Delayed surgical Intervention after Chemoradiotherapy in Esophageal cancer: (DICE) study

Running Title: Prolonged interval to surgery may be associated with reduced survival after chemoradiotherapy

Swathikan Chidambaram[1], Richard Owen[2,3], Bruno Sgromo[2], Magdalena Chmura[2], Aaron Kisiel[4], Richard Evans[4], Ewen A Griffiths[4], Carlo Castoro[5], Caroline Gronnier[6], M MaoAwyes[7], Christian A Gutschow[7], Guillaume Piessen[8], Sébastien Degisors[8], Rita Alvieri[9], H Feldman[10], Giovanni Capovilla[11], Peter P Grimminger[11], Shiwei Han[12], Donald E Low[12], Jonathan Moore[13], James Gossage[13], Dan Voeten[14], Suzanne S. Gisbertz[14], Jelle Ruurda[15], Richard van Hillegersberg[15], Xavier Benoit D'journo[16], Alexander W Phillips[17], Ricardo Rosati[18], George B Hanna[1], Nick Maynard[2], W Hofstetter[10], Lorenzo Ferri[19], Mark I. Berge Henegouwen[14*], Sheraz R. Markar[2,20]

***Sponsoring ESA Member**

1. Academic Surgical Unit, Department of Surgery and Cancer, Imperial College London, St Mary's Hospital, London, UK
2. Department of Surgery, Churchill Hospital, Oxford University Hospitals NHS Trust, Old Road, Oxford, OX3 7LE, UK
3. The Ludwig Institute for Cancer Research, University of Oxford, Old Road Campus Research Building Roosevelt Drive, Oxford, OX3 7DQ, UK
4. Department of Surgery, Birmingham University Hospitals NHS Foundation Trust, Queen Elizabeth Hospital, Mindelsohn Way, Edgbaston, Birmingham, B15 2GW, UK
5. General Gastric and Esophagus Surgery Unit, Humanitas Research Hospital, Italy
6. Esophageal and endocrine surgery unit, digestive surgery department, centre Magellan, CHU de Bordeaux, France
7. Stomach and Oesophageal Tumor Centre, Comprehensive Cancer Center, University Hospital Zuric, Zurich, Switzerland
8. Department of Digestive and General Surgery, University Hospital Claude Huriez, Lille, Cedex, France
9. Oncological Surgery Unit, Veneto Institute of Oncology, IOV – IRCCS, Padua, Italy
10. University of Texas, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 445, Houston, TX, United States
11. Department of Surgery, University Medical Centre, Johannes Gutenberg University Mainz. Mainz, Germany

12. Department of Thoracic Surgery and Thoracic Oncology, Virginia Mason Hospital & Seattle Medical Center, 1100 Ninth Avenue, Seattle, WA 98101
13. Department of Surgery, Guy's and St Thomas' Hospitals NHS Foundation Trust, Westminster Bridge Road, London SE1 7EH, UK
14. Department of Surgery, Amsterdam UMC, Cancer Center Amsterdam, University of Amsterdam, Amsterdam, the Netherlands
15. Department of Upper Gastrointestinal Surgery, University Medical Center Utrecht, Netherlands
16. Department of Thoracic Surgery, Diseases of the Esophagus & Lung Transplantations. Chemin des Bourrely, North Hospital, Marseille, France
17. Northern Esophago-Gastric Unit, Newcastle upon Tyne Hospitals NHS Foundation Trust, Freeman Hospital, Freeman Road, Newcastle upon Tyne, NE7 7DN, UK
18. Department of GI Surgery, San Raffaele Hospital, Milan, Italy
19. Departments of Surgery and Oncology, McGill University, Montreal General Hospital, Cedar Avenue, Montreal, Canada
20. Nuffield Department of Surgery, University of Oxford, UK

Correspondence to:
Sheraz R Markar
Nuffield Department of Surgery, Churchill Hospital, Old Road, Headington, Oxford OX3 7LE
Email: sheraz.markar@nds.ox.ac.uk
Phone: +44 (0)20 3312 7657

Word count (excluding abstract and references): 3,949 words
Abstract: 244 words
Tables: 4 Figures: 3 Supplementary tables: 26 Supplementary figures: 12

Keywords: esophagectomy, chemoradiotherapy, esophageal cancer, salvage esophagectomy

Funding: The research was supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Mini-abstract

This international multi-center cohort study included 2,867 patients who underwent esophagectomy after chemoradiotherapy (CRT). Prolonged interval following CRT prior to surgery was associated with an increased 90-day mortality of up to a three-fold increase in patients more than 200 days after chemoradiotherapy, and furthermore poorer 5-year overall survival.

Word count: 48

Structured Abstract

Background

Chemoradiotherapy (CRT) is a core component of multimodality treatment for locally advanced esophageal cancer. The timing of surgery following CRT may influence the probability of performing an oncological resection and the associated operative morbidity.

Objective

To determine the impact of delayed surgical intervention following CRT on survival from esophageal cancer.

Methods

This was an international, multi-center, cohort study, including patients from seventeen centers who received CRT followed by surgery between 2010-2020. In the main analysis patients were divided into four groups based upon the interval between chemoradiotherapy and surgery (0-50, 51-100, 101-200 and >200 days) to assess the impact upon 90-day mortality and 5-year overall survival (OS). Multivariable logistic and Cox regression provided hazard rations (HRs) with 95% confidence intervals (95%CI) adjusted for relevant patient, oncological and pathological confounding factors.

Results

2,867 patients who underwent esophagectomy after CRT were included. After adjustment for relevant confounders, prolonged interval following CRT was associated with an increased 90-day mortality compared to 0-50 days (reference): 51-100 days (HR=1.54, 95%CI 1.04-2.29), 101-200 days (HR=2.14, 95%CI 1.37-3.35) and >200 days (HR=3.06, 95%CI 1.64-5.69). Similarly, a poorer 5-year OS was also observed with prolonged interval following CRT compared to 0-50 days (reference): 101-200 days (HR=1.41, 95%CI 1.17-1.70) and >200 days (HR=1.64, 95%CI 1.24-2.17).

Conclusion

Prolonged interval following CRT before esophagectomy is associated with increased 90-day mortality and poorer long-term survival. Further investigation is needed to understand the mechanism that underpins these adverse outcomes observed with a prolonged interval to surgery.

Word count: 244

Introduction

Esophageal cancer is the eighth most common cancer worldwide, with an estimated annual incidence of 572, 000 new cases[1,2]. With the publication of the CROSS study, chemoradiotherapy (CRT) followed by surgery became the mainstay of curative treatment for locally advanced esophageal cancer in many tertiary, high-volume centers across the world [3]. Since then, more combinations of CRT regimes and surgery have also come to the forefront as effective alternatives [4,5]. Previous studies have reported this tailored, multimodal approach to substantially improve survival outcomes [6]. Currently, the National Comprehensive Cancer Network (NCCN) guidelines for esophageal cancer recommend several therapeutic approaches, including neoadjuvant chemoradiotherapy with surgery (NCRS), neoadjuvant chemotherapy with surgery, definitive chemoradiotherapy, or primary esophagectomy [7]. The final treatment decision is often based on the patient's performance status, the hospital facility, physician and patient preferences, and oncological characteristics of the tumor. While esophagectomy remains a principal component of treatment, it is often associated with significant morbidity and substantial impact upon quality of life [8]. In recent times, this has led to greater consideration of an organ-sparing approach that is reliant on primary chemoradiotherapy with curative intent, and esophagectomy reserved as salvage when required for residual or recurrent disease [9].

Given that approximately 50% of patients with squamous cell carcinoma and 25% of patients with adenocarcinoma have a pathological complete response of the primary tumour following neoadjuvant CRT, the need for an esophagectomy has been called to question in patients who respond sufficiently [10,11]. Although randomized clinical trials have shown equivalence in survival outcomes between CRT alone and NCRS, the recurrence rate as high as 75% in some series outweighs the morbidity of esophagectomy [12-15]. Since then, many of the studies have reported inconsistent results, and are limited by small sample sizes

and overlapping tumor histopathology. In patients with recurrent or residual cancer, the only remaining option of salvage esophagectomy has historically suffered from poor outcomes, partly due to very high doses of radiation as well as results published prior to centralisation of esophageal cancer surgical services with concentration of expertise. Previous studies have also shown a large degree of heterogeneity in clinical outcomes associated with the length of interval after chemoradiotherapy prior to esophagectomy for residual or recurrent esophageal cancer [16–18].

The objective of this large multi-center international cohort study was to evaluate the importance of the interval to surgical intervention following chemoradiotherapy on short and long-term mortality in patients with esophageal cancer with subset analyses patients with adenocarcinoma and squamous cell carcinoma.

Methods

Data sources

The Delayed surgical Intervention after Chemoradiotherapy in Esophageal cancer (DICE) study was created to collate data from seventeen high-volume tertiary centers based across Europe and North America. Data from consecutive patients undergoing chemoradiotherapy followed by surgical resection for esophageal cancer with curative intent between 2010 and 2020 in these centers were retrospectively entered into a dedicated RedCap platform. Centers uploaded data directly onto the platform, and an independent monitoring team audited data capture to minimize missing data and control concordance and data quality. Missing or inconsistent data were obtained from e-mail exchanges with the referral center. Ethical approval was waived as no patient identifiable data was collected, and the necessary materials transfer agreements to enable data transfer was formalized between Imperial College London and the respective centers.

Inclusion and exclusion criteria

This cohort study included all adult patients who underwent surgery after chemoradiotherapy and had complete follow-up data for mortality. The data was collected for all patients admitted during a ten-year study period between 2010-2020. Patients who did not undergo both surgery and CRT or did not have follow-up data for primary outcome measures were excluded. Other exclusion criteria are as follows: other histology subtypes such as mucinous and neuroendocrine tumors; patients who underwent simultaneous endoscopic resections; other concurrent cancer diagnoses; and patients with metastatic esophageal cancer.

Data collection

The DICE database contains specific details about patient demographics, including the age, sex, body mass index, American Society of Anesthesiologists (ASA) grade. Tumor-level characteristics including stage (pathological TNM staging), histology and location were also collected. Details of local staging were recorded, including imaging (computed tomography and positron emission tomography), endoscopy, endoscopic ultrasound and endobronchial ultrasound. Operative data such as surgical technique and

approach as well as data on chemoradiotherapy (including agents, dose, regime and duration) were also collected.

Exposure; Interval between chemoradiotherapy and surgery

The interval was the time elapsed, measured in number of days, between completion of chemoradiotherapy and surgical intervention. Within the study cohort, patients were categorised into four groups based on this interval: <50 days, 51-100 days, 101-200 days and >200 days.

Covariates

Other confounding variables in multivariate statistical models included radiation dose (<50 or >50Gy), age (continuous), sex (male or female), body mass index (BMI) (continuous), ASA (1, 2, or 3), pathological T stage (0, 1, 2, 3, or 4) or pathological N stage (0, 1, 2, or 3), histological subtype (adenocarcinoma or squamous cell carcinoma), resection margin (R0 or R1/2), tumor location (upper 1/3, middle 1/3, distal 1/3 and Siewert I, Siewert II and Siewert III junctional), surgical approach (totally minimally invasive, open, hybrid (thoracoscopic chest and open abdomen or laparoscopic abdomen and open chest, or robotic) and surgical technique (transhiatal, Ivor-Lewis, three-stage or left thoraco-abdominal).

Outcomes

The outcomes evaluated included 90-day mortality, 5-year overall survival (OS) and 5-year recurrence-free survival (RFS) from date of surgery.

Statistical analysis

Statistical analysis was performed using SPSS (version 27.0; SPSS, Chicago, IL) and R (version 4.2.2). Continuous variables are expressed as mean and standard deviation, and categorical variables as number and percentage. Categorical variables were compared using the chi-squared test. Non-parametric continuous data were analyzed using the Mann-Whitney U test. Five-year overall survival was estimated using the Kaplan-Meier survival curves and compared using the log-rank test. Multivariable analyses using logistic regression and Cox proportional hazards models were performed to derive odds ratios (OR) and hazard ratios (HR) as effect-size measures, with 95% CIs. Statistical significance was set at $p<0.05$ for all

analyses. Machine learning techniques were applied to the data to develop a risk prediction model associated with 90-day mortality, and 5-year OS and 5-year RFS, using only preoperative variables. For mortality prediction, raw data were pre-processed as follows: variables with greater than 5% missing data were removed, patients with incomplete mortality, recurrence or interval-to-surgery data were excluded, and then random forest imputation used to complete the dataset. Backward selection was performed with logistic regression using the Akaike Information Criterion to identify the most informative variables, and the variance inflation factor (VIF) was used to assess for collinearity, keeping variables with a VIF <2. Data were then split into a train and test sets in a ratio of 3:1. Model training was performed using random forest, tuned random forest, support vector machines and logistic regression. Model performance was assessed on test data sets using receiver operating characteristics (ROC) and area under the curve (AUC). Raw and processed data and R code are available (DOI: 10.17632/j2ngv924sv.1).

Results

Demographics and study population

A total of 2,867 patients underwent surgical resection after chemoradiotherapy and were included in the study. From this cohort, 795 patients received surgery 0-50 days following chemoradiotherapy, 1278 patients between 51 and 100 days, 599 patients between 101 and 200 days and 153 more than 200 days. Comparison of patient demographics revealed no significant differences in age, sex or BMI; however, the proportion of patients with ASA grade 3 was increased in patients within the longest interval group (>200 days) (Table 1). Analysis of pathology showed significant differences across the groups in ypT stage, and a higher proportion of patients with SCC and upper or middle third tumours in the longest interval group (>200 days) (Table 1). Importantly, patients in the longer interval groups had a higher proportion of R1/2 resection margin: 13.7% (>200 days) and 12.9% (101-200 days) compared to 5% (0-50 days) and 6% (51-100 days). Treatment approach also varied with a greater proportion of patients in the longest interval group (>200 days) receiving a radiation dose of >50Gy, open surgery and three-stage esophagectomy. Multivariate analysis confirmed factors associated with delayed interval after chemoradiotherapy before surgery (defined as more than 12 weeks) included increasing age and body mass index, greater nodal stage, higher tumour location, surgical approach and technique (Supplementary table S1).

90-day mortality

Univariate analysis of 90-day mortality showed a stepwise increasing pattern with increasing interval between chemoradiotherapy and surgery: 6.3% (0-50 days) vs. 7.1% (51-100 days) vs. 10.2% (101-200 days) vs. 13.2% (>200 days); P=0.001. Multivariate analysis after adjustment for relevant confounders (table 2) showed that an increasing interval was associated with a greater 90-day mortality: OR=1.51 (95%CI 1.02-2.24) (51-100 days), OR=2.01 (95%CI 1.29-3.13) (101-200days) and OR=2.95 (95%CI 1.59-5.46) (>200 days) compared with 0-50 day (reference).

Patient demographics associated with increased 90-day mortality included advancing age, male sex, lower BMI and ASA grade 3. Greater pathological nodal status, R1/2 resection margin status and SCC histology were also associated with increased 90-day mortality. Importantly, a higher radiation dose of >50Gy was associated with an increase in 90-day mortality (OR=1.73, 95%CI 1.17-2.55).

These results were consistent in all subgroup analyses with increasing interval after CRT before surgery associated with increased 90-day mortality in subset analyses for patients with: SCC (OR=3.00, 95%CI 1.62-5.55; >200days) (Supplementary table S2), adenocarcinoma (OR=2.92, 95%CI 1.22-6.99); >200days) (Supplementary table S5) and R0 resection margin (OR=3.00, 95%CI 1.52-5.91; >200 days) (Supplementary table S8).

5-year overall survival (OS)

5-year OS showed a stepwise decreasing pattern within increasing interval between chemoradiotherapy and surgery (65.9% (0-50 days) vs. 64.4% (50-100 days) vs. 58.9% (101-200 days) vs. 54.3% (>200 days); P=0.002) (Table 1) (Figure 1). Multivariate analysis after adjustment for relevant confounders showed that increasing interval after chemoradiotherapy before surgery was associated with a decreasing pattern of 5-year OS: 101-200 days (HR=1.38, 95%CI 1.14-1.66) and >200 days (HR=1.61, 95%CI 1.22-2.13) (Table 3). Patient demographics associated with decreased 5-year OS included advanced age and male sex. Higher pathological tumor stage, R1/2 resection margin and nodal status were associated with decreasing 5-year OS. Left thoracoabdominal approach to esophagectomy was associated with an improved 5-year OS (HR=0.63, 95%CI 0.41-0.98).

These results were consistent in all subgroup analyses with increasing interval after CRT before surgery associated with decreased 5year overall survival in subset analyses for patients with: SCC (HR=1.60, 95%CI 1.21-2.12; >200days) (Supplementary table S3) (Supplementary figure S1), adenocarcinoma (HR=1.59, 95%CI 1.12-2.25; >200days) (Supplementary table S6) (Supplementary figure S3) and R0 resection margin (HR=1.62, 95%CI 1.20-2.21; >200 days) (Supplementary table S9) (Supplementary figure S5).

5-year recurrence-free survival

The interval between chemoradiotherapy and surgery was not significantly associated with 5-year recurrence-free survival (Table 4) (Figure 2). Important co-variates significantly associated with poorer 5-year recurrence-free survival included radiation dose >50Gy (HR=3.19, 95% CI 2.49-4.09), increasing pathological T and N Stage, R1/2 resection margin (HR=1.66, 95%CI 1.28-2.14), and robotic surgical approach (HR=1.91, 95%CI 1.15-3.18). These results were consistent in all subgroup analyses for patients with: SCC (Supplementary table S4) (Supplementary figure S2), adenocarcinoma (Supplementary table S7) (Supplementary figure S4) and R0 resection margin (HR=1.62, 95%CI 1.20-2.21; >200 days) (Supplementary table S10) (Supplementary figure S6).

Mortality prediction

After data pre-processing, logistic regression generally performed well in comparison to random forest with little benefit from model tuning, and therefore logistic regression was preferred due to its simplicity and the transparency of variable relevance (Supplementary figure S7,8,9). Area under curves of logistic regression for 90-day mortality, 5-year OS and 5-year RFS were 0.594, 0.604 and 0.697 respectively. Predictive variables included for 90-day mortality were age, BMI, interval after chemoradiotherapy, sex, ASA grade and radiation dose (Supplementary figure S7). Predictive variables included for 5-year OS were interval after age, interval after chemoradiotherapy, sex, ASA grade, pathological T and N stage, tumor location, operative approach and technique (Supplementary figure S8). Predictive variables included for 5-year RFS were smoking, pathological T and N stage, surgical approach and technique, ASA grade and radiation dose (Supplementary figure S9).

Subset analyses

Subset analyses were included for specific patient cohorts (Supplementary tables S11 to S22) including; patient age >70 years, ASA 3 or greater, clinical T4 stage, and excluding those receiving left thoraco-

abdominal esophagectomy. Within the subset analysis for patients aged > 70 years, a delayed interval after chemoradiotherapy before surgery of 51-100 days was associated with significantly poor 5-year OS, and a delay of >200 days was associated with a significantly greater 90-day mortality. Within subset of patients ASA 3 or greater or clinical T4 stage, a delayed interval after chemoradiotherapy before surgery was not associated with any significant changes in 90-day mortality, 5-year OS or 5-year RFS. Within subset excluding patients receiving left thoracoabdominal esophagectomy, a delay of >200 days was associated with a significantly greater 90-day mortality. A further subset analysis was performed of the high-volume centers contributing more than 100 patients to the study cohort (n=8) [supplementary table S23]. There was no difference in frequency of distribution of intervals after chemoradiotherapy before surgery between these high volume centers and the overall cohort [Supplementary figure S10] Survival analysis from these high volume centers paralleled the overall findings of the study with a delayed interval after chemoradiotherapy before surgery adversely affecting 5-year overall survival [Supplementary figure S11].

Radiation dose (≥50Gy)

A correlation analysis between radiation dose and chemoradiotherapy interval (Supplementary figure S12), showed a Spearman rank coefficient of 0.30 and thus no real correlation between these two variables. Radiation dose was not associated with overall survival (Figure 3). Upon exclusion of patients receiving radiation dose ≥50Gy, analysis of 1645 patients showed, prolonged delay after chemoradiotherapy was associated with a trend towards increased 90-day mortality [supplementary tables S24 to S26].

Discussion

The results of this large international multi-center cohort study suggest that both 90-day and 5-year overall survival outcomes for esophageal cancer are consistently worse in patients with a prolonged interval between surgical intervention and completion of chemoradiotherapy. However, this increased interval did not significantly affect 5-year recurrence-free survival. These results were consistent in subset analyses of patients with adenocarcinoma and SCC. In this cohort advancing age, male sex, lower BMI, increasing ASA grade, resection margin status, pathological T and N stage were all factors associated with poorer short- and long-term survival. A higher radiation dose of >50Gy was also associated with an increase in 90-day mortality. The mechanisms that underpin the adverse prognostic outcomes seen with a prolonged interval after chemoradiotherapy remain unknown and are an important area for future investigation. However, given the outcomes observed in the present study, careful consideration should be made regarding any delay after chemoradiotherapy before undertaking surgery. Furthermore, in patients with a long delay after chemoradiotherapy (>200 days), patients must be adequately counselled with a careful preoperative physiological assessment prior to undertaking salvage surgery given the adverse outcomes observed in this study with a 90-day mortality of 13% v 6% and 5-year OS of 54% v 66%.

Neoadjuvant chemoradiotherapy followed by surgery is currently the most commonly utilized treatment regime for locally advanced esophageal cancer worldwide [19]. Nevertheless, the role of surgery as an imperative component of the curative treatment pathway is increasingly being challenged due to the development of safer and more effective CRT regimes. Currently, the ongoing SANO trial is investigating a watch-and-wait strategy following CRT. Such an approach remains controversial given the risk of undetected recurrence or residual cancer and current ability to accurately identify a complete response following chemoradiotherapy [19]. Failure to detect recurrence following chemoradiotherapy in an accurate and timely fashion may delay surgical intervention leading to stage migration and potentially adverse impact upon postoperative morbidity and long-term survival [20].

In this present study, a prolonged interval between chemoradiotherapy and surgery of greater than 100 days doubled the 90-day mortality, and at 200 days, this was more than three times greater than in patients with an interval of less than 50 days. Given that median time to recurrence of most esophageal cancers is typically beyond 100 days after CRT, delayed esophagectomy may translate to worse outcomes despite an initial complete response to CRT. The mechanism for this increase in 90-day mortality with a prolonged interval between chemoradiotherapy and surgery is unknown from the present available data. Potentially important factors include unmeasured patient factors including cachexia, physical fitness and frailty following chemoradiotherapy, are all clearly important factors that must be evaluated in these complex patients before embarking on salvage esophagectomy. Furthermore, it may be hypothesized that a prolonged delay in timing of surgery increases the degree of radiation-induced fibrosis, thus making tissue dissection during salvage esophagectomy more technically challenging. This may also be reflected by the observed strong positive correlation between proportion of R1/2 resection margin and increasing interval between chemoradiotherapy and surgery. However, this remains a hypothesis to explain the findings of this study, and does require further robust scientific investigation. We do await the long-term results of the NeoRes II trial, which will randomise 249 patients to either a standard delay of 4-6 weeks or a prolong delay of 10-12 weeks after chemoradiotherapy prior to surgery [21]. However this present study does include over 25% of patients operated on with a more than 100 day interval after chemoradiotherapy and thus does test a different hypothesis.

The results of this study also identified a poorer 5-year overall survival associated with a prolonged interval between chemoradiotherapy and surgical intervention. Surgical complexity is often increased following a prolonged delay after chemoradiotherapy, with increasing fibrosis, making distinguishing residual tumor from fibrosis from airway structures often very challenging. Thus, there is an unmeasured mechanism that is mediating the poorer survival seen in these patients undergoing esophagectomy with a substantial interval (>200 days) after CRT. As 5-year RFS was not affected by the interval following CRT, the observed difference in 5yr OS is unlikely to be mediated by cancer recurrence. Thus, this most likely represents a further issue associated with patient physiology or surgical complexity associated with salvage

esophagectomy. It is important to acknowledge the context of the present results, with patients included in this study preceding the results and implementation of Checkmate 577 [22]. Thus it may be of further importance in future studies to assess the delay to surgery after chemoradiotherapy in the context of further delay in the initiation of adjuvant immunotherapy.

Previous investigations have suggested that more modern practices including a minimally invasive approach to esophagectomy and centralization of complex cancer services can reduce the morbidity and mortality attributed to esophagectomy [23-27]. Although all the centers participating in this study were high volume esophageal surgical centers, the experience with salvage esophagectomy did vary, which is an important consideration in interpreting the results of the present study with real-world data. Given the adverse outcomes in terms of 90-day mortality and 5-year survival, the logical argument remains that esophagectomy after a prolonged interval following CRT should be centralized to high-volume centers with an experience in salvage esophagectomy. Interestingly robotic surgery was associated with poorer 90-day mortality and 5-year RFS, which is most likely a reflection of the complex learning curve associated with robotic surgery.

Currently, there is no widely accepted definition of salvage or delayed esophagectomy. In our preliminary discussions to design the study, we identified the difficulty in characterizing the definition of salvage esophagectomy. We have previously discussed its clinical validity and feasibility, and other studies have addressed the variation in how salvage esophagectomy is performed [20]. Our study has outlined several features that can be selectively optimized to improve survival. This will be especially relevant in situations where recurrent or residual cancers are detected in patients whom an organ sparing approach was initially undertaken, and now require esophagectomy [28].

The optimum dose of radiation to achieve sustained pathological complete response (pCR) without recurrence and minimal toxicity has been a topic of controversy within the field. Different doses and regimes have been trialled and reported with varying success [3,14,29,30] . Although 40.4Gy is the dose used in the CROSS regime for neoadjuvant intent(ref), the dose recommended for CRT alone is typically much

higher at 50-55Gy, and at times, extending beyond 60Gy. In the US, the current standard suggested dose of 50-50.4 Gy for CRT alone was based on the landmark INT0123 (RTOG 9405) phase III trial [14]. Dose intensification above 50.4Gy does not confer any additional marginal benefit but does increase the incidence of toxicity [31,32] . Higher doses of radiation effect a combination of vascular and epithelial damage that is heightened in radio-sensitive gastrointestinal mucosal tissues [33]. Acute-responding tissues in gastrointestinal mucosa are forced to enter pre-mitotic apoptosis or undergo mitotic catastrophe early on. The ensuing chronic inflammation leads to extensive fibrogenesis due to a persistent and exaggerated wound healing response that not only has a deleterious effect on the structure and functionality of esophageal tissue, but inadvertently also hostilizes the tumor microenvironment [34,35]. Within this present study total radiation dose of greater than 50Gy was also associated with an increased 90-day mortality, which may be an effect of radiation increasing fibrosis and surgical complexity or alternatively increased pulmonary fibrosis and poorer patient physical fitness following high doses of radiotherapy.

Our study is topical in the current era, and pertinent within the context of currently ongoing work that may transform the management of esophageal cancer to an organ-sparing, surveillance-based approach. The generalizability of our results is based on the largest and most diverse dataset with comprehensive follow-up from seventeen international high-volume centers. Nevertheless, this setup has important limitations. As a retrospective multi-center cohort study, it is dependent on reliable data collection of measurable prognostic factors. Approach to clinical staging did vary as would be expected in an international study such as this, which may be reflected by 1% of cases within the dataset being Siewert type III on pathological analysis and thus would not have been intended to typically receive chemoradiotherapy prior to surgery. Despite the use of multivariate analysis to address confounding and selection bias of measured co-variates, residual bias will exist due to geographic variations in practice and fundamental differences in the underlying population. Furthermore, the precise reason of delay of surgical intervention is unknown from the present study, this could be due to a primary treatment approach with CRT alone and esophagectomy for residual or recurrent disease, or potentially in some cases poorer patient physiology delaying surgical intervention, which is an important consideration when interpreting the main findings of

the study. However, in the current times of COVID-related delays to surgical intervention these results may become increasing more relevant and important when counselling patients regarding salvage surgery. Our database is largely limited to European and North American centers and did not incorporate the variation in tumor pathology and subsequent treatment response seen in the Eastern hemisphere. Lastly, this study did not assess the morbidity or health related quality of life effects of surgery and CRT, although this will be reported outside the scope of this paper in future work. Further work is still required to understand the mechanisms underlying the poor survival associated with delayed surgery after CRT. If a primary organ-sparing approach does become the future status quo, our study definitively highlights the need for modelling of risk-stratification tools to predict the profile of patients who may benefit from delayed or salvage surgery.

Conclusion

Oncological and patient-related characteristics are most pertinent in attaining the best short and long-term survival outcomes in patients undergoing chemoradiotherapy and esophagectomy. A prolonged interval between completion of chemoradiotherapy and surgical intervention was shown to be a highly important prognostic factor adversely affecting 90-day mortality and 5-year overall survival. The results of this multi-center international study do provide important data to inform patients regarding the risks of a potential watch and wait strategy after chemoradiotherapy with salvage esophagectomy reserved for recurrent cancer. There remains a need to contextualize these results and identify the precise mechanisms that underpin the adverse clinical outcomes observed with a delayed interval after chemoradiotherapy.

Funding

There are no funding sources to disclose.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that there is no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

Ethical approval was waived by the Imperial College London as the data was collected as part of clinical service evaluation processes. Materials transfer agreements were formally set up for data transfer with the respective institutions from outside of the United Kingdom.

Data sharing

Not applicable.

References

1. Arnold M, Ferlay J, Van Berge Henegouwen MI, et al. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. *Gut*.;69 . Epub ahead of print 2020. DOI: 10.1136/gutjnl-2020-321600.
2. Kamangar F, Nasrollahzadeh D, Safiri S, et al. The global, regional, and national burden of oesophageal cancer and its attributable risk factors in 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*.;5 . Epub ahead of print 2020. DOI: 10.1016/S2468-1253(20)30007-8.
3. van Hagen P, Hulshof MCCM, van Lanschot JJB, et al. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. *N Engl J Med*.;366 . Epub ahead of print 2012. DOI: 10.1056/nejmoa1112088.
4. Cunningham D, Allum WH, Stenning SP, et al. Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. *N Engl J Med*.;355 . Epub ahead of print 2006. DOI: 10.1056/nejmoa055531.
5. Reynolds J V., Preston SR, O'Neill B, et al. Neo-AEGIS (Neoadjuvant trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): Preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (Modified MAGIC or FLOT protocol). (NCT01726452). *J Clin Oncol*.;39 . Epub ahead of print 2021. DOI: 10.1200/jco.2021.39.15_suppl.4004.
6. Eyck BM, van Lanschot JJB, Hulshof MCCM, et al. Ten-Year Outcome of Neoadjuvant Chemoradiotherapy Plus Surgery for Esophageal Cancer: The Randomized Controlled CROSS Trial. *J Clin Oncol*.;39 . Epub ahead of print 2021. DOI: 10.1200/JCO.20.03614.
7. Ajani JA, D'Amico TA, Bentrem DJ, et al. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw*.;17 . Epub ahead of print 2019. DOI: 10.6004/jnccn.2019.0033. Updated in 2022
8. Piessen G, Messager M, Mirabel X, et al. Is there a role for surgery for patients with a complete clinical response after chemoradiation for esophageal cancer? An intention-to-treat case-control

study. *Ann Surg*.;258 . Epub ahead of print 2013. DOI: 10.1097/SLA.0000000000000228.

9. Eyck BM, van der Wilk BJ, Noordman BJ, et al. Updated protocol of the SANO trial: a stepped-wedge cluster randomised trial comparing surgery with active surveillance after neoadjuvant chemoradiotherapy for oesophageal cancer. *Trials*.;22 . Epub ahead of print 2021. DOI: 10.1186/s13063-021-05274-w.

10. Noordman BJ, Spaander MCW, Valkema R, et al. Detection of residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer (preSANO): a prospective multicentre, diagnostic cohort study. *Lancet Oncol*.;19 . Epub ahead of print 2018. DOI: 10.1016/S1470-2045(18)30201-8.

11. Chidambaram S, Sounderajah V, Maynard N, et al. Evaluation of tumor regression by neoadjuvant chemotherapy regimens for esophageal adenocarcinoma: a systematic review and meta-analysis. Dis Esophagus 2023; 36(2): doac058

12. Teoh AYB, Chiu PWY, Yeung WK, et al. Long-term survival outcomes after definitive chemoradiation versus surgery in patients with resectable squamous carcinoma of the esophagus: Results from a randomized controlled trial. *Ann Oncol*.;24 . Epub ahead of print 2013. DOI: 10.1093/annonc/mds206.

12. Bedenne L, Michel P, Bouché O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol*.;25 . Epub ahead of print 2007. DOI: 10.1200/JCO.2005.04.7118.

13. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: Long-term follow-up of a prospective randomized trial (RTOG 85-01). *J Am Med Assoc*.;281 . Epub ahead of print 1999. DOI: 10.1001/jama.281.17.1623.

14. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation therapy oncology group 94-05) phase III trial of combined-modality therapy for esophageal cancer: High-dose versus standard-dose radiation therapy. *J Clin Oncol*.;20 . Epub ahead of print 2002. DOI: 10.1200/JCO.20.5.1167.

15. Kamarajah SK, Phillips AW, Hanna GB, et al. Definitive Chemoradiotherapy Compared to

Neoadjuvant Chemoradiotherapy With Esophagectomy for Locoregional Esophageal Cancer: National Population-Based Cohort Study. *Ann Surg*.202; 275; 275(3): 526 - 533.

16. Kim JY, Correa AM, Vaporchiyan AA, et al. Does timing of esophagectomy after chemoradiation affect outcome? Ann Thorac Surg 2012; 93: 207 - 212.

17. Baja SS, Shah KM, Potter AL, et al. Early vs. Delayed Surgery for esophageal cancer during the COVID-19 pandemic. J Am Coll Surg 2022; 235: 174 - 184.

18. Tsang JS, Tong DKH, Lam KO, et al. Appropriate timing for surgery after neoadjuvant chemoradiation for esophageal cancer. Dis Esophagus 2017; 30: 1 - 8.

19. Ajani JA, Bhutani MS, Swisher SG. Oesophageal preservation in locally advanced oesophageal cancer. *The Lancet Oncology*.;19 . Epub ahead of print 2018. DOI: 10.1016/S1470-2045(18)30617-X.

20. Markar S, Gronnier C, Duhamel A, et al. Salvage surgery after chemoradiotherapy in the management of esophageal cancer: Is it a viable therapeutic option? *J Clin Oncol*.;33 . Epub ahead of print 2015. DOI: 10.1200/JCO.2014.59.9092.

21. Nilsson K, Klevebro F, Rouvelas I, et al. Surgical morbidity and mortality from the multicenter randomized controlled NeoRes II Trial: standard versus prolonged time to surgery after neoadjuvant chemoradiotherapy for esophageal cancer. Ann Surg 2020; 272: 684 - 689.

22. Kelly RJ, Ajani JA, Kuzdal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med 2021; 384: 1191 - 1203.

23. Ha JS, Fraser C, Zhou X, et al. Morbidity and mortality outcomes after esophagectomy following chemoradiation using a standardized operative technique. *J Clin Oncol*.;36 . Epub ahead of print 2018. DOI: 10.1200/jco.2018.36.4_suppl.166.

24. Markar SR, Mackenzie H, Lagergren P, et al. Surgical proficiency gain and survival after esophagectomy for cancer. *J Clin Oncol*.;34 . Epub ahead of print 2016. DOI: 10.1200/JCO.2015.65.2875.

25. Mariette C, Markar SR, Dabakuyo-Yonli TS, et al. Hybrid Minimally Invasive Esophagectomy for Esophageal Cancer. *N Engl J Med*. 2019;380:152–162.

26. Mariette C, Meunier B, Pezet D, et al. Hybrid minimally invasive versus open oesophagectomy for patients with oesophageal cancer: A multicenter, open-label, randomized phase III controlled trial, the MIRO trial. *J Clin Oncol*.;33 . Epub ahead of print 2015. DOI: 10.1200/jco.2015.33.3_suppl.5.

27. Straatman J, van der Wielen N, Cuesta MA, et al. Minimally Invasive Versus Open Esophageal Resection: Three-year Follow-up of the Previously Reported Randomized Controlled Trial: the TIME Trial. *Ann Surg*. . Epub ahead of print 2017. DOI: 10.1097/SLA.0000000000002171.

28. Hofstetter WL. Salvage esophagectomy. *Journal of Thoracic Disease*.;6 . Epub ahead of print 2014. DOI: 10.3978/j.issn.2072-1439.2014.03.29.

29. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol*.;26 . Epub ahead of print 2008. DOI: 10.1200/JCO.2007.12.9593.

30. Burmeister B, Smithers M, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: A randomised controlled phase III trial. *Lancet Oncol*.;6 . Epub ahead of print 2005. DOI: 10.1016/S1470-2045(05)70288-6.

31. Crehange G, Bonnetain F, Peiffert D, et al. Phase II/III randomized trial of exclusive chemoradiotherapy with or without dose escalation in locally advanced esophageal carcinoma: The CONCORDE study (PRODIGE 26). *Journal of Clinical Oncology*.;34.

32. Hulshof MCCM, Geijsen ED, Rozema T, et al. Randomized Study on Dose Escalation in Definitive Chemoradiation for Patients With Locally Advanced Esophageal Cancer (ARTDECO Study). *J Clin Oncol*.;39 . Epub ahead of print 2021. DOI: 10.1200/JCO.20.03697.

33. De Ruysscher D, Niedermann G, Burnet NG, et al. Radiotherapy toxicity. *Nat Rev Dis Prim*.;5 . Epub ahead of print 2019. DOI: 10.1038/s41572-019-0064-5.

34. Bentzen SM. Preventing or reducing late side effects of radiation therapy: Radiobiology meets molecular pathology. *Nature Reviews Cancer*.;6 . Epub ahead of print 2006. DOI: 10.1038/nrc1950.

35. Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: A paradigm shift.

Journal of the National Cancer Institute.;105 . Epub ahead of print 2013. DOI: 10.1093/jnci/djs629.

Figure legends

Figure 1: DICE interval as a predictive factor of overall survival at five years (0 = 0-50 days; 1 = 51-100 days; 2 = 101 – 200 days; 3 = >200 days) (p-value = <0.001)

Figure 2: DICE interval as a predictive factor of recurrence-free survival at five years (0 = 0-50 days; 1 = 51-100 days; 2 = 101 – 200 days; 3 = >200 days) (p-value = 0.242)

Figure 3: Dose of radiation as a predictive factor of overall survival at five years (p-value = 0.984)