Clinical and Translational Radiation Oncology 36 (2022) 70–76

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Original Research Article

Excessive esophageal toxicity in patients with locally advanced non-small cell lung cancer treated with concurrent hypofractionated chemoradiotherapy and 3-weekly platinum doublet chemotherapy

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ARTICLE INFO

Keywords:
Non-small cell lung cancer (NSCLC)
Concurrent chemoradiation
Hypofractionation
Platinum doublet chemotherapy
Esophageal toxicity

ABSTRACT

Introduction: Concurrent chemoradiation followed by immunotherapy is the standard of care for patients with stage III non-small cell lung cancer (NSCLC). Prior to the introduction of adjuvant immunotherapy, we treated patients with stage III NSCLC with concurrent platinum doublet chemotherapy and 66 Gy in 24 fractions. We determined the toxicity of this treatment.

Methods: A retrospective observational study was performed in a cohort of patients with stage III NSCLC, <70 years old, and WHO performance score 0–1. Patients were treated with concurrent platinum doublet chemotherapy and 66 Gy in 24 fractions. All patients were staged with a PET-scan and brain MRI-scan. Toxicity was scored using the common criteria for adverse events (CTCAE v4.03).

Results: Between 2012 and 2017, 41 patients were treated with mildly hypofractionated radiotherapy and platinum doublet chemotherapy. The median follow-up was 4.7 years. The median age was 57 and 58% of patients were male. The majority of patients had stage IIIB disease (68%). The median total Gross Tumor Volume (GTV) was 104 cc (range: 15–367 cc). The median lymph node GTV was 59 cc (10–341 cc). Five patients died: four due to an esophagus perforation or fistula, and one due to pulmonary bleeding. Grade $\geq$ 3 esophageal toxicity occurred in 16 patients. Five patients had late grade $\geq$ 3 esophageal toxicity (12%). The median overall survival was 19 months.

Conclusion: Toxicity was unexpectedly high in patients with stage III NSCLC (WHO 0–1) after concurrent platinum doublet chemotherapy and 66 Gy in 24 fractions.

Introduction

The standard treatment for patients with stage III non-small cell lung cancer (NSCLC) is concurrent chemoradiation, followed by adjuvant immunotherapy. During the pre-immunotherapy era, strategies to intensify local treatment and improve overall survival included: concurrent chemoradiation [1], dose escalation [2], accelerated radiotherapy [3] and mildly hypofractionated radiotherapy [4–6]. In the EORTC 08972 phase III trial a mildly hypofractionated radiotherapy regimen (66 Gy in 24 fractions) combined with daily cisplatin (6 mg/m^2) was used [4]. Survival outcome is comparable to conventional concurrent chemoradiation (median survival 28–36 months) [5,6]. At our institute, we treated selected stage III NSCLC patients with concurrent platinum doublet chemotherapy and the mildly hypofractionated radiotherapy regimen. They were treated between 2012 and 2017, prior to the introduction of immunotherapy. Our multidisciplinary oncology team decided to treat selected patients with full dose platinum doublet chemotherapy (rather than the radiosensitizing daily cisplatin) as the

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https://doi.org/10.1016/j.ctro.2022.07.002
Received 1 July 2022; Accepted 4 July 2022
Available online 7 July 2022

incidence of distant metastases is high (>40%) in patients with stage III NSCLC [1]. Although platinum doublet chemotherapy combined with mildly hypofractionated radiotherapy (24x2.75 Gy) is not a commonly used regimen, it was allowed in the international randomized phase II PET boost trial (NCT01024829), in which isotoxic dose escalation was assessed in patients treated with 24 fractions of at least 3 Gy and concurrent cisplatin-etoposide, cisplatin-pemetrexed or daily low dose cisplatin [7,8]. We retrospectively determined the toxicity in patients with stage III NSCLC treated with concurrent mildly hypofractionated chemoradiotherapy and platinum doublet chemotherapy.

Materials and methods

We retrospectively assessed all patients with stage III NSCLC treated in two medical centers with 3-weekly platinum doublet chemotherapy and concurrent hypofractionated radiotherapy between 2012 and 2017. Patients were excluded if they had single N2 disease and scheduled for surgery after chemoradiation. Patients were eligible for platinum doublet chemoradiation if they met the following criteria: age <70 years, WHO performance score 0–1, adequate renal and hepatic function for chemotherapy. The diagnostic work-up consisted of a contrast enhanced CT-scan, PET-scan, MRI-scan of the brain and cytology of clinical suspect lymph nodes on imaging and histology of the primary tumor. All patients were discussed in the multidisciplinary tumor board meeting. This study was approved by the institutional review board.

Chemotherapy

The first cycle of chemotherapy was based on tumor histology. Patients with an adenocarcinoma received intravenous cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2, while patients with a squamous cell carcinoma received intravenous gemcitabine 1250 mg/m^2 (day 1 and day 8) and cisplatin 75 mg/m^2 (day 2). This was followed by 2–3 cycles of intravenous cisplatin 75 mg/m^2 and etoposide 100 mg/m^2. Cisplatin was replaced by carboplatin in patients with poor hearing or reduced renal function. Chemotherapy was delayed or the dose was reduced according to guidelines [9]. Growth colony stimulating factor was not administered.

Radiotherapy

Treatment planning was initially based on a contrast-enhanced 3DCT-scan. As of 2014, a four-dimensional CT-scan (4DCT) was made in addition to the contrast enhanced CT-scan. A planning PET-CT-scan was made in radiotherapy treatment position and fused to the contrast enhanced CT-scan to facilitate tumor delineation. Elective nodal irradiation was not performed. The planning target volume (PTV) consisted of the involved lymph nodes +10 mm margin and the tumor + 10–15 mm margin (larger margin for lower lobe tumors). After the introduction of the 4DCT-scan an internal target volume (ITV) was determined for the tumor and lymph nodes based on all phases of the 4DCT-scan. PTV = ITV + 6 mm margin for the tumor and an 8 mm margin for lymph nodes. The organs at risk were contoured according to RTOG guidelines and checked by a dedicated lung radiation oncologist [10].

Prescription dose (24×2.75 Gy) was calculated using the collapsed cone algorithm. Dose was prescribed such that 95% of the prescribed dose covered 90% of the PTV and 90% of the prescribed dose covered 99% of the PTV. Two percent of the PTV was allowed to receive >107% of the prescribed dose according to ICRU 83 [11]. The following constraints were used for the organs at risk (physical dose): D_{max} spinal cord ≤ 50 Gy, mean lung dose (MLD) ≤ 20 Gy, D_{max} brachial plexus ≤ 66 Gy. A constraint for the esophagus was introduced at our center after the majority of the cohort had completed treatment: 66 Gy was allowed in the esophagus +0.5 cm (D_{max} esophagus +0.5 cm ≤ 66 Gy). Despite the lack of a universal constraint for the esophagus, we implemented this parameter as it is predictive for late esophageal toxicity in patients treated with concurrent mildly hypofractionated radiotherapy and daily cisplatin [12]. No dose constraint for the heart was applied. Patients were treated with three-dimensional conformal radiotherapy (3DCRT) and from 2014 onwards with intensity modulated radiotherapy (IMRT). Electronic portal imaging was used in 27 patients. From 2016 onwards daily cone-beam CT-scans were used (n = 14).

The Dose Volume Histogram of the esophagus and esophagus +0.5 cm was exported and various dosimetric parameters (previously predictive for esophagitis after mildly hypofractionated radiotherapy) were derived: D_{max}, $D_{0.1\%}$[7], V_{66}[12], V_{35} [7,14], V_{50}[13], and length of the esophagus receiving 66 Gy[15]. The D_{mean} was also derived (esophagus constraint in the RTOG 0617 trial: D_{mean} <34 Gy)[2].

Toxicity was retrospectively reviewed from digital medical records. Follow-up was generally performed at 3, 6, 9, and 12 months after radiotherapy, every four months the 2nd year after radiotherapy and every six months thereafter. The Common Terminology Criteria for Adverse Events (version 4.03) was used to score toxicity. Toxicity was acute if it occurred within 90 days after the start of radiotherapy, and late if it occurred thereafter.

Statistical analysis

Descriptive statistics described patient and treatment characteristics. Overall survival was calculated from the first day of radiotherapy treatment until the date of death, or the date of the last hospital visit (last visit determined on 21–10-2021). Median follow-up was estimated using the reversed Kaplan-Meier method. Analyses were performed using SPSS version 26 (IBM SPSS for Windows, Armonk, NY).

Results

Between 2012 and 2017, 60 NSCLC patients were selected for concurrent chemoradiation. Forty-one patients were included in this analysis (Table 1). Nineteen patients were excluded for the following reasons: surgery after chemoradiation in patients with single N2 nodal disease (n = 9), stage IV oligometastatic NSCLC (n = 6), palliative radiotherapy after a cerebrovascular incident following the first chemotherapy (n = 1), and radiotherapy monotherapy due to either acute renal insufficiency after one cycle of chemotherapy (n = 2), or an allergic reaction to chemotherapy (n = 1). Two patients were treated for a prior malignancy: one patient had a lobectomy in 2009 for an adenocarcinoma in the right upper lobe (pT1aN0M0) and the other patient had breast cancer in 2016 treated with breast conserving therapy. There was no overlap with current radiation fields in this patient, as the breast cancer was located contralateral to the involved lung. All but one patient had a PET-scan (98%). This patient had an anxiety disorder and had a bone scintigraphy instead. A brain MRI-scan was made in all but three patients (93%). One of these patients had a CT-scan of the brain with contrast.

The majority of patients received chemoradiation per protocol. All patients received at least 3 cycles of chemotherapy, on time (80%) and with the intended dose (73%). Reasons for delay of chemotherapy were neutropenia (n = 1), leucopenia (n = 1), granulocytopenia (n = 1), inadequate blood count not further specified (n = 1) and unknown (n = 2). Reasons for dose reduction were trombopenia (n = 2), neutropenia (n = 1), and leucopenia (n = 1).

All patients completed radiotherapy per protocol (66 Gy in 24 daily fractions). Radiotherapy treatment planning characteristics are listed in Table 2. Ten patients had a short radiotherapy interruption (1 day n = 7 or 2 days n = 3). All treatment plans met the criteria for tumor coverage. In one patient, 8% of the PTV received >107% of the prescribed dose. Eight patients had a MLD >20 Gy (20.6–23.6 Gy). The treating physician accepted a violation of the MLD constraint based on the pulmonary condition of the patient. In one patient, the spinal cord constraint was exceeded (D_{max} = 55 Gy, volume receiving >50 Gy = 0.38 cc/1.1%) as was the MLD (23.6 Gy rather than ≤ 20 Gy).

Table 1
Patient, tumor and treatment characteristics.

No. of patients = 41	
Mean age (range)	57 (37–70)
Male/Female ratio	24/17
%	58%/42%
COPD GOLD	
0	34 (83%)
1	4 (10%)
2	1 (2%)
3	2 (5%)
Mean FEV1 (%) (range)	80% (45–113)
Mena DLCO (%) (range)	74% (50–105)
Smoking status	
Current smoker	13 (32%)
Never	5 (12%)
Former smoker*	22 (54%)
Unknown	1 (2%)
Weight loss	
None	30 (73%)
1–5%	4 (10%)
6–10%	2 (5%)
>10%	5 (12%)
Mean BMI at baseline (range)	25 (17–37)
T stage	
T0	1 (2%)
T1	10 (25%)
T2	13 (32%)
T3	5 (12%)
T4	12 (29%)
N stage	
N0	1 (2%)
N1	0
N2	26 (64%)
N3	14 (34%)
Number of Involved lymph nodes stations*	
0	1 (2%)
1–3	22 (54%)
4–7	18 (44%)
Naruke 7 included (No., %)	23 (58%)
TNM stage	13
IIIA	(32%)28
IIIB	(68%)
Histology	
Squamous cell carcinoma	16 (39%)
Adenocarcinoma	18 (44%)
Other	7 (17%)
GTV tumor mean (range)	65 (2–239)
Median [IQR]	44 [9 – 97]
GTV lymph nodes mean (range)	70 (10–341)
Median [IQR]	59 [19 – 82]
GTV total mean (range)	120 (15–367)
Median [IQR]	104 [68–163]
PTV total mean (range)	450 (128–943)
Median [IQR]	406 [336 – 509]
Technique	
3D-CRT	17%
IMRT	83%

* Stopped smoking prior to treatment.

The D_{max} Esophagus +0.5 cm was exceeded in 90% of patients (>66 Gy in 35/39 patients). The D_{max} Esophagus +0.5 cm was on average 2.5 Gy above the 66 Gy limit (range: 0–6.4 Gy above the limit) and the median percentage of the esophagus volume receiving >66 Gy (V_{66Gy}) was 4.9% (range 0–39.5%). The V_{35} <65% (predictive for esophagitis after 3D-conformal radiotherapy [14]) was met in 90% (37/41) of our cohort and the $D_{mean\ EQD2}$ <34 Gy (esophagus constraint in the RTOG 0617 trial) was met in 73% of patients (30/41). The length of the esophagus in the radiation field <12 cm (constraint in the EORTC 08972 trial [15] and the SOCCAR trial [16]) was exceeded in 39% of our cohort (Table 2).

The median follow-up was 4.7 years (75th percentile 4.4 years). The median overall survival was 19 months [IQR 10.8–45.6] (66% at one year and 37% at two years). Locoregional control and overall survival are given in supplementary Table A.

Table 2
Radiotherapy treatment planning characteristics. All dose parameters are physical doses unless otherwise mentioned.

	Median	Mean (Range)
Time between planning CT-scan and start treatment [days]		14.9 (3.0–28.0)
PTV coverage with 95% of the prescribed dose [%]		96 (93.8–98.9)
PTV coverage with 90% of the prescribed dose [%]		99.7 (98.5–100)
PTV Dose [Gy]		69.0
$D_{1\%}$		(64.2–71.7)60.8
$D_{99\%}$		(55.7–62.5)65.9
D_{mean}		(61.3–67.4)
D_{max} spinal cord [Gy]		34.5 (4.5–55.0)
Mean lung dose (MLD) [Gy]		17.0 (10.5–23.6)
D_{max} esophagus +0.5 cm [Gy]	68.5	68.1 (63.3–72.4)
D_{max} esophagus [Gy]	67.7	66.2
		(42.2–70.3)
$D_{0.1\%}$ esophagus +0.5 cm [Gy]	68.0	67.8 (63.0–72.1)
$D_{0.1\%}$ esophagus [Gy]	67.3	66.9
		(55.5–70.5)
V_{66Gy} esophagus +0.5 cm [%]	4.9	7.8 (0–39.5)7.8
V_{66Gy} esophagus [%]	3.4	(0–42.7)
V_{35Gy} esophagus +0.5 cm [%]	42.0	41.0 (13.5–66.8)
V_{35Gy} esophagus [%]	41.437	40.9
V_{35Gy} esophagus <65%	patients	(1.6–72.7)
	(90%)	
V_{50Gy} esophagus +0.5 cm [%]	34.5	31.6 (4.2–61.4)
V_{50Gy} esophagus [%]	34.2	31.1
		(0–66.6)
D_{mean} esophagus +0.5[Gy]	28.2	28.3 (13.0–45.2)
D_{mean} esophagus [Gy]	28.526	28.6 (8.0–48.5)
D_{mean} <34 Gy	patients	
$D_{mean\ EQD2}$ <34 Gy	(63%)30	27.1
Mean esophageal dose [Gy]	patients	(6.9–48.5)
(EQD2 with an a/b = 10)	(73%)	
	26.5	
Overlap PTV and esophagus >12 cm	16 patients	
	(39%)	

Grade 3 or higher toxicity occurred in 21 patients (51.2%) of whom the majority had esophageal toxicity (n = 16, 39%) (Fig. 1). Grade 3 non-esophageal toxicity included hospitalization during or within 3 months of chemoradiation due to: neutropenic fever (n = 5), vomiting and diarrhea (n = 1), radiation pneumonitis (n = 1), and suspected acute coronary syndrome for which heart catheterization was performed (n = 1, no stenosis was seen). Possible cardiovascular toxicity occurred in 3 patients including: myocardial infarction 3 months after chemoradiation requiring stents, replacement of a leaking heart valve 23 months after chemoradiation in a patient with pre-existent heart valve leakage, and a cerebrovascular event 4 years after chemoradiation.

Grade 5 esophagus toxicity occurred in five patients. Four patients died due to an esophageal fistula/perforation and one patient died due to hemorrhage. All five patients had bulky centrally located tumors (5–8 cm; range 253 cm^3 – 749 cm^3) (supplementary Fig. 1/supplementary Table B).

Grade 3 esophageal toxicity was acute in 14 patients (34.1%) and late in 5 patients (12.2%). Five of the 14 patients (36%) with acute grade 3 toxicity developed late esophageal toxicity including 3 deaths. Comparison of patients with and without serious esophageal toxicity and naruke 7 involvement is provided (supplementary Table C).

Discussion

The combination of three-weekly platinum doublet chemotherapy and mildly hypofractionated radiotherapy (24×2.75 Gy) resulted in excessive esophageal toxicity in our patients: 12% grade 5 toxicity, 34% acute and 12% late grade 3 toxicity. This excessive toxicity may result from: a higher radiation dose to a large volume of the esophagus in our cohort (Table 3), the combination of full dose platinum doublet

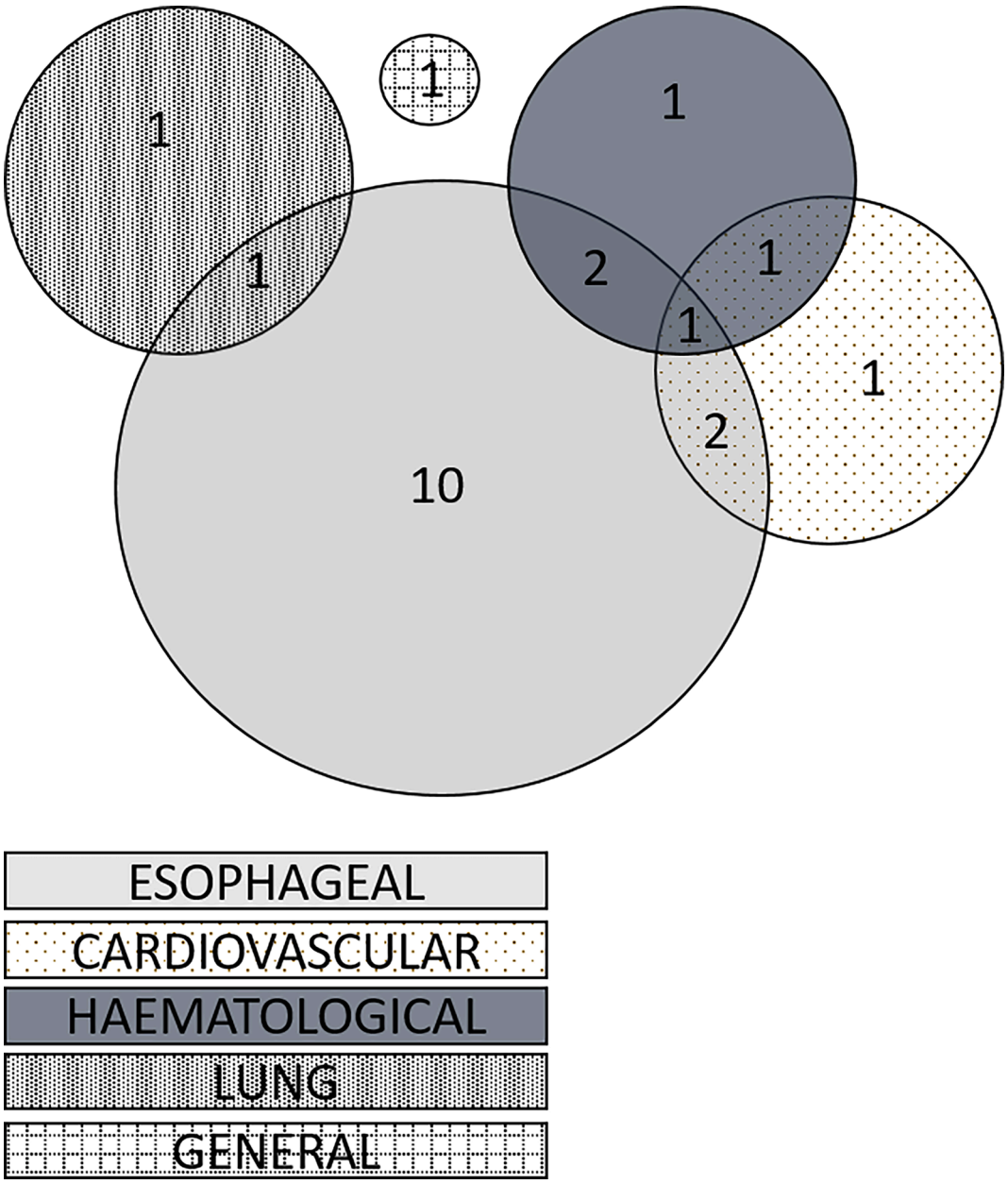

Fig. 1. Grade 3 or higher toxicity.

chemotherapy, biologically high dose mildly hypofractionated radiotherapy (Table 4), and less stringent patient selection and constraints than in clinical trials. Esophageal toxicity in our cohort was almost twice that reported in Auperin's *meta*-analysis of concurrent chemoradiation [1]. Toxicity was also twice that reported by the EORTC 08,972 trial in which the same radiotherapy regimen was combined with daily cisplatin (34% versus 14%) [4]. Patient selection probably influenced toxicity. Patients generally had multiple involved lymph nodes leading to large radiation fields. The patients who died all had bulky disease at Naruke 7, or abutting the bronchus and esophagus (supplementary Fig. 1/Table C). Two of the five patients who died, had tumor growth into the esophagus and bronchus at the time of death (shown by autopsy (n = 1) or gastroscopy (n = 1). These patients may have developed a fistula even in the absence of treatment. A third patient died 6.5 months after re-irradiation for a recurrence (supplementary fig. 2). This death may have been prevented if the patient was not re-irradiated. The remaining two patients had dilatation of an esophagus stricture or biopsy in the irradiated part of the esophagus. As one of the patients died shortly after esophageal dilatation, we are cautious to dilate esophageal strictures after chemoradiation.

Besides grade 5 toxicity, another concern is the high incidence of grade 3 esophageal toxicity (Table 4). Acute esophageal toxicity was almost twice that reported in Auperin's concurrent chemoradiation *meta*-analysis (34% versus 18%) [1]. This may lead to less treatment completion [17], increased late toxicity [12] and delay treatment with adjuvant immunotherapy. Late esophageal toxicity was 12% in our cohort as opposed to <1% in the RTOG 0617 trial, 6% after concurrent hypofractionated chemoradiation with low dose cisplatin [12] and none after individualized isotoxic accelerated concurrent chemoradiation [3]. As persistent esophageal toxicity (grade $\geq$ 2 toxicity in the 42 days after the last radiation dose) is an exclusion criteria for immunotherapy in the PACIF trial [18], these patients cannot start adjuvant immunotherapy. They will potentially miss out on the survival benefit (median 47.5 versus 29 months) [19]. In the era of immunotherapy, toxicity prevention is even more important during concurrent chemotherapy [20].

Similar rates of late toxicity (10%) were reported by the randomized

Table 3
Esophagus dose parameters our cohort compared to literature data.

Esophagus parameters	Our Cohort	PET-boost trial* [7]
	Median (IQR)	Median (IQR)
V_{66Gy} esophagus +0.5 cm [%]** V_{66Gy} esophagus [%]**	4.9 [0.7 – 10.4] 3.4 [0.07 – 10.6]	Dmax below 66 Gy. Thus V66 = 0 [Protocol PET Boost trial version 4 2014]
$D_{0.1\%}$ esophagus	67.3 [66.4 – 68.5]	65.7 [63.9–70.3]
V_{35Gy} esophagus [%]	41.4 [28.0 – 54.0]	34.7 [25.2 – 46.7] (EQD2 with an a/b = 10)
Mean esophageal dose [Gy](EQD2 with an a/b = 10)	26.5 [19.1–34.7]	23.2 [18.4–30.5]
Predictive parameters for Esophagitis		
	Our Cohort	EORTC 08972 [15]	SOCCAR[16,21–23]
Radiation schedule	24×2.75 Gy	24×2.75 Gy	20×2.75 Gy
Chemotherapy schedule	Platinum doublet chemotherapy	Daily low dose cisplatin	Platinum doublet chemotherapy
Overlap PTV and esophagus >12 cm	16/41 patients (39%)		None (all <12 cm)
Length of field <7 cm	7 (17%)	–	–
7–10 cm	8 (20%)	19 (48%)	–
>10–14 cm	16 (39%)	17 (43%)	–
>14–20 cm	10 (24%)	4 (10%)	–
Mean length of the esophagus in the PTV (cm)	11 (1.2–17.1)	–	–

* Mediastinal lymph nodes treated with 24x2.75 Gy, primary tumor boosted to at least 24x3Gy. Concurrent with chemotherapy (platinum doublet or daily low dose cisplatin).

** V76.6 most predictive of late toxicity. It corresponds to a physical dose of 66 Gy in 24 fractions (V66)[12].

phase II PET boost trial, in which the primary tumor was boosted and mediastinal lymph nodes were treated with the same radiotherapy schedule as in our cohort (24x2.75 Gy) [7,8]. This trial reported high local tumor control after hypofractionated radiotherapy and individualized isotoxic dose escalation to the entire tumor or to tumor regions having high pre-treatment FDG uptake (89% local tumor control at 2 years) [8]. Fatal pulmonary bleeding or esophageal fistula were observed in 10% of patients treated with concurrent chemoradiation (8 of 77 patients). Four patients died of fatal bleeding, and 4 patients died due to an esophageal fistula. One of the stopping criteria of the trial (no >10% grade ≥ 4 pulmonary toxicity) was almost exceeded when considering patients treated with concurrent chemoradiation only. Compared to our cohort, acute esophageal toxicity was surprisingly low in the PET boost trial (14% versus 34%), while the PTV tumor dose was higher (78 Gy and 84 Gy versus 66 Gy). Plausible explanations are that the PET-boost trial had: less platinum doublet chemotherapy (56% platinum doublet chemotherapy versus 100% in our cohort), less nodal disease (N3: 14% versus 34% in our cohort, N0: 12% versus 2%), smaller median lymph node GTV (18 cc versus 59 cc in our cohort), more VMAT radiotherapy planning (40% versus none in our cohort), and lower esophageal radiation doses: (median $D_{0.1\%}$ 1.6 Gy lower, D_{mean} 3.3 Gy lower, V_{35} 6% lower, and the V_{66} 5% lower) (Table 3).

The majority of experience with concurrent mildly hypofractionated chemoradiation is with the phase III EORTC-08972 schedule (24×2.75 Gy within 32 days and daily 6 mg/m^{2,}) [4–6,12,13], the SOCCAR schedule: 20×2.75 Gy in four weeks with cisplatin/vinorelbine [16,21–23] and the Polish trial regimen: 21×2.8 Gy in four weeks with cisplatin/vinorelbine [24]. All report excellent median overall survival with FDG-PET staging and modern radiotherapy techniques (supplementary Table A). The favorable outcome and low toxicity profile of the EORTC-08972 schedule has been established in both randomized [4,5], prospective [13] and retrospective studies [6,12]. Evidence for concurrent chemoradiation using the SOCCAR schedule is based on a randomized trial including 70 patients (prior to modern staging and radiotherapy) [16] and retrospective studies including 30, 100 and 163 patients, some of which used FDG-PET staging and image guided radiotherapy techniques [21–23]. Prospective data on toxicity are limited for the SOCCAR schedule [16]. The retrospective data have reported some ongoing esophagitis (n = 2/30), and one patient with a trachea-esophageal fistula [21]. The SOCCAR schedule is deemed tolerable. In contrast to our cohort, the presecribed dose was lower ($BED_{a/b=10}$ = 70.1 Gy versus 84.2 Gy). In addition to this, the length of the esophagus receiving the prescribed dose was limited to 12 cm. These patients presumably had limited nodal disease. The Polish trial raised concern on the rate of (probable) toxic deaths (7.6%) and the longer duration of severe esophageal toxicity (30 versus 7 days). Persistent severe esophageal toxicity after 3 months was also high in our cohort (36%, 5/14 patients with severe acute esophagitis) and in the EORTC-08972 regimen (52%) [25]. A publication of the EORTC-08972 regimen showed that maximum grade of acute esophageal toxicity and recovery rate of acute esophageal toxicity are significantly associated with late esophageal toxicity [12]. The COVID pandemic has increased the interest in hypofractionated irradiation and platinum doublet chemotherapy, as short schedules put less strain on medical resources and may reduce the risk of acquiring COVID during hospital visits [26]. It is however crucial to select patients based on the risks of esophageal toxicity (limited nodal disease).

Since the publication of the EORTC-08972 trial, esophageal toxicity has been reduced (12.9% to 3.6%) by lowering the dose to the mediastinum with a simultaneous integrated boost technique: 58.08 Gy to the involved mediastinal lymfnodes and 66 Gy to the tumor in 24 fractions with daily cisplatin 6 mg/m^2 [27]. A lower mediastinum dose was safe, as isolated regional recurrences were rare [28]. As such, a lower mediastinal dose can be prescribed safely to reduce esophageal toxicity without compromising outcome. Lin et al. published data supporting dose reduction to the mediastinum in patients treated with concurrent hypofractionated radiotherapy: severe esophagitis was more frequent in patients who received >2.7 Gy per fraction to the esophagus than those receiving less (80% versus 0%) [29]. They observed no severe esophageal toxicity if the dose per fraction was ≤ 2.4 Gy [17,29]. In addition to the radiotherapy schedule, the incidence of severe esophagitis is determined by the toxicity profile of the chemotherapy regimen. Severe esophagitis is more common after concurrent chemoradiation with cisplatin/etoposide than for instance carboplatin/paclitaxel (20% versus 6%) [30]. A concern of mono-chemotherapy is a potential higher risk of metastases. This concern appears to be ungrounded in case of brain metastases, as Hendriks et al. found no difference in brain metastases in two large cohorts treated with either concurrent chemoradiation using doublet chemotherapy, or mildly hypofractionated radiotherapy and low dose cisplatin [31].

Based on the unforeseen increased toxicity in our cohort, we stopped treating patients with doublet chemotherapy and mildly hypofractionated radiotherapy. Patients are treated either with platinum doublet chemotherapy and 30x2Gy or with mildly hypofractionated radiotherapy (66 Gy primary tumor/58.08 Gy lymph nodes in 24 fractions) and daily low dose cisplatin. In our experience, the latter schedule allows for treatment of frail elderly patients.

Conclusion

Mildly hypofractionated radiotherapy (24x2.75 Gy) in combination with platinum doublet chemotherapy was too toxic in our patients with inoperable mostly stage IIIB NSCLC. A median $D_{0.1\%}$ of 68 Gy (71.7 Gy EQD2 a/b = 10) to the esophagus was not tolerated. Esophageal tolerance is important to consider in future trials, and the volume of involved

Table 4
Maximal esophagus toxicity and any grade 5 toxicity: cohort results compared with literature. CCRT = concurrent chemo radiation; NR not reported.

	Our cohort	PET boost [7] (homogeneous arm)	EORTC-08972 regimen [12,13]	SOCCAR regimen[16]	Polish AHRT Trial [24]	RTOG 0617 [2]	INDAR [3]
Radiotherapy regimen		24x2.75 Gy mediastinal nodes	24x2.75 Gy	20x2.75 Gy	21x2.8 Gy	30x2Gy* Versus 37×2Gy	45 Gy/30 fractions BID followed by isotoxic dose escalation.
Chemotherapy regimen		CCRT arm: Cisplatin/ Etoposide OR Cisplatin/ Pemetrexed OR daily Cisplatin	daily Cisplatin	Cisplatin/ Vinorelbine	Cisplatin/ Vinorelbine	Cisplatin/ Etoposide	Cisplatin/Vinorelbine OR Cisplatin/Etoposide OR Carboplatin/Etoposide
BED ($\alpha/\beta = 10$)#	73	73	73	76	81	38 versus 23	77
BED ($\alpha/\beta = 3$)#	115	115	115	111	119	66 versus 58	93
Esophagus constraint used	$D_{2\%}$ Oes + 5 mm ≤ 66 Gy	<66 Gy in 24 fractions $V_{36Gy} < 80\%$	$V_{35Gy} < 65\%$ [13]	Esophagus ≤ 12 cm the PTV [16]	$D_{mean} < 34$ Gy¥	$D_{mean} < 34$ Gy	$V_{35Gy} < 65\%$ $D_{max} < 74$ Gy
Acute Gr 3 Dysphagia/ esophagitis	34.1%	14.3%	22%[13]	Acute/Late grade 3. Max grade 4	14% (first 6 months)	10% versus 25%	22%
Late Gr 3 esophagitis/ dysphagia	12.2%	13.0%	6%[12]	9-15% [16,22]**,$	0	<1% versus 1%	0
Max Grade 4 esophagitis/ dysphagia	0	2.6%			NR	0% in both arms	0
Grade 5	5/41 (12.2%)	8/77 (10%)		2.9%[16]	2/92 (2.2%) 5/92 (5.4%) probably treatment related deaths	3/131 (2%) Versus 9/107 (8%)	0

* Patients treated in the radiotherapy only arm (not with Cetuximab).
\# BED = $E/\alpha = nd(1 + d/(\alpha/\beta)) - (\ln 2)(T - Tk)/\alpha Tp$ (Fowler JF. Biological factors influencing optimum fractionation in radiation therapy. Acta Oncol. 2001;40:712–7. https://doi.org/10.1080/02841860152619124).
** No differentiation between acute and late esophageal toxicity.
$ Dose constraint used in the phase II trial. Constraint not mentioned in report by Iqbal et al.[22].
¥ Not mentioned whether this is a physical dose of 34 Gy of a EQD2 corrected dose.

mediastinal disease, should be reported.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2022.07.002.

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