Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

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

C.M. Jones [*†‡], K. Spencer [*‡§], C. Hitchen [¶], T. Pelly [¶], B. Wood [¶], P. Hatfield [*], A. Crellin [*], D. Sebag-Montefiore [*‡], R. Goody [*], T. Crosby [||], G. Radhakrishna [***]

[*] Radiotherapy Research Group, Leeds Cancer Centre, The Leeds Teaching Hospitals NHS Trust, Leeds, UK
[†] School of Molecular & Cellular Biology, Faculty of Biological Sciences, University of Leeds, Leeds, UK
[‡] Leeds Institute of Medical Research at St James's, Faculty of Medicine & Health, University of Leeds, Leeds, UK
[§] Leeds Institute of Health Sciences, Faculty of Medicine & Health, University of Leeds, Leeds, UK
[¶] School of Medicine, Faculty of Medicine & Health, University of Leeds, Leeds, UK
[||] Velindre Cancer Centre, Velindre Hospital, Cardiff, UK

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) regimen.
Materials and methods: A retrospective UK single-centre analysis of 61 consecutive patients with lower- or middle-third adenocarcinoma (OAC; 61%) or squamous cell carcinoma of the oesophagus managed using HRT with radical intent between April 2009 and 2014. Treatment consisted of 50 Gy in 16 fractions ($n = 49$, 80.3%) or 50–52.5 Gy 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 were, respectively, 56.9% and 29 months with HRT compared with 55.5% and 26 months for CRT; adjusted hazard ratio 0.79 (95% confidence interval 0.48–1.28). Grade 3 and 4 toxicity rates were low at 16.4% ($n = 10$) for those receiving HRT and 40.2% ($n = 32$) for the CRT group. In patients with OAC, CRT delivered superior overall survival (hazard ratio 0.46; 95% confidence interval 0.25–0.85) and progression-free survival (hazard ratio 0.45; 95% confidence interval 0.23–0.88) when compared with HRT.
Conclusions: The HRT regimen 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.
© 2019 The Royal College of Radiologists. Published by Elsevier Ltd. All rights reserved.

Introduction

Oesophageal cancer is the sixth most common cause of death from malignancy worldwide and results in 440 000 deaths annually [1]. Most 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, although 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 represents their only radical treatment option, yet reported outcomes after single-modality

Author for correspondence: G. Radhakrishna, The Christie Hospital, Wilmslow Road, Manchester M20 4BX, UK. Tel: +44-113-2068522; Fax: +44-113-2068474.
E-mail address: g.radhakrishna@leeds.ac.uk (G. Radhakrishna).
[**] Present address: The Christie Hospital, Manchester, UK.

treatment are historically very poor [2,4,5]. Strategies to improve the efficacy of radiotherapy as a single treatment modality for oesophageal cancer have received little focus and there is no prevailing consensus on an optimal radical radiotherapy regimen. In addition, although both hyper-fractionated and hypofractionated radiotherapy regimens 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 the 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 regimen 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.

Materials and 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 1 April 2009 and 1 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 Figure 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 anticancer and palliative interventions. The gross tumour volume (GTV) was identified through a 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 seventh edition of the AJCC *Cancer Staging Manual* [10].

Setting and Treatment Selection

Over the 5-year study period, all patients received treatment directed by a site-specialist multidisciplinary team. 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 comorbidity, 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 10 cm. A small proportion of patients undergo endoscopic mucosal resection for early T1 tumours before CRT or HRT. A summary of treatments, including the year in which patients received initial therapy, is shown in Table S1.

Hypofractionated Radiotherapy

Dose fractionation used for single-modality HRT consisted of 50 Gy in 16 fractions ($n = 49$, 80.3%) for most. 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 used ($n = 12$, 19.7%).

Chemoradiotherapy

CRT consisted of 50 Gy in 25 fractions with concurrent systemic treatment. For most ($n = 76$; 96%) patients, the chemotherapy regimen consisted of cisplatin (60–80 mg/m^2) or carboplatin (AUC 3.3) with either capecitabine (625 mg/m^2 bid) or 5-fluorouracil (600–800 mg/m^2), prescribed as two concurrent 3- or 4-weekly cycles with two preceding induction cycles at identical doses in 14 (17.5%) patients. Four (5%) patients received an alternative regimen consisting of 5 × 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) 3-weekly.

Radiotherapy Planning

All patients received three-dimensional conformal image-guided radiotherapy (IGRT). Those with middle-third tumours underwent a three-dimensional planning computed tomography, as did patients with lower-third tumours until September 2010. From this date four-dimensional contrast-enhanced planning computed tomography was used. Cone beam computed tomography was used for treatment verification as per National Radiotherapy Implementation Group 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 and planning target volume margins for planned three-dimensional cases were as per the SCOPE-1 study protocol [12]. Four-dimensional planning with the creation of clinical target volumes, internal target volume and planning
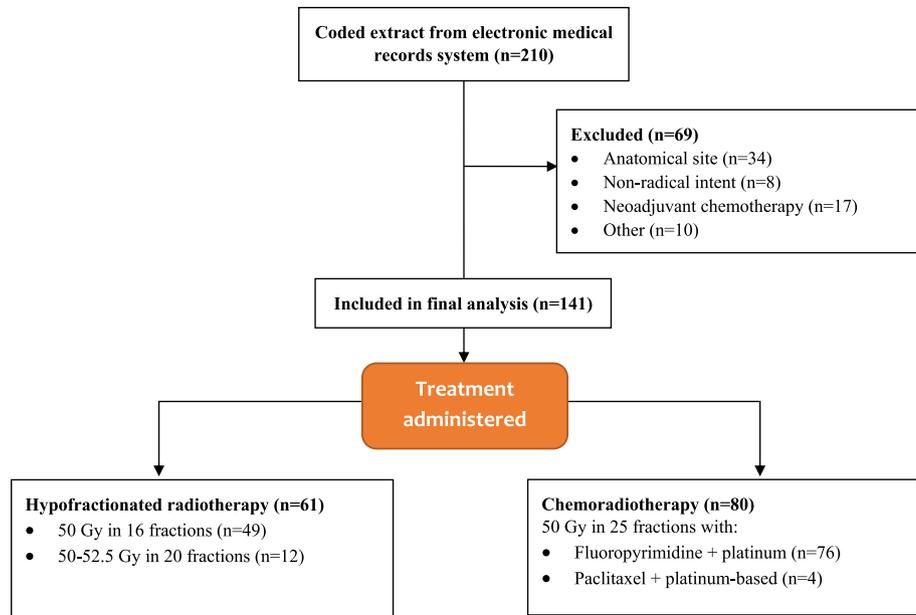
Fig 1. Study profile indicating selection of patients for analysis. Following initial identification of potentially eligible patients through an informatics search, 69 were excluded due to ineligible cancer site (upper thoracic oesophageal or gastric), administration of neoadjuvant chemotherapy with initial surgical intent, treatment with palliative intent, administration of trial-specific treatment or previous oesophagectomy.

target volume was carried out 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 5 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 3 months after the completion of treatment, followed by further clinical assessment at 3—6-monthly intervals for the first 24 months after treatment and 6-monthly intervals thereafter. The timing of repeat imaging was determined by clinical assessment. Patients alive at 4 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 was measured from the date of diagnosis. For patients lost to follow-up, data for overall survival 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 overall survival and PFS were assessed using the Cox proportional hazards model. This multivariable model assumes that the impact of treatment is constant within a covariable. 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 was used 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 with HRT treatment. The Stata 14 (StataCorp, TX, USA) 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 on 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% versus 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 years 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% versus 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 ($P < 0.05$). Most 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. The median GTV was higher in the CRT cohort (37.4 cm^3 versus 24.5 cm^3). The median tumour

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

		Hypofractionated radiotherapy ($n = 61$)		Combination chemoradiotherapy ($n = 80$)	
Demographics		No.	%	No.	%
Gender	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 comorbidity index	0	25	41.0	55	68.8
	1	15	24.6	19	23.8
	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	Adenocarcinoma	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	1	10	16.4	7	8.8
	2	24	39.3	29	36.3
	3	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

CT, computed tomography; PET–CT, positron emission tomography–computed tomography; EUS, endoscopic ultrasound.

length was 5.0 (IQR 4.0–6.0) cm in the CRT cohort and 4.5 (IQR 2.3–5.8) in the 57/61 (91.8%) of the HRT cohort for whom data for this value were available. All patients underwent computed tomography staging, whereas positron emission tomography-computed tomography was used more frequently in the CRT cohort (93.8% versus 80.3%; $P < 0.05$) and endoscopic ultrasound was used more frequently in the HRT cohort (68.9% versus 56.3%; $P < 0.05$).

Outcome Measures

Overall Survival

There was no evidence of a difference in overall survival between the cohorts (see Figure 2). The median survival for patients receiving CRT was 29 months, compared with 26 months for patients who received HRT; adjusted hazard ratio 0.79 (95% confidence interval 0.48–1.28). Similarly, there was no evidence of a difference in 1-year (80.3% versus 85.0%), 2-year (56.9% versus 55.5%) or 3-year (38.8% versus 43.5%) survival. On univariable analysis, age greater than 80 years and AJCC stage III were associated with worse overall survival. The importance of AJCC stage was confirmed on multivariable analysis with an adjusted hazard ratio of 1.99 (95% confidence interval 1.08–3.69) and 2.11 (95% confidence interval 1.08–4.12) for stages II and III. Treatment type was not associated with significant change in overall survival, as shown in Tables 2 and 3.

The fit of the multivariable Cox model for overall survival 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% confidence interval 0.819–3.700) for SCCs and 0.464 (95% confidence interval 0.253–0.848) for OAC (see Figures S1 and S2). This indicates a differential treatment effect with histological subtype; CRT being associated with improved overall survival in OAC, but no evidence of a difference between the treatment modalities in SCC.

Progression-free Survival and Recurrence Patterns

As seen in Figure 3, the median time to treatment failure was 25 months for patients who received HRT and 23 months for patients prescribed CRT; adjusted hazard ratio 0.98 (95% confidence interval 0.57–1.67). There were comparable proportions of patients with local recurrence in the HRT and CRT cohorts (26.2% versus 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; $P < 0.001$), showing 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 (hazard ratio 0.449; 95% confidence interval 0.230–0.879). Conversely, there was no evidence of a difference in PFS by treatment type in patients with SCC (hazard ratio 0.977; 95% confidence interval 0.574–1.665).

Time-To-Stent Insertion

Figure 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 and Compliance

There were no deaths within 30 days of treatment and overall rates of treatment toxicity were low. As summarised in Table S2, grade 3 toxicities were seen in 29 (36.3%) patients managed with CRT and nine (14.8%) patients treated using HRT. Grade 4 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 3 toxicity in those managed with both HRT ($n = 6$; 9.8%) and CRT ($n = 10$; 12.5%), additionally accounting for an episode of grade 4 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.

In total, 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
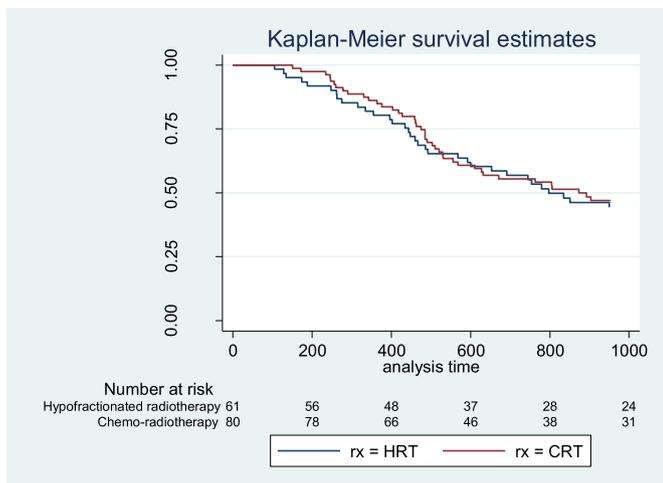

Fig 2. Overall survival by treatment modality. Survival calculated from date of diagnosis for patients who received either hypofractionated radiotherapy (HRT) and chemoradiotherapy (CRT). Data censored at 3 years OF follow-up. There was no significant difference between treatment modalities.

Table 2
Univariable Cox proportional hazards analysis by study population characteristics. Results shown for overall survival, progression-free survival and stent-free survival. Overall survival was calculated from the date of diagnosis; progression-free and stent-free survival were calculated from the date of first radiotherapy treatment

	Overall survival		Progression-free survival		Stent-free survival	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Gender						
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	
Adenocarcinoma	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*						
I	1.00		1.00		1.00	
II	1.68 (0.96–2.92)	0.07	2.05 (1.06–3.99)	*0.03*	2.51 (0.90–6.97)	0.08
III	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

HR, hazard ratio; CI, confidence interval; SCC, squamous cell carcinoma; HRT, hypofractionated radiotherapy; CRT, chemoradiotherapy.
 * AJCC not known for all patients.

Table 3
Multivariable analysis by study population characteristics. Results shown for overall survival, progression-free survival and stent-free survival. Overall survival was calculated from the date of diagnosis; progression-free and stent-free survival were calculated from the date of first radiotherapy treatment

	Overall survival		Progression-free survival		Stent-free survival	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Gender						
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	
Adenocarcinoma	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*						
I	1.00		1.00		1.00	
II	1.99 (1.08–3.69)	*0.03*	2.21 (1.07–4.56)	*0.03*	2.216 (0.74–6.65)	0.16
III	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

HR, hazard ratio; CI, confidence interval; SCC, squamous cell carcinoma; HRT, hypofractionated radiotherapy; CRT, chemoradiotherapy.
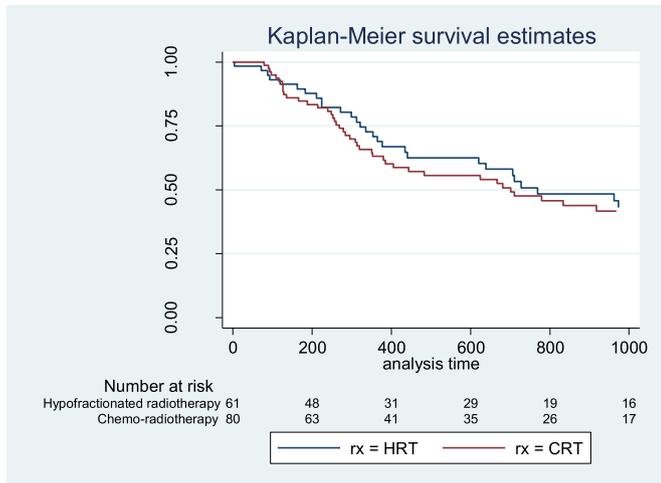 * AJCC not known for all patients.

Fig 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 of follow-up. There was no significant difference between treatment modalities.

switched following the first cycle in view of adverse effects. For one patient, chemotherapy was dose reduced. No change to the planned radiotherapy dose or fractionation was required in either cohort.

Discussion

The Radiation Therapy Oncology Group (RTOG) 85-01 trial showed significantly superior survival outcomes with CRT compared with those achieved using single-modality conventionally fractioned radiotherapy in patients with
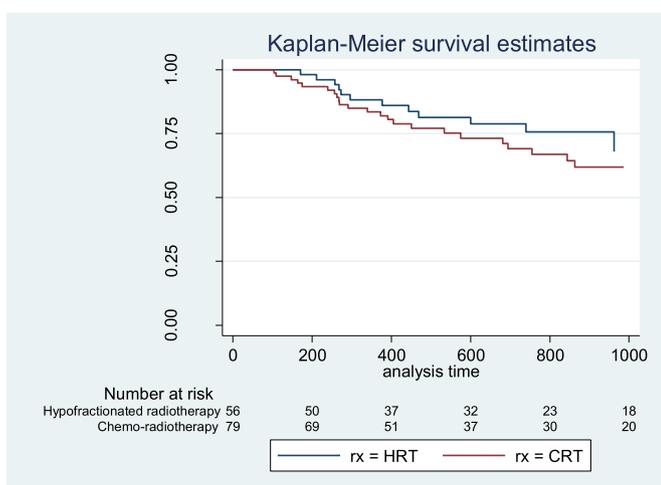

Fig 4. Time-to-stent insertion by treatment modality. Time-to-stent insertion calculated from the start of radiotherapy to the date of oesophageal stent insertion and/or dilatation for patients who received either hypofractionated radiotherapy (HRT) or chemo-radiotherapy (CRT). Patients for whom an oesophageal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

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 64 Gy/32 fraction regimen used within RTOG 85-01 is the most commonly adopted treatment approach despite achieving very poor survival of as low as 0% at 5 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 radiotherapy may be improved by adjusting dose fractionation (see Table S3) [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 comorbid patients with both OAC and SCC, use of a convenient, well-tolerated HRT regimen resulted in outcomes superior to those seen in historical analyses of definitive radiotherapy [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 overall survival 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 a significantly greater burden of comorbidity. By 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, the median overall survival and PFS were 34.5 and 24.1 months, respectively. At 26 and 25 months, the overall survival and PFS for the cohort presented here approach that seen in SCOPE-1, despite a greater proportion of patients aged over 70 years (72% versus 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 regimen may be explained by both increased dose delivery and 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 2 Gy fractions (EQD2) of 54.69 Gy. This is a modest yet clinically relevant increase in dose compared with the 50 Gy received by the comparator CRT cohort yet remains lower than the 64 Gy received in RTOG 85-01. Delivered in either 16 or 20 fractions, the HRT regimen was also accelerated, potentially resulting in reduced accelerated repopulation.

There are several important implications of these data for the care of patients with oesophageal cancer. First, these results provide a proof-of-principle for an effective treatment approach for patients who are suitable for radical treatment but are 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.

Second, 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 magnetic resonance-based IGRT (MR-Linac), which permits the delivery of more precise radiotherapy 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 in oesophageal cancer, an approach that is supported by recent evidence in the neoadjuvant setting [25–27]. This treatment involves the use of particles to deliver high doses of radiotherapy to a tumour with high accuracy and with limited normal tissue exposure. The dose-escalated regimen 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 carried out exploratory subanalyses to determine whether there was any relationship between tumour histological subtype and the effectiveness of each treatment approach. Interestingly, although 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 showing benefit from chemotherapy in the adjuvant setting in gastric cancer, both with and without radiotherapy [28,29]. Whether chemotherapy would add further benefit in addition to radiotherapy 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 was 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 positron emission tomography-computed tomography. 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 multidisciplinary team, 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 radiotherapy technology, including magnetic resonance-based IGRT and proton beam therapy, may provide additional scope for improving outcomes in oesophageal cancer using HRT-based approaches and should be evaluated.

Conflict of interest

The authors confirm that they have no relevant conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.01.010.

References

[1] Global Burden of Disease Cancer CollaborationFitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, *et al.* The Global Burden of Cancer 2013. *JAMA Oncol* 2015; 1(4):505–527.

[2] Zhang Y. Epidemiology of esophageal cancer. *World J Gastroenterol* 2013;19(34):5598–5606.

[3] Rackley T, Leong T, Foo M, Crosby T. Definitive chemoradiotherapy for oesophageal cancer – a promising start on an exciting journey. *Clin Oncol* 2014;26:533–540.

[4] Herskovic A, Martz K, al-Sarraf M, *et al.* Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992; 326(24):1593–1598.

[5] Kleinberg L, Gibson MK, Forastiere AA. Chemoradiotherapy for localised esophageal cancer: regimen selection and molecular mechanisms of radiosensitization. *Nat Rev Clin Onc* 2007;4:282—294.

[6] Slabber AF, Nel JS, Shcoeman L, Burger W, Falkson G, Falkson CI. A randomized study of radiotherapy alone versus radiotherapy plus 5-fluorouracil and platinum in patients with inoperable, locally advanced squamous cancer of the esophagus. *Am J Clin Oncol* 1998;21(5):462—465.

[7] Wobbes T, Baron B, Paillot B, *et al*. Prospective randomised study of split-course radiotherapy versus cisplatin plus split-course radiotherapy in inoperable squamous cell carcinoma of the oesophagus. *Eur J Cancer* 2001;37(4):470—477.

[8] Araujo CM, Souhami L, Gil RA, *et al*. A randomized trial comparing radiation therapy versus concomitant radiation therapy and chemotherapy in carcinoma of the thoracic esophagus. *Cancer* 1991;67(9):2258—2261.

[9] Smith TJ, Ryan LM, Douglass Jr HO, *et al*. Combined chemo-radiotherapy vs. radiotherapy alone for early stage squamous cell carcinoma of the esophagus: a study of the Eastern Cooperative Oncology Group. *Int J Radiat Oncol Biol Phys* 1998;42:269—276.

[10] Rice TW, Blackstone EH, Rusch VW. 7th Edition of the AJCC Cancer Staging Manual: Esophagus and Esophagogastric Junction. *Ann Surg Oncol* 2010;17:1721—1724.

[11] The Royal College of Radiologists, Society and College of Radiographers. *Institute of Physics and Engineering in Medicine. On target: ensuring geometric accuracy in radiotherapy*. London: The Royal College of Radiologists; 2008.

[12] Hurt CN, Nion LS, Griffiths GO, *et al*. SCOPE1: a randomised phase II/III multicentre clinical trial of definitive chemo-radiation, with or without cetuximab, in carcinoma of the esophagus. *BMC Cancer* 2011;11:466.

[13] Mukherjee S, Hurt CN, Gwynne S, *et al*. NEOSCOPE: a randomised phase II study of induction chemotherapy followed by either oxaliplatin/capecitabine or paclitaxel/carboplatin based chemoradiation as pre-operative regimen for resectable oesophageal adenocarcinoma. *BMC Cancer* 2015;15:48.

[14] ICRU. . In: *ICRU Report*, vol. 62. International Commission on Radiation Units and Measurements; 1999. Prescribing, recording and reporting photon beam therapy (supplement to ICRU report 50).

[15] 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). Radiation Therapy Oncology Group. *JAMA* 1999;281(17):1623—1627.

[16] Cunningham D, Starling N, Rao S, *et al*. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008;358(1):36—46.

[17] Zhu L-L, Yuan L, Wang H, *et al*. A meta-analysis of concurrent chemoradiotherapy for advanced esophageal cancer. *PLoS One* 2015;10(6):e0128616.

[18] Ma J-B, Wei L, Chen E-C, *et al*. Moderately hypofractionated conformal radiation treatment of thoracic esophageal carcinoma. *Asian Pac J Cancer Prev* 2012;13:4163—4167.

[19] Oh D, Noh JM, Nam H, Lee H, Kim TG, Ahn YC. High-dose radiation therapy alone by moderate hypofractionation for patients with thoracic esophageal squamous cell carcinoma. *Medicine* 2016;95(e4591):33.

[20] Amdal CD, Jacobsen AB, Tausjo JE, *et al*. Radical treatment for oesophageal cancer patients unfit for surgery and chemotherapy. A 10-year experience from the Norwegian Radium Hospital. *Acta Oncol* 2010;49(2):209—218.

[21] Sun XD, Yu JM, Fan XL, Ren RM, Li MH, Zhang GL. Randomized clinical study of surgery versus radiotherapy alone in the treatment of resectable esophageal cancer in the chest. *Zhonghua Zhong Liu Za Zhi* 2006;28:784—787.

[22] Zhao KL, Shi XH, Jiang GL, Wang Y. Late-course accelerated hyperfractionated radiotherapy for localized esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 2004;60:123—129.

[23] Sykes AJ, Burt PA, Slevin NJ, Stout R, Marrs JE. Radical radiotherapy for carcinoma of the oesophagus: an effective alternative to surgery. *Radiother Oncol* 1998;48:15—21.

[24] Harrington K, Hall E, Hawkins M, *et al*. Introducing the Cancer Research UK Advanced Radiotherapy Technologies Network (ART-NET). *Clin Oncol* 2017;29(11):707—710.

[25] National Cancer Research Institute Clinical and Translational Radiotherapy Research Working Group (CTRad), Proton Beam Clinical Trial Strategy Group. Proton beam therapy — the challenges of delivering high-quality evidence of clinical benefit. *Clin Oncol* 2018;30(5):280—284.

[26] Wang J, Wei C, Tucker SL, *et al*. Predictors of post-operative complications after trimodality therapy for esophageal cancer. *Int J Radiat Oncol Biol Phys* 2013; 86(5):885—891.

[27] Hallemeier CL, Chuong M, Merrell KW, *et al*. Impact of neo-adjuvant proton vs photon chemoradiotherapy on post-operative outcomes in patients with esophageal cancer treatment with trimodality therapy: a multi-institutional analysis. *Int J Part. Ther* 2015;2:79—80.

[28] Cunningham D, Allum WH, Stenning SP, *et al*. Perioperative chemotherapy versus surgery alone for resectable gastro-esophageal cancer. *N Eng J Med* 2006;355:11—20.

[29] MacDonald JS, Smalley SR, Benedetti J, *et al*. Chemo-radiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Eng J Med* 2001;345:725—730.