.19. ECOG performance status at time of surgery	0: Fully active 1: Restricted in strenuous physical activity 2: Ambulatory, self-caring 3: Limited self-care, chair/bed bound >50% of waking hr *(only 1 answer allowed)*	1st oncology notes

P4. Preoperative treatment		
P4.1. First histological diagnosis date (DD/MM/YYYY)	dd/mm/yyyy	Pathology report
P4.2. Completed 4 neoadjuvant FLOT cycles	Yes, No *(only 1 answer allowed)*	Oncology notes
P4.3. If no, total number of cycles completed (Branching logic, if No to P4.2)	1, 2, 3, unknown *(only 1 answer allowed)*	
P4.4. If no, reason for early cessation (Branching logic, if No to P4.2)	Patient refusal Clinician decision Decreased performance status Drug toxicity Progressive disease Other (describe) *(Can be any number of the above)*	
P4.5. More than 4 cycles FLOT preoperatively (Branching logic, if YES to P4.2)	No, Yes (5 cycles), Yes (6 cycles), Yes (7 cycles), Yes (8 cycles), Yes (>8 cycles) *(only 1 answer allowed)*	
P4.6. Preoperative radiation	Yes, No *(only 1 answer allowed)*	
P5. Surgery and postoperative care		
P5.1. Duration of surgery (minutes)	min	Anaesthetic chart
P5.2. Date of surgery (DD/MM/YYYY)	dd/mm/yyyy	Operation notes
P5.3. Surgical approach	Open, Hybrid, Total minimally invasive *(only 1 answer allowed)*	
P5.4. Type of resection	Transthoracic oesophagectomy Transhiatal oesophagectomy 3-stage oesophagectomy Extended total gastrectomy (Oesophago-gastrectomy) Total gastrectomy Subtotal gastrectomy Proximal partial gastrectomy Other (describe) *(only 1 answer allowed)*	
P5.5. Type of lymphadenectomy – oesophagectomy	Not applicable 2 field: mediastinal & abdominal 3 field: neck, mediastinal & abdominal *(only 1 answer allowed)*	
P5.6. Type of lymphadenectomy – gastrectomy	Not applicable Sub-D1: less than perigastric nodes D1: perigastric nodes D1+: D1 & left gastric, common hepatic, coeliac, proximal splenic artery nodes D2: D1+ & splenic hilum, distal splenic artery nodes D3: D2 & hepaticoduodenal, retropancreatic nodes *(only 1 answer allowed)*	
P5.7. Intraoperative complication	Yes, No *(only 1 answer allowed)*	
P5.8. ICU/HDU admission	Yes, No *(only 1 answer allowed)*	Progress notes
P5.9. Total length of stay (Days)	Days *(only 1 answer allowed)*	Discharge summary
P5.10. 30-day return to theatre	Yes, No *(only 1 answer allowed)*	
P5.11. 30-day hospital readmission	Yes, No *(only 1 answer allowed)*	
P5.12. 30-day ICU/HDU readmission	Yes, No *(only 1 answer allowed)*	
P5.13. 30-day mortality	Yes, No *(only 1 answer allowed)*	
P6. Complications within 30 days post-op		
Respiratory		Discharge summary Unit audit Hospital coding service Progress notes
P6.1. Pneumonia	Yes, No *(only 1 answer allowed)*	
P6.2. Pleural effusion requiring drainage	Yes, No *(only 1 answer allowed)*	
P6.3. Pneumothorax requiring intervention	Yes, No *(only 1 answer allowed)*	
P6.4. Atelectasis requiring bronchoscopy	Yes, No *(only 1 answer allowed)*	
P6.5. Respiratory failure requiring reintubation	Yes, No *(only 1 answer allowed)*	
P6.6. Acute respiratory distress syndrome	Yes, No *(only 1 answer allowed)*	

P6.7. Acute aspiration	Yes, No *(only 1 answer allowed)*	
P6.8. Tracheobronchial injury	Yes, No *(only 1 answer allowed)*	
P6.9. Air leak > 10 days post-op	Yes, No *(only 1 answer allowed)*	
Cardiac		
P6.10. Myocardial infarction	Yes, No *(only 1 answer allowed)*	
P6.11. Arrhythmia requiring intervention	Yes, No *(only 1 answer allowed)*	
P6.12. Congestive heart failure requiring intervention	Yes, No *(only 1 answer allowed)*	
P6.13. Cardiac arrest requiring CPR	Yes, No *(only 1 answer allowed)*	
Gastrointestinal		
P6.14. Anastomotic leak	Yes, No *(only 1 answer allowed)*	
P6.15. Ileus	Yes, No *(only 1 answer allowed)*	
P6.16. Small bowel obstruction	Yes, No *(only 1 answer allowed)*	
P6.17. Pancreatitis	Yes, No *(only 1 answer allowed)*	
Infection		
P6.18. General sepsis	Yes, No *(only 1 answer allowed)*	
P6.19. Clostridium difficile infection	Yes, No *(only 1 answer allowed)*	
P6.20. Surgical site infection requiring intervention or antibiotics	Yes, No *(only 1 answer allowed)*	
P6.21. Intrathoracic abscess	Yes, No *(only 1 answer allowed)*	
P6.22. Intra-abdominal abscess	Yes, No *(only 1 answer allowed)*	
Neurological		
P6.23. Delirium	Yes, No *(only 1 answer allowed)*	
P6.24. Cerebrovascular accident (ischaemic or bleed)	Yes, No *(only 1 answer allowed)*	
Haematological		
P6.25. Venous thromboembolism	Yes, No *(only 1 answer allowed)*	
P6.26. Bleeding requiring intervention or transfusion	Yes, No *(only 1 answer allowed)*	
Urological		
P6.27. Acute kidney injury (x2 baseline creatinine)	Yes, No *(only 1 answer allowed)*	
P6.28. Urinary tract infection	Yes, No *(only 1 answer allowed)*	
Other complications		
P6.29. Wound dehiscence	Yes, No *(only 1 answer allowed)*	
P6.30. Acute diaphragmatic hernia	Yes, No *(only 1 answer allowed)*	
P6.31. Acute abdominal wall hernia	Yes, No *(only 1 answer allowed)*	
P6.32. Chyle leak	Yes, No *(only 1 answer allowed)*	
P6.33. Clavien-Dindo grade (for most severe complication)	1: complication with no change in patient management 2: complication requiring pharmacological treatment 3: complication requiring reintervention 4a: complication needing ICU admission and 1 organ failure 4b: complication needing ICU admission and >1 organ failure 5: complication resulting in death *(only 1 answer allowed)*	
P7. Histology		
P7.1. Tumour type	Adenocarcinoma, squamous cell carcinoma, other *(only 1 answer allowed)*	Pathology report
P7.2. Tumour site	GOJ, Cardia, Fundus, Body, Antrum, Pre-pylorus *(only 1 answer allowed)*	

P7.3. Tumour size (mm longest axis)	mm (describe), Not reported *(only 1 answer allowed)*	
P7.4. Lauren type	Intestinal, Diffuse, Mixed, Not reported *(only 1 answer allowed)*	
P7.5. Grade	Well differentiated, Moderately differentiated, Poorly differentiated, Undifferentiated, Not reported *(only 1 answer allowed)*	
P7.6. Lymph-vascular invasion	Yes, No, Not reported *(only 1 answer allowed)*	
P7.7. Perineural invasion	Yes, No, Not reported *(only 1 answer allowed)*	
P7.8. Resection margins	R0: radial, proximal and distal margins clear R1: microscopically tumour extends to/involving any margin R2: macroscopically tumour at any margin *(only 1 answer allowed)*	
P7.9. ypT status	T0, Tis, T1a, T1b, T2, T3, T4a, T4b *(only 1 answer allowed)*	
P7.10. ypN status	N0, N1, N2, N3 *(only 1 answer allowed)*	
P7.11. ypM status	M0, M1 *(only 1 answer allowed)*	
P7.12. Number of lymph nodes examined	Number	
P7.13. Number of lymph nodes with cancer	Number	
P7.14. Her2 immunohistochemistry	IHC 0, 1+, 2+, 3+, Not reported *(only 1 answer allowed)*	
Mismatch repair status		
P7.15. MLH1 staining	Present, Absent, Not reported *(only 1 answer allowed)*	
P7.16. PMS2 staining	Present, Absent, Not reported *(only 1 answer allowed)*	
P7.17. MSH2 staining	Present, Absent, Not reported *(only 1 answer allowed)*	
P7.18. MSH6 staining	Present, Absent, Not reported *(only 1 answer allowed)*	
P7.19. Tumour regression grade	TRG1: complete pathological response TRG2: near-complete pathological response TRG3: partial pathological response TRG4: poor/no pathological response *(only 1 answer allowed)*	
P8. Adjuvant treatment		
P8.1. Any adjuvant treatment	Yes, No *(only 1 answer allowed)*	Oncology notes and letters
P8.2. Reason for no adjuvant treatment (Branching logic, if NO to P8.1) → section P9	Patient refusal Clinician decision Decreased performance status Drug toxicity Progressive disease Death Other (describe) *(Can be any number of the above)*	
P8.3. Adjuvant FLOT (Branching logic, if YES to P8.1)	Yes, No *(only 1 answer allowed)*	
P8.4. Number of adjuvant FLOT cycles completed (Branching logic, if YES to P8.3)	1, 2, 3, 4 completed, not reported *(only 1 answer allowed)*	
P8.5. Reason not completing 4 cycles of adjuvant FLOT (Branching logic, if YES to P8.3)	Completed FLOT - Not applicable Patient refusal Clinician decision Decreased performance status Drug toxicity Progressive disease Death Other (describe) *(Can be more than one of the above)*	
P8.6. Adjuvant treatment in addition to FLOT (Branching logic, if YES to P8.3)	Radiotherapy (describe) Chemotherapy (describe) Radiation and chemotherapy (describe) Molecular therapy (describe) Immunotherapy (describe) Clinical trial (describe) Other (describe) *(only 1 answer allowed)*	

P8.7. Adjuvant treatment NOT involving FLOT (Branching logic, if NO to P8.3)	Radiotherapy only (describe) Radiation and chemotherapy (describe) Non-FLOT chemotherapy (describe) Molecular therapy (describe) Immunotherapy (describe) Clinical trial (describe) Other (describe) *(only 1 answer allowed)*	
P9. Survival endpoints		
P9.1. Disease recurrence (clinical OR tumour marker OR radiological OR endoscopic evidence, does NOT require biopsy evidence)	Yes, No *(only 1 answer allowed)*	Surgery/oncology notes and letters
P9.2. Date of recurrence (DD/MM/YYYY) (Branching logic, if YES to P9.1)	dd/mm/yyyy	
P9.3. Site(s) of recurrence (Branching logic, if YES to P9.1)	Describe	
P9.4. ECOG at recurrence (Branching logic, if YES to P9.1)	0: Fully active 1: Restricted in strenuous physical activity 2: Ambulatory, self-caring 3: Limited self-care, chair/bed bound >50% of waking hr 4: Completely disable *(only 1 answer allowed)*	
P9.5. 1st line treatment for recurrence (Branching logic, if YES to P9.1)	Yes, No *(only 1 answer allowed)*	
P9.6. Describe 1st line treatment for recurrence (Branching logic, if YES to P9.5)	Describe	
P9.7. 1stline treatment for recurrence start date (DD/MM/YYYY) (Branching logic, if YES to P9.5)	dd/mm/yyyy	
P9.8. 1stline treatment for recurrence stop date (DD/MM/YYYY) (Branching logic, if YES to P9.5)	dd/mm/yyyy	
P9.9. 2nd line treatment for recurrence	Yes, No *(only 1 answer allowed)*	
P9.10. Describe 2nd line treatment for recurrence (Branching logic, if YES to P9.9)	Describe	
P9.11. 2nd line treatment for recurrence start date (DD/MM/YYYY) (Branching logic, if YES to P9.9)	dd/mm/yyyy	
P9.12. 2nd line treatment for recurrence stop date (DD/MM/YYYY) (Branching logic, if YES to P9.9)	dd/mm/yyyy	
P9.13. 3rd line treatment for recurrence	Yes, No *(only 1 answer allowed)*	
P9.14 Describe 3rd line treatment for recurrence (Branching logic, if YES to P9.13)	Describe	
P9.15 3rd line treatment for recurrence start date (DD/MM/YYYY) (Branching logic, if YES to P9.13)	dd/mm/yyyy	
P9.16 3rd line treatment for recurrence stop date (DD/MM/YYYY) (Branching logic, if YES to P9.13)	dd/mm/yyyy	
P9.17. Date of death (DD/MM/YYYY)	dd/mm/yyyy	
P9.18. If date of death unknown, last seen alive (censored date, DD/MM/YYYY)	dd/mm/yyyy	

Table 16.2. Sites involved (current to date-stamp)

Hospital	State/Region	Country	Participation status	Lead investigator/ Contact person
Canberra Hospital	ACT	Australia	Confirmed	A/Prof. Sivakumar Gananadha
Bankstown/Liverpool Hospital	NSW	Australia	Confirmed	Prof. Neil Merrett
The Royal Northshore Hospital	NSW	Australia	Confirmed	A/Prof. Garett Smith
Princess Alexandra Hospital	Queensland	Australia	Confirmed	Prof. Mark Smithers
Royal Brisbane Hospital	Queensland	Australia	Confirmed	Dr. Rob Finch
Flinders Medical Centre	South Australia	Australia	Confirmed	Dr. Tim Bright Prof. David Watson
Lyell McEwin Hospital	South Australia	Australia	Confirmed	Dr. Lachlan Dandie
Royal Adelaide Hospital	South Australia	Australia	Confirmed	Dr. Harsh Kanhere Dr. Ahmed Barazanchi
Austin Hospital	Victoria	Australia	Confirmed	Dr. David Liu A/Prof. Ahmad Aly
Bendigo Hospital	Victoria	Australia	Confirmed	Dr. Chon Hann Liew
Eastern Hospital	Victoria	Australia	Confirmed	Dr. Mary-Ann Johnson
Monash Medical Centre	Victoria	Australia	Confirmed	Dr. Sarah Martin
Northern Health	Victoria	Australia	Confirmed	Dr. Krinal Mori
Peter MacCallum Cancer Centre	Victoria	Australia	Confirmed	A/Prof Cuong Duong
St Vincent's Hospital	Victoria	Australia	Confirmed	Dr. Matthew Read
Western Health	Victoria	Australia	Confirmed	Dr. Yayha Al-Hallal A/Prof. Val UsatoffA Dr. Rodney Jacobs
Royal Hobart Hospital	Tasmania	Australia	Confirmed	Dr. Rob Bohmer
Launceston General Hospital	Tasmania	Australia	Confirmed	Dr. Jurstine Daruwalla Dr. Girish Pande
Fiona Stanley Hospital	Western Australia	Australia	Confirmed	A/Prof. Mo Ballal
Middlemore Hospital	Auckland	New Zealand	Confirmed	Dr. Andrew McCormick
Christchurch Hospital	Christchurch	New Zealand	Confirmed	Dr. Ross Robert
Dunedin Hospital	Dunedin	New Zealand	Confirmed	Dr. Sharon Pattison
Queen Elizabeth Hospital	Birmingham	England	Confirmed	Dr. Ewen Griffiths
Salford Group	Greater Manchester	England	Confirmed	Dr. Jav Sultan
Royal Victoria Infirmary	Newcastle-upon-Tyne	England	Confirmed	Dr. Alex Phillips
Norfolk and Norwich University Hospital	Norwich	England	Confirmed	Dr. Bhaskar Kumar
Imperial College London	London	England	Confirmed	Dr. Sheraz Markar
Oxford University Hospital	London	England	Confirmed	Dr. Sheraz Markar
University Hospital Plymouth	London	England	Confirmed	Dr. David Chan
Mercy University Hospital	Cork City	Ireland	Confirmed	Dr. Thomas Murphy
St James Hospital	Dublin	Ireland	Confirmed	Prof. John Reynolds Dr. Claire Donohoe
Karolinska Comprehensive Cancer Centre	Stockholm	Sweden	Confirmed	Prof. Magnus Nilsson
Lille University Hospital	Lille	France	Confirmed	Prof. Guillaume Piessen
Erasmus University Medical Center	Rotterdam	Netherlands	Confirmed	Prof. Bas Wijnhoven
Utrecht Medical Center	Utrecht	Netherlands	Confirmed	Prof. Richard van Hillegersberg Dr. Jelle Ruurda

Queen Mary Hospital	Hong Kong	China	Confirmed	Prof. Simon Law
Christian Medical College	Vellore	India	Confirmed	Prof. Inian Samarasam
Sunway Medical Centre	Selangor	Malaysia	Confirmed	Dr. Ramesh Gurunathan
National University Cancer Institute	Singapore	Singapore	Confirmed	Prof. Jimmy So
University Medical Center	Ho Chi Minh City	Vietnam	Confirmed	Dr. Long Duy Vo
Toronto University Hospital	Toronto	Canada	Confirmed	Prof. Gail Darling
Montreal General Hospital	Montreal	Canada	Confirmed	Prof. Lorenzo Ferri