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Original Article

Hypofractionated Concomitant Chemoradiation in Inoperable Locally Advanced Non-small Cell Lung Cancer: A Report on 100 Patients and a Systematic Review☆

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Abstract

Aims: Concomitant chemoradiation is the standard of care in patients with inoperable non-small cell lung cancer. The purpose of this study was to analyse the survival outcome and toxicity data of using hypofractionated chemoradiation.
Materials and methods: One hundred patients were treated from June 2011 to November 2016. Treatment consisted of 55 Gy in 20 daily fractions concurrently with split-dose cisplatin vinorelbine chemotherapy over 4 weeks followed by two cycles of cisplatin vinorelbine only. Survival was estimated using Kaplan–Meier and Cox regression was carried out for known prognostic factors. A systematic search of literature was conducted using Medline, Embase and Cochrane databases and relevant references included.
Results: In total, 97% of patients completed radiotherapy and 73% of patients completed all four cycles of chemotherapy. One patient died of a cardiac event during consolidative chemotherapy. There were two cases of grade 4 toxicities (one sepsis, one renal impairment). Grade 3 toxicities included nausea/vomiting (17%), oesophagitis (15%), infection with neutropenia (12%) and pneumonitis (4%). Clinical benefit was seen in 86%. Two-year progression-free survival and overall survival rates were 49% and 58%, respectively. The median progression-free survival and overall survival were 23.4 and 43.4 months, respectively. The only significant prognostic factor was the number of chemotherapy cycles received ($P = 0.02$). The systematic review identified 13 relevant studies; a variety of regimens were assessed with variable reporting of outcomes and toxicity but with overall an improvement in survival over time.
Conclusion: Our experience compared with the original phase II trial showed improved treatment completion rates and survival with acceptable morbidity. With appropriate patient selection this regimen is an effective treatment option for locally advanced non-small cell lung cancer. This study helps to benchmark efficacy and toxicity rates while considering the addition of new agents to hypofractionated concurrent chemoradiotherapy. The agreement of a standard regimen for assessment in future trials would be beneficial.

Key words: Chemoradiation; hypofractionated; non-small cell lung cancer

Introduction

Lung cancer is the most commonly diagnosed cancer and remains the leading cause of cancer-related deaths worldwide, with 1.6 million deaths per year [1]. Non-small cell lung cancer (NSCLC) represents more than 80% of lung cancers and about one-third of these present with non-metastatic locally advanced disease [2]. Bimodal combination treatment of radiotherapy and chemotherapy is the standard of care for patients with inoperable non-metastatic locally advanced disease and with good performance status [2,3]. A meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced NSCLC showed superior results of concomitant therapy, with an

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absolute survival benefit of 5.7% at 3 years and 4.5% at 5 years [2].

Hypofractionated radiotherapy has been shown to have similar outcomes to conventional fractionation in prostate cancer and breast cancer, with shorter treatment times and fewer patient visits. It has not been directly compared with conventional fractionation when used for treatment with concurrent chemotherapy in inoperable stage III NSCLC. In the UK, the hypofractionated regimen of 55 Gy in 20 daily fractions over 4 weeks is one of the most commonly used [4]. SOCCAR, a randomised phase II trial comparing sequential versus concurrent chemotherapy and radical hypofractionated radiotherapy (55 Gy in 20 daily fractions) in patients with inoperable stage III NSCLC and good performance status, showed an improvement in 2-year overall survival rate (50% with concomitant therapy versus 46% with sequential therapy) [5].

The purpose of the current study was to evaluate the tolerability and outcome of the SOCCAR regimen using modern staging and radiotherapy techniques in a real-world setting from a single institute. In order to set this in context we reviewed the present evidence of concurrent chemoradiation using hypofractionated radiotherapy regimens to treat NSCLC.

Materials and Methods

Patient Population

Between 1 June 2011 and 30 November 2016, 103 patients received the SOCCAR regimen treatment. Two patients with a recurrent disease and one with oligometastatic disease at presentation were excluded. The data were collected retrospectively on 100 patients. All patients had a histological confirmation of NSCLC, were fully staged using computed tomography head, chest, abdomen and positron emission tomography-computed tomography (PET-CT), were World Health Organization (WHO) performance status 0/1, had a reasonable respiratory reserve, i.e. a forced expiratory volume in 1 s $\geq$ 40% predicted with an absolute value $\geq$ 1 l/s and a transfer factor $\geq$40% predicted and adequate renal function (EDTA glomerular filtration rate $\geq$ 60 ml/min).

Radiotherapy

All patients received 55 Gy in 20 daily fractions of 2.75 Gy per fraction over 4 weeks. The patients underwent a planning computed tomography scan using 3–5 mm thick slices. A gross tumour volume was drawn on each slice and a 5 mm circumferential margin was then applied to grow a clinical target volume. From clinical target volume to planning target volume the following margins were used: 10 mm margins in axial and 15 mm margins in superior–inferior directions. Elective nodal irradiation was not used. Until December 2015, treatment was delivered using three-dimensional conformal radiotherapy (n = 73); after this date, the volumetric arc therapy technique was used (n = 27). A beam energy of 6 MV photons was used.

Chemotherapy

Chemotherapy was started on day 1 of radiotherapy. Cisplatin 20 mg/m^2 was given intravenously with fractions 1–4 and 16–19. Vinorelbine 15 mg/m^2 was given intravenously on the day of fractions 1, 6, 15 and 20. Chemotherapy was given as an inpatient during the first and last weeks of chemoradiotherapy. Four weeks after completion of the concomitant phase, two more cycles of cisplatin (80 mg/m^2 day 1) and vinorelbine (25 mg/m^2 days 1 and 8) were given as an outpatient 3 weeks apart.

Clinical Assessments

All patients were monitored weekly during radiotherapy and before each cycle of subsequent chemotherapy. A computed tomography scan was carried out 4–6 weeks after the completion of treatment. Patients were then regularly followed up at 3-month intervals with a chest X-ray. Further investigations including computed tomography and PET-CT $\pm$ biopsy were carried out if there was any suspicion of progression on clinical or radiological grounds.

Literature Search Strategy

A systematic literature search was carried out using the following keywords; 'non-small cell lung cancer', 'NSCLC', 'hypofractionated', 'hypofractionation', 'concurrent', 'concomitant', 'chemoradiotherapy' and 'chemoradiation' (date of search 6 February 2018). The literature search was restricted to studies published from 1990 to 2017. Two authors (MSI/AG) collected the literature data, assessed the quality and its applicability to the patient population of interest.

Results

The median age of patients treated was 63 years (range 43–75) and all patients had a WHO performance status of 0/1 (53% 0, 47% 1). Stage IIIA disease was the most common (63%), followed by stage IIIB (32%). Adenocarcinoma was the most common histology (43%), followed by squamous cell carcinoma (41%). The patient demographics and their disease characteristics are summarised in Table 1.

Ninety-seven per cent of patients completed radiotherapy, similar to the 95% rate in SOCCAR. Three patients could not complete all 20 fractions of planned radiotherapy. One patient became ill with renal failure after the first cycle of chemoradiotherapy, in the second patient, it was stopped due to patient wishes (he also developed grade 3 oesophagitis) and in the third patient, the disease progressed during chemoradiotherapy. Seventy-three per cent of patients completed all four cycles of chemotherapy (as compared with only 9% in the concurrent cohort of SOCCAR). Eighty-six per cent of patients completed at least

Table 1
Patients demographics and their disease characteristics

Characteristic	*n*	%
Number of patients	100	–
Age: median (range)	63 (43–75)	–
Gender		
Male	56	56
Female	44	44
PET available for staging	99	99
WHO performance status		
0	53	53
1	47	47
Stage (TNM 7th Edition)		
IIA	2	2
IIB	3	3
IIIA	63	63
IIIB	32	32
Histology		
Adenocarcinoma	43	43
Squamous cell carcinoma*	41	41
Large cell carcinoma	1	1
Adenosquamous	2	2
NSCLC NOS	13	13

PET, positron emission tomography; WHO, World Health Organization; NSCLC NOS, Non-small cell lung cancer-not otherwise specified.

* One patient had a mixed histology of squamous and small cell carcinoma.

three cycles of chemotherapy, i.e. a cumulative cisplatin dose of 240 mg/m^2 (compared with 88% in the SOCCAR trial). In eight patients, cisplatin was replaced with carboplatin due to toxicities (after the concomitant phase).

With a median follow-up of 27 months, a total of 43 patients had died. Response was available in 96 patients: complete response 5%, partial response 77%, stable disease 4% and progressive disease 13% (one patient with histologically proven progressive disease had salvage surgery). Of 83 patients with a response, the disease had relapsed in 33 patients (40%) (Table 2). One-year progression-free survival (PFS) and overall survival were 69% and 81%, respectively, with 2-year PFS and overall survival 49% and 58%, respectively. The median PFS was 23.4 months and the median overall survival was 43.4 months (Figures 1 and 2). This exceeds the results from SOCCAR, where 2-year PFS and overall survival were 34% and 50%, respectively, and the median PFS and overall survival were 12.9 months and 24.3 months, respectively [5].

Table 2
Response to treatment

	Number	%
Response (available in 96 patients)		(out of 96)
Complete response	5	5
Partial response	74	77
Stable disease	4	4
Progressive disease	13	14
Relapse (out of 83 patients with response)		(out of 83)
No	55	60
Yes	33	40
Pattern of relapse (out of 33)		(out of 33)
Locoregional only	10	30
Distant ± local	23	70
Survival (out of total 100)		
Alive	56	56
Dead	43	43
Lost to follow-up	1	1

There was no significant impact of gender or age (assessed as either a continuous variable or >65 years) on survival. Performance status (0 versus 1, $P = 0.17$), histology (squamous cell versus adenocarcinoma and not otherwise specified (NOS), $P = 0.08$) or stage (II, IIIA and IIIB) did not influence survival ($P = 0.77$). The only significant prognostic factor was the number of chemotherapy cycles received (cycles 0–4 as a continuous variable, $P = 0.02$). There was one death on treatment after the third cycle of chemotherapy due to a cardiac event. The patient did not have any previous cardiac history. The incidence of grade 3/4 oesophagitis was 14% and radiation pneumonitis was 4%. Other

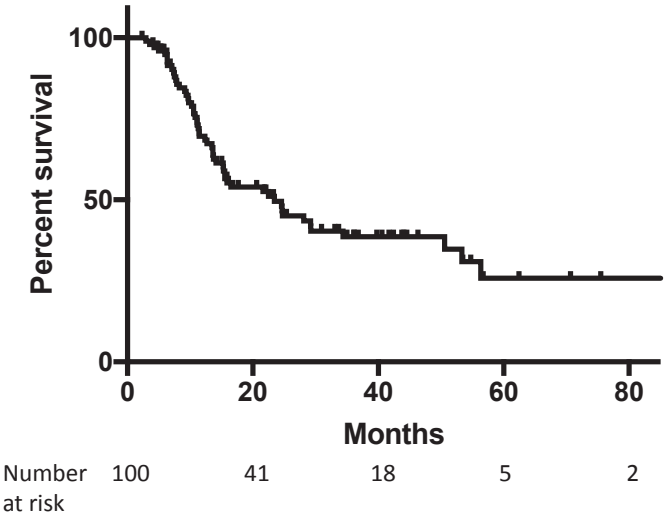

Fig 1. Kaplan–Meier estimation of progression-free survival.

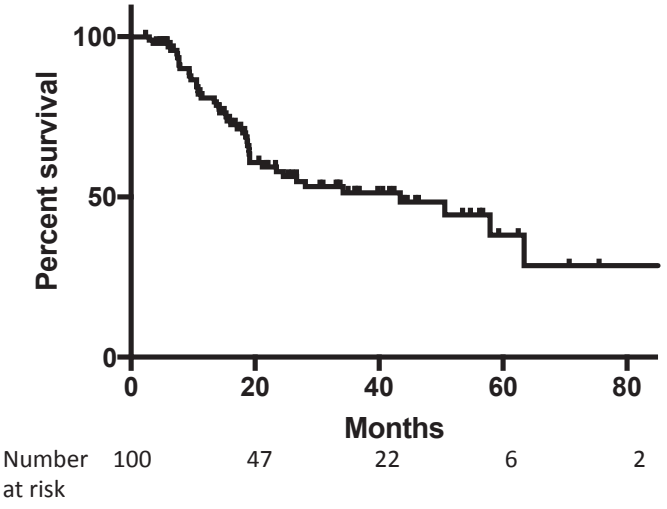

Fig 2. Kaplan–Meier estimation of overall survival.

frequent grade 3/4 toxicities were nausea/vomiting (17%) and infection with neutropenia (12%) (Table 3).

Results of the Literature Search

A flow diagram of the search and inclusion and exclusion criteria is shown in Figure 3. We found 13 studies that were applicable; five feasibility or phase I trials, four phase II trials and four retrospective case series. These have assessed a variety of chemotherapy regimens in conjunction with different radiotherapy schedules (see Table 4). The range of radiotherapy doses ranged from 48 to 75 Gy with a fraction size between 2 and 3 Gy with 2.75 Gy being the most commonly used, as in this study. Most studies used platinum, either as a single agent or in conjunction with a vinca alkaloid/taxane, with only one study looking at docetaxel as a single agent. Only one study looked at a targeted therapy (cetuximab).

Table 3
Treatment delivery and toxicity

Characteristic	*n*	%
Radiotherapy completed		
Yes	97	97
No*	3	3
Chemotherapy cycles completed†		
4	73	73
3	13	13
2	11	11
1	5	5
Toxicities (grades 3–5 only)		
Grade 5 cardiac arrest	1	1
Grade 4 acute kidney injury	1	1
Grade 4 sepsis	1	1
Grade 3 oesophagitis	15	15
Grade 3 pneumonitis	4	4
Grade 3 nausea/vomiting	17	17
Grade 3 neutropenia/sepsis	12	12
Grade 3 acute kidney injury	7	7
Grade 3 anaemia	5	5
Grade 3 diarrhoea	4	4
Grade 3 fatigue/tiredness	4	4
Grade 3 pyrexia (not neutropenic)	3	3
Grade 3 extravasation	2	2
Grade 3 rectal bleed	1	1
Grade 3 atrial fibrillation (required pacemaker)	1	1
Grade 3 urinary sepsis	1	1
Grade 3 epigastric pain	1	1

† Split course of cisplatin and vinorelbine given concomitantly with radiotherapy was considered as two cycles.

Although some studies were very rigorous in reporting both acute and late toxicities, including deaths after treatment (which could have been related to cancer progression or toxicity from the chemoradiotherapy), it was unclear from other studies exactly what the oesophageal and pulmonary toxicity rates were. In general, the number of patients treated was small. The outcomes in our retrospective series were significantly better than previously reported. However, some of this may have been due to improved selection and treatment delivery in recent times. Overall median survival significantly improved over time ($P < 0.05$; Figure 4).

The largest randomised trial by Belderbos *et al.* [9] compared sequential chemotherapy (two cycles of cisplatin/gemcitabine) against concurrent low-dose cisplatin daily ($n = 80$) with 66 Gy in 24 fractions (2.75 Gy per fraction). Unfortunately, the trial was closed prematurely due to poor accrual. The outcomes in both arms were similar but with different toxicity profiles (a higher incidence of oesophagitis in the concurrent arm and haematological toxicities in the sequential arm). The SOCCAR trial [5] was a randomised phase II study that compared sequential versus concurrent chemotherapy when given with hypofractionated radiotherapy 55 Gy in 20 fractions (2.75 Gy per fraction) together with a split-dose of cisplatin/vinorelbine followed by two cycles of the same

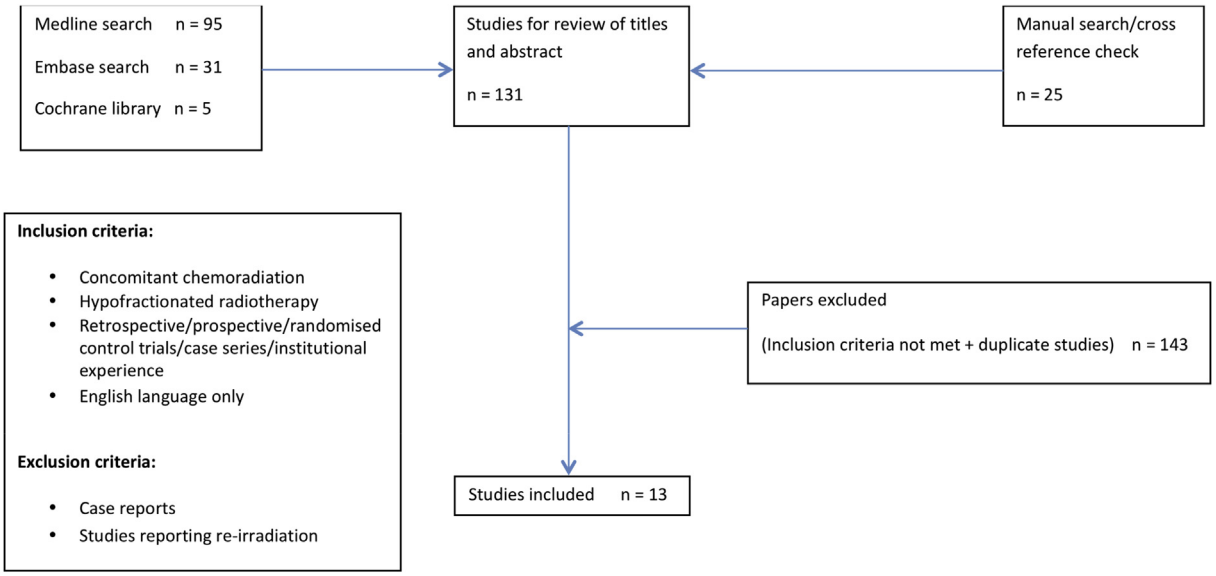

Fig 3. Flow chart of search strategy and identification of applicable studies in systematic review.

Table 4
Studies using hypofractionated concomitant chemoradiation

Reference	Type of study/comparative arm	No. patients received hypofractionated CRT	Chemotherapy	Radiotherapy [EQD2]	Outcome	Toxicity	Additional comments
Phase II trials							
[6]	Phase II neoadjuvant chemotherapy (paclitaxel carboplatin) followed by either 60 Gy in 30 fractions (arm A) or hypofractionated CRT (arm B).	18 in each arm.	Cisplatin 30 mg/m^2 weekly.	48 Gy in 20 fractions over 4 weeks.	ORR at first follow-up was 72.2% for arm B versus 44% for arm A ($P = 0.06$) and at 1 year 61% versus 5.5% ($P = 0.04$). Median PFS for arm A 5.36 months and 17 months for arm B ($P = 0.053$). Median overall survival 12.33 months versus 24.73 months for arm B ($P = 0.007$).	Grade ≥3 acute pharyngitis/ oesophagitis: 17% in arm A versus 6% in arm B ($P = 0.05$).	Small study. Improved outcome due to addition of low-dose weekly cisplatin as radiosensitiser despite lower biological effective dose.
[7] (This was an updated result of a previously published study [8])	Phase II trial. Hypofractionated radiotherapy with low-dose daily cisplatin (arm A) ± cetuximab (arm B).	102 (51 patients in each arm).	Daily low-dose cisplatin (6 mg/m^2) ± weekly cetuximab.	66 Gy in 24 fractions (2.75 Gy/fraction).	Median overall survival of whole cohort was 31.5 months (not significantly different between 2 arms, 33 and 30 months, $P = 0.72$). 1-, 2- and 5-year overall survival for whole cohort 92.2%, 74.5% and 37.3% (no significant difference in 2 arms).	Grade ≥3 acute toxicity: 45% in arm A versus 65% in arm B ($P = 0.03$). 2 patients (4%) in arm B had treatment-related deaths (neutropenic sepsis). Late toxicity: Grade ≥3 pulmonary and oesophageal toxicities: 0% and 4%, 6% and 8% in arm A and arm B, respectively.	Overall good survival results. However, addition of cetuximab was not better. In multivariate analysis, worse performance status, V35 of oesophagus and existence of comorbidities were associated with shorter overall survival.
[5]	Phase II trial. Sequential (seq arm) versus concurrent CRT (CRT arm) (seq arm: 4 cycles of 3 weekly cisplatin 80 mg/m^2 on day 1 and vinorelbine 25 mg/m^2 days 1 and 8).	130 ($n = 70$ in concurrent arm versus 60 patients in sequential arm).	Cisplatin 20 mg/m^2 on radiotherapy fractions 1–4 and 16–19. Vinorelbine 15 mg/m^2 on radiotherapy fractions 1, 6, 15 and 20.2 more cycles of cisplarin/ vinorelbine (doses as per seq arm) 4–6 weeks after concurrent phase.	55 Gy in 20 daily fractions (2.75 Gy/fraction).	1- and 2-year overall survival rates were 70% versus 83%, and 50% versus 46% in CRT and seq arm, respectively. Median PFS was 12.9 months for CRT, 12.1 months for seq arm. Median overall survival for CRT versus seq arm was 24.3 months and 18.4 months.	Grade ≥3 neutropenia: 35% in CRT arm versus 53% in seq arm ($P = 0.05$). Grade ≥3 lung toxicity: 18% versus 15% in seq arm ($P = 0.7$). Grade ≥3 oesophagitis: 9% in both arms. All grade 3–5 toxicities: 32% versus 41% in seq arm ($P = 0.3$).	Treatment-related mortality 2.9% in CRT arm versus 1.7% in seq arm ($P = 0.65$). Authors concluded that CRT was safe and effective.

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Table 4 (*continued*)

Reference	Type of study/comparative arm	No. patients received hypofractionated CRT	Chemotherapy	Radiotherapy [EQD2]	Outcome	Toxicity	Additional comments
[9]	Randomised trial (EORTC) CRT (arm CRT) versus sequential chemotherapy followed by radiotherapy (arm seq).	158 (arm CRT; $n = 80$) (arm seq; $n = 78$).	Daily low-dose cisplatin (6 mg/m^2) in arm CRT. 2 cycles of gemcitabine (1250 mg/m^2 days 1, 8) cisplatin (75 mg/m^2 day 2) in arm seq	66 Gy in 24 fractions in 32 days (2.75 Gy/fraction) (EQD2 = 70 Gy). Elective nodal irradiation was also given (40 Gy in 20 fractions).	CR or PR: 69.7% in arm seq and 60.8% in arm CRT ($P = 0.29$). At 39 months of median follow-up, locoregional progression (43% in arm seq and 46% in arm CRT) and rate of DM (50% in both) were similar. Median overall survival 16.2 months for arm CRT and 16.5 months for arm seq. 1-year PFS and overall survival 36.3% and 69% for arm seq and 44.5% and 55.9% for arm CRT.	Grade 3/4 haematological toxicities: 30% in arm seq versus 6% in arm CRT. Grade 3/4 oesophagitis: 14% in arm CRT versus 5% in arm seq. Late grade 3/4 pneumonitis: 14% in arm seq and 18% in arm CRT.	Higher rates of oesophagitis in arm CRT but higher rates of haematological toxicities in arm seq. Overall well tolerated but definitive results cannot be drawn as the trial was closed prematurely due to poor accrual.
Retrospective studies							
[10]	Retrospective study	61 Concurrent CRT ($n = 29$). 2 cycles of induction chemotherapy (cisplatin or carboplatin + gemcitabine) followed by either 2 more cycles of such chemotherapy and radiotherapy or concurrent CRT.	Concurrent chemotherapy: cisplatin 40 mg/m^2 days 2 and 9, vinorelbine 15 mg/m^2 days 2 and 9, cisplatin 40 mg/m^2 day 23, vinorelbine 15 mg/m^2 days 23 and 30).	Radiotherapy began within 7 days after completion of induction chemotherapy. 30 fractions of 2.25–2.28 Gy to a total dose of 67.5–68.4 Gy (range 64.5–71.3 Gy). EQD2 70–72 Gy.	All patients: CR: 6% PR: 48% SD: 20% Median overall survival 18.6 months in sequential and 24.1 months in concurrent group.	All patients: No grade 4 toxicity. Acute grade 3 pneumonitis: 10%. 2 patients developed grade 3 acute oesophagitis (both in concurrent group).	The authors concluded that 'high BED delivered in a standard time frame may be safely administered with or without chemotherapy, provided high conformal radiotherapy techniques used'.
[11]	Retrospective	171	Cisplatin 6 mg/m^2 with a maximum dose of 12 mg.	IMRT 66 Gy in 24 fractions.	Median overall survival 24 months.	Grade 3 acute oesophageal toxicity: 18.7%. Severe late oesophageal toxicity: 6%.	This study was aimed at reporting oesophageal toxicity.
[12]	Retrospective	30	Cisplatin 20 mg/m^2 fractions 1–4 and 16–19, vinorelbine 15 mg/m^2 fractions 1, 6, 15 and 20 (SOCCAR regimen as in reference [5])	55 Gy in 20 fractions (2.75 Gy per fraction).	No information given.	Grade 3 oesophagitis: 13% Grade 3 dyspnoea: 3% Grade 3 lethargy: 3% No deaths with 3 months of treatment	Well tolerated regimen. The authors concluded that it compared well with reported toxicity of conventional regimen of CRT 66 Gy in 33 fractions

Table 4 (*continued*)

Reference	Type of study/comparative arm	No. patients received hypofractionated CRT	Chemotherapy	Radiotherapy [EQD2]	Outcome	Toxicity	Additional comments
[13]	Retrospective study. 3 comparative arms (CRT versus sequential versus radiotherapy only)	131 (in total) Group CRT: 66 Gy in 24 fractions (2.75 Gy/fraction) + cisplatin 6 mg/m^2 daily ($n = 56$). Group sequential: 2 cycles of cisplatin/gemcitabine followed by radiotherapy alone 66 Gy in 24 fractions ($n = 26$). Group radiotherapy: 66 Gy in 24 fractions or 60 Gy in 20 fractions. No chemotherapy ($n = 49$)	In CRT group, cisplatin 6 mg/m^2 daily.	In CRT group, 66 Gy in 24 fractions (2.75 Gy/fraction).	All groups: 1-, 2- and 5-year overall survival were 46%, 24% and 15%. 5-year overall survival in CRT group was 23%.	4 patients with late grade 4 toxicities (all in CRT group). Severe late toxicity: 27% in CRT, 23% in sequential and 8% in radiotherapy-alone group.	Addition of chemotherapy to radiotherapy was prognostic factor ($P = 0.01$). However, no statistical difference in overall survival between CRT or sequential chemotherapy followed by radiotherapy.
Feasibility studies/phase I trial							
[14]	Phase I	22 (21 were evaluable)	Concurrent weekly carboplatin AUC2 and paclitaxel 45 mg/m^2. Consolidation chemotherapy was 2 cycles of 3-weekly carboplatin AUC6 and paclitaxel 200 mg/m^2.	Cohort 1 = 60 Gy in 27 fractions. Cohort 2 = 60 Gy in 24 fractions. Cohort 3 = 60 Gy in 22 fractions. Cohort 4 = 60 Gy in 20 fractions.	CR = 14.3%. PR = 52.4%. SD = 23.8%. PD = 9.5%. With a median follow-up of 23 months, the median PFS was 12.2 months and the median overall survival was 19.3 months.	Grade 5 toxicities in 3 patients (1 patient in cohort 2 − haemoptysis and 2 patients in cohort 3 − haemoptysis and pneumonitis). Time to grade 5 toxicity was 9 months, 6 months and 9 months.	MTD was defined by cohort 2 (60 Gy in 2.5 Gy/fractions. 86% of patients completed the consolidative cycles of chemotherapy.
[15]	Feasibility study − single arm	26 (19 untreated and 7 cases with recurrent disease).	Vinorelbine (25 mg/m^2) days 1, 8; carboplatin AUC5 day 8. Cycle repeated every 28 days (4 cycles − at least 1 cycle concurrently).	60−75 Gy in 3 Gy/fraction with 5 fractions per week.	With a median follow-up of 11.5 months, median PFS was 10 months, median overall survival was 13 months. 1-year PFS was 37% and overall survival was 60.9%.	Grade 4 fatigue: 11.5%. Grade 3 toxicities: fatigue 19.2%, radiation oesophagitis 15.4%, radiation pneumonia 7.7%, nausea 23.1%. Late grade 3 oesophageal toxicity 7.7%.	A feasibility study with high oesophageal toxicity.
[16]	Phase I trial	13	Vinorelbine (25 mg/m^2 on days 1 and 8) and carboplatin AUC5 on day 8. At least 1 cycle of this concurrent chemotherapy followed by consolidative chemotherapy (median 4 cycles).	66−72 Gy in 3 Gy/fraction (3 patients received 66 Gy, 2 received 69 Gy and 4 received 72 Gy).	CR: 23.1%. PR: 61.5%. SD: 15.4%. With a median follow-up of 10 months, 1-year PFS was 49.4% and median PFS was 12 months.	Grade 4 neutropenia: 8%. Grade 3 neutropenia: 15.3%. 1 grade 3 radiotherapy pneumonia and 2 grade 3 oesophagitis in 72 Gy group.	MTD was 69 Gy in 23 fractions.
[17]	Phase I trial (dose-finding study to determine dose of weekly docetaxel concurrent with radiotherapy after induction chemotherapy (3 cycles of cisplatin and docetaxel).	37 enrolled (4 did not receive CRT: 2 PD and 2 withdrew consent).	Docetaxel (stopping the accrual at dose of 38 mg/m^2 weekly).	60 Gy in 25 daily fractions (2.4 Gy/fraction) using Tomotherapy.	Who completed CRT: median PFS was 20 months and median overall survival was 24 months.	In CRT phase: Grade 3 oesophagitis in 1 patient (3%). No grade 3 pneumonitis or haematological toxicity.	MTD was not reached as no life-threatening toxicity, however accrual was stopped at 38 mg/m^2.

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Table 4 (*continued*)

Reference	Type of study/comparative arm	No. patients received hypofractionated CRT	Chemotherapy	Radiotherapy [EQD2]	Outcome	Toxicity	Additional comments
[18]	Phase I/II to determine MTD of radiotherapy	34	Fixed-dose chemotherapy (docetaxel and cisplatin each at a dose 20 mg/m^2 starting on day 1 of radiotherapy on a weekly basis for 6 weeks).	60–74.4 Gy in 30 fractions using Tomotherapy.	PR: 52%. SD: 30%. PD: 18%. With a median follow-up of 17 months, median overall survival was 17.9 months.	Cumulative incidence of grade ≥3 oesophageal toxicity 36%. Cumulative late lung toxicity grade ≥3 was 21%.	MTD for CRT was set at 67.2 Gy in 30 fractions. Following chemoradiation, 2 cycles of consolidative chemotherapy (cisplatin and docetaxel).
[19]	Feasibility study. Hypofractionated radiotherapy with cytoprotection.	14 (9 patients had resistant or refractory disease to previous platinum or taxane).	Vinorelbine (20–30 mg/m^2) and liposomal doxorubicin (20 mg/m^2 every 2 weeks, for 3 consecutive cycles).	15 fractions for 3.5 Gy within 4 consecutive weeks (1 week split after the 10th fractions) + subcutaneous amifostine 500–1000 mg/day.	PR: 64%. Minimal response: 22%. SD: 14%. Median local PFS: 12 months. Median overall survival: 8 months.	Grade 3 neutropenia in 2/5 and 2/4 patients receiving vinorelbine 25 mg/m^2 and 30 mg/m^2, respectively. Grade 2 radiotherapy-induced pneumonitis: 42.8%.	MTD of oral vinorelbine concurrent with radiotherapy is 25 mg/m^2.
Current study							
Current study	Retrospective	100	Cisplatin 20 mg/m^2 on radiotherapy fractions 1–4 and 16–19. Vinorelbine 15 mg/m^2 on radiotherapy fractions 1, 6, 15 and 20.2 more cycles of cisplatin/vinorelbine (doses as per seq arm) 4–6 weeks after concurrent phase (as per [5]).	55 Gy in 20 daily fractions (2.75 Gy/fraction).	Clinical benefit was seen in 86% (CR 5%, PR 77%, SD 4%). 1-year PFS and overall survival were 69% and 81%. 2-year PFS and overall survival were 49% and 58%. Median PFS and overall survival were 23.4 months and 43.4 months.	1 grade 5 event (death on treatment due to cardiac event). Grade 3/4 esophagitis was 14% and radiation pneumonitis was 4%. Grade 3/4 nausea/vomiting was 17% and infection with neutropenia was 12%.	97% of patients completed radiotherapy. 73% of patients completed all 4 cycles of chemotherapy (86% completed at least 3 cycles, i.e. a cumulative cisplatin dose of 240 mg/m^2).

ORR, overall locoregional response rate; PFS, progression-free survival; CRT, chemoradiotherapy; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; DM, distant metastases; V35, volume of organ receiving 35 Gy; AUC, area under concentration–time curve; IMRT, intensity-modulated radiotherapy; MTD, maximum tolerated dose.

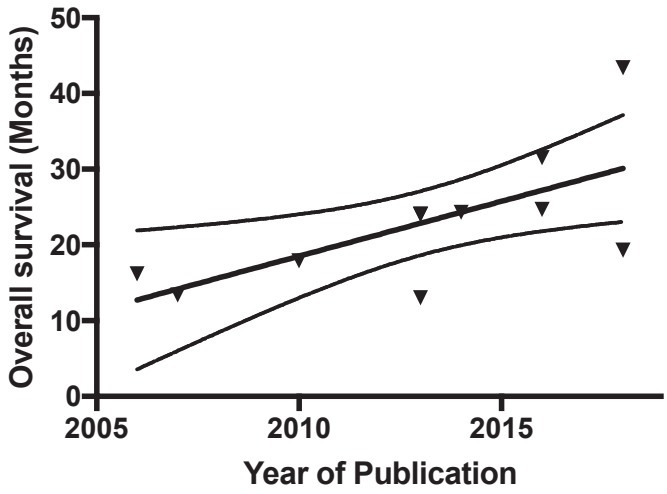

Fig 4. Median overall survival in hypofractionated chemoradiotherapy studies in stage III non-small cell lung cancer by year of publication.

chemotherapy was safe and effective. Walraven *et al.* [7] added weekly cetuximab to daily low-dose cisplatin concomitantly with 66 Gy in 24 fractions (2.75 Gy per fraction). Overall it showed good results (the median overall survival of the whole cohort was 31.5 months) but the addition of cetuximab was not found to be beneficial.

The largest retrospective study to date by Chen *et al.* [11] ($n = 171$) concentrated on the incidence of oesophageal toxicity and included some of the patients treated in the study by Walraven *et al.* [7]. The regimen used was 66 Gy in 24 fractions using intensity-modulated radiotherapy (2.75 Gy per fraction) with daily low-dose cisplatin chemotherapy. Grade 3 acute oesophageal toxicity was 18.7% and grade 3 late oesophageal toxicity was 13%. The median overall survival was 24 months [11]. This study highlights the importance of accurately capturing late toxicity data in this potentially curative setting.

Discussion

Hypofractionated radiotherapy reduces treatment times and may be associated with improved outcome, with less repopulation of tumour cells [20]. It also allows more effective use of limited capacity in radiotherapy centres and can therefore increase the cost-effectiveness of treatment. However, it is important that this is not associated with an increase in toxicity, particularly in the concurrent setting.

To the best of the authors' knowledge, this is the biggest case series of patients treated with hypofractionated chemoradiation with the SOCCAR regimen using up-to-date staging and radiotherapy techniques. The original trial showed that this approach was feasible and safe for patients. We have now shown efficacy that seems to be superior to the SOCCAR trial and in addition higher treatment completion rates and lower morbidity. This improvement in survival may be due to improved staging (99% patients had PET staging, which was not mandated in SOCCAR), less stage IIIB (32% versus 56% in SOCCAR), improved treatment delivery or a combination of these factors.

We would also highlight that in our study 73% of patients completed four cycles of chemotherapy (only 9% in the SOCCAR concurrent arm) and 97% of patients managed to complete radiotherapy, which was higher than in the original trial result (89% in the concurrent arm).

Treatment was well tolerated. There were only two cases of grade 4 toxicity (acute kidney injury and sepsis) and one possible treatment-related death. The incidence of grade 3 oesophagitis was 15%, slightly higher than the original reported data (9%); similarly, the rate of grade 3 nausea and vomiting was slightly higher and this could reflect the higher number of patients completing all four cycles of chemotherapy and 20 fractions of planned radiotherapy.

These data are important as they allow an accurate benchmark of efficacy and toxicity. This is vital before considering the addition of additional systemic agents such as immuno-oncology agents or DNA damage response inhibitors to concurrent chemoradiation. These data provide an outcome analysis using high-quality radiotherapy techniques to benchmark results to help interpret contemporary studies, such as PACIFIC, where radiotherapy is relatively sparsely described [21].

The literature search revealed a wide discrepancy in both the radiotherapy and chemotherapy schedules evaluated. Our data suggest that 55 Gy in 20 fractions (2.75 Gy per fraction) using modern radiotherapy techniques together with concomitant split-dose combination chemotherapy (cisplatin/vinorelbine) is safe and effective. Using a higher dose of radiotherapy, i.e. 66 Gy in 24 fractions (2.75 Gy per fraction), can also be safe and effective when given with single-agent cisplatin chemotherapy administered on a daily basis.

Conclusion

We have shown that our outcomes are slightly superior to the SOCCAR trial, with improved treatment completion rates and acceptable morbidity. Accepting problems with retrospective cohorts, we feel that we have shown with appropriate patient selection that this regimen is an effective treatment option for locally advanced NSCLC. In general, previous studies and retrospective series have evaluated different radiotherapy and chemotherapy regimens and sometimes it has not been clear what the oesophageal and pulmonary toxicity rates are. For the future it would be beneficial if a standardised hypofractionated regimen is agreed. This regimen can then be evaluated to determine the safety and efficacy of the addition of consolidation immunotherapy.

Conflict of interest

Author MSI has received honorarium from Ipsen for clinician steering committee role.

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