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Quality of life in patients with upper GI malignancies managed by a strategy of chemoradiotherapy alone versus surgery

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ABSTRACT

Background and objectives: Neoadjuvant chemoradiotherapy (nCRT) induces a pathological complete response (pCR) in 25–85% of oesophago-gastric cancer. As surgery entails morbidity and mortality risks and quality of life (QL) impairment, its avoidance in patients without residual disease is desirable.

This study aimed to compare quality of life of patients with a cCR who chose surveillance with those who chose surgery.

Methods: Four groups of patients were studied. Group 1(n = 31) were controls; Group 2 (n = 26) had chemoradiotherapy only; Group 3 (n = 31) had oesophagectomy after nCRT; Group 4 (n = 26) had gastrectomy alone. A 33-point novel questionnaire was administered at two 3 month time points. Participants were also interviewed with a validated questionnaire.

Results: Mean(± sd) quality of life scores in cCR patients offered surveillance (28.9 ± 4.5) were superior to patients undergoing oesophagectomy (32.3 ± 58. $p=0.042$) or gastrectomy (33.19 ± 5.9, $p=0.004$). This result was replicated in the validated questionnaire ($p=0.017$). There was a trend towards increased reflux-related respiratory symptoms in the oesophagectomy group (7.3 ± 2.2 *vs* 6.5 ± 1.9; $p=0.396$) and towards early dumping (8.2 ± 1.4 vs 7.1 ± 1.; $p=0.239$) and vagotomy-related symptoms (1.82 ± 0.9 vs 1.4 ± 0.6; $p=0.438$) in the gastrectomy group.

Conclusions: Avoidance of surgery in cCR patients is rewarded with a superior quality of life to those undergoing surgery.

1. Introduction

Carcinoma of the upper gastrointestinal tract is an aggressive malignancy, with oesophageal and gastric cardia subtypes increasing in incidence in the Western world [1]. The prognosis is poor [1–3], and surgical resection, historically the only curative option, represents a major undertaking with the potential for serious morbidity and in-hospital mortality rates approaching 10% worldwide [4]. Since the advent of promising randomised trials in the 1990s [5] and subsequent trials in the 2000s [6–8] many centres treat patients with oesophageal and gastric carcinoma with neoadjuvant chemotherapy or chemoradiotherapy as standard and a number of meta-analyses have confirmed the superiority of this approach over surgery alone [9,10].

Neoadjuvant chemoradiotherapy induces a pathological complete response (pCR) in 25–50% of cancers depending on disease subtype, stage and chosen regimen. Complete response rates of up to 87% of oesophageal cancer patients with earliest stage disease have been reported [11], with an associated significantly improved 5-year survival rate of up to 60% [11–16].

Patients with a pathological complete response (pCR) after NCRT cannot benefit from resection but are exposed to the significant risks of morbidity and mortality and to a lifetime impairment of quality of life. Ideally these patients should not be subjected to surgery but it is currently not possible preoperatively to accurately identify patients with a complete pathological response from those patients harboring resectable residual microscopic disease. The CROSS trial data suggests that if residual disease is present it will lie in the mucosa or submucosa in 89% of cases and is thus potentially identifiable on endoscopic biopsy.

As all pathological complete responders will have had a complete clinical response (cCR) at restaging it would appear reasonable to offer a selected cohort of clinically complete responders the option of avoiding surgery and instead entering them into a surveillance program with the option of salvage resection if the disease reemerges [17]. The

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selection of patients for surveillance would be based on patient preference, operative risk score and risk of disease recurrence and allow the patient to choose between resection and surveillance and to support their decision with active surveillance in those wishing to avoid surgery [18,19].

Given the variation in physiological cost of the different treatment strategies, it is intuitive that quality of life (QL) should represent a significant factor in patient choice. Patients may suffer side-effects and a negative quality of life impact from neoadjuvant chemo-radiotherapy [20,21]. The addition of surgery is associated with a further physiological hit with morbidity and mortality risks [22–27], a long recovery time [28–30] and with a further significant QL impact [31,32]. Furthermore, division of the vagal nerve trunks, and resection of the lower oesophageal sphincter anti-reflux mechanism, increase the potential complications and quality of life risks [31–34].

The value of recording QL outcomes is well recognised. A number of studies have noted that quality of life indices in patients with oesophageal cancer represent an independent prognostic factor in terms of survival [35–37]. In addition, quality of life questionnaires provide information to the clinician regarding patient's physical symptoms, psychological wellbeing and functional status [38–40]. This in turn may influence choice when offering various treatment modalities, highlight health issues in patients actively undergoing or post treatment, and monitor changes in QL over time [41,42].

A number of studies have compared the role of definitive chemoradiotherapy with surgery as treatment for oesophageal cancer, predominantly as treatment for SCC but also for adenocarcinoma [43–46], with a small number specifically analysing health-related quality of life differences [47–49]. To our knowledge, however, there have been no studies to date comparing the quality of life outcomes in patients with either squamous or adenocarcinoma of the upper GI tract undergoing chemoradiotherapy only versus patients undergoing neoadjuvant chemoradiotherapy followed by surgical resection. The aims of this study were to assess QL outcomes in a cohort of oesophageal carcinoma patients undergoing chemoradiotherapy only with a cohort receiving neoadjuvant chemoradiotherapy followed by surgery and with a cohort of patients undergoing surgery alone for gastric cancer.

2. Materials and methods

2.1. Recruitment

All eligible patients were identified from a prospectively maintained upper gastrointestinal oncology databases of patients with oesophageal and gastric cancer treated for cure at both Connolly and Beaumont Hospitals.

2.2. Inclusion criteria

Patients with a confirmed diagnosis of gastric or oesophageal malignancy who had undergone treatment with curative intent in the form of either surgery alone, neo-adjuvant chemoradiotherapy followed by surgery or neoadjuvant or definitive chemoradiotherapy alone and who were alive and disease-free 3 or more months after completion of treatment. The chemoradiotherapy protocol used was the CROSS regimen for all patients. Of those who had undergone chemoradiotherapy alone, all had had a clinical complete response (cCR) and had chosen surveillance, or were deemed at higher risk for resection based on age or operative risk assessment. In addition, a group of 31 healthy patients with no history of upper gastrointestinal disorders were recruited from attendees at an orthopaedic fracture clinic to act as a control group. The control group patients were attending 2–12 weeks post fractures involving the upper limb (predominantly radial and scaphoid; also humerus, ulnar, carpal and phalangeal fractures.

2.3. Exclusion criteria

Exclusion criteria were patients who were within 3 months of treatment or surgery, patients undergoing palliative treatment and patients with disease recurrence.

2.4. Study groups

Four groups of patients were studied. **Group 1** (n = 31) were a control group of healthy individuals, age and gender matched for the treatment groups, attending an orthopaedic fracture clinic at 2–12 weeks post injury, who denied any history of upper GI disorders. **Group 2** (n = 26) were patients with oesophageal carcinoma with a complete clinical response following chemoradiotherapy who did not undergo surgery; **Group 3** (n = 31) were patients with oesophageal cancer who underwent neoadjuvant chemoradiotherapy and also underwent oesophagectomy; **Group 4** (n = 26) were gastric cancer patients who underwent gastrectomy only.

A 33-point questionnaire, assessing five functional domains with specific focus on symptoms of respiratory reflux, antro-pyloric function, and post-vagotomy symptoms, was performed. The data were then aggregated to produce a total score ranging from 20 to 93, with 20 representing the least symptomatic.

2.5. Instruments – questionnaire administration

Patients were assessed using the standard QL instrument - EORTC-QLQ C30 and the site specific instruments OES-18 and STO-22 in addition to a novel - Connolly - questionnaire.

Initial pilot interviews were performed with controls and patients identified as suitable via the above criteria using the novel questionnaire to assess its utility as a quality of life instrument.

Follow-up interviews were performed at 2 separate time points with a 3-month interval. The initial time point for the first administration of the questionnaire was at 6 months post completion of primary treatment, for all treatment groups. Interviews consisted of the novel questionnaire in combination with the European Organisation for Research and Treatment of Cancer validated quality of life instruments EORTC-QLQ C30 [50–52] and the appropriate site-specific module OES-18 [53] or STO-22 [54]. This allowed us to correlate self-reported quality of life scores from the novel questionnaire with scores from a validated quality of life tool and also to assess intra-observer variability with the self-reported novel questionnaire over a 3-month time interval.

Quality of life outcomes were measured by administration of the novel questionnaire in conjunction with the (EORTC) core questionnaire (QLQ-C30). The EORTC QLQ-C30 has been validated for use in many treatment groups, including in patients with gastric and oesophageal malignancies [50–52]. It consists of 30 questions in total. The majority of these are scaled and assess function (physical, emotional, role, social and cognitive), symptomatic status (pain, nausea/vomiting, fatigue) and general health status. There are also six questions regarding dyspnoea, constipation, diarrhoea, insomnia, anorexia and financial concerns.

In addition the appropriate site specific module for either gastric or oesophageal carcinoma (OES-18 and ST0-22 respectively) was administered. The oesophageal and gastric site specific modules each have 18 and 22 additional questions respectively. [53,54] The oesophageal module comprises four symptom scales relating to dysphagia, difficulty with eating, reflux symptoms and pain, and a further six single questions related to difficulty with saliva, choking while eating, dry mouth, coughing and difficulty with speech. The gastric module again comprises symptom scales in relation to dysphagia, eating, reflux and pain, with additional questions regarding taste, dry mouth, early satiety, weight loss, hair loss and health-related anxiety.

The Connolly questionnaire was devised to assess specific problems secondary to the effects of surgery; the need for hospital readmission, the need for repeat procedures and the effect of resection of the lower oesophageal anti-reflux sphincter mechanism, and the effects of vagotomy. Symptoms referable to resection and vagotomy included symptoms of reflux or aspiration, antro-pyloric function, and early and late dumping and diarrhoea. It comprises 29 questions in total, the first 19 of which relate to the domains described above and a further 10 questions regarding changes in diet, and overall subjective quality of life.

2.6. *Ethics committee approval*

Ethics committee approval was sought and granted prior to embarking on the study. Consent was obtained from all patients prior to the interview.

2.7. *Data analysis*

The Chi-squared test was used to compare means in demographic data (age, sex, histology). For the questionnaire data, the data were transferred from the original MS Excel questionnaire file to IBM SPSS Version 25.

Variables were recoded to categorical values. New summary variables were created to provide sub-domain analysis. Cases in which data were missing or unknown were excluded from the final analysis. Frequency tables were used for the display of observational data. Levene's test for homogeneity of variance was applied to all the final variables to determine whether the data were normally distributed. The choice of hypothesis test was predicated in each case on the results from Levene's test.

For normally distributed data in two groups, the parametric independent *t*-test was applied to compare two means. For normally distributed data in three groups, the parametric One-way Analysis of Variance (ANOVA) was used to compare three means. For non-normally distributed data the non-parametric Kruskal-Wallis ANOVA was used to compare medians in two or more groups. Statistical significance was set at 5% ($p = 0.05$).

Repeated-measures ANOVA was used to compare the result of our 33-point patient-reported symptom questionnaire delivered to each patient twice, 3 months apart. A paired *t*-test was used to compare the results of our questionnaire with the externally-validated EORTC quality of life questionnaires QLQ-C30 and OES-18/STO22.

3. Results

3.1. *Demographics and disease characteristics*

A total of 114 patients completed the questionnaires at the first time point, of whom 31 **(Group 1)** were healthy controls, 26 **(Group 2)** had received chemoradiotherapy only, 31 **(Group 3)** had undergone neoadjuvant chemoradiotherapy and oesophagectomy, and 26 **(Group 4)** had undergone gastrectomy.

The mean(± SD, median, range years) values for age for the entire cohort (including controls) was 66.5 (± 10.7, 68.5, 36–86) years. The age distribution (median, mean (SD) and min-max values) according to the groups was as follows [1]: Control group, 63.6 (± 11.31, 62, 36–86) years [2]; Group 2, 68.46 (± 9.3, 67, 52–86) years [3]; Group 3, 67.39 (± 10.53, 70, 37–85) years [4]; Group 4, 67.27 (± 11.3, 70, 43–85) years ($p = 0.32$). The values for age for the cohort who received treatment (Group 2, 3 and 4) were: 67.7 (± 10.3, 70, 37–86); while the mean age of the control group was 63.6 years, which did not differ significantly from the treatment cohorts ($p = 0.068$).

Of the oesophageal carcinomas, 68% were adenocarcinomas and 32% squamous cell carcinomas. The majority of patients (93%) had stage II-III tumours while 7% were stage I. In the cohort of patients undergoing chemoradiotherapy only (Group 2), the histology was squamous cell 15/26(57.6%), adenocarcinoma 11/26(42.3%) whilst in the cohort of patients with oesophageal cancer who underwent trimodality therapy (Group 3) the majority 25/31(80.6%) were adenocarcinomas, with the remainder represented by squamous cell carcinomas.

3.2. *Questionnaire compliance/missing data*

A total of 114 patients completed the questionnaires at the first time point. At the subsequent 3-month follow-up interval, four patients were excluded due to disease recurrence and a further 7 were not contactable for the duration of the study. Therefore, a total of 103 ($n = 103$) patients completed all 3 questionnaires and were recruited for purposes of comparison of the novel questionnaire against the validated questionnaires.

3.3. *Novel questionnaire - controls versus treatment groups*

The mean score for the control group administered the novel questionnaire was 20.74(± 1.09), approaching the lowest possible score of 20. This was significantly lower than scores for any of the cohorts who received treatment (28.9 ± 4.5, 32.3 ± 5.8 and 33.19 ± 5.9) for Group 2 (CRT only), Group 3 (oesophagectomy) and Group 4 (gastrectomy) respectively ($p < 0.001$).

3.4. *Validated questionnaire – overall health*

There was a statistically significant difference in favour of the CRT only group for self-reported overall health comparative to either of the oesophagectomy or gastrectomy operative groups (2.88 ± 1.166 versus 3.33 ± 1.269 and 4.20 ± 1.871, $p = 0.033$). The gastrectomy group reported the poorest health in this category.

3.5. *Validated questionnaire – quality of life*

The CRT only group reported the best quality of life comparative to the oesophagectomy and gastrectomy groups (2.65 ± 1.115 vs 3.37 ± 1.426 vs 4.28 ± 2.011). This difference was statistically significant ($p = 0.017$).

3.6. *Validated questionnaire – site specific modules*

Results for the OES-18 and STO-22 questionnaires demonstrated no significant differences between any groups (34.57 ± 8.423 vs 31.41 ± 8.352 vs 38.56 ± 11.903, $p = 0.066$) (see Fig. 1).

3.7. *Novel questionnaire - quality of life after surgery*

Scores did not differ significantly between patients undergoing either oesophagectomy or gastrectomy (32.3 ± 5.8 *vs* 33.19 ± 5.9, *$p=0.889$), (*Fig. 2*).* There was a trend, however, in the symptom burden between the two cohorts, with oesophagectomy associated with a greater proportion of reflux-related respiratory symptoms (7.3 ± 2.2 *vs* 6.5 ± 1.9; $p=0.396$) while the gastrectomy cohort reported more symptoms related to their post-vagotomy status, namely diarrhoea ((1.82 ± 0.9 vs 1.4 ± 0.6; $p=0.438$ and early dumping *((*8.2 ± 1.4 vs 7.1 ± 1.; $p=0.239$) but these trends did not reach statistical significance. Neither was there a significant difference in scores for anxiety/mental wellbeing between the groups ($p = 0.125$).

3.8. *Novel questionnaire - quality of life after chemo-radiotherapy*

The mean(± sd) overall QL scores were significantly-better in all domains (antro-pyloric function; respiratory reflux; post-vagotomy diarrhoea; early and late dumping) in patients avoiding resection (28.9 ± 4.5) *vs* oesophagectomy (32.3 ± 5.8 $p=0.042$) and *vs* gastrectomy(33.19 ± 5.9, $p=0.004$) *(*Fig. 3*).* Patients who underwent

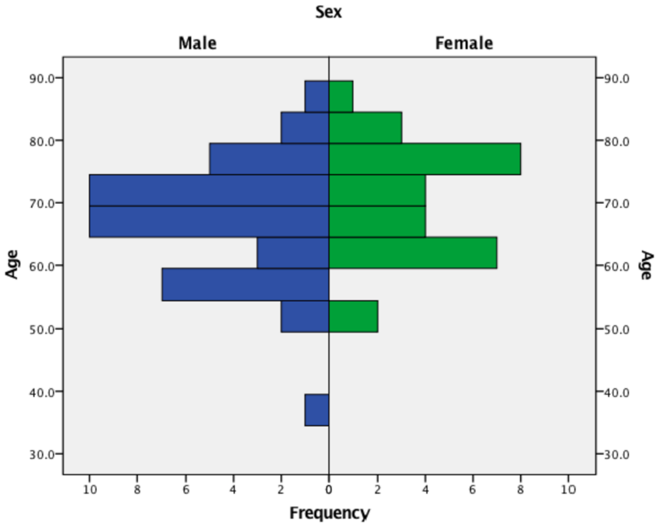

Fig. 1. Age and sex distribution of included patients.

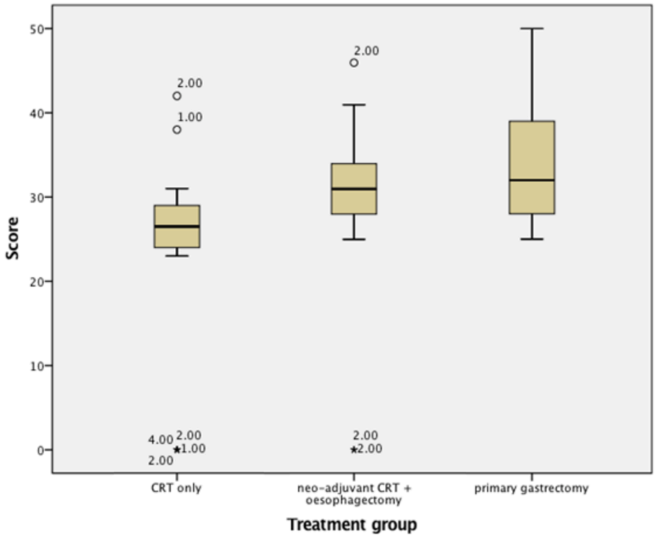

Fig. 2. Boxplot of Overall symptom score for each treatment group.

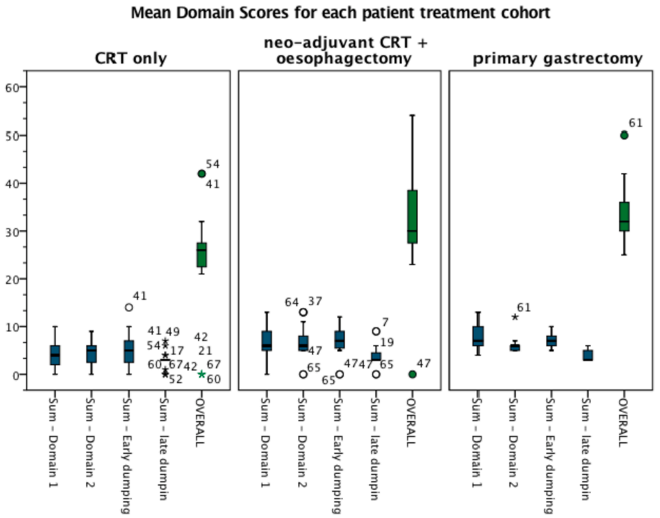

Fig. 3. Box plot displaying Mean symptom scores (for each domain in the 33-point questionnaire, and overall) for each cohort of patients.

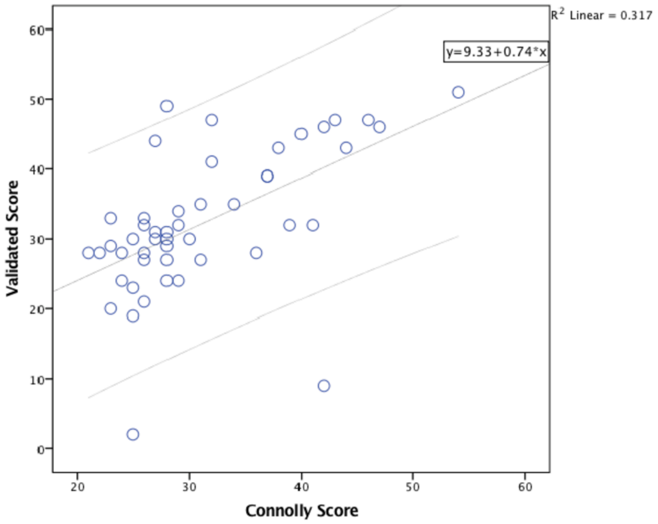

Fig. 4. Correlation between overall sum score in the 33-point Connolly symptom score questionnaire when presented to patients on second visit (X-axis) and externally validated symptom score (Y- axis).

resection did not differ statistically significantly from one another in terms of symptoms, but performed comparatively poorly versus non-operated patients.

3.9. Comparison at 3-month interval and against externally validated instruments

At a 3-month interval the novel questionnaire was repeated in order to assess variability of self-reported symptoms at two distinct time points. The total sum scores reported at this time were also compared against total sum scores from the externally validated instruments described above with appropriate linear transformation to ensure a like-for-like comparison *(*Fig. 4*)* Individual and overall scores reported from the novel questionnaire were consistent at a 3 month interval on repeated measures ANOVA, with no significant difference from those reported at the initial interview *($p = 0.647$)(*Fig. 5*)*.

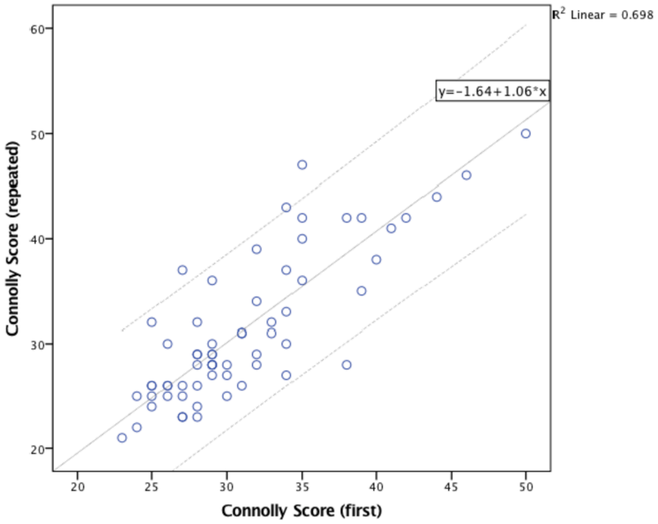

Fig. 5. Correlation between overall sum score in the 33 – point Connolly symptom score questionnaire when presented to patients on first visit (X – axis) and subsequently (Y-axis).

4. Discussion

This study compared the health-related quality of life of patients who had undergone treatment for upper GI malignancy with normal controls, using both standard instruments and a novel instrument focusing on the specific side-effects of different surgical interventions. Using standard instruments [50,53,54] patients who had undergone chemoradiotherapy alone and avoided surgery scored insignificantly different from controls and significantly better than patients receiving neoadjuvant/definitive chemoradiotherapy followed by surgery or surgery (gastrectomy) alone for individual and overall outcomes. Emotional function was similar between all groups.

This study also used a novel consequence-specific questionnaire. It was felt that two major and unique consequences of oesophagectomy – resection of the anti-reflux mechanism and division of the vagal trunks – are not reflected in current questionnaires. Of the surgical groups, gastrectomy and oesophagectomy produced differing local symptoms but overall similar quality of life metrics. The oesophagectomy cohort predominantly complained of reflux and aspiration symptoms whereas the symptoms reported by the gastrectomy cohort centred on post-vagotomy diarrhoea and dumping. General symptoms such as fatigue, pain and anxiety were similar in both surgical arms. Although only insignificant differences were noted between groups for the specific symptom complexes related to anti-reflux mechanism resection, anastomosis and vagotomy, this may have been due to the relatively small numbers in each cohort.

Symptom scores for the control group, however, were significantly better compared to those in any of the treatment groups ($p = 0.001$). Furthermore, quality of life scores remained significantly better in the chemoradiotherapy alone group versus the chemoradiotherapy followed by oesophagectomy and the gastrectomy cohorts on the second delivery of the questionnaire, ($p = 0.002$) supporting the findings of the first. This internal validation suggests both that the questionnaire is robust in our cohort of patients and that the QL issues experienced are chronic in nature.

Oesophageal and gastric malignancies typically affect an older population with age related and upper GI risk factor such as smoking and alcohol, increasing the incidence of significant comorbidity, such as heart disease, obstructive pulmonary disorders, diabetes and arteriopathy. The 5-year survival rate is poor as most patients have advanced disease at presentation [1–3]. In patients with potentially curable disease, however, treatment historically entailed major surgical resection, with significant morbidity often involving deterioration of cardiorespiratory function in already compromised patients. The recognition that neoadjuvant chemoradiotherapy offered a complete pathological response in a significant percentage of patients [5,6,8–10,55,56] led to a new way of thinking about this disease. No longer were patients committed to surgery on completion of chemoradiotherapy as a significant percentage could be salvaged by chemoradiotherapy alone. This was true of both squamous cell carcinoma where a 49% pathological complete response may be anticipated[14], but also in adenocarcinoma[19] where the complete response rate is half of this[14]. As the percentage of complete pathological responders increase with more effective neoadjuvant regimens, offered for earlier stage of disease, a growing number of surgeons are offering surveillance for selected complete clinical responders with increased confidence [18,57–60]. This is necessarily dependent on performance status and informed patient choice but appropriately selected patients can have equivalent overall survival to those who have surgery [46,61,62]. For the oldest patients, especially those with comorbidity, quality of life is at a premium [42]. In addition to the morbidity and mortality risks of differing treatment approaches patients desire quality of life information [41,63–67], and it is recommended that where two treatments offer no difference in overall survival the quality of life should be used to determine which is superior [68,69].

Surgery for upper GI malignancies has a negative impact on multiple aspects of quality of life. A meta-analysis by Jacobs et al. [70] found that symptoms such as cough, reflux, dyspnoea and fatigue were increased at 3–9 months after surgery and were sustained for over 12 months while Scarpa et al. [56] found a decline in quality of life due to worsened fatigue, dyspnoea and diarrhoea at 6 months but these had returned to baseline at 12 months [71]. While HRQL may recover over time for survivors, surveillance and avoidance of surgery avoids altogether the surgery-associated impairment in quality of life in those with the least ability to tolerate it, with the option of salvage in the event of disease recurrence. In trials designed to examine QL as an end-point in comparison between definitive chemoradiotherapy and chemoradiotherapy followed by surgery, all have found QL to be superior in patients avoiding surgery, without a concomitant survival disadvantage [47–49]. Opinion is divided as to whether this benefit is sustained [47] or the two approaches equilibrate after 1–2 years [48,49] but it must be remembered that the majority of patients undergoing resection do not survive beyond 3 years.

Our study supports the findings of previous studies reporting that chemoradiotherapy results in increased fatigue and declined physical function, although the effect is less marked than with surgery [48], and global QL indices are consistently superior to patients who have undergone surgical resection [47,49,62]. Blazeby in 2005 also found that in regard to specific symptoms such as dyspnoea, cough and fatigue, again chemoradiotherapy had a negative effect, but as in our study, this remained superior to the effect of chemoradiotherapy when followed by surgery [72].

The use of a non-validated questionnaire for QL assessment may be considered a shortcoming of the study but this was controlled for by co-administration with both a separate externally validated and well accepted assessment tool (the EORTC questionnaire) and recruitment of a control group of healthy individuals. There was no significant difference between the total sum scores of our novel questionnaire and those of the externally validated instruments ($p = 0.405$) indicating a good correlation between the two. Karnofsky performance status was not specifically evaluated which may be considered a further shortcoming but there was no significant difference in age or stage between the cohorts, indicating reasonable homogeneity. And study sample sizes were necessarily small, which may lack sufficient power to detect subtle differences between the groups, such as the trend towards respiratory problems in those undergoing resection of the LOS and diarrhoea and dumping in the gastrectomy cohort; trends towards significance which a larger sample size may have uncovered. Nevertheless, the study found a significant QL difference favouring surveillance over surgery, which was consistent across the spectrum of symptom domains evaluated and over two separate time points. This supports the belief that avoidance of surgery in selected patients results in superior QL outcome for this cohort.

5. Conclusions

Avoidance of surgery in clinically complete responders to neoadjuvant chemoradiotherapy is rewarded with a superior quality of life than those undergoing resection. As the literature demonstrates equivalent long-term recurrence rates and mortality between definitive chemoradiotherapy and nCRT plus surgery in responding patients, we feel that consideration should be given to forgoing surgery in selected patients with a complete clinical response after nCRT in favour of a strategy of ongoing surveillance, with the option of salvage surgery if the disease recurs.

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Conflicts of interest

None declared.

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