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Hypofractionated Radiotherapy in Oesophageal Cancer for Patients Unfit for Systemic Therapy: a Retrospective Single-Centre Analysis

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Highlights

- In oesophageal cancer, hypofractionated radiotherapy is safe and tolerable.
- Outcomes following hypofractionated radiotherapy are very encouraging.
- Response to treatment in oesophageal cancer dependent on tissue subtype.
- Potential to combine this approach and precision radiotherapy approaches.
- Findings relevant to the use of proton-beam therapy.

ABSTRACT

Aims: Chemoradiotherapy (CRT) is established as a superior treatment option to definitive radiotherapy in the non-surgical management of oesophageal cancer. For patients precluded from CRT through choice or comorbidity there is little evidence to guide delivery of single-modality radiotherapy. In this study we outline outcomes for patients unfit for CRT who received a hypofractionated radiotherapy (HRT) regime.

Methods: Retrospective UK single-centre analysis of 61 consecutive patients with lower or middle third adenocarcinoma (OAC; 61%) or squamous cell carcinoma (SCC) of the oesophagus managed using HRT with radical-intent between April 2009 and 2014. Treatment consisted of 50Gy in 16 fractions (n=49, 80.3%) or 50-52.5Gy in 20 fractions (n=12, 19.7%). Outcomes were referenced against a contemporaneous comparator cohort of 80 (54% OAC) consecutive patients managed with conventionally-fractionated CRT within the same centre.

Results: Three-year and median overall survival (OS) were respectively 56.9% and 29 months with HRT, compared with 55.5% and 26 months for CRT; adjusted HR 0.79 (95%CI 0.48-1.28). Grade III and IV toxicity rates were low at 16.4% (n=10) of those receiving HRT, and 40.2% (n=32) of the CRT group. In patients with OAC, CRT delivered superior overall survival (HR 0.46; 95%CI 0.25-0.85) and progression-free survival (HR 0.45; 95%CI 0.23-0.88) when compared to HRT.

Conclusions: The HRT regime described here was safe and tolerable in patients unable to receive CRT, and delivered promising survival outcomes. The use of HRT for the treatment of oesophageal cancer, both alone and as a sequential or concurrent treatment with chemotherapy, requires further study. New precision radiotherapy technologies may provide additional scope for improving outcomes in oesophageal cancer using HRT-based approaches and should be evaluated.

INTRODUCTION

Oesophageal cancer is the sixth most common cause of death from malignancy worldwide and results in 440000 deaths annually.[1] A majority of patients present with advanced disease, with localised disease present in only 20% and regional spread seen in a further 30%.[2]. Surgery remains the most widely accepted management approach in the setting of locally advanced disease, though definitive concurrent chemoradiotherapy (CRT) is a standard of care for squamous cell carcinoma (SCC). For patients unwilling to undergo or precluded from surgery as a consequence of their functional status or locoregional disease extent, CRT is the most widely accepted treatment approach.[3]

A proportion of patients will however be unfit for chemotherapy despite potentially curable disease. For this group radiotherapy (RT) represents their only radical treatment option yet reported outcomes following single modality treatment are historically very poor.[2,4,5] Strategies to improve the efficacy of RT as a single treatment modality for oesophageal cancer have received little focus and there is no prevailing consensus on an optimal radical radiotherapy regime. In addition, whilst both hyperfractionated and hypofractionated radiotherapy regimes have been linked with possible benefit in a small number of studies, these have almost exclusively focussed on SCCs with a paucity of evidence to guide treatment decisions in oesophageal adenocarcinoma (OAC).[6-9]

Within Leeds Cancer Centre (LCC) hypofractionated radiotherapy (HRT) is established as the standard of care for patients with lower and middle oesophageal SCC and OAC who are unfit for CRT. In this retrospective analysis we provide evidence for the efficacy and toxicity of this regime, and reference these outcomes to those seen in a contemporaneous reference cohort of patients managed with the non-surgical standard-of-care, CRT, within the same centre.

METHODS

Patient population

All patients receiving HRT (n=61; 37 (61%) OAC) or CRT (n=80; 42 (54%) OAC) with curative intent for lower- or middle- third oesophageal cancer (ICD-10 codes C15.4 and C15.5) within LCC between 1st April 2009 and 1st April 2014 were included. Patients for whom there was diagnostic uncertainty, who had undergone previous upper gastrointestinal surgery or prior treatment for oesophageal cancer, or who had an upper thoracic or cervical oesophageal malignancy were excluded.

Study design

Patients were identified via an informatics query. Each identified patient's electronic health record was then manually reviewed to assess eligibility. An outline of the study approach is provided in **Fig. 1**. Data were extracted by three medically-trained investigators and cross-checked for accuracy. Extracted data included patient demographics, comorbidities at the time of diagnosis, tumour characteristics and both surgical and non-surgical anti-cancer and palliative interventions. The gross tumour volume (GTV) was identified through review of treatment contours and used as an indicator of tumour bulk. American Joint Committee on Cancer (AJCC) stage was calculated using criteria from the 7th edition of the AJCC *Cancer Staging Manual*.[10]

Setting & treatment selection

Over the five-year study period all patients received treatment directed by a site-specialist multidisciplinary team (MDT). At LCC, patients with potentially curable disease but who have declined or who are unsuitable for oesophagectomy are referred either for CRT or, if unwilling or unable to receive chemotherapy due to poor performance status or co-morbidity, HRT. For both treatments disease length, measured as the tumour length plus that of the length of any outlying nodes, is required to be less than 10cm. A small proportion of patients undergo endoscopic mucosal resection for early T1 tumours prior to CRT or HRT. A summary of treatments, including the year in which patients received initial therapy, is shown in **Supp. Table 1**.

Hypofractionated radiotherapy (HRT)

Dose fractionation used for single modality HRT consisted of 50 Gy in 16 fractions (n=49, 80.3%) for the majority. In those for whom dose constraints for the lung, heart or stomach could not be met an alternative dose of 50-52.5 Gy in 20 fractions was employed (n=12, 19.7%).

Chemoradiotherapy (CRT)

CRT consisted of 50 Gy in 25 fractions with concurrent systemic treatment. For the majority (n=76; 96%) of patients, chemotherapy regimen consisted of cisplatin (60-80 mg m^{-2}) or carboplatin (AUC 3.3) with either capecitabine (625 mg m^{-2} B.I.D.) or 5-fluorouracil (5FU; 600-800 mg m^{-2}), prescribed as two concurrent three or four-weekly cycles with two preceding induction cycles at identical doses in 14 (17.5%) patients. Four (5%) patients received an alternative regimen consisting of five weekly doses of concurrent carboplatin (AUC 2.0) and paclitaxel (50 mg m^{-2}), or carboplatin (AUC 3.0) and paclitaxel (175 mg m^{-2}) three-weekly.

Radiotherapy planning

All patients received 3D conformal Image Guided Radiotherapy (IGRT). Those with middle-third tumours underwent a 3D planning CT, as did patients with lower-third tumours until September 2010. From this date 4D contrast-enhanced planning CT was used. Cone Beam CT was utilised for treatment verification as per National Radiotherapy Implementation Group (NRIG) Guidelines.[11] The GTV was planned to include the primary tumour, the circumference of the oesophagus at the level of the disease and para-oesophageal nodal disease in proximity to the primary tumour. The circumference of the oesophagus was included at the level of involved para-oesophageal nodes, and where nodal involvement was superior or inferior to the primary tumour, the radial margin of the oesophagus between these structures formed the radial margin of the GTV. Involved nodes below the gastro-oesophageal junction were contoured separately. Creation of clinical target volume (CTV) and planning target volume (PTV) margins for planned 3D cases were as per the SCOPE-1 study protocol.[12] 4D planning with creation of CTVs, internal target volume (ITV) and PTV was performed as per the NeoSCOPE trial protocol.[13] Dose to the target volume was prescribed as per International Commission on Radiation Units & Measurements (ICRU) 62 recommendations (95-107% isodose coverage), and organ at risk (lung, cord and heart) constraints defined as per institutional protocols. In the case of CRT this was as per the SCOPE1 trial protocol.[12,14] Radiotherapy was administered once daily for five days per week in all cases. Selected clinical cases were subject to departmental quality assurance rounds in which volumes were reviewed by consultant clinical oncologists and radiologists specialising in upper gastrointestinal cancer.

Follow-up

Follow-up included clinical assessment and imaging at three months after completion of treatment, followed by further clinical assessment at three-to-six monthly intervals for the first 24 months following treatment, and six-monthly intervals thereafter. The timing of repeat imaging was determined by clinical assessment. Patients alive at four years were either seen annually or discharged to their primary care practitioner. The timing of subsequent investigations was determined by the outcome of clinical assessments. Treatment options for recurrence included salvage oesophagectomy, systemic therapy or supportive care.

Outcome measures

Progression free survival (PFS) and time-to-stent insertion (TTS) were calculated from the date on which treatment with radiotherapy commenced. Overall survival (OS) was measured from the date of diagnosis. For patients lost to follow-up, data for OS were censored on the date the patient was last seen alive and data for TTS and PFS on the dates on which the patient was last known to have respectively not undergone oesophageal stent insertion or exhibited disease recurrence. Toxicity data were retrieved from medical records and graded retrospectively based on Common Terminology Criteria for Adverse Events v4.0.

Statistical analysis

The distribution of categorical variables was assessed using Fisher's Exact test. The impact of case-mix and treatment upon OS and PFS were assessed using Cox proportional hazards model. This multivariable model assumes the impact of treatment is constant within a co-variable. In the case of histology this may not be the case i.e. CRT may have a different effect on OAC compared with oesophageal SCC. The possibility of an interaction between histological subtype and treatment was therefore considered. Akaike's Information Criteria (AIC) was used to assess the fit of the model and the log-likelihood ratio to determine the significance of improved fit once histological subtype was considered. Linear combination was used to determine the hazard ratios for each of the histological subtypes with CRT as compared to HRT treatment. The Stata 14 (StataCorp, TX) software package was used to analyse these data. Two-sided p-values of less than 0.05 were considered significant.

Study approval was granted by The Leeds Teaching Hospitals NHS Trust Research & Innovation department.

RESULTS

Patient characteristics

Baseline characteristics are shown in **Table 1**. Reflecting patient selection for each treatment modality, a significantly greater proportion of patients undergoing HRT had one or more moderate-severe comorbidity when compared with those receiving CRT (59.0% vs. 31.3%; p=0.001). The age distribution reflected oesophageal cancer as a disease of the elderly; 55.0% of patients in the CRT cohort were aged over 70 versus 72.2% of those receiving HRT (p=0.004), with respective median ages of 70 (interquartile range; IQR 62-76) years and 76 (IQR 69-80) years. There was a preponderance of males in the HRT cohort (73.8% vs. 52.5%; p<0.05).

Tumour characteristics

Staging investigations are shown in **Table 1**. Twelve (24.5%) of the 61 patients who received HRT had a middle third tumour compared with 30 (60%) of those receiving CRT (p<0.05). The majority of patients in the HRT cohort were AJCC stage I (41%) or II (31.1%), whereas 47.5% in the CRT cohort were AJCC stage II and 26.3% AJCC stage III (p=0.001). Histological subtype, grade and nodal stage were comparable between cohorts. Median GTV was higher in the CRT cohort (37.4 cm^3 vs. 24.5 cm^3). Median tumour length was 5.0 (IQR 4.0-6.0) cm in the CRT cohort and 4.5 (IQR 2.3-5.8) cm in the 57/61 (91.8%) of the HRT cohort for whom data for this value were available. All patients underwent computed tomography (CT) staging whereas positron emission tomography (PET)-CT was used more frequently in the CRT cohort (93.8% vs. 80.3%; p<0.05) and endoscopic ultrasound (EUS) more frequently in the HRT cohort (68.9% vs. 56.3%; p<0.05).

Outcome measures

Overall survival (OS)

There was no evidence of a difference in overall survival between the cohorts (see **Fig. 2).** Median survival for patients receiving CRT was 29 months, compared with 26 months for patients who received HRT; adjusted HR 0.79 (95% CI 0.48-1.28). Similarly, there was no evidence of a difference in one year (80.3% vs 85.0%), two

year (56.9% vs 55.5%) or three year (38.8% vs 43.5%) survival. On univariable analysis age greater than 80 years and AJCC stage of 3 were associated with worse OS. The importance of AJCC stage was confirmed on multivariable analysis with adjusted HR of 1.99 (95% CI 1.08 – 3.69) and 2.11 (95% CI 1.08 – 4.12) for stages 2 and 3 respectively. Treatment type was not associated with significant change in OS, as shown in **Table 2** and **Table 3**.

The fit of the multivariable Cox model for OS improved significantly with the addition of an interaction term between survival and histology, reflected by a reduction in AIC from 821.86 to 815.65 (log likelihood ratio p=0.004). When this term was included within the multivariable model, CRT was associated with a hazard ratio of 1.733 (95%CI 0.819-3.700) for SCCs and 0.464 (95%CI 0.253-0.848) for OAC **(Supp. Fig. 1 & Supp. Fig. 2)**. This indicates a differential treatment effect with histological subtype; CRT being associated with improved OS in OAC, but no evidence of a difference between the treatment modalities in SCC.

Progression free survival (PFS) and recurrence patterns

As seen in **Fig. 3**, median time to treatment failure was 25 months for patients who received HRT and 23 months for patients prescribed CRT; adjusted HR 0.98 (95% CI 0.57-1.67). There were a comparable proportion of patients with local recurrence in the HRT and CRT cohorts (26.2% vs. 28.8%). Distant relapse was seen in seven (11.5%) patients who received HRT and 14 (17.5%) managed with CRT. In both cohorts, 10% of patients presented with simultaneous distant and locoregional relapse. Treatment type did not adversely affect PFS on either univariable or multivariable analysis. Inclusion of an interaction term between histology and treatment type resulted in significant improvement in the model fit (AIC 646.01 from 656.44; p<0.001), demonstrating that local control rates achieved by each treatment modality were at least partly dependent on disease histology. In patients with adenocarcinoma, PFS was significantly better in patients treated with CRT (HR 0.449; 95%CI 0.230-0.879). Conversely, there was no evidence of a difference in PFS by treatment type in patients with SCC (HR 0.977; 95%CI 0.574-1.665).

Time-to-stent (TTS) insertion

Fig. 4 represents TTS and excludes the one patient who received CRT and two who received HRT who had a stent in-situ at the start of treatment. No evidence of a difference in TTS was seen between treatment groups. As with PFS, AJCC score but not treatment type adversely affected TTS. Five (6%) patients who received CRT required a stent for benign structuring and 20 (24%) for a malignant indication. A comparable proportion of patients who received HRT required stent insertion; five (8%) for a benign stricture and nine (15%) for malignant disease.

Treatment toxicity & compliance

There were no deaths within 30 days of treatment and overall rates of treatment toxicity were low. As summarised in **Supp. Table 2**, grade III toxicities were seen in 29 (36.3%) patients managed with CRT and nine (14.8%) patients treated using HRT. Grade IV toxicity was rare and reported for just three (3.8%) patients receiving CRT and one (1.6%) managed with HRT. Dysphagia was the most common cause of grade III toxicity in those managed with both HRT (n=6; 9.8%) and CRT (n=10; 12.5%), additionally accounting for an episode of grade IV toxicity in patients receiving CRT. Enteral feeding support was required by 10 (12.5%) patients in the CRT cohort and four (6.6%) receiving HRT. In line with commonly seen side effects from chemotherapy, gastrointestinal side effects were common in the CRT group.

A total of 13 patients required changes to their chemotherapy protocol; for six (7.3% of the CRT cohort) chemotherapy was stopped earlier than initially planned and for an identical proportion the chemotherapeutic agent was switched following the first cycle in view of adverse effects. For one patient chemotherapy was dose reduced. No change to planned radiotherapy dose or fractionation was required in either cohort.

DISCUSSION

The RTOG 85-01 trial demonstrated significantly superior survival outcomes with CRT compared with those achieved using single-modality conventionally fractioned RT in patients with oesophageal cancer.[15] CRT consequently forms the non-surgical standard-of-care and the added benefit derived from the addition of chemotherapy has been supported by a number of subsequent series.[15-17] However, for patients unfit for chemotherapy the 64Gy/32# regime employed within RTOG 85-01 is the most commonly adopted treatment

approach despite achieving very poor survival of as low as 0% at five years in both RTOG 85-01 and subsequent series. A small number of highly-selective series in patients with oesophageal SCC have however suggested that outcomes for patients receiving definitive RT may be improved by adjusting dose fractionation (see **Supp. Table 3**).[18-22] In our series, 45% of patients were unfit for CRT but remained suitable for radical therapy. We show that in this large, elderly cohort of co-morbid patients with both OAC and SCC, use of a convenient, well-tolerated HRT regime resulted in outcomes superior to those seen in historical analyses of definitive RT.[4,6-8,23]

There are two contemporaneous cohorts against which these outcomes may be further benchmarked. The first is the CRT cohort described here. At 29 and 23 months for CRT and HRT respectively, there was no evidence of a difference in OS between treatment modalities. There were however important differences in the baseline characteristics of the two cohorts. Those treated with HRT had a greater median age and significantly greater burden of comorbidity. In contrast, disease stage and tumour bulk were less favourable in the CRT cohort.

The recent SCOPE-1 trial of cetuximab used alongside conventionally-fractionated CRT provides a second comparator cohort.[18] For patients within this trial treated with CRT alone, median OS and PFS were 34.5 and 24.1 months respectively. At 26 and 25 months, the OS and PFS for the cohort presented here approach that seen in SCOPE-1 despite a greater proportion of patients aged over 70 years (72% vs 39%) and 59% of the cohort having been diagnosed with one or more major comorbidity. In contrast to the SCOPE-1 trial, our analysis additionally excludes the more favourable prognostic groups of the upper oesophagus.

The efficacy of this novel HRT regime may be explained both by increased dose delivery and by the shorter duration over which it is delivered. Assuming an α/β ratio of 10 for oesophageal tumours, the HRT we describe provides an equivalent dose in 2Gy fractions (EQD2) of 54.69 Gy,. This is a modest yet clinically relevant increase in dose compared to the 50Gy received by the comparator CRT cohort yet remains lower than the 64Gy received in RTOG 85-01. Delivered in either 16 or 20 fractions, the HRT regime was also accelerated, potentially resulting in reduced accelerated repopulation.

There are a number of important implications of these data for the care of patients with oesophageal cancer. Firstly, these results provide a proof-of-principle for an effective treatment approach for patients who are suitable for radical treatment but unfit for chemotherapy. There is at present no good evidence to support best practice for this cohort yet in the population studied here, 45% of those amenable to radical therapy were unfit for or declined CRT. This points to a significant area of unmet need in which trial analyses incorporating a HRT comparator arm should be considered.

Secondly, the data presented here also support the use of dose escalation and hypofractionation in the treatment of oesophageal cancer. This may be achieved through the use of MR-based IGRT (MR-Linac), which permits the delivery of more precise RT and on-treatment adaptation of volumes to reflect treatment response; thereby facilitating dose escalated, shorter duration approaches such as the HRT schedule outlined here.[24] Similarly, our data also provide a signal for the use of proton beam therapy (PBT) in oesophageal cancer, an approach which is supported by recent evidence in the neoadjuvant setting.[25-27]. This treatment involves the use of particles to deliver high doses of RT to a tumour with high accuracy and with limited normal tissue exposure. The dose escalated regime outlined here suggests that such an approach may be efficacious, and could be achieved via a schedule with limited resource implications.

In keeping with previous analyses of radiotherapy in this context, we performed exploratory subanalyses to determine whether there was any relationship between tumour histological subtype and the effectiveness of each treatment approach. Interestingly, whilst comparable outcomes were seen in SCC, CRT was associated with superior outcomes when compared with HRT in patients with OAC. This evidence for additional benefit from the addition of chemotherapy in patients with lower or middle-third OAC is in keeping with data demonstrating benefit from chemotherapy in the adjuvant setting in gastric cancer, both with and without RT.[28,29] Whether chemotherapy would add further benefit in addition to RT dose escalation by hypofractionation is of additional interest and is under review within the SCOPE-2 trial.

Limitations

This was a retrospective analysis and the number of included participants is limited, reducing power to identify treatment differences. That significant differences were still identified is notable. Case selection was made within a single multidisciplinary team following standardised staging techniques. Selection bias is nevertheless inevitable given different treatment toxicities, a higher proportion of patients aged over 70 years, a greater burden of comorbidity and the larger proportion of males seen in the HRT cohort. Conversely, a greater median tumour size and larger proportion of more advanced tumours were seen in the CRT cohort, constituents of which were more likely to undergo enhanced staging with PET-CT. We cannot therefore conclude on the relative efficacy or toxicity of HRT when compared with CRT. However, these and demographic differences between the treatment groups were as far as possible adjusted for within multivariable analyses, thereby providing a real-world comparator cohort against which to benchmark the efficacy of HRT. Standardised clinical protocols were in addition used throughout the study period and treatment overseen by a single highly-site-specialised MDT, limiting the potential for impact from inter-clinician heterogeneity. The shorter fractionation schedule for HRT may impact on both patient experience and resource expenditure. Quality of life and health economic analyses would therefore be of interest but could not be assessed here. Finally, toxicity data were collated retrospectively and may therefore be prone to bias, although it is unclear what effect this would have had on the data presented here.

CONCLUSION

These data concerning the use of HRT in oesophageal cancer provide evidence for encouraging efficacy and reassuring rates of toxicity. The use of HRT for the treatment of oesophageal cancer, both alone and as a sequential or concurrent treatment with chemotherapy, requires further study. The advent of newer precision RT technology, including MR-based IGRT and PBT, may provide additional scope for improving outcomes in oesophageal cancer using HRT-based approaches and should be evaluated.

AUTHOR CONTRIBUTIONS

CMJ contributed to the collection and analysis of data, in addition to authoring the first draft of the manuscript and leading subsequent revisions. KS supported data collection and led data analysis. CH, BW and TP contributed to data collection. PH, DSM and AC devised the hypofractionation protocol on which this study is

based. PH, DSM, AC, RG and TC supported the collection and analysis of study data. GR devised the study and supported data analysis. All authors contributed to revisions of the manuscript and all have read and approved the final version of the manuscript.

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TABLES

Table 1: Baseline characteristics for patients with oesophageal adenocarcinoma and squamous cell carcinoma treated with radical intent using either hypofractionated radiotherapy or combination chemoradiotherapy between 2009 and 2014 (n=141).

		Hypofractionated radiotherapy n=61		**Combination chemo-radiotherapy n=80**	
		No.	%	No.	%
Demographics					
Sex	Male	45	73.8	42	52.5
	Female	16	26.2	38	47.5
Age (years)	40-49	1	1.6	1	1.25
	50-59	0	0.0	8	10.0
	60-69	16	26.2	27	33.8
	70-79	24	39.3	36	45.0
	80-89	20	32.8	8	10.0
Charlson	0	25	41.0	55	68.8
comorbidity	1	15	24.6	19	23.8
index	2	13	21.3	3	3.8
	≥3	8	13.1	3	3.8
Tumour-characteristics					

Investigations	CT	61	100.0	80	100.0
	PET-CT	49	80.3	75	93.8
	EUS	42	68.9	45	56.3
Histology	Adeno	37	60.7	42	53.8
	SCC	24	39.3	36	46.2
Location	Middle	12	19.7	30	37.5
	Lower	49	80.3	50	62.5
T stage	T1	12	19.7	3	3.75
	T2	26	42.6	21	26.3
	T3	22	36.0	53	66.3
	T4a	0	0.0	1	1.25
	T4b	0	0.0	2	2.5
	Unknown	1	1.6	0	0.0
N stage	N0	43	70.5	51	63.8
	N1	13	21.3	26	32.5
	N2	4	6.6	3	3.8
	Unknown	1	1.6	0	0.0
Grade	G1	10	16.4	7	8.8
	G2	24	39.3	29	36.3
	G3	15	24.6	26	32.5
	U	12	19.7	17	21.3
AJCC	I	25	41.0	9	11.3
	II	19	31.1	38	47.5
	III	11	18.0	21	26.3
	Unknown	6	9.8	12	15.0

Table 2: Univariable cox proportional hazards analysis by study population characteristics. Results shown for overall survival (OS), progression-free survival (PFS) and stent-free survival (SFS). OS calculated from date

of diagnosis, PFS and SFS from date of first radiotherapy treatment. HR: Hazard Ratio; HRT: Hypofractionated radiotherapy; Chemoradiotherapy. *AJCC not known for all patients.

	OS		PFS		SFS	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Sex						
Male	0.92 (0.60-1.39)	0.68	1.05 (0.65-1.68)	0.84	0.72 (0.39-1.36)	0.31
Female	1.00		1.00		1.00	
Age (years)						
<60	1.08 (0.45-2.62)	0.87	1.13 (0.46-2.77)	0.79	0.60 (0.14-2.58)	0.49
60-69	1.00		1.00		1.00	
70-79	1.43 (0.89-2.29)	0.14	1.26 (0.74-2.13)	0.34	0.78 (0.39-1.57)	0.49
80-89	1.99 (1.07-3.69)	*0.03*	1.88 (0.93-3.78)	0.08	1.21 (0.47-3.09)	0.69
Histology						
SCC	1.00		1.00		1.00	
Adeno	1.13 (0.75-1.71)	0.56	1.02 (0.65-1.61)	0.93	0.67 (0.36-1.24)	0.20
AJCC*						
1	1.00		1.00		1.00	
2	1.68 (0.96-2.92)	0.07	2.05 (1.06-3.99)	*0.03*	2.51 (0.90-6.97)	0.08
3	1.94 (1.05-3.59)	*0.03*	2.39 (1.16-4.95)	*0.03*	5.00 (1.55-15.65)	*0.01*
Charlson						
0	1.00		1.00		1.00	
≥1	0.99 (0.66-1.49)	0.96	0.83 (0.53-1.35)	0.43	0.72 (0.38-1.36)	0.31
Treatment						
HRT	1.00		1.00		1.00	
CRT	0.95 (0.63-1.43)	0.81	1.21 (0.76-1.92)	0.43	1.26 (0.67-2.40)	0.48

Table 3: Multivariable analysis by study population characteristics. Results shown for overall survival (OS), progression-free survival (PFS) and stent-free survival (SFS). OS calculated from date of diagnosis, PFS and SFS from date of first radiotherapy treatment. HR: Hazard Ratio; HRT: Hypofractionated radiotherapy; CRT: Chemoradiotherapy. *AJCC not known for all patients.

	OS		PFS		SFS	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Sex						
Male	0.92 (0.57-1.48)	0.73	1.12 (0.67-1.87)	0.68	0.67 (0.34-1.34)	0.26
Female	1.00		1.00		1.00	
Age (years)						
<60	0.98 (0.39-2.49)	0.97	0.92 (0.36-2.37)	0.86	0.27 (0.06-1.23)	0.09
60-69	1.00		1.00		1.00	
70-79	1.23 (0.73-2.08)	0.44	1.06 (0.58-1.94)	0.86	0.57 (0.26-1.28)	0.17
80-89	1.77 (0.89-3.53)	0.10	1.69 (0.78-3.67)	0.18	0.90 (0.33-2.48)	0.84
Histology						
SCC	1.00		1.00		1.00	
Adeno	1.29 (0.78-2.12)	0.33	1.19 (0.67-2.10)	0.55	0.96 (0.44-2.09)	0.91
AJCC*						
1	1.00		1.00		1.00	
2	1.99 (1.08-3.69)	*0.03*	2.21 (1.07-4.56)	*0.03*	2.216 (0.74-6.65)	0.16
3	2.10 (1.08-4.12)	*0.03*	2.33 (1.06-5.12)	*0.04*	6.35 (2.08-19.41)	*<0.01*
Charlson						
0	1.00		1.00		1.00	
≥1	1.08 (0.70-1.67)	0.73	0.92 (0.56-1.52)	0.92	0.86 (0.43-1.71)	0.66
Treatment						
HRT	1.00		1.00		1.00	
CRT	0.79 (0.48-1.28)	0.34	0.98 (0.57-1.67)	0.93	0.82 (0.39-1.71)	0.60

FIGURE LEGENDS

Figure 1: Study profile indicating selection of patients for analysis. Following initial identification of potentially eligible patients through an informatics search 69 were excluded due to ineligible cancer site (upper thoracic oesophageal or gastric), administration of neoadjuvant chemotherapy with initial surgical intent, treatment with palliative intent, administration of trial-specific treatment or previous oesophagectomy.

Figure 2: Overall survival by treatment modality. Survival calculated from date of diagnosis for patients who received either hypofractionated radiotherapy (HRT) and chemoradiotherapy (CRT). Data censored at 3-years follow-up. There was no significant difference between treatment modalities.

Figure 3: Progression-free survival by treatment modality. Progression-free survival calculated from the start of radiotherapy to the date of disease progression for patients who received either hypofractionated radiotherapy (HRT) or chemoradiotherapy (CRT). Data censored at 3-years follow-up. There was no significant difference between treatment modalities.

Figure 4: Time-to-stent insertion by treatment modality. Time-to-stent insertion calculated from the start of radiotherapy to the date of oesophageal stent insertion and/or dilatation for patients who received either hypofractionated radiotherapy (HRT) or chemoradiotherapy (CRT). Patients for whom an oesophageal stent was inserted prior to receiving HRT or CRT were excluded from analysis.

Figure 1: Study profile indicating selection of patients for analysis.

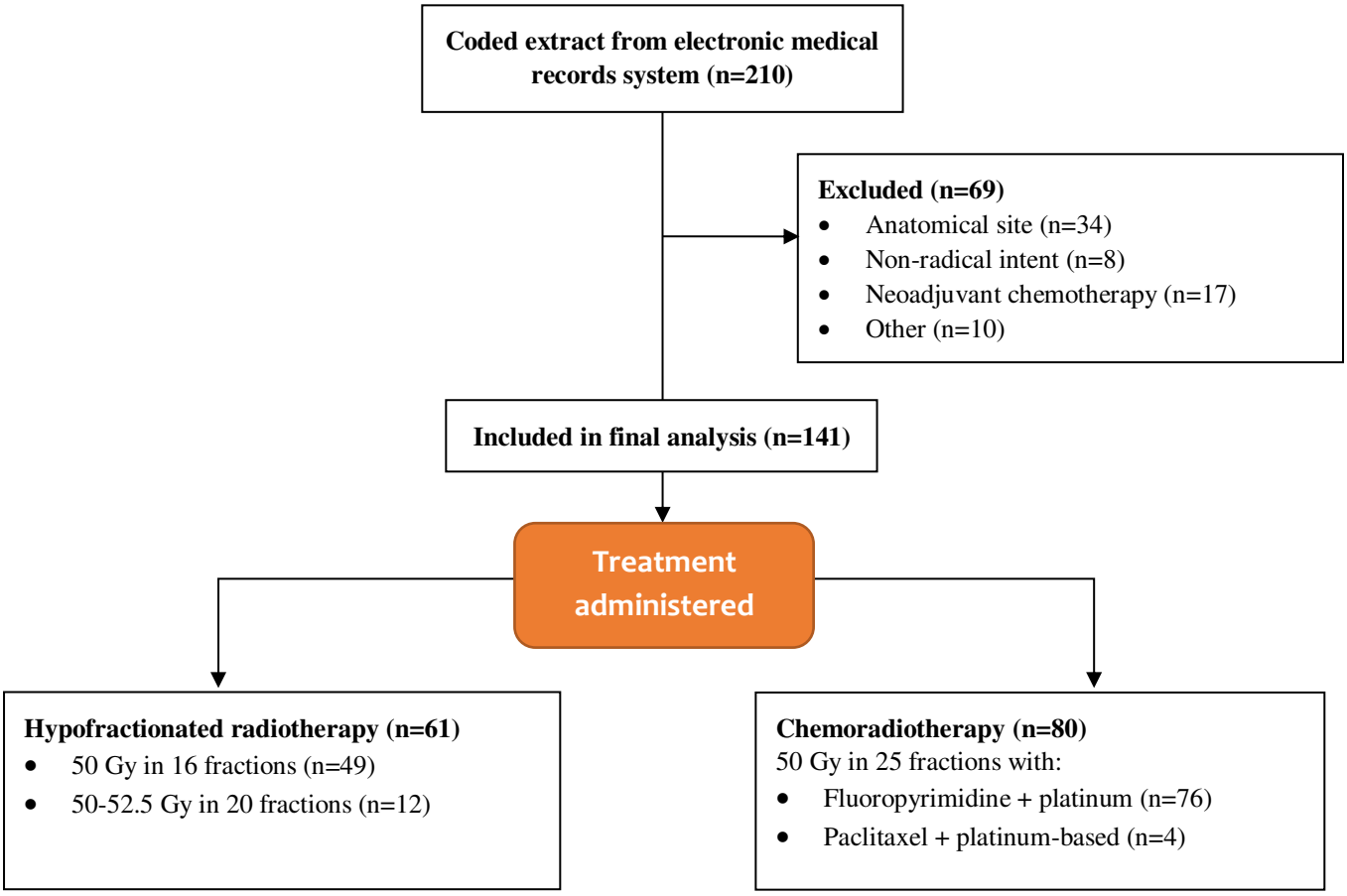


Figure 2: Overall survival by treatment modality.

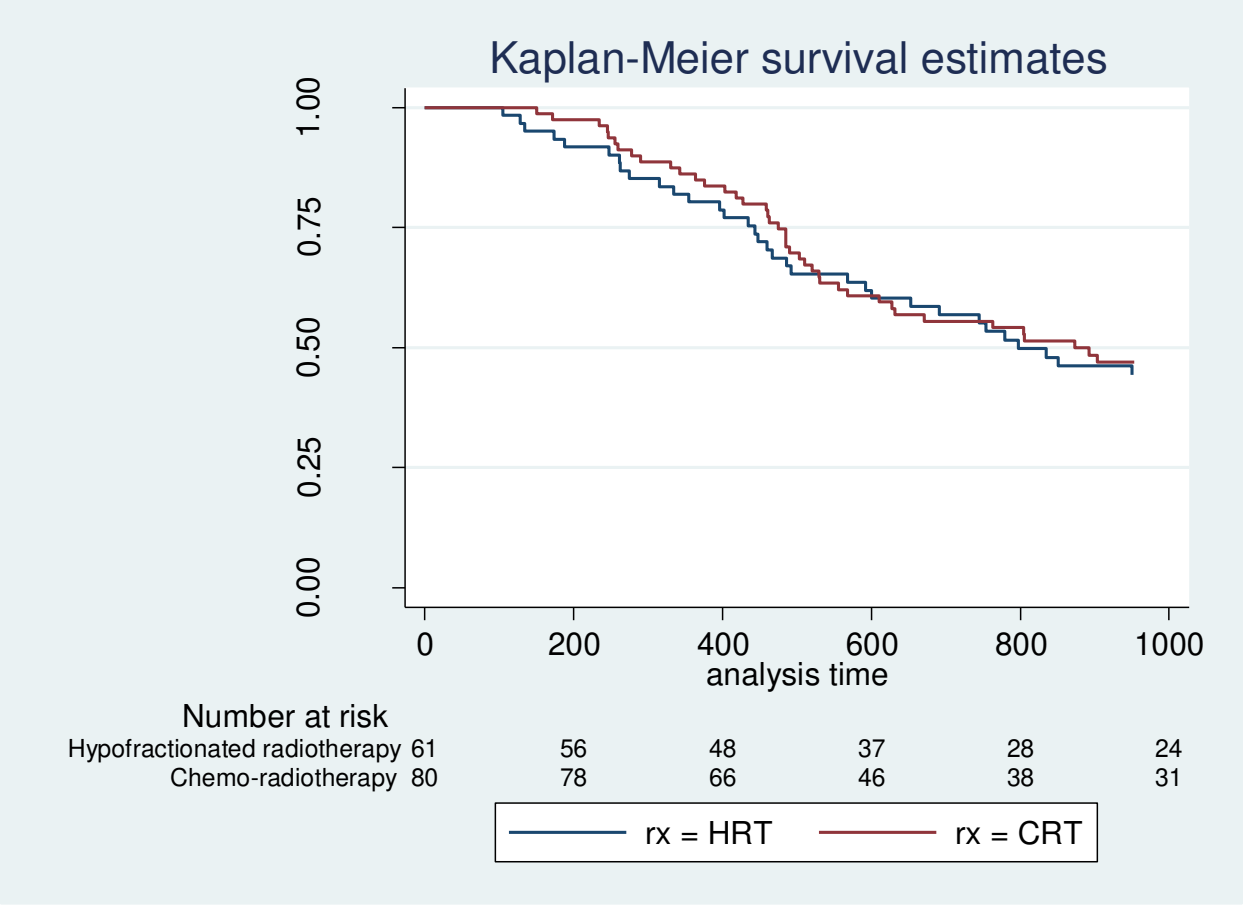


Figure 3: Progression-free survival by treatment modality.

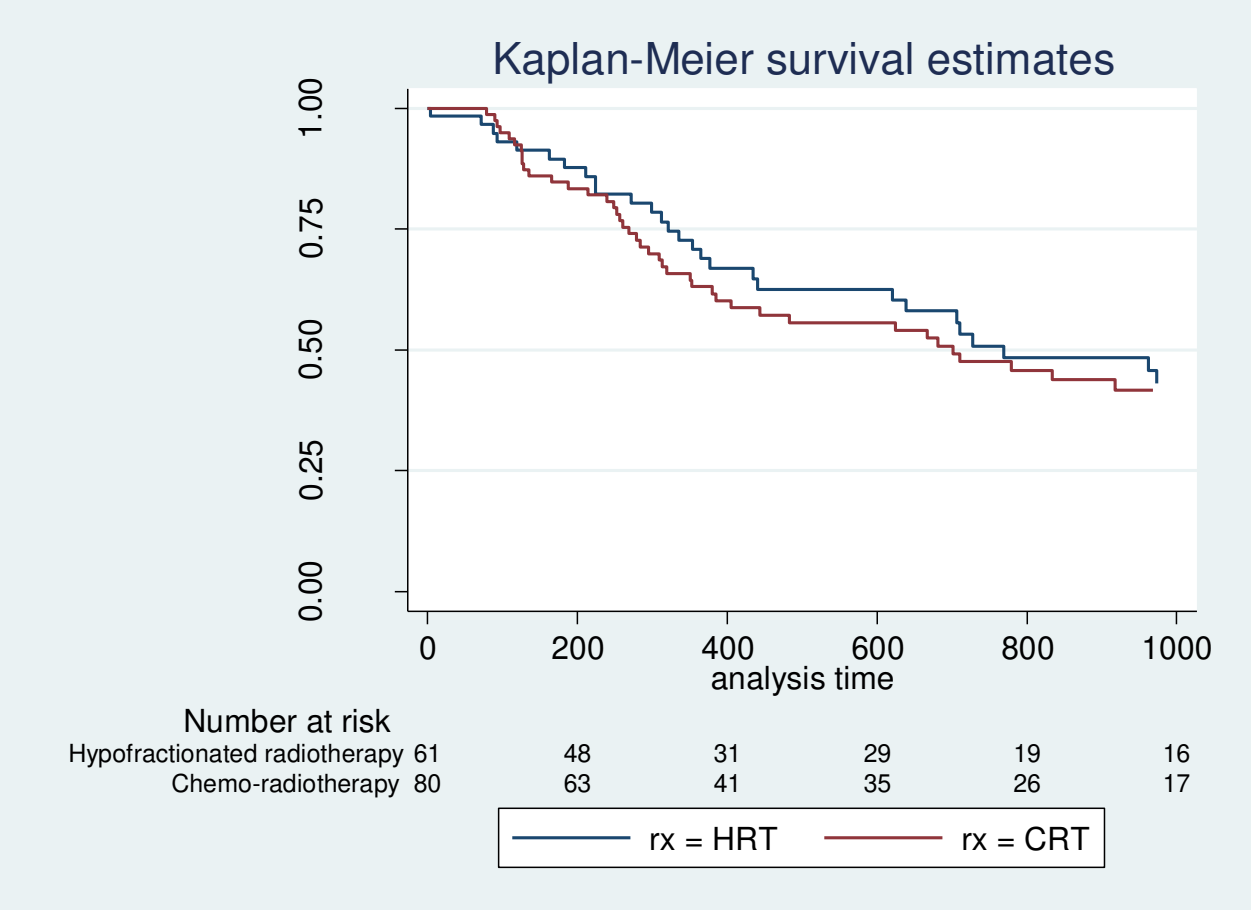
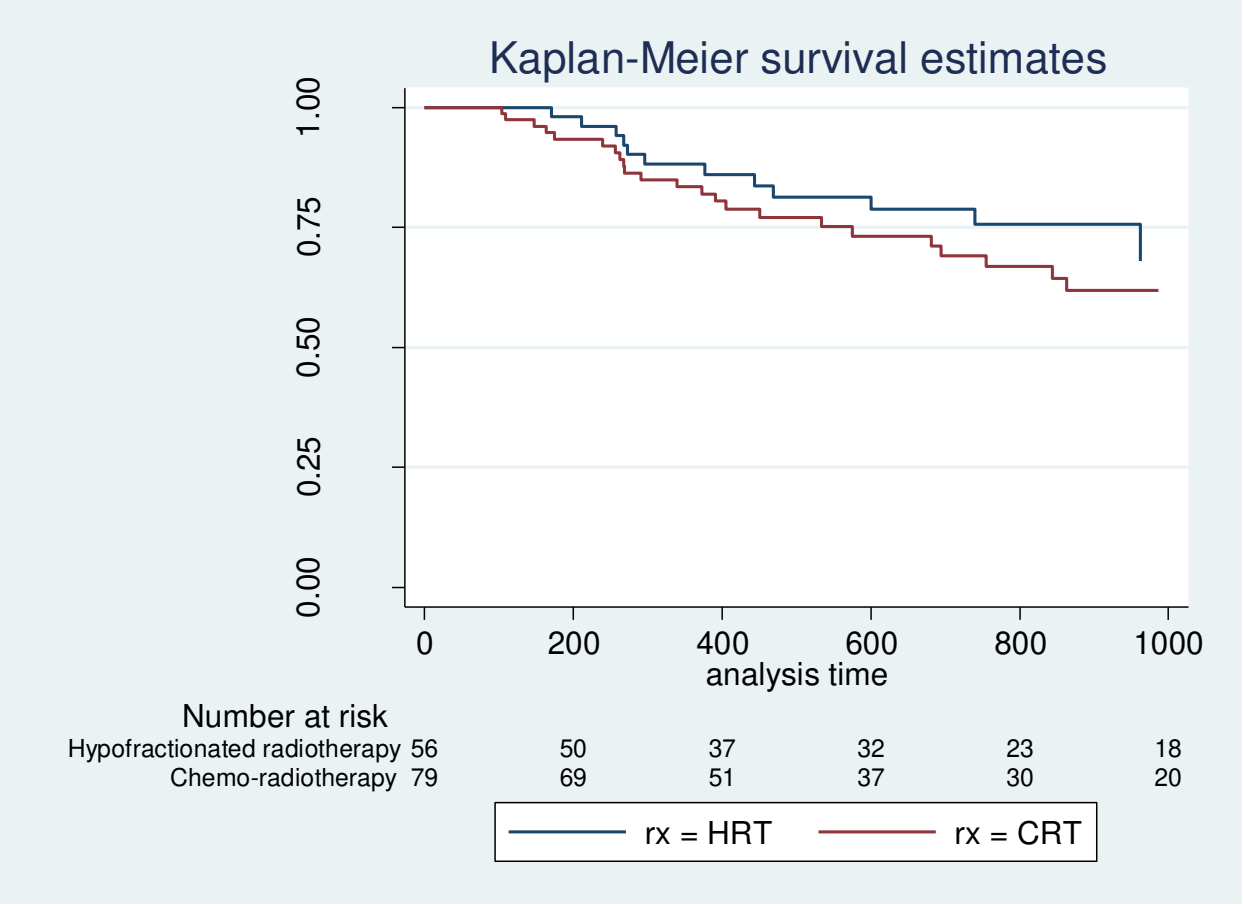
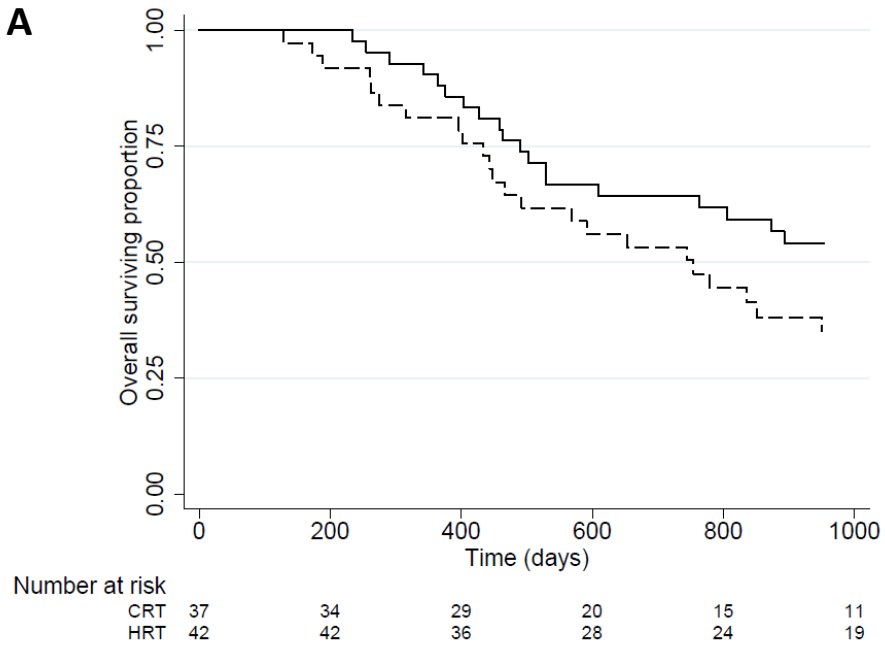


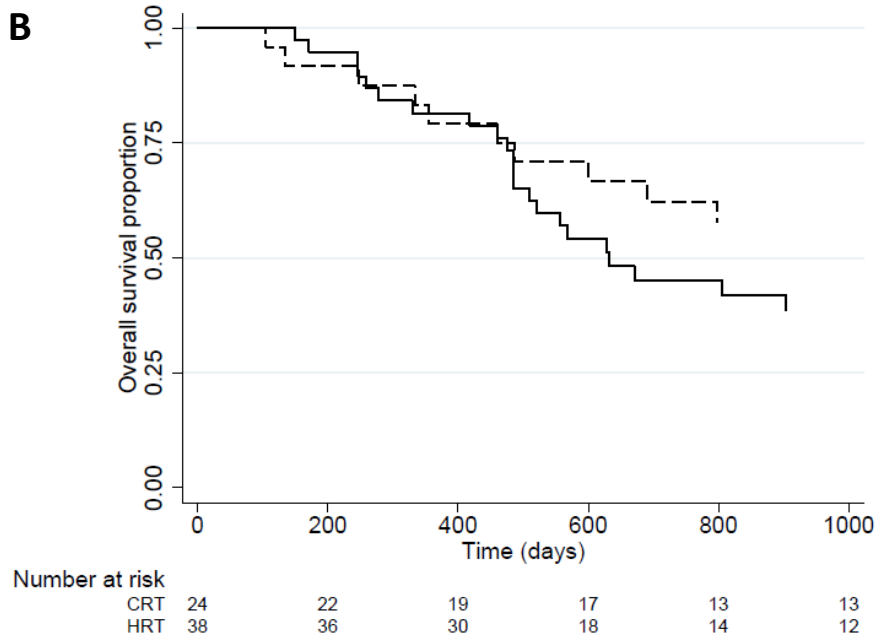
Figure 4: Time-to-stent insertion by treatment modality.



Supplementary Figure 1: Overall survival by treatment modality for patients with oesophageal adenocarcinoma. Thirty-seven patients with oesophageal adenocarcinoma received chemoradiotherapy (solid line), compared with 42 who received hypofractionated radiotherapy (dotted line).



Supplementary Figure 2: Overall survival by treatment modality for patients with oesophageal squamous cell carcinoma. Twenty four patients with oesophageal squamous cell carcinoma received chemoradiotherapy (solid line), compared with 38 who received hypofractionated radiotherapy (dotted line).



SUPPLEMENTARY FILES

Supplementary Table 1: Overview of surgical and non-surgical management interventions in the radical treatment of patients with oesophageal adenocarcinoma and squamous cell carcinoma between 2009 and 2014 (n=141).

	Hypofractionated radiotherapy n=61		**Combination chemo-radiotherapy n=80**	
	No.	%	No.	%
Year of initial treatment				
2009	2	3.3	4	5
2010	8	13.1	14	17.5
2011	15	24.6	14	17.5
2012	15	24.6	16	20.0
2013	12	19.7	19	23.8
2014	9	14.8	13	16.3
EMR	8	13.1	6	7.5
Radiotherapy dose				
50 Gy/16#	49	80.3	-	-
50-52.5 Gy/20#	12	19.7	-	-
50 Gy/25#	-	-	80	100.0
Initial chemotherapy regimen				
Fluoropyrimidine + platinum	-	-	76	95
Taxol + platinum	-	-	4	5
Salvage oesophagectomy	1	1.6	4	5

Supplementary Table 2: Treatment toxicity and compliance for patients with oesophageal cancer managed with CRT and HRT administered with curative intent between 2009 and 2014 in a single centre.

	Hypofractionated radiotherapy n=61		**Combination chemo-radiotherapy n=80**	
	No.	%	No.	%
Toxicity				
Grade III	9	14.8	29	36.3
Gastrointestinal				
Dysphagia	6	9.8	10	12.5
Nausea	0	0	5	6.25
Vomiting	0	0	4	5
Mucositis	0	0	1	1.25
Infection	0	0	5	6.25
Haematological				
Neutropenia	0	0	1	1.25
Thrombocytopenia	0	0	1	1.25
Acute kidney injury	2	3.3	2	2.5
Metabolic	0	0	1	1.25
Fatigue	2	3.3	0	0
Grade IV	1	1.6	3	3.8
Gastrointestinal				
Dysphagia	0	0	1	1.25
Vomiting	0	0	1	1.25
Infection	0	0	1	1.25
Hypotension	1	1.6	0	0
Compliance				
Chemotherapy				
Dose reduction	-	-	1	1.25
Shortened course	-	-	6	7.3
Agent change	-	-	6	7.3
Radiotherapy				
Reduced dose intensity	0	0	0	0
Shortened course	0	0	0	0
Enteral feeding support required	4	6.6	10	12.5

Supplementary Table 3: Dose escalation in oesophageal cancer.

Author, Year	Study type	Patient number		Chemotherapy regimen	Radiotherapy regimen	Median PFS (months)	Overall survival		
		OAC	SCC				Median (months)	3 year (%)	5 year (%)
Hypofractionated Radiotherapy									
Current series	Cohort	37	24	-	50 – 52.5Gy / 16-20#	25	29	56.9	-
Oh, 2016 [25]	Cohort	0	70	-	60Gy / 20#	-	36	-	-
Ma, 2012 [24]	RCT	0	74	Paclitaxel + Cisplatin	54-60Gy / 18-20#	-	27.8	38.2	28.0
Sykes, 1998 [23]	Cohort	11*	81*	-	45-52.5Gy / 15-16#	-	15	27	21
Hyperfractionated Radiotherapy									
Amdal, 2010 [26]	Cohort	17	83**		>60 Gy***	-	7	11	-
Sun, 2006 [27]	RCT	0	134	-	68.4-71Gy / 37-42#	-	-	61	-
Zhao, 2004 [28]	Cohort		201		68.4 Gy / 41#	-	-	34	26

Key

* An additional nine patients with oesophageal carcinoma of unknown histopathological subtype were included in this analysis.

** One additional case of small cell carcinoma was included in the final study analysis.

*** Forty four patients were managed with EBRT and brachytherapy boost, with 58 receiving greater than 60 Gy without brachytherapy boost