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ORIGINAL ARTICLE

Prognostic factors in patients after definitive chemoradiation using involved-field radiotherapy for esophageal cancer in a phase II study

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Keywords
Definitive chemoradiotherapy; esophageal cancer; gross tumor volume; involved-field radiotherapy; relative dose intensity.

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Abstract

Background: A prospective study was performed on the use of chemoradiotherapy (CRT) for esophageal cancer (EC) with involved-field radiation therapy (IFRT), based on 18-fluorodeoxyglucose positron-emission tomography. Prognostic factors for overall survival (OS) were analyzed.

Methods: Eligible patients included 63 adults with newly diagnosed, untreated, inoperable stage I–IV EC with lymph node metastases. Patients received 80 mg/m^2 nedaplatin per day on day 1, 800 mg/m^2 5-fluorouracil on days 1–4 intravenously repeated every 28 days for two to four cycles, and combined IFRT. Irradiation was applied only to the primary tumor and positive lymph nodes.

Results: Three-year progression-free survival and OS rates were 44.9% and 47.5%, respectively. The median survival time was 31.5 months. In univariate analyses for OS, Karnofsy Performance Scale <90% (P = 0.027), initial stage (P = 0.0087), T stage (P = 0.066), N stage (P = 0.000086), M stage of M1 (P = 0.0042), dysphagia score (P = 0.00017), tumor marker squamous cell carcinoma antigen >1.5 ng/mL (P = 0.0054), gross tumor volume (GTV) > 60 cc (P = 0.00011), and relative dose intensity (RDI) of chemotherapy ≤50% (P = 0.063) were found to be associated with significantly or marginally worse OS. In multivariate analyses for OS, GTV ≥ 60 cc (P = 0.00040), RDI < 50% (P = 0.00034), and cN2-3 (P = 0.0020) were associated with significantly worse OS.

Conclusion: GTV, RDI and N grading, were associated with OS after definitive CRT using IFRT for EC.

Introduction

Our prospective phase II study of chemoradiation therapy (CRT) for esophageal cancer (EC) using involved-field radiation therapy (IFRT), based on 18-fluorodeoxyglucose (^{18}FDG) positron-emission tomography (PET), indicated the efficacy of IFRT in the treatment of inoperable EC, primarily squamous cell carcinoma.[1] The primary end point was to determine that isolated out-of-field loco-regional nodal recurrence did not occur in more than six cases. Recent studies have examined prognostic factors in EC. According to Yutong *et al.*, multivariate analysis indicated that age, pathological type, tumor node metastasis (TNM) stage, surgery and neutrophil-lymphocyte ratio were independent risk factors for 820 pathologically confirmed cases of EC (odds ratio ≥ 3.5/< 3.5 = 1.29).[2] According to Boggs, in 67 patients treated for EC with CRT followed by esophagectomy, gross tumor volume (GTV)-primary was the only multivariate predictor of progression-free survival (PFS; P = 0.030) and overall survival (OS; P = 0.0012) at five years, rather than traditional TNM staging.[3] In this study, the prognostic factors affecting survival after this treatment method are reported as a secondary endpoint. We sought to determine prognostic factors in patients that received homogenous treatment for EC, such as IFRT and concurrent chemotherapy, to ascertain the treatment method with the worst prognosis in

order to improve the survival in these patients. At present, three-year OS is only around 50%.

Methods

Eligible patients included adults with newly diagnosed, untreated, inoperable stage I–IV EC. Stage IV cases included had supraclavicular and/or para-aortic lymph nodes (LNs) only, without distant organ metastasis. Patients received 80 mg/m^2 nedaplatin per day on day 1, 800 mg/m^2 5-fluorouracil on days 1–4 intravenously repeated every 28 days for two to four cycles, and combined IFRT. Elective nodal irradiation was not performed. Irradiation was applied only to the primary tumor and positive lymph nodes. Age criteria were 20–85 years old.

Radiotherapy planning and target volume definition

Enhanced computed tomography (CT) and/or PET and endoscopic extension were used to define GTV for each patient. All LNs with a diameter at least 1 cm in the short axis in CT or positive by ^{18}FDG-PET (excluding physiological accumulation) were included in the GTV. The positive was defined as more than 2.5 of maximum standardized uptake value (SUVmax). The GTV was contoured on the planning CT by referring to the PET/CT images on the monitor adjacent to the Pinnacle^3 planning machine. We did not co-register the PET/CT images with the planning-CT in Pinnacle. All patients had available PET/CT information. The clinical target volume (CTV)-GTV margin was 2 cm in the craniocaudal direction and 0 cm in the other four directions for the primary tumor. CTV was equal to GTV for metastatic LNs. The planning target volume (PTV)-CTV margin was 1 cm in the craniocaudal direction and 0.5 cm in the other four directions. The heterogeneity corrections of collapsed cones convolution superposition were used. Volumetric modulated arc therapy was also used when necessary in terms of dose constraints for both target volume and organ at risk. All patients received selective LN irradiation and were treated with 50.4 Gy delivered over 5.6 weeks at 1.8 Gy per fraction or 50 Gy in 25 fractions over five weeks.

Patients

Serum tumor markers, carcinoembryonic antigen (CEA), squamous cell carcinoma-related antigen (SCC), cytokeratin 19 fragment (CYFRA), and p53 antibody, were obtained before CRT.

The chemotherapy relative dose intensity (RDI) was calculated as follows:[4]

RDI = (total chemotherapy cycle number administered/4 cycles) × (chemotherapy dose administered per cycle/100% dose) × (28 days/interval between chemotherapy cycles) × 100 (%).

Karnofsky performance status (KPS) before treatment was 70–80% in 19 cases. The subsites of the primary tumors included cervical (Ce), upper (Ut), middle (Mt), and lower thoracic (Lt) portions, with distributions at 5%, 19%, 49%, and 27%, respectively (Table 1). Tumor length in the craniocaudal direction before CRT was over 5.0 cm in 33 cases. The positive rates of SCC, CYFRA, CEA, and p53 tumor markers were 48.4% (32/62 cases), 16.7% (10/60), 27.9% (17/61), and 17.7% (11/62), respectively (Table 1).

Statistical analysis

Kaplan–Meier method was used for OS estimation and log-rank for P value in comparisons with each group. Survival durations were calculated from the start of CRT. The proportional hazard model was used for multivariate analyses of OS. Multivariate analysis was performed by stepwise variable selection using Bayesian information criterion. The explanatory variables included age (<68 vs. ≥68 years), tumor length (≥5 cm vs. <5 cm), cT stage, cN stage, cM stage, GTV (≥ 60cc vs. < 60cc), KPS (<90% vs. ≥90%), histopathological type (SCC vs. other), and RDI (≥50% vs. <50%). $P < 0.05$ was considered statistically significant. The final follow-up date was 25 April 2016.

Results

From September 2009 to July 2012, 63 patients were enrolled. The primary end point of isolated out-of-field loco-regional nodal recurrence was seen in only three patients.

The mean ± standard error (SE) for PTV was 293.0 ± 25.1 cc. The average ± SE for GTV, CTV, and irradiated volume was 82.4 ± 9.6 cc, 116.3 ± 13.1 cc, and 421.9 ± 30.2 cc, respectively. Chemotherapy RDI was 0–24% in four cases, 25–49% in 24, 50–74% in nine, and 75–100% in 26 cases. Salvage surgery was performed in 11 patients (17.5%) as a result of residual (3 cases) or recurrent (8) disease. Two of these cases received exploratory laparotomy as salvage surgery.

The median follow-up duration in the 23 (37%) living patients was 56.7 months (range 30.7–76.2). Estimated two, three, and four-year OS for all 63 cases by Kaplan–Meier method were 57.1% (95% confidence interval [CI]) 44–68.3%), 47.5% (95% CI 34.8–59.2%), and 44.2% (95% CI 31.8–56%), respectively. Median OS duration was 31.5 months (95% CI 17.5–53.8). PFS rates at two, three,

Table 1 Clinicopathological characteristics of patients with esophageal cancer

Factors	N	1-year OS (%)	SE	2-year OS (%)	SE	3-year OS (%)	SE	MST (month)	*P* (log-rank)
Total	63	68.3	5.9	57.1	6.2	47.5	6.3	31.5	
Age									
<68 years	32	65.6	8.4	56.2	8.8	50.0	8.8	41.8	0.20
≥68 years	31	71.0	8.2	58.1	8.9	45.2	8.9	31.5	
KPS									
≥90%	44	79.5	6.1	65.9	7.2	54.4	7.5	39.2	0.027
<90%	19	42.1	11.3	36.8	11.1	31.6	10.7	7.6	
Stage									
I	9	88.9	10.5	88.9	10.5	88.9	10.5	NE	0.0087
II	10	100		100		70.0	14.5	53.5	
III	27	59.3	9.5	48.1	9.6	44.1	9.6	22.0	
IV	17	52.9	12.1	29.4	11.1	17.6	9.3	13.0	
T stage									
T1	10	90.0	9.5	90.0	9.5	80.0	12.7	NE	0.066
T2	7	100		100		85.7	13.2	51.1	
T3	22	68.2	9.9	54.5	10.6	40.0	10.6	28.6	
T4	24	50.0	10.2	33.3	9.6	29.2	9.3	11.8	
N stage									
N0	17	94.1	5.7	94.1	5.7	88.2	7.8	NE	0.000086
N1	15	80.0	10.3	66.7	12.2	53.3	12.9	53.5	
N2	18	50.0	11.8	38.9	11.5	26.7	10.7	14.8	
N3	13	46.2	13.8	23.1	11.7	15.4	10.0	9.2	
M stage									
M0	46	73.9	6.5	67.4	6.9	58.5	7.3	51.1	0.0042
M1	17	52.9	12.1	29.4	11.1	17.6	9.3	13.0	
Tumor location									
Ce	3	66.7	27.2	66.7	27.2	66.7	27.2	NE	0.29
Ut	12	58.3	14.2	41.7	14.2	25.0	12.5	51.1	
Mt	31	74.2	7.9	58.1	8.9	51.6	9.0	39.4	
Lt	17	64.7	11.6	64.7	11.6	52.9	12.1	15.7	
Pathological type									
SqCC	59	67.8	6.1	55.9	6.5	45.6	6.5	29.8	0.37
AC	4	75.0	21.7	75.0	21.7	75.0	21.7	53.8	
Dysphagia score									
1	9	66.7	15.7	66.7	15.7	55.6	16.6	NE	0.00017
2	17	41.2	11.9	17.6	9.3	17.6	9.3	10.6	
3	9	66.7	15.7	44.4	16.6	11.1	10.5	13.9	
4(normal)	28	85.7	6.6	82.1	7.2	75.0	8.2	NA	
Tumor length									
≤ 5.0 cm	37	67.6	7.7	56.8	8.1	45.9	8.2	31.5	0.91
> 5.0 cm	26	69.2	9.1	57.7	9.7	50.0	9.8	33.0	
SCC									
Low	30	73.3	8.1	73.3	8.1	66.7	8.6	NE	0.0054
High	32	62.5	8.6	43.8	8.8	30.7	8.3	17.6	
NE	1								
CYFRA									
Low	50	72.0	6.4	64.0	6.8	53.9	7.1	39.2	0.13
High	11	54.5	15.0	36.4	14.5	27.3	13.4	12.3	
NE	2								
CEA									
Low	44	68.2	7.0	56.8	7.5	45.2	7.5	30.7	0.77
High	17	70.6	11.1	64.7	11.6	58.8	11.9	42.7	
NE	2								
p53									
Low	51	68.6	6.5	58.8	6.9	48.9	7.0	35.6	0.43

Table 1 Continued

Factors	N	1-year OS (%)	SE	2-year OS (%)	SE	3-year OS (%)	SE	MST (month)	*P* (log-rank)
High	11	63.6	14.5	54.5	15.0	45.5	15.0	29.8	
NE	1								
GTV-60 cc									
≤ 60 cc	29	86.2	6.4	82.8	7.0	75.9	8.0	NE	0.00011
> 60 cc	34	52.9	8.6	35.3	8.2	22.9	7.3	13.4	
RDI-50%									
≤ 50%	28	57.1	9.4	42.9	9.4	35.7	9.1	15.4	0.063
> 50%	35	77.1	7.1	68.6	7.9	56.9	8.4	51.1	
RDI-60%									
≤ 60%	29	58.6	9.2	44.8	9.2	34.5	8.8	17.8	0.052
> 60%	34	76.5	7.3	67.6	8.0	58.7	8.5	53.5	
RDI-70%									
≤ 70%	32	59.4	8.7	46.9	8.8	37.5	8.6	18.1	0.064
> 70%	31	77.4	7.5	67.7	8.4	57.9	8.9	51.1	

AC, adenocaricinoma; Ce, cervix; CEA, carcino-embryonic antigen; CYFRA, cytokeratin 19 fragment; GTV, gross tumor volume; KPS, Karnofsky Performance Status; Lt, lower thoracic; MST ,median survival time; Mt, middle thoracic; NE, not evaluated; OS, overall survival; RDI, relative dose intensity; SCC, squamous cell carcinoma-related antigen; SE, standard error; SqCC, squamous cell carcinoma; SE, standard error; Ut, upper thoracic.

and four-years were 50.7%, 44.9%, and 43%, respectively, and the median PFS was 27.3 months (95% CI 12-NA).

Univariate analyses for OS by log-rank test were performed according to age, KPS, initial stage (including T, N, and M stage), tumor location, pathological type, dysphagia score, tumor length, initial tumor markers, GTV (= primary tumor plus positive LNs), and RDI (Table 1). Among these factors, KPS < 90% (3-year OS 54.4% vs. 31.6%; $P = 0.027$), initial stage ($P = 0.0087$), T stage ($P = 0.066$), N stage ($P = 0.000086$), M stage of M1 (58.5% vs. 17.6%; $P = 0.0042$), dysphagia score ($P = 0.00017$), SCC > 1.5 ng/mL (66.7% vs. 30.7%; $P = 0.0054$), GTV > 60cc (75.9% vs. 22.9%; $P = 0.00011$; Fig 1), and RDI ≤ 50% (56.9% vs. 35.7%; $P = 0.063$; Fig 2) were found to be associated with significantly or marginally poor prognosis. There was no significant correlation between OS and age ($P = 0.20$),

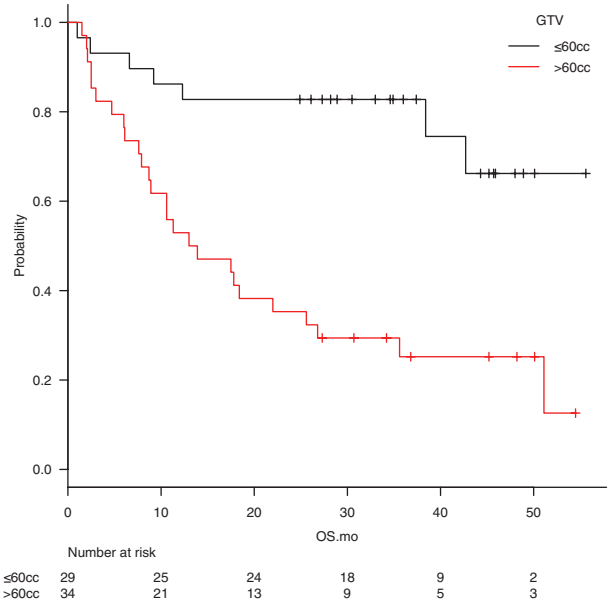

Figure 1 Kaplan–Meier survival curves in 63 patients with esophageal carcinoma, comparing gross tumor volume ≤60 cc and >60 cc ($P = 0.00011$). OS, overall survival.

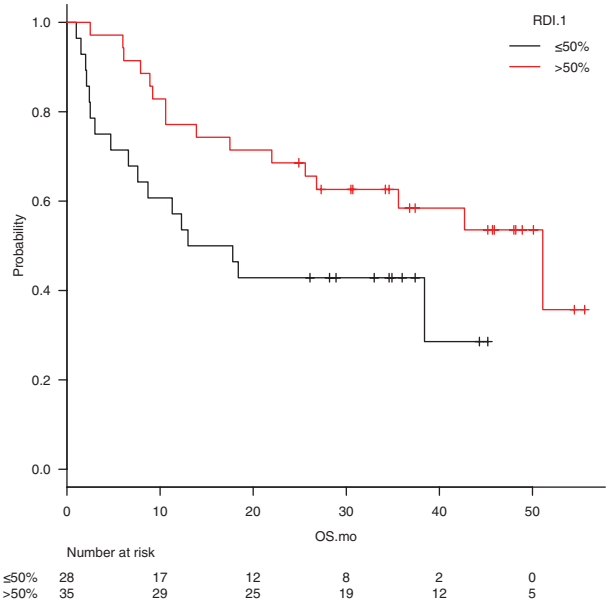

Figure 2 Kaplan–Meier survival curves in 63 patients with esophageal carcinoma, comparing relative dose intensity of ≤50% and >50% ($P = 0.063$). OS, overall survival.

Table 2 Multivariate analyses for overall survival

Factors	Hazard ratio	Lower 95% CI	Upper 95% CI	*P*
cN2-3	3.40	1.57	7.37	0.0020
GTV ≥ 60cc	0.23	0.10	0.52	0.00040
RDI ≤ 50%	3.52	1.77	7.00	0.00034

CI, confidence interval; GTV, gross tumor volume; RDI, relative dose intensity.

tumor location ($P = 0.29$), pathological type ($P = 0.37$), tumor length ($P = 0.91$), CYFRA ($P = 0.13$), CEA ($P = 0.77$), or p53 ($P = 0.43$).

Multivariate analyses for OS by proportional hazard model were performed (Table 2). GTV ≥ 60cc (hazard ratio [HR] 4.35; $P = 0.00040$), RDI ≤ 50% (HR 3.52; $P = 0.00034$), and cN-stage (HR 3.40; $P = 0.0020$) remained associated with significantly poor prognosis. However, the significant differences disappeared in KPS, and cT and cM stages.

Discussion

We present a secondary analysis of a data set from a prospective, single institution phase II trial evaluating a large number of potential prognostic features for EC treated with IFRT and concurrent chemotherapy. This study found prognostic factors that predicted OS in the 63 patients enrolled. Elective nodal irradiation is unnecessary and, thus, is omitted in the radiation field when using concurrent CRT combined with nedaplatin plus 5-fluorouracil. The finding that GTV60cc is a prognostic factor was limited to this particular CRT method in our study; however, we believe our results apply to all CRT for EC. Our primary end point of isolated out-of-field loco-regional nodal recurrence after CRT for EC using IFRT based on ^{18}FDG-PET was seen in only three patients; the expected rate was less than 5%, based on our previous research.[1] In this study, RDI ≤ 50% (28 cases) and GTV in addition to clinical T and cN stages were associated with a significantly poor OS prognosis after definitive CRT using IFRT for EC. The overall impact of such findings is small given the size of the patient sample size. As expected, TNM staging and KPS were prognostic factors.

Tumor length was determined as a prognostic factor of EC.[5–12] Data from the Japanese esophageal carcinoma registration database between 1969 and 1980 demonstrated that the depth of tumor invasion correlated with the 10-year survival of EC patients more than the superficial extent of the tumor.[6,13] Recent publications have suggested that pathologic esophageal tumor length is directly correlated with long-term survival; however, most of these data originated in western countries, and the cancer type was predominantly adenocarcinoma.[8,11,12,14–16] The finding that GTV > 60 cc was associated with a significantly poor OS prognosis may be related to the fact that tumor length is a prognostic factor for survival. However, tumor length >5 cm was not a prognostic factor for OS in the present study.

Recently, Boggs *et al.* reported that GTV-primary was a significant multivariate predictor for improved local control ($P = 0.034$), PFS ($P = 0.030$), and OS ($P = 0.0012$) in locally advanced EC patients treated with tri-modality therapy of CRT followed by esophagectomy.[3] Additionally, they reported that GTV-primary >85 cc was the best predictor for local failure (33% vs. 9% if ≤85 cc). They concluded that GTV-primary was a more powerful predictor of patient outcome than traditional TNM staging. Our results are consistent with their conclusion; however Boggs *et al.* contoured primary and nodal GTV as separate regions of interest rather than together and they adopted preoperative CRT, not definitive CRT.

Bollschweiler *et al.* demonstrated a strong correlation between tumor length and T stage, with tumors measuring less than 3 cm associated with improved survival rates.[17] Although univariate analysis revealed T, N, and M grading and tumor length were of significant prognostic relevance, multivariate analysis concluded that only T, N, and M grading were independent prognostic factors. This remains a controversial area and further research is required to clarify the relevance of tumor length in EC prognosis. In the present study, T and N grading were determined as prognostic factors.

Many previous studies did not distinguish between EC stages II and III. Our stage II clinical results were very good, with a three-year OS rate of 100%; however, only 10 patients were included.

In the present study, RDI ≤ 50% was a prognostic factor for OS. Therefore, it may be important to administer at least to two cycles of chemotherapy as a standard schedule. However, our results are limited in that it prior to the study we decided that elderly patients would only be treated with two cycles and 80% of the dose administered to younger patients. It has been reported that a higher chemotherapy RDI improves survival in colon cancer, metastatic solid tumors, early stage breast cancer, epithelial ovarian cancer, and renal cell carcinoma.[18–22]

This study had a number of limitations. GTV is a somewhat subjective measure because it relies on the physician's judgment. Inter-observer variability in the GTV definition is well known, which could limit the generalizability of the results.[23] Other authors have used only the volume of the primary tumor to predict survival.[24] However, in the present study, the PTV and involved nodes were added to calculate GTV. Because this was a prospective study, cases with poor performance status or with serious complications were excluded.

The results of this study indicated that GTV (>60 cc), RDI (≤50%), T, and N grading were unfavorable prognostic factors for OS after definitive CRT using IFRT for EC.

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Disclosure

No authors report any conflict of interest.

Reference

1 Yamashita H, Omori M, Takenaka R *et al.* Involved-field irradiation concurrently combined with nedaplatin/5-fluorouracil for inoperable esophageal cancer on basis of ^{18}FDG-PET scans: A phase II study. *Radiother Oncol* 2014; **113**: 182–7.
2 Yutong H, Xiaoli X, Shumei L, Shan S, Di L, Baoen S. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with esophageal cancer in a high incidence area in China. *Arch Med Res* 2015; **46**: 557–63.
3 Boggs DH, Hanna A, Burrows W, Horiba N, Suntharalingam M. Primary gross tumor volume is an important prognostic factor in locally advanced esophageal cancer patients treated with trimodality therapy. *J Gastrointest Cancer* 2015; **46**: 131–7.
4 Lenhart C. Relative dose intensity: Improving cancer treatment and outcomes. *Oncol Nurs Forum* 2005; **32**: 757–64.
5 Beahrs OH, Myers MH. Esophageal cancer. In: OH B, MH M (eds). *Manual for staging cancer*, American Joint Committee on Cancer, 2nd edn. J. B. Lippincott Company, Philadelphia, PA 1983; 61–6.
6 Sobin LH, Hermanek P, Hutter RV. TNM classification of malignant tumors. A comparison between the new (1987) and the old editions. *Cancer* 1988; **61**: 2310–4.
7 Edge SB, Compton CC. The American Joint Committee on Cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010; **17**: 1471–4.
8 Gaur P, Sepesi B, Hofstetter WL *et al.* Endoscopic esophageal tumor length: A prognostic factor for patients with esophageal cancer. *Cancer* 2011; **117**: 63–9.
9 Wang BY, Goan YG, Hsu PK, WH H, YC W. Tumor length as a prognostic factor in esophageal squamous cell carcinoma. *Ann Thorac Surg* 2011; **91**: 887–93.
10 Song Z, Wang J, Lin B, Zhang Y. Analysis of the tumor length and other prognosis factors in pT1-2 node-negative esophageal squamous cell carcinoma in a Chinese population. *World J Surg Oncol* 2012; **10**: 273.
11 Mirinezhad SK, Jangjoo AG, Seyednejad F *et al.* Impact of tumor length on survival for patients with resected esophageal cancer. *Asian Pac J Cancer Prev* 2014; **15**: 691–4.
12 Eloubeidi MA, Desmond R, Arguedas MR, Reed CE, Wilcox CM. Prognostic factors for the survival of patients with esophageal carcinoma in the U. S.: The importance of tumor length and lymph node status. *Cancer* 2002; **95**: 1434–3.
13 Iizuka T, Isono K, Kakegawa T, Watanabe H. Parameters linked to ten year survival in Japan of resected esophageal carcinoma. Japanese Committee for Registration of Esophageal Carcinoma Cases. *Chest* 1989; **96**: 1005–11.
14 Griffiths EA, Brummell Z, Gorthi G, Pritchard SA, Welch IM. Tumor length as a prognostic factor in esophageal malignancy: Univariate and multivariate survival analyses. *J Surg Oncol* 2006; **93**: 258–67.
15 Bolton WD, Hofstetter WL, Francis AM *et al.* Impact of tumor length on long-term survival of pT1 esophageal adenocarcinoma. *J Thorac Cardiovasc Surg* 2009; **138**: 831–6.
16 Davies L, Mason JD, Roberts SA *et al.* Prognostic significance of total disease length in esophageal cancer. *Surg Endosc* 2012; **26**: 2810–6.
17 Bollschweiler E, Baldus SE, Schröder W, Schneider PM, Hölscher AH. Staging of esophageal carcinoma: Length of tumor and number of involved regional lymph nodes. Are these independent prognostic factors? *J Surg Oncol* 2006; **94**: 355–63.
18 Aspinall SL, Good CB, Zhao X *et al.* Adjuvant chemotherapy for stage III colon cancer: Relative dose intensity and survival among veterans. *BMC Cancer* 2015; **15**: 62.
19 Havrilesky LJ, Reiner M, Morrow PK, Watson H, Crawford J. A review of relative dose intensity and survival in patients with metastatic solid tumors. *Crit Rev Oncol Hematol* 2015; **93**: 203–10.
20 Sandy J, Della-Fiorentina S. Relative dose intensity in early stage breast cancer chemotherapy: A retrospective analysis of incidence, risk factors and outcomes at a South-West Sydney cancer clinic. *Asia Pac J Clin Oncol* 2013; **9**: 365–72.
21 Hanna RK, Poniewierski MS, Laskey RA *et al.* Predictors of reduced relative dose intensity and its relationship to mortality in women receiving multi-agent chemotherapy for epithelial ovarian cancer. *Gynecol Oncol* 2013; **129**: 74–80.
22 Kawashima A, Tsujimura A, Takayama H *et al.* Importance of continuing therapy and maintaining one-month relative dose intensity in sunitinib therapy for metastatic renal cell carcinoma. *Med Oncol* 2012; **29**: 3298–305.
23 Schreurs LM, Busz DM, Paardekooper GM *et al.* Impact of 18-fluorodeoxyglucose positron emission tomography on computed tomography defined target volumes in radiation treatment planning of esophageal cancer: Reduction in geographic misses with equal inter-observer variability: PET/CT improves esophageal target definition. *Dis Esophagus* 2010; **23**: 493–501.
24 Hyun SH, Choi JY, Shim YM *et al.* Prognostic value of metabolic tumor volume measured by 18F-fluorodeoxyglucose positron emission tomography in patients with esophageal carcinoma. *Ann Surg Oncol* 2010; **17**: 115–22.

