Clinical and Translational Radiation Oncology 2 (2017) 76–82

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Follow up results of a prospective study to evaluate the impact of FDG-PET on CT-based radiotherapy treatment planning for oesophageal cancer

Sweet Ping Ng [a,b,*], Jennifer Tan [a], Glen Osbourne [c], Luke Williams [d], Mathias A.B. Bressel [e], Rodney J. Hicks [f,g], Eddie W.F. Lau [f], Julie Chu [a], Samuel Y.K. Ngan [a,g], Trevor Leong [a,g]

[a] Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
[b] Department of Radiation Oncology, MD Anderson Cancer Center, Houston, TX, USA
[c] Department of Radiation Therapy, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
[d] Department of Radiation Therapy, Radiation Oncology Victoria, GenesisCare, Melbourne, Victoria, Australia
[e] Centre for Biostatistics and Clinical Trials, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
[f] Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
[g] The University of Melbourne, Parkville, Victoria, Australia

ARTICLE INFO

Article history:
Received 20 November 2016
Revised 12 January 2017
Accepted 12 January 2017
Available online 7 March 2017

Keywords:
Oesophageal cancer
PET
Radiotherapy
Planning

ABSTRACT

Background: This prospective study aims to determine the impact of PET/CT on radiotherapy planning and outcomes in patients with oesophageal cancer.
Methods: All patients underwent PET/CT scanning in the radiotherapy treatment position, and received treatment planned using the PET/CT dataset. GTV was defined separately on PET/CT (GTV-PET) and CT (GTV-CT) datasets. A corresponding PTV was generated for each patient. Volumetric and spatial analysis quantified the proportion of FDG-avid disease not included in CT-based volumes. Clinical data was collected to determine locoregional control and overall survival rates.
Results: 13 (24.1%) of 57 accrued patients had metastatic disease detected on PET. Median follow up was 4 years. FDG-avid disease would have been excluded from GTV-CT in 29 of 38 patients (76%). In 5 patients, FDG-avid disease would have been completely excluded from the PTV-CT. GTV-CT underestimated the cranial and caudal extent of FDG-avid tumour in 14 (36%) and 10 (26%) patients. 4-Year overall survival and locoregional failure free survival were 37% and 65%.
Conclusions: PET/CT altered the delineation of tumour volumes when compared to CT alone, and should be considered standard for treatment planning. Although clinical outcomes were not improved with PET/CT planning, it did allow the use of smaller radiotherapy volumes.

Introduction

Oesophageal cancer is often treated with radiotherapy (RT), both in the radical and palliative settings. Accurate localisation of the tumour is imperative to ensure optimal radiation field design and avoid geographic miss. Currently there is no universally accepted method to accurately define the cranial and caudal limits of the primary oesophageal tumour when delineating the gross tumour volume (GTV) for radiotherapy planning. Oesophagography was once routinely used to determine the cranial and caudal extent of the tumour; however it does not define the radial extent of disease [1]. With computed tomography (CT) planning, it is possible to better define the radial extent of the primary tumour but it is less accurate in defining the cranial and caudal extent of the tumour than oesophagography [2]. Furthermore, oesophagography provides no assessment of regional nodal status, while the sensitivity of CT imaging for detecting lymph node involvement is low compared to surgical pathology [3,4].

The role and potential value of positron emission tomography (PET) scanning in certain tumours, including oesophageal cancer, has been widely investigated in recent years [5–14]. Most of these

* Corresponding author at: Department of Radiation Oncology, Peter MacCallum Cancer Centre, Locked Bag 1 A'Beckett Street, Victoria 8006, Australia. Fax: +61 3 8559 7729.
E-mail address: sweet.ng@petermac.org (S.P. Ng).

http://dx.doi.org/10.1016/j.ctro.2017.01.008

studies have investigated the role of PET in cancer staging, evaluating treatment response, monitoring disease status and estimating prognosis. Our study aims to evaluate the contribution of PET/CT imaging in radiotherapy treatment planning and its impact on outcomes. In 2006 we reported preliminary results of the first 16 patients recruited to the study, which demonstrated that FDG-avid disease was excluded from the GTV in 11 of 16 patients (69%) when the GTV was based on CT alone [15]. Modifications based on PET were mainly seen in the longitudinal direction in keeping with the known limitations of soft tissue definition on CT imaging alone. In this article, we report final results for the full cohort of patients who completed the study protocol. In addition to evaluating the contribution of PET//CT to radiotherapy treatment planning, we also determined treatment outcomes for patients treated according to PET/CT planning.

Materials and methods

Study participants

From June 2003–May 2008, patients with localised oesophageal cancer suitable for definitive chemoradiotherapy were recruited, following ethics approval from the Peter MacCallum Cancer Centre Human Research and Ethics Committee. Exclusion criteria were metastatic disease detected on conventional imaging or clinically, significant comorbidities that might be exacerbated by or impacting the planned delivery of chemotherapy and/or radiotherapy. All patients were discussed at the institutional multidisciplinary meeting and were considered suitable for definitive radiotherapy. Informed consent was obtained from all participants in this study.

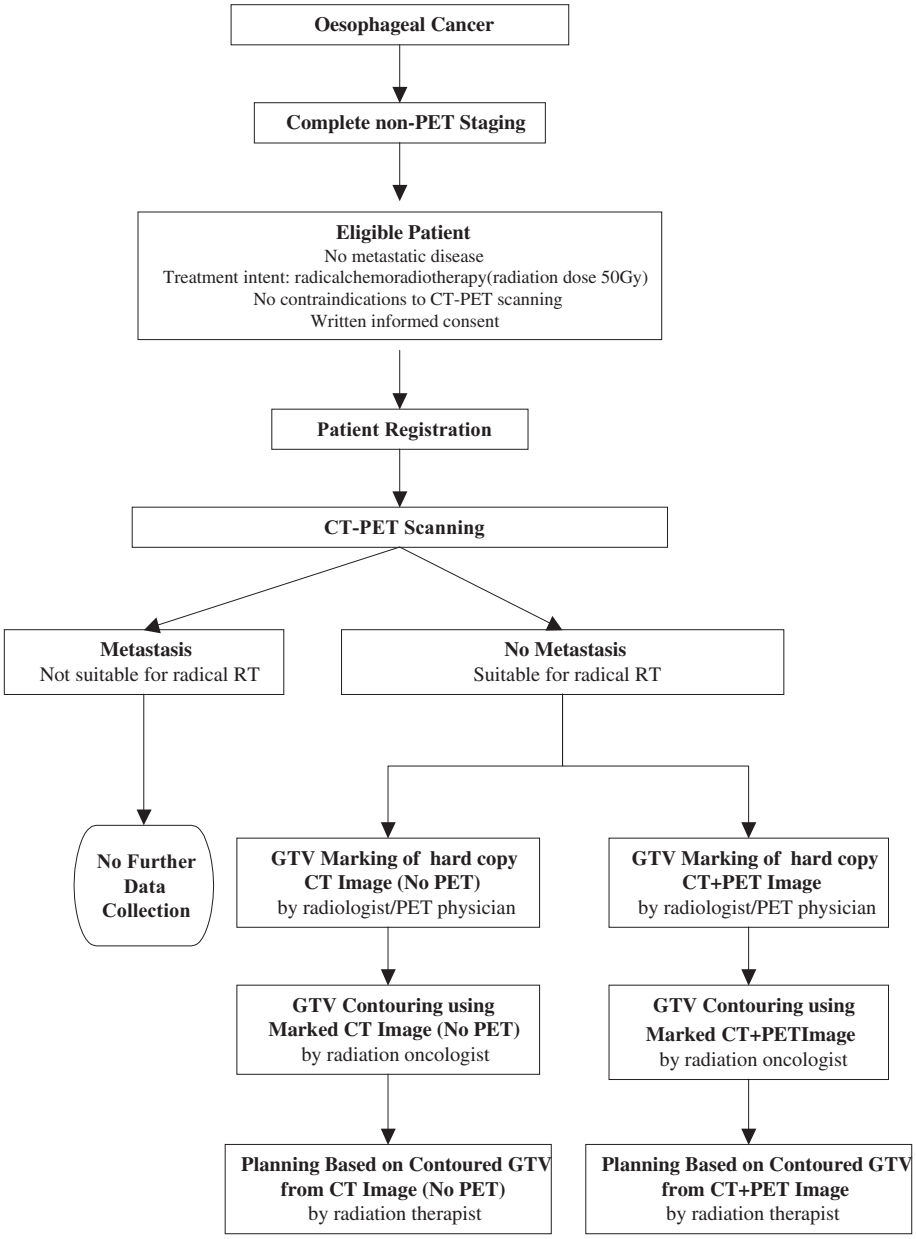


Fig. 1. Study schema.

Imaging techniques

All patients had PET/CT scan performed in the radiotherapy treatment position on the combined PET/CT scanner (Discovery LS, GE Medical System, Milwaukee, Wisconsin) that served as both a diagnostic and planning PET/CT scan. The detailed study design is discussed elsewhere [15] (Fig. 1).

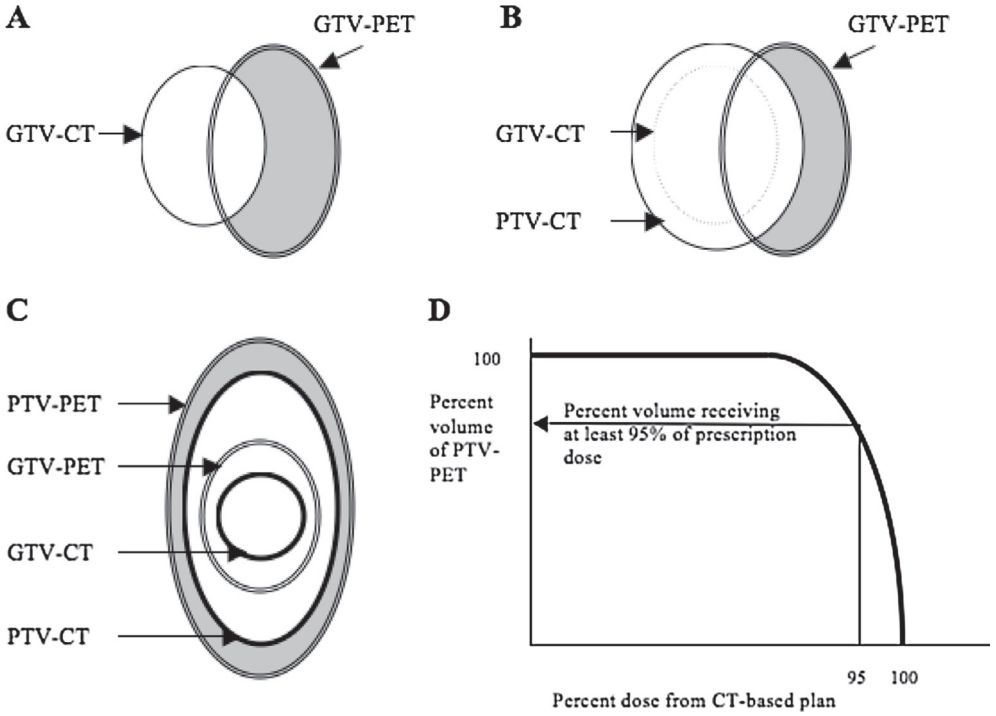
Patients were positioned supine for scanning with arms raised above their head and crossed to allow for clearance through the CT/PET scanner aperture. An adjustable arm and neck support was located on a carbon fibre, flat bed top to simulate treatment conditions. CT and PET data sets were transferred to the treatment planning workstation in the radiotherapy department for tumour volume localisation and treatment planning.

Contouring methods

For each patient, two radiologist/PET imaging (dual qualified) specialists contoured all gross tumour volumes (GTVs) on either planning CT (GTV-CT) or PET (GTV-PET) scans in a blinded fashion. The contoured GTV was subsequently copied onto the treatment planning system. Clinical information, diagnostic CT scans, barium swallow studies, and oesophagoscopy, bronchoscopy and pathology reports were made available when marking the planning CT scan and PET scan.

Following marking of each image (CT or PET), a radiation oncologist used the information to contour the corresponding GTV on the treatment-planning computer. When contouring the GTV-PET, a greyscale was used to display the PET data on the treatment-planning computer, in accordance with guidelines recommended by the PET centre. Briefly, the visual interpretation of standard uptake unit (SUV) was used, normalising to normal tissues (the liver was used in these cases). On the 256-level grey scale, the liver was set to mid-grey. The liver was then set at the interface between blue and green on the rainbow colour scale for the fused PET/CT scan. Tumour boundaries were defined at the junction between yellow and orange on the rainbow scale. Using these parameters, the normal tissue intensity such as mediastinal blood pool and bone marrow, can be compared to the liver reproducibly and the relative intensity of the tumour can be appreciated. The detailed contouring method is described in our previous paper [15]. If two or more tumour masses were separated by more than 1 cm (for example, primary tumour and involved lymph node), they were contoured as separate GTVs. When contouring the GTV-CT, regional lymph nodes greater than or equal to 1 cm in maximal diameter were contoured in the GTV. When contouring the GTV-PET, it was assumed that PET-avid regions correlating with possible location of tumour on CT were true positives, and enlarged lymph nodes on CT that were not PET-avid were considered to be true negatives. The same radiation oncologist was permitted to contour both GTVs for the same patient. An appropriate clinical target volume (CTV) was generated for each GTV by applying 0.5 cm radial and 4 cm longitudinal margins.

A PTV was subsequently generated for each GTV by applying standard margins according to institutional guidelines (1 cm volumetric margin). Patients were treated to a dose of 50–50.4 Gy in 25–28 fractions, 5 per week for 5 weeks. Separate treatment plans were generated for the PTV from CT data alone (PTV-CT) and from combined PET/CT data (PTV-PET). Patients were treated with plans generated from CT-PET data.



***A**. Proportion of GTV-PET excluded from CTV-CT. **B**. Grade 1 geographic miss defined as GTV-PET excluded from PTV-CT. **C**. PTV-PET excluded from PTV-CT. **D**. DVH for PTV-CT; Grade 2 geographic miss scored if <95% of PTV-PET received <95% of prescribed dose*

Fig. 2. Treatment plans comparison.

Plan comparison

GTV-CT and GTV-PET measurements were compared to determine if there was any change in defining active disease resulting from PET data. The cranial and caudal limits of the primary tumour as defined by CT alone and PET/CT were also recorded.

Volumetric analysis of GTV-CT and GTV-PET, as well as the overlap region was performed to quantify the proportion of PET-avid disease that would not be included in the GTV if CT data alone were used for radiotherapy planning (Fig. 2A).

For the purpose of this study, we have defined grade 1 geographic miss as any PET-avid disease not included in the PTV-CT (Fig. 2B). A grade 2 geographic miss was defined as less than 95% of the PTV-PET receiving at least 95% of the prescription dose based on planning with CT data alone (Fig. 2C, D) [15].

The impact of PET information on dose limiting normal structures such as the lungs, liver and spinal cord was also evaluated from final dose volume histograms.

Clinical data

Clinical outcome data including post-treatment response, dates of local and distant progression as evidenced by pathological or radiological confirmation and date of last follow up was collected retrospectively on patients treated with radical intent with a study close-out date of 31st March 2011. Treatment response assessment was based on at least one of post-treatment CT, PET/CT or gastroscopy results obtained at 3 months after completion of radiotherapy. Locoregional failure was defined as a failure at the primary site and/or regional node and was measured from the end of radiotherapy to the date of first locoregional failure. Death and distant failure were considered as censoring events. Relapse free survival was measured from the end of radiotherapy to the date of first relapse (any site) or date of death for patients that did not relapse. Overall survival was measured from the end of radiotherapy to the date of death.

Statistical analysis

PET/CT planning results were described using simple descriptive statistics. Response was described as a rate with 95% (Wilson) confidence interval. Overall survival, relapse free survival and time to locoregional failure were described using Kaplan–Meier methods with 95% confidence intervals.

Results

Patient characteristics

57 patients were initially recruited. 16 patients were subsequently excluded from the study: 13 had metastatic disease detected on PET scan (upstaged to M1 disease), 2 had gastric cancer as determined on PET/CT, and 1 did tolerate PET/CT planning or radical radiotherapy.

A total of 41 patients were eligible for the study. Three patients were excluded from the planning component analysis as 1 patient's computer data was corrupted and 2 did not tolerate the PET/CT in the treatment position but had radical radiotherapy. 3 patients were excluded from the clinical analysis because they did not commence radical radiotherapy even though they underwent radiotherapy planning, due to exacerbation of comorbidities, and/or decline in performance status. Therefore, in total, there were 38 patients eligible for each of the planning and clinical analyses (Fig. 3).

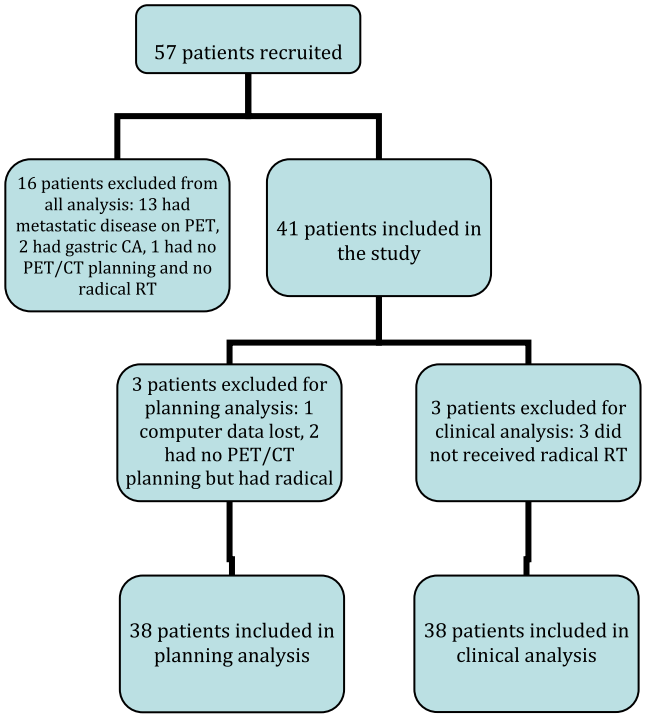


Fig. 3. Patients schema.

Mean age of 57 patients in the study was 67 years (range: 32–88). Patient, tumour characteristics and treatment regimen are described in Table 1. Majority of patients had T3 primary disease (33 patients, 87%). There is an almost equal distribution of patients

Table 1
Clinical characteristics.

Variable	Category	Count	%
Diagnosis ECOG	0	9	24
	1	28	74
	2	1	3
Histology	Adenocarcinoma	15	39
	Squamous cell carcinoma	23	61
Disease site	Upper	10	26
	Middle	8	21
	Lower	12	32
	GOJ	8	21
T stage	T1	1	3
	T2	1	3
	T3	33	87
	T4	2	5
	Tx	1	3
N stage	N0	18	47
	N1	20	53
Radiotherapy total dose	50	17	45
	50.4	20	53
	60	1	3
No. of fractions	20	1	3
	25	16	42
	28	20	53
	30	1	3
Concurrent chemotherapy	No	1	3
	Yes	37	97
Surgery	No	26	68
	Yes	12	32
Surgery type	Oesophagectomy	8	67
	Stent	4	33

with N0 (18 patients, 47%) and N1 (20 patients, 53%) disease. All except one patient received concurrent chemotherapy (cisplatin/5-fluorouracil).

Metastatic disease – change of treatment plan

13 patients (22.8%) had occult distant metastatic disease detected on PET scan which rendered them unsuitable for radical treatment. Their treatment intent was changed to palliative.

Comparison of tumour length

Assuming that GTV-PET represents true extent of disease, GTV-CT overestimated the cranial and caudal extent, respectively, in 11 (29%; median: 1.28 cm, range: 0.33–3.40 cm) and 19 (50%; median: 0.66 cm, range: 0.3–5.52 cm) patients. GTV-CT underestimated the cranial and caudal extent, respectively, of FDG-avid tumour in 14 (36%; median: 1.14, range: 0.3–2.85) and 10 (26%; median: 1.03 cm, range: 0.4–4.25) patients.

Geographic misses and dose to critical normal tissues

GTV-PET was excluded from the GTV-CT in 29 patients (76%) with a median percentage volume excluded of 17% (range: 1–100%). In 1 patient, 100% of the GTV-PET was excluded from GTV-CT. Grade 1 geographic miss was detected in 5 patients (13.1%) where any PET-avid disease was excluded from the PTV-CT. The median percentage volume of PET-avid disease excluded was 6% (range: 2–92%). In 8 patients (21.1%), there was a grade 2 geographic miss detected where the PTV-PET did not receive adequate dosimetric coverage. The median percentage volume of PTV-PET receiving at least 95% of the prescription dose for these patients was 81.5% (range: 63–92%). There were no clinically significant differences in radiation dose to the lungs, liver and spinal cord between CT and PET/CT treatment plans for the group.

Clinical outcomes – treatment response, patterns of failure, survival

Median follow up time was 4 years (range: 2.7–6.8). 36 patients were assessed for treatment response, as 1 patient refused follow up and another died prior to response assessment. Clinical responses were assessed using a combination of imaging (CT and/or PET) with/without gastroscopy. 18 patients (50%, 95% CI [34–66]) achieved a clinical complete response, 14 (39%, 95% CI [25–55]) had a partial response, 3 had stable disease and 1 had progressive disease.

In our cohort, 21 patients relapsed post treatment. The type and sequence of relapses are described in Fig. 4. All locoregional failures are within the radiation treatment fields. The 4-year overall survival and locoregional failure free survival for this cohort of 38 patients were 37% (95% CI [5–42]), and 65% (95% CI [47–90]) respectively (Fig. 5 and Table 2).

Discussion

Our initial report published in 2006 was the first prospective study to evaluate the impact of PET/CT on radiotherapy treatment planning for oesophageal cancer. These early results showed that 69% of CT-based plans excluded PET-avid disease from the GTV, which would have resulted in a grade 1 geographic miss (gross tumour) in 31% of patients and a grade 2 geographic miss in 38% of patients [15]. Since that time, there have been further publications demonstrating the utility of PET/CT for radiotherapy treatment planning in oesophageal cancer, and PET/CT has become more commonly used in many centres. Building on our earlier results, the current report describes our findings in the full cohort of study patients who now have longer follow up.

This study demonstrates that PET/CT imaging provides important staging information that has major clinical impact in terms of the patients' overall management plan and treatment intent. In this cohort, PET/CT detected metastatic disease not seen on conventional imaging in 22.8% of patients. This is consistent with other PET staging studies in oesophageal cancer [5,15,16], including our own evaluation of the impact of stand-alone FDG PET in staging oesophageal cancer [17]. Treatment with radical radiotherapy would have been futile in these patients as they will subsequently fail distantly. With this knowledge, treatment intent was consequently changed to palliative with the aim of preserving quality of life and limiting toxicity.

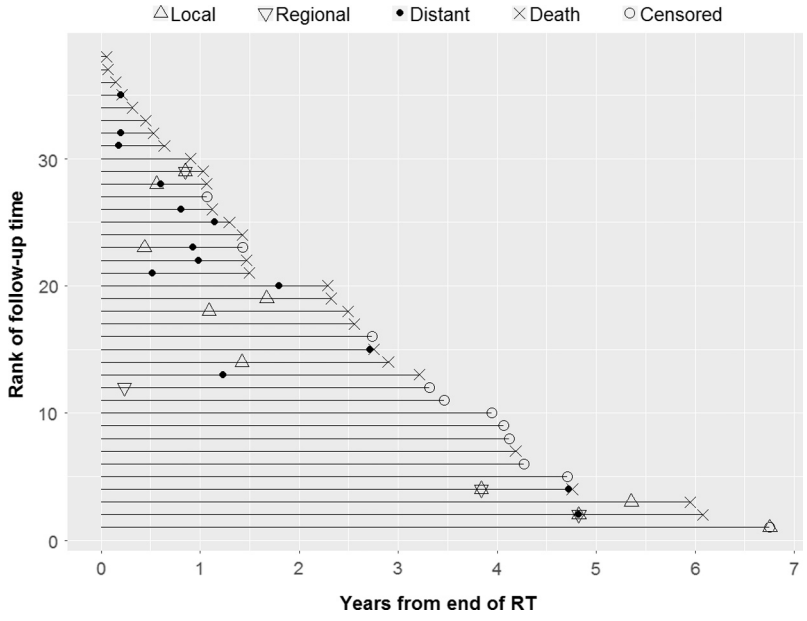


Fig. 4. Event plot.

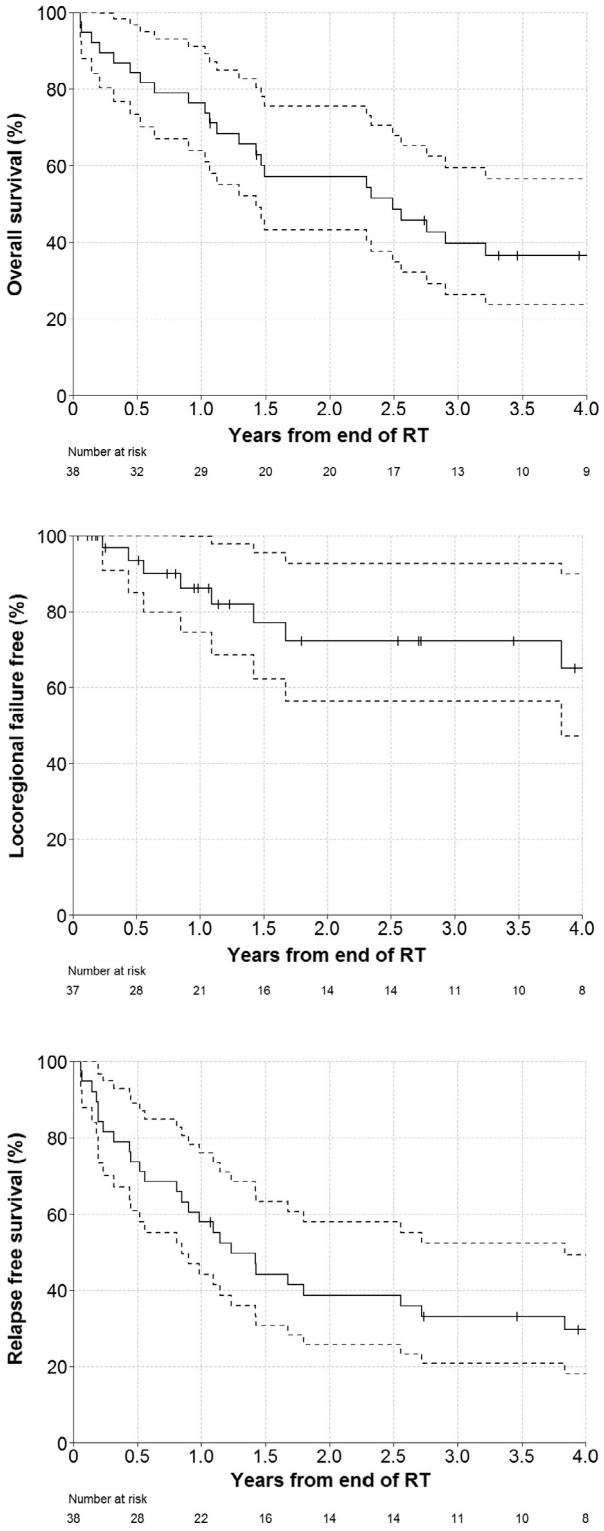


Fig. 5. Overall survival, locoregional failure free and relapse free survival curves. Dashed lines represent 95% confidence intervals.

With regard to radiotherapy planning, we have demonstrated that the discordance between CT and PET/CT relates mainly to the longitudinal extent of disease with a difference in the cranial extent detected in 25 patients (65.8%) and in the caudal extent in 29 patients (76.3%). Although we did not perform histopathological confirmation of the extent of tumour, there are several lines of evidence to suggest that PET/CT provides the most accurate delineation of cranio-caudal tumour extent in the oesophagus. Rollins et al. [18] have shown that PET/CT has the best correlation with histopathological length compared with endoscopic ultrasound and oesophago-gastroduodenoscopy. Konski et al. [19] have also reported that PET/CT correlated well with histology and endoscopic ultrasound findings. In addition, none of our study patients relapsed in the oesophagus out-of-field, thereby providing further evidence that the true extent of disease in the oesophagus was corrected delineated using PET/CT. Nevertheless, it should be noted that the presence of respiratory motion, especially at the level of the diaphragm may lead to discordance between the PET and CT image sets and more accurate delineation of may require more sophisticated planning techniques including respiratory gating [20].

Table 2
Overall survival, locoregional failure free and relapse free survival estimates.

Analysis	Time (year)	Percentage (%)	95% confidence interval
Overall survival	1	76	(64–91)
	2s	57	(43–76)
	3	40	(26–60)
	4	37	(24–57)
Locoregional failure free	1	86	(75–99)
	2	72	(56–93)
	3	72	(56–93)
	4	65	(47–90)
Relapse free survival	1	58	(44–76)
	2	39	(26–58)
	3	33	(21–52)
	4	30	(18–49)

Assuming that PET/CT represents the true extent of disease, CT planning alone would have resulted in geographic miss of gross tumour (grade 1 geographic miss) in 5 patients (13.1%) and inadequate dosimetric coverage of the 'true' PTV based on PET (grade 2 geographic miss) in 8 patients (21.1%) in our cohort. These results based on a larger cohort of patients are lower than our earlier findings, but nevertheless demonstrate potential undertreatment in a significant proportion of patients. The longitudinal extent of disease and involved nodal disease can be difficult to detect on CT imaging alone [2–4]. Approximately 3 in 4 patients had FDG-avid disease excluded from the GTV-CT. A study by Muijs et al. [21] found that 36% of patients had >5% of GTV-PET excluded from GTV-CT. In comparison, our study detected 21 patients (55.3%) with >5% of GTV-PET excluded from GTV-CT.

To our knowledge, this is the first prospective study of PET/CT planning in oesophageal cancer to report long-term clinical outcomes. The 4-year overall survival in our cohort was 37%, which is similar to that reported in RTOG 85-01 where the 5-year overall survival for the combined chemoradiation arm was 26% [22]. The RTOG study reported a locoregional failure rate at 5 years of 38%, which is comparable to our reported rate of 35% at 4 years. However, it should be noted that the radiation fields used in our study are smaller than those used in RTOG 85-01, whereby the radiation fields included most of the mediastinum and these patients did not have PET staging. The high rates of in-field locoregional failure suggest that the poor outcome of patients with oesophageal cancer treated with radical radiotherapy may not be improved simply with better delineation of FDG-avid tumour volumes and treatment planning, noting that patients on RTOG 85-01 did not have PET/CT staging. All locoregional failures in our study occurred in-field, which indicates a failure of the chemoradiation regimen (50 Gy of radiation with concurrent cisplatin/5-fluorouracil) to eradicate all gross disease. However, given the similar rates of locoregional failure to RTOG 85-01, it is be reasonable to assume that PET/CT planning allows the use of smaller but more targeted

radiation volumes, which has the potential to reduce both acute and late toxicity.

Reduction in radiotherapy treatment volumes, together with improved techniques for treatment delivery, may allow for radiation dose escalation. Although some previous studies [23–25] have historically failed to show any significant benefit for higher radiation doses, this question remains the subject of an ongoing trial (SCOPE 2, ClinicalTrials.gov Identifier: NCT02741856), which aims to investigate the role of radiation dose escalation in the modern era of intensity-modulated radiation therapy (IMRT). Similarly, another study (CONCORDE, ClinicalTrials.gov Identifier: NCT01348217) utilising 3D conformal radiotherapy with larger fields to a lower dose (40 Gy) encompassing elective nodal volumes is underway. Given the high rate of distant relapse in oesophageal cancer, studies investigating improved systemic therapy are also required.

In conclusion, the results of this study demonstrated that PET/CT altered the delineation of tumour volumes when compared to CT alone in a significant proportion of patients. Although we were unable to demonstrate any improvement in long-term clinical outcomes with PET/CT planning, it did allow the use of smaller radiotherapy volumes. PET has now become a standard staging procedure for oesophageal cancer, and if resources allow, it should also be considered standard for treatment planning in patients undergoing radical radiotherapy.

Conflicts of interest

None.

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