Radiotherapy and Oncology 118 (2016) 465–470

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Acute esophagitis

Acute esophagitis for patients with local–regional advanced non small cell lung cancer treated with concurrent chemoradiotherapy

Yi Pan [a,b], Carsten Brink [b,c], Marianne Knap [d], Azza A. Khalil [d], Christa H. Nyhus [e], Tine McCulloch [f], Bente Holm [g], Yi-long Wu [h], Tine Schytte [i], Olfred Hansen [b,i,*]

[a] Department of Radiation Oncology, Guangdong General Hospital & Guangdong Academy of Medical Science, PR China; [b] Institute of Clinical Research, University of Southern Denmark, Odense; [c] Laboratory of Radiation Physics, Odense University Hospital; [d] Department of Oncology, Aarhus University Hospital; [e] Department of Oncology, Vejle Hospital, Sygehus Lillebaelt; [f] Department of Oncology, Aalborg University Hospital; [g] Department of Oncology, Herlev University Hospital, Denmark; [h] Guangdong Lung Cancer Institute, PR China; and [i] Department of Oncology, Odense University Hospital, Denmark

ARTICLE INFO

Article history:
Received 4 October 2015
Received in revised form 8 January 2016
Accepted 10 January 2016
Available online 20 January 2016

Keywords:
Acute esophagitis
Non small cell lung cancer
IMRT
Concurrent chemoradiotherapy

ABSTRACT

Purpose: Esophagitis is common in patients treated with definitive radiotherapy for local–regional advanced non small cell lung cancer (NSCLC). The purpose of this study was to estimate the dose–effect relationship using clinical and dosimetric parameters in patients receiving intensity modulated radiotherapy (IMRT) and concomitant chemotherapy (CCT).

Methods: Between 2009 and 2013, 117 patients with stages IIB–IIIB NSCLC were treated in a multicenter randomized phase II trial with 2 cycles of induction chemotherapy followed by IMRT and CCT. The esophagitis was prospectively scored using the Common Toxicity Criteria 3.0. Clinical and dosimetric variables were analyzed for the correlation with grade $\geqslant 2$ esophagitis through logistic regression.

Results: Grade 2 esophagitis was experienced by 31 (27%). All models including gender, institution, a dosimetric parameter and a position parameter were significantly associated with esophagitis. The two models using the relative esophagus volume irradiated above 40 Gy (V_{40}, OR = 2.18/10% volume) or the length of esophagus irradiated above 40 Gy (L_{40}, OR = 4.03/5 cm) were optimal. The upper part of esophagus was more sensitive and females experienced more toxicity than men.

Conclusion: V_{40} and L_{40} were most effective dosimetric predictors of grade $\geqslant 2$ esophagitis. The upper part of esophagus was more sensitive.

 Radiotherapy and Oncology 118 (2016) 465–470

Thirty-five percent of patients with non small cell lung cancer (NSCLC) are irresectable at diagnosis due to being in loco-regional advanced stage [1]. Definitive concomitant chemoradiotherapy (CCRT) is the standard of care for this group of patients if they are in good performance status. Overall survival is improved by 5% by CCRT compared to sequential chemoradiotherapy, which may be caused by an increased local–regional control [1]. Although CCRT has a better therapeutic effect, the risk and severity of acute toxicity, especially the acute esophagitis may increase. In a meta-analysis performed by the NSCLC Collaborative Group containing 6 randomized clinical trials, the incidence of grade 3–4 esophagitis in CCRT (18%) was higher than observed in sequential chemoradiotherapy (4%), with a relative ratio of 4.9 ($p < 0.01$) [1]. For patients treated with radiotherapy alone, the incidence of esophagitis $\geqslant$grade 3 is $\approx$1%, but it is markedly increased to 6–24% with CCT [2].

The symptoms of esophagitis include retrosternal pain, dysphagia and odynophagia. It often occurs 2–4 week after the start of radiation therapy and may persist 2–7 weeks [3,4]. Severe esophagitis may induce hospitalization, and require parenteral nutrition, naso-gastric tube and analgetics. It may lead to treatment interruptions, which may have a negative impact on the quality of life of the patients, lower the chance of local tumor control, and thus impact survival negatively.

Intensity modulated radiotherapy (IMRT) facilitates a more conform radiation dose distribution allowing for shaping the dose of the tumor and sparing esophagus more than 3-dimensional radiation (3DCRT) may be able to do. For NSCLC, IMRT has the potential to escalate target dose without a corresponding increase to the lung and esophagus [5–7]. In many centers IMRT has become the principal radiation technique for NSCLC to reduce local relapse and protect critical organ at risk (OAR).

Although a number of clinical and dosimetric risk factors for esophagitis have been reported in previous studies [8–13], no dosimetric parameter has been generally accepted as the best predictor. In addition, most of these studies were based on 3DCRT. The

* Corresponding author at: Department of Oncology, Odense University Hospital, DK-5000 Odense, Denmark.
E-mail address: olfred.hansen@rsyd.dk (O. Hansen).

http://dx.doi.org/10.1016/j.radonc.2016.01.007
0167-8140/

objective of this study was to estimate the dose–effect relation between esophagitis and clinical as well as dosimetric parameters in patients with local–regional advanced NSCLC receiving IMRT and CCT.

Materials and methods

Patients

Between May 2009 and August 2013, 117 patients with NSCLC were enrolled in the Danish multicenter randomized phase II trial (NARLAL). The inclusion criteria were histologically or cytologically confirmed NSCLC, clinical American Joint Committee of Cancer stage (the seventh edition) IIB–IIIB, performance status (PS) <2 on the ECOG scale, weight loss $\leqslant$10%, adequate hepatic and renal function, forced expiratory volume in 1 s (FEV1) $\geqslant$1.0. Patients with pleural effusion, prior chemotherapy for lung cancer and any other active malignancy within the last 5 years were excluded. Each patient underwent basic laboratory studies, computed tomography (CT) scan of the chest and upper abdomen with contrast and whole body positron emission tomography (PET) before treatment. Approval was granted by the Institutional Review Board for conducting this study. The NARLAL clinic cohort study was filed at clinicaltrials.gov (No. NCT00887783).

The medium age was 66 years (44–82 years). The patient characteristics are presented in Table 1.

Table 1
Patient characteristics (N = 117).

Characteristics	Number	Percentage
Gender		
Male	68	58
Female	49	42
Age (years)		
Median (range)	65.5 (44–82)	
Smoking		
Never and former smokers	89	76
Current smoker	28	24
Histology		
SCC	47	40
NSCC	70	60
Performance status		
0	62	53
1	55	47
T stage		
T1 + 2	74	63
T3 + 4	43	37
N stage		
N0–1	18	15
N2	85	73
N3	14	12
Stage		
IIB	6	5
IIIA	81	69
IIIB	30	26
Prescribed Radiation Dose (Gy)		
66	57	49
60	60	51
Length of esophagus (cm)		
Median (range)	26 (20–31)	
Volume of esophagus (cm^3)		
Median (range)	35 (19–141)	
Mean esophagus dose (Gy)		
Median (range)	23 (3–42)	
Maximum esophagus dose (Gy)		
Median (range)	63 (9–72)	
Median esophagus dose (Gy)		
Median (range)	10 (1–60)	
Esophagus V_{20} (%)		
Median (range)	43 (0–70)	
Esophagus V_{30} (%)		
Median (range)	36 (0–70)	
Esophagus V_{40} (%)		
Median (range)	32 (0–68)	
Esophagus V_{50} (%)		
Median (range)	26 (0–66)	
Esophagus V_{60} (%)		
Median (range)	8 (0–50)	

Abbreviations: SCC = squamous cell carcinoma; NSCC = non squamous cell carcinoma; V_{20}–V_{60}: percentage of esophageal volume receiving at least 20–60 Gy.

NARLAL protocol

All patients were treated with induction chemotherapy followed by CCRT. The induction chemotherapy consisted of 2 cycles of Carboplatin (AUC = 5, day 1) and Vinorelbine oral (60–80 mg/m^2, day 1 and 8). After completing induction chemotherapy, patients were randomized into two groups: 60 Gy in 30 fractions (Arm A) and 66 Gy in 33 fractions (Arm B), once daily, 5 times per week. The concomitant chemotherapy regimen consisted of Vinorelbine oral 50 mg 3 times a week for 6—6$\frac{1}{2}$ weeks. Eighty-three percent of the patients received the scheduled doses of concomitant chemotherapy (Supplementary Table 1).

Radiotherapy preparation

IMRT was planned for all patients. Gross tumor volume including the lung tumor and involved mediastinal lymph node was defined on CT of the chest and PET-CT.

A treatment planning CT scan was performed with 2.5–3 mm slice thickness from upper neck to mid-abdomen. Radiotherapy was delivered with a linear accelerator using energy of 6 MV X-rays. The planning technique was based on ICRU62 recommendations [14]. Critical organ dose tolerances were defined as maximum dose of esophagus $\leqslant$ 66 Gy, lung $V_{20} \leqslant 40\%$, spinal cord $\leqslant$ 45 Gy, heart $V_{50} \leqslant 20\%$.

Esophageal contours and dosimetric data

For the consistency, the esophagus was re-delineated in all patients by the same oncologist (Y.P.). The external surface of esophagus was contoured on each axial plane of the planning CT scan from the inferior margin of cricoid cartilage to the gastro-esophageal junction. Dose-volumetric values were calculated from Dose Volume Histogram (DVH) for each patient. The following esophageal dosimetric parameters were extracted from the dose data set in treatment planning system: maximum, median and mean dose, the entire length and volume, series of dose-volumetric values from DVH such as: the percentage of the volume of esophagus receiving from $\geqslant$20 Gy (V_{20}) and in 10 Gy increments up to $\geqslant$60 Gy (V_{60}).

Based on the hypothesis that length and positional information, which is discarded in traditional DVH, might be important to predict grade 2 or greater esophagitis, the following metrics were calculated: the length of the part of esophagus for which the median dose within a transversal CT slices was above 20 Gy, 30 Gy, 40 Gy, 50 Gy, or 60 Gy (L_{20}, L_{30}, L_{40}, L_{50}, or L_{60}) and mean relative position of the volume related to L_{20}–L_{60} (P_{20}, P_{30}, P_{40}, P_{50}, and P_{60}) defined as 0 at the most cranial located esophagus delineation and 1 at the most caudal located delineation.