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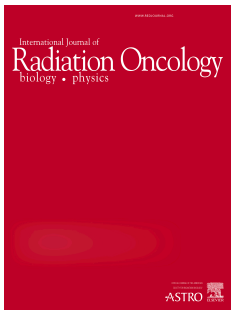

IDEAL-CRT: A phase I/II trial of isotoxic dose-escalated radiotherapy and concurrent chemotherapy in patients with stage II/III non-small cell lung cancer

David B. Landau, MRCP, Laura Hughes, Angela Baker, MSc, Andrew T. Bates, MBBS, Michael C. Bayne, MD, Nicholas Counsell, MSc, Ange Garcia-Alonso, MDI, Susan V. Harden, DM, Jonathan D. Hicks, FRCR, Simon R. Hughes, FRCR, Marianne C. Illsley, MA, Iftekhar Khan, PhD, Virginia Laurence, FRCR, Zafar Malik, FRCR, Helen Mayles, MSc, William PM. Mayles, PhD, Elizabeth Miles, Mphil, Nazia Mohammed, FRCR, Yenting Ngai, BSc, Emma Parsons, BHSc, James Spicer, FRCP, Paula Wells, PhD, Dean Wilkinson, MSc, John D. Fenwick, PhD

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IDEAL-CRT: A phase I/II trial of isotoxic dose-escalated radiotherapy and concurrent chemotherapy in patients with stage II/III non-small cell lung cancer

Running Title: Dose Escalated Radiotherapy

Landau David B.,MRCP[1], Hughes Laura[2], Baker Angela, MSc[3], Bates Andrew T, MBBS[4], Bayne Michael C, MD[5], Counsell Nicholas, MSc[2], Garcia-Alonso Ange, MDl[6], Harden Susan V, DM[7], Hicks Jonathan D, FRCR[8], Hughes Simon R, FRCR[1], Illsley Marianne C, MA[9], Khan Iftekhar, PhD[2], Laurence Virginia, FRCR[5], Malik Zafar, FRCR[3], Mayles Helen, MSc[3], Mayles William PM, PhD[3], Miles Elizabeth, Mphil[10], Mohammed Nazia, FRCR[7], Ngai Yenting, BSc[2], Parsons Emma, BHSc[10], Spicer James, FRCP[1], Wells Paula, PhD[11], Wilkinson Dean, MSc[10] and Fenwick John D., PhD[12]

1. Guy's & St.Thomas' NHS Trust; King's College London

2. Cancer Research UK & UCL Cancer Trials Centre

3. Clatterbridge Cancer Centre

4. Southampton General Hospital

5. Poole Hospital

6. North Wales Cancer Centre

7. Addenbrookes Hospital

8. Beatson West of Scotland Cancer Centre

9. Royal Surrey County Hospital

10. Mount Vernon Hospital

11. St. Bartholomew's Hospital

12. University of Oxford

Corresponding author:

Dr David Landau

Oncology Management Offices

4th Floor Bermondsey Wing

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Guy's Hospital

Great Maze Pond

London

SE1 9RT

Tel: +44(0) 2071883761

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Corresponding author:

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Summary

Eighty-four patients (6 IIB, 57 IIIA, 21 IIIB) were recruited to IDEAL-CRT, an early phase trial of dose-per-fraction-escalated concurrent chemoradiation for NSCLC. Tumor doses of 63-73Gy (mean 67.6Gy) were isotoxically prescribed to the ICRU reference-point and delivered in 30 fractions over 40 days. Toxicity was acceptable. At 35 months median follow-up, median OS was 36.9 months, 1 year OS and PFS were 87.8% and 72.0%, and 2 year OS and PFS were 68.0% and 48.5%.

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Abstract

Background and Purpose

Toxicity and early efficacy data are presented for IDEAL-CRT, a trial of an escalated, concurrent chemoradiotherapy schedule for advanced stage non-small cell lung cancer (NSCLC). Tumor dose-per-fraction-escalation was used in IDEAL-CRT to achieve therapy intensification without prolongation, and tumor doses were prescribed isotoxically to maximum levels consistent with normal tissue dose constraints.

Patients and Methods

Patients received tumor doses of 63-73Gy in 30 once-daily fractions over 6 weeks with two concurrent cycles of cisplatin and vinorelbine. They were assigned to one of two groups according to esophageal dose. In Group 1, tumor doses were determined by an experimental constraint on maximum esophageal dose which was escalated following a 6+6 design from 65Gy through 68Gy to 71Gy, allowing an esophageal maximum tolerated dose (MTD) to be determined from early and late toxicities. Tumor doses for Group 2 patients were determined by other tissue constraints, often lung. Overall survival (OS), progression-free survival (PFS), tumor response and toxicity were evaluated for both groups combined.

Results

Eight centres recruited 84 patients: 13, 12 and 10 in the 65Gy, 68Gy and 71Gy cohorts of Group 1, and 49 in Group 2. The mean prescribed tumor dose was 67.6Gy. Five grade 3 esophagitis and three grade 3 pneumonitis events were observed across both groups. Following one fatal esophageal perforation in the 71Gy

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cohort, 68Gy was declared the esophageal MTD. With a median follow-up of 35 months, median OS was 36.9 months, and OS and PFS were 87.8% and 72.0% at 1 year and 68.0% and 48.5% at 2 years.

Conclusions

IDEAL-CRT achieved significant treatment intensification with acceptable toxicity and promising survival. The isotoxic design allowed the esophageal MTD to be identified from relatively few patients.

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Introduction

Intensification of local treatment has been associated with increased local control and overall survival (OS) for non-small cell lung cancer (NSCLC) patients. Improved 2-year OS was reported for CHART trial patients treated using 54Gy delivered in just 12 days compared to the standard 60Gy in 40 days (29% versus 20%)[1], while a recent meta-analysis has reported a hazard ratio (HR) of 0.86 for intensification of radiation-only or sequential chemo-radiotherapy (CRT) treatments compared to control arms[2]. A meta-analysis of trials of concurrent versus sequential CRT found an advantage for concurrent delivery of radiation and chemotherapy, with an HR of 0.77 for local progression-free survival (PFS) and 5.7% and 4.5% absolute benefit in OS at 3 and 5 years[3].

RTOG 0617 recently examined the effect of increasing radiotherapy (RT) tumor doses from 60 to 74Gy given in five 2Gy fractions per week[4]. Unexpectedly, survival was significantly lower in the 74Gy arm, perhaps partly because the 11 day increase in total treatment time required for additional fractions reduced the effectiveness of tumor dose-escalation. Dose-per-fraction-escalation circumvents this by fixing the number of fractions and treatment duration, hypofractionating and effectively accelerating RT[5-7]. It may therefore provide a more effective means of local treatment intensification[8–10].

RT toxicity is determined by doses delivered to normal tissues. Early phase trials testing the toxicity of intensified CRT or RT combined with novel agents should control these normal tissue doses, while allowing prescribed tumor doses to vary within an acceptable range. Isotoxic dose-escalation accomplishes this by prescribing the highest deliverable tumor doses without exceeding pre-determined normal tissue limits.

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We report toxicity and early survival data for IDEAL-CRT, a trial of tumor dose-escalated concurrent CRT for NSCLC. Dose-per-fraction-escalation was used to achieve intensification without schedule protraction; tumor doses were prescribed isotoxically; and selected patients were prospectively assigned to cohorts receiving incrementally increasing esophageal RT doses.

Patients and methods

This non-randomized phase I/II trial enrolled stage II and III NSCLC patients, who received tumor RT doses between 63Gy and 73Gy in 30 once-daily fractions over 40 days, concurrent with two cycles of cisplatin and vinorelbine.

Patients

Inclusion criteria were histologically/cytologically confirmed stage IIA-IIIB NSCLC, WHO performance status (PS) 0-1, suitability for CRT agreed by multidisciplinary team, no prior anti-cancer therapy, forced expiratory volume (FEV_1) ≥40% predicted or ≥1L, carbon monoxide diffusing capacity (D_{LCO}) ≥40% predicted, hematology and biochemistry baselines suitable for chemotherapy, and glomerular filtration rate ≥60 ml/min. Patients with chronic liver disease and/or bilirubin >35μmol/l, connective tissue disorders (e.g. scleroderma, systemic lupus) or history of prior malignancy likely to interfere with protocol treatment were excluded.

Design

Patients received the highest prescribed tumor doses between 63-73Gy deliverable while meeting the normal tissue dose constraints shown in Table 1. For lungs, spinal cord, brachial plexus and heart these constraints were held at levels determined from an earlier review[11]. However, insufficient data linking dose to toxicity existed for

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an esophageal constraint to be defined up-front, and so an incrementally increasing esophageal limit was used during the trial. To facilitate this process, patients were split after RT treatment planning but before tumor dose prescription into two non-randomized groups based on dosimetric findings. In Group 1, prescribed tumor doses were limited by an escalating esophageal constraint, while in Group 2 prescribed tumor doses were limited by lung and other normal tissue constraints. Allocation of patients to these groups was therefore determined purely on the basis of dosimetry and not clinician choice.

Group 1 was designed as a phase I study to establish an esophageal maximum tolerated dose (MTD), patients' prescribed tumor doses being limited by an escalating experimental constraint on dose delivered to the most highly irradiated 1cc of esophagus. This esophageal dose constraint was progressively raised from 65Gy to 68Gy and then 71Gy following a 6+6 design (Supplementary Figure 1), treating 6 or 12 patients at each level. It was initially planned to include a 73Gy esophageal dose cohort, but the 73Gy upper limit on prescribed tumor dose meant that in practice it was not feasible to deliver 73Gy to 1cc of oesophagus. Dose-limiting toxicities (DLTs) were grade ≥3 esophagitis (CTCAE v4.0) occurring during or within 4 weeks of completing RT and late esophageal toxicity which was monitored closely.

Group 2 comprised all trial patients whose prescribed tumor doses were limited by other dose constraints, often lung or cord, and was designed to provide further toxicity data, particularly for radiation pneumonitis (RTPN). For some Group 2 patients, however, prescribed tumor dose was limited by a lower esophageal constraint, already known to be safe, initially set at 63Gy to 1cc (Table 1). As the trial

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recruited, this Group 2 esophageal limit was progressively raised to levels for which early toxicity had been found to be acceptable in cohorts of 12 patients in Group 1.

Feasibility and survival data were analyzed jointly across both groups, comprising the phase II element of the study.

Interventions

Concurrent chemotherapy was 2 cycles of i.v. cisplatin 75 mg/m^2 on days 1 and 29 of RT, and i.v. vinorelbine 15 mg/m^2 on days 1, 8, 29 and 36. No induction or consolidation chemotherapy was allowed.

RT planning was the same for Groups 1 and 2. 3D- or 4D-CT images were collected during quiet breathing, and on 3D-CT images the gross tumor volume (GTV) was contoured and then expanded by 5mm to create a clinical target volume (CTV), and by a further 5mm minimum radial and 10mm minimum cranio-caudal to form a planning target volume (PTV). On 4D-CT a composite volume was formed by merging GTVs outlined on the different scan phases, then expanded by 5mm to form a CTV and by 5mm minimum further in all directions to form a PTV. Most patients were treated using 3D conformal plans comprising 3-5 photon fields of energy 5-8MV. Some were treated using volumetric modulated arc therapy (VMAT), according to available centre resources. Dose-distributions were calculated using 'type-b' superposition-convolution algorithms[12] and all tumor doses were prescribed to the International Commission on Radiation Units (ICRU) reference-point.

The tumor dose prescription process is summarized in Table 1. For each patient an initial prescribed tumor dose was selected to achieve a target value of 18.2Gy for lung EQD_{2mean}, the average equivalent dose in 2Gy fractions delivered to all CT voxels of both lungs excluding the GTV[13,14]. This level is associated with a 20% rate

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of Southwest Oncology Group (SWOG) G2-5 RTPN and a presumed G3-5 rate of <10%[13,15]. The prescribed tumor dose was then reduced by 10% to allow for toxicity caused by concurrent chemotherapy, and further if necessary to meet the tabulated dose constraints for esophagus, brachial plexus, heart and spinal cord[11]. If this caused the prescribed tumor dose to fall below the trial minimum of 63Gy, the lung EQD_{2mean} limit was relaxed to 19.3Gy, and the patient would still receive a prescribed tumor dose of 63Gy provided this relaxed lung limit and all the other normal tissue constraints listed in Table 1 could be met. Prescribed tumor doses were capped at 73Gy to limit damage to central blood vessels and airways.

Quality assurance was overseen by the Radiotherapy Trials Quality Assurance Group of the National Cancer Research Institute. Before starting the trial, clinicians and physicists from each centre attended an outlining and dose prescription workshop. Clinicians outlined two benchmark cases[16] which were checked against contours drawn by the Principal Investigator, and planned two pre-outlined benchmark cases which were reviewed to ensure that trial dosimetric aims were met. An additional arc-planned case was checked for centres introducing VMAT. Equipment details were collected via an on-line questionnaire. Contouring and dosimetry of each centre's first recruited case was independently reviewed prior to treatment. Further reviews were requested, where deemed necessary, to ensure protocol compliance. Subsequently all treatment plan data was collected centrally and analyzed retrospectively to verify conformance to the trial protocol.

Staging CT of the thorax and abdomen and PET scanning were performed for all patients, either one within 42 days of commencing RT. Clinical assessments of PS, hematology, weight and dyspnoea score were made weekly during RT. Post-treatment PS, weight, dyspnoea score, pulmonary function, adverse events and

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toxicity data were collected at clinical reviews held weekly during the first month, monthly to 6 months, 3-monthly to 24 months, 6-monthly to 36 months and annually thereafter. CT thorax and abdomen and lung function tests were carried out 3, 6, 12 and 24 months after completion of RT, chest x-ray at 1, 3, 6, 12, 18 and 24 months, and ECG at 6 and 12 months.

Outcomes and statistics

Trial endpoints were toxicity, particularly grade 3-5 esophagitis and grade 2-5 RTPN, OS, PFS and tumor response (RECIST version 1.1). Attribution of toxicity to treatment was overseen by an independent data monitoring committee. OS and PFS rates were estimated using Kaplan-Meier methods. All patients who received at least one fraction of RT were included in this analysis. The database cut-off date was July 31st 2015.

The Group 1 sample size depended on toxicity seen: up to 36 patients were possible, 12 each in the three feasible cohorts. In Group 2, assuming a G2-5 RTPN rate of 20% was of further interest, 45 patients were required to exclude an unacceptable rate of 40% with a 1-sided 5% significance level and 90% power[17].

Role of the funding source

The funder, Cancer Research UK, was not involved in the conduct, analysis or interpretation of the trial, or the writing of this paper. The trial sponsor, responsible for trial conduct and analysis, was University College London. The corresponding author had full access to all the data in the study and final responsibility to submit for publication. The trial was run in accordance with the Declaration of Helsinki and with the approval of all relevant ethical bodies and regulatory authorities.

Results

Between September 2010 and March 2013, 84 patients from eight UK centres were enrolled, 35 in Group 1 and 49 in Group 2, with the baseline characteristics shown in Table 2. Of these, 34 patients (40.5%) were planned using 4DCT and 50 (59.5%) with intravenous contrast. Three patients were treated using VMAT. An extra patient was recruited to the 65Gy cohort of Group 1 as re-planning during treatment was required for one of the patients initially recruited, adding uncertainty to the delivered maximum esophageal dose. Twelve patients were recruited to the 68Gy cohort of Group 1 but only ten to 71Gy before trial funding ended (Figure 1).

Two patients in Group 2 did not begin treatment following clinical deterioration. Of the 82 patients starting CRT, 81 (98.8%) completed both cycles of chemotherapy and 81 (97.6%) received all 30 RT fractions (Figure 1): one patient withdrew due to toxicity (Group 2). Median relative dose intensity was 99.6% for cisplatin and 99.0% for vinorelbine, and RT was generally delivered as scheduled with a median duration of 5.6 weeks (range 5.1-6.6 weeks, Supplementary Table 1). Prescribed tumor doses are shown in Figure 2 and have an overall mean of 67.7Gy, with means of 68.9Gy and 66.8Gy for Groups 1 and 2 respectively.

Toxicity

Grade 2-5 RTPN was seen in 30.5% of patients who received trial treatment (1-sided upper 95% confidence limit: 39.9%; 2-sided 95% confidence interval (CI): 20.8-41.6%). Three of these RTPN events were Grade 3 (3.7%, 95% CI: 0.8-10.3%).

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The Grade 2-5 esophagitis rate overall was 82.9% (2-sided 95% CI: 73.0-90.3%), with five Grade 3 toxicities (6.1%, 2-sided 95% CI: 2.0-13.7%). A fatal esophageal perforation occurred in one patient in the 71Gy cohort of Group 1, 7 months post-RT (Table 3), and was considered directly related to treatment. The esophageal MTD was therefore set at 68Gy to 1cc of esophagus.

A further three patients had fatal events, (Table 3), all hemoptysis. One occurred 14 months post-RT with tumor recurrence and was considered possibly treatment-related (Group 1, prescribed tumor dose 72.6Gy); another at 4.5 months post-RT with residual tumor was considered unrelated (Group 2, prescribed tumor dose 68.5Gy); and the third at 4 weeks post-RT was also considered unrelated (Group 2, prescribed tumor dose 67.6Gy).

Incidences of esophagitis and RTPN are listed by grade and trial group in Table 3, alongside a summary of other toxicities. Rates of other complications are listed in more detail in Supplementary Table 2, whilst the latency of Grade 3-5 toxicities is summarized in Supplementary Table 3. Supplementary Table 4 summarizes the trial dosimetrically, listing prescribed tumour doses for all three cohorts of Group 1 and for Group 2, alongside details of delivered doses to the constrained normal tissues.

Efficacy

At the 3 months post-RT visit, 52 patients (63.4%) had a partial response, 21 (25.6%) stable disease, 4 (4.9%) had progressive disease, 4 (4.9%) had non-evaluable disease and 1 (1.2%) patient had died.

After a median follow-up of 34.9 months (range: 2.2-51.2) there were 40 deaths, the remaining 42 patients being censored at the last date known to be alive. One- and two-year OS was 87.8% (95% CI: 80.7-94.9%) and 68.0% (95% CI: 57.8-78.1%),

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and median OS was 36.9 months (95% CI: 31.7-42.1 months) (Figure 3a). OS is plotted by tumor stage in Figure 3b. Figure 3c shows OS for the 82 patients split into two subgroups having prescribed tumor doses greater or less than the 68Gy median; the risk of death was lower for the higher tumor dose subgroup (HR=0.53, 95% CI: 0.28-1.02, p=.06). There were 49 PFS events overall. One- and two-year PFS was 72.0% (95% CI: 62.2-81.7%) and 48.5% (95% CI: 37.6-59.3%), and median PFS was 21.1 months (95% CI: 11.5-30.6 months) (Figure 3d).

Discussion

IDEAL-CRT tested a novel, individualized, tumor-dose-per-fraction-escalated concurrent CRT schedule for NSCLC. The trial demonstrated acceptable toxicity, feasibility and promising clinical outcomes as well as defining an esophageal MTD for the schedule.

The 6% rate of G3-5 esophagitis in IDEAL-CRT is lower than the 18% and 25% average rates found in two meta-analyses of concurrent CRT[3,18], and the 7%, 19% and 26% rates of the two dose arms of RTOG 0617[4] and the MAASTRO study of isotoxically individualized concurrent CRT[10]. Intensive clinical input resulting from mandated weekly patient assessments may have reduced the number of G3-5 cases in IDEAL-CRT, and the study's dosimetric focus may also have limited esophageal irradiation.

There was one late G3-5 esophageal toxicity, a fatal perforation in the 71Gy cohort of trial Group 1, and 68Gy was defined as the esophageal MTD. Of 171 patients treated using concurrent CRT at Netherlands Cancer Institute (NKI), Amsterdam, three suffered esophageal fistula and eight grade 3 stenosis[19]. In the high dose arm of RTOG 0617 three of 206 patients died of gastro-intestinal (GI) toxicity[20] and an

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additional nine of 442 patients overall experienced late grade 3-5 GI toxicity[4]. The most significant predictor of late esophageal toxicity in the NKI series was esophageal volume receiving an EQD_2 ≥76.7Gy. Using the linear-quadratic model with an α/β ratio of 3Gy to account for fractionation differences[14], this equates to the 71Gy esophageal dose-level of the IDEAL-CRT cohort in which the esophageal perforation occurred.

The ability of the isotoxic escalation scheme to limit the incidence of RTPN was confirmed by the G2-5 RTPN and G3-5 RTPN rates of 30.5% (95% CI: 20.8-41.6%) and 3.7% (95% CI: 0.8-10.3%) respectively in the patients who received trial treatment, similar to the 7% and 4% G3-5 rates of the control and escalated arms of RTOG 0617, and the 7% rate in the Cochrane review of concurrent CRT[18]. A detailed analysis of possible associations between dosimetry, observed pulmonary, cardiac and esophageal toxicities and survival is underway.

Two deaths in IDEAL-CRT were treatment-related. In the Cochrane review treatment-related deaths were recorded in 3% of patients receiving concurrent CRT[18]. In RTOG 0617, eight treatment-related deaths occurred in the 74Gy group versus seven in the 60Gy group, and ten patients receiving cetuximab had treatment-related deaths versus five not receiving cetuximab[4]. Overall, despite substantial treatment intensification, toxicity in IDEAL-CRT does not appear higher than in other relevant concurrent CRT studies.

IDEAL-CRT patients were recruited and treated at multiple sites, supported by a rigorous quality assurance program[21]. Their demographics and tumor characteristics were roughly comparable to those of patients in previous studies (Table 2)[3,4]. The average prescribed tumor dose of 67.7Gy in 30 fractions corresponds to a 15%

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increase in EQD_2 above the 60Gy dose given in 30 fractions in the control arm of RTOG0617, assuming a 10Gy α/β ratio for NSCLC[14,15]. While it remains to be proven in randomized trials whether this degree of intensification improves survival, the 36.9 month median OS seen in IDEAL-CRT is promising and compares well with median OS times of 28.7 and 20.3 months in the control and escalated arms of RTOG 0617, and with 24.3 months in the concurrent CRT arm of the UK SOCCAR trial[4,22].

The relatively high survival seen in IDEAL-CRT may originate from strict adherence to the CRT protocol, as well as from treatment intensification. It might also reflect the stage-mix of patients (7% stage IIB, more stage IIIA than IIIB), although we found no evidence of a difference in OS between IIIA and IIIB patients (HR=1.23; 95% CI:0.59-2.57; p=0.58) (Figure 3b). The borderline-significant survival advantage seen for patients treated with prescribed doses greater than the median could be interpreted as showing an increase in tumor control either with rising dose or with falling tumor size, since isotoxic schemes tend to prescribe higher doses to smaller tumors.

A key feature of IDEAL-CRT was its focus on doses to organs-at-risk, particularly in determining the safety of progressively increasing esophageal doses in a sequence of patient cohorts. While it is not possible to plan exactly the same RT dose-distribution in each patient, we have nevertheless demonstrated the feasibility of structured patient recruitment to cohorts defined by key dosimetric predictors of toxicity. This aspect of trial design proved to be effective and efficient in prospectively identifying an MTD for esophagus using relatively few patients, and is highly relevant to early phase studies investigating intensified RT across many tumor

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types and sites, and to studies exploring the addition to RT of systemic therapies, radiosensitizers or radioprotectors.

Conclusions

Toxicity results and survival data from IDEAL-CRT are promising. Dose-limits have been determined efficiently using the study's approach to dose-escalation, namely by incrementally increasing key dose-metrics in specific normal tissues. We have recently completed recruitment to a 5-week form of the IDEAL-CRT schedule, designed to further limit tumor repopulation during treatment, and are presently planning a randomized trial of the 6-week schedule described here versus standard dose CRT.

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Table 1: Summary of the RT planning and dose prescription process.

Process steps				
Tumor coverage aim				
PTV	90% isodose to cover 98% of PTV			
Tumor dose prescribed to the ICRU reference-point initially selected to achieve				
Lung	EQD_{2mean}[†] 18.2Gy			
Prescribed tumor dose reduced by 10%, and further if needed to meet the limits				
Heart	$D_{100\%}$[††] <45Gy, $D_{67\%}$ <53Gy, $D_{33\%}$ <60Gy			
Spinal Cord	$D_{0.1cc}$ ≤47Gy			
Brachial plexus	$D_{30\%}$ ≤60Gy, $D_{0.1cc}$ ≤65Gy			
Esophagus	Dose to1cc = 65Gy	Dose to 1cc = 68Gy	Dose to 1cc = 71Gy	Dose to 1cc ≤ 63Gy*
Limit for	Group 1	Group 1	Group 1	Group 2
Prescribed tumor dose finally limited to 63-73Gy, patients being ineligible for the trial if this causes lung V_{20Gy}[**] or $EQD2_{mean}$ to exceed 35% or 19.3Gy respectively.				

[†] Equivalent dose in 2Gy fractions averaged across lung excluding gross tumor volume (GTV).

[††] $D_{X[\%or\ cc]}$ denotes the minimum dose delivered to the most highly irradiated X% or X cc of the tissue.

* This dose-level increased to 65Gy, and then 68Gy as safety data became available from Group 1.

** V_{20Gy} is the volume of lung excluding GTV receiving more than 20Gy.

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Table 2: Demographics and baseline characteristics of all patients.

		Group 1 (N= 35)	Group 2 (N= 49)	Total (N=84)
Age (# patients)	≥ 70	10 (29%)	13 (27%)	23 (27%)
(years)	< 70	25 (71%)	36 (74%)	61 (73%)
	Mean (SD)	65.6 (8.0)	65.4 (8.0)	65.5 (8.0)
	Median (range)	66 (46-84)	66 (43-78)	66 (43-84)
Gender	Female	9 (26%)	13 (27%)	22 (26%)
	Male	26 (74%)	36 (73%)	62 (74%)
WHO PS	0	12 (34%)	20 (41%)	32 (38%)
	1	23 (66%)	29 (59%)	52 (62%)
Histology	Adenocarcinoma	12 (34%)	14 (29%)	26 (31%)
	Squamous	17 (49%)	30 (61%)	47 (56%)
	Other NSCLC	6 (17%)	5 (10%)	11 (13%)
Stage	IIA	0	0	0
	IIB	0	6 (12%)	6 (7%)
	IIIA	24 (69%)	33 (67%)	57 (68%)
	IIIB	11 (31%)	10 (20%)	21 (25%)
GTV size	Mean (SD)	127.7 (118.9)	118.0 (83.3)	122.1 (99.4)
(cm^3)	Median (range)	110 (14-602)	92 (15-329)	109 (14-602)

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Table 3: Selected toxicities by grade amongst the 82 patients who began RT (safety population), according to trial group.

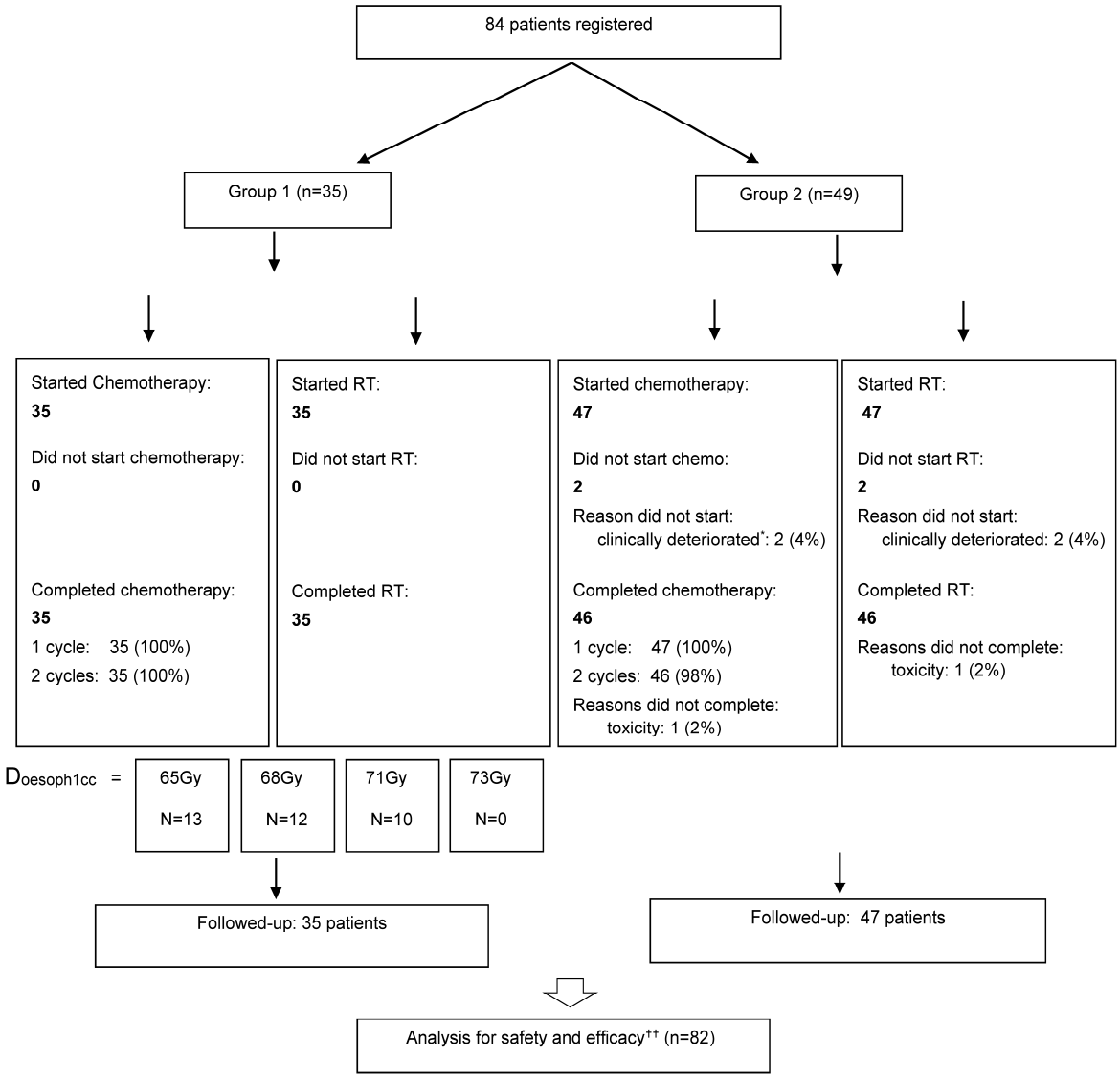
Toxicity	Grade	Group 1 (N=35)	Group 2 (N=47)	Total (N=82)
Esophagitis	**0**	2 (6%)	7 (15%)	9 (11%)
	1	1 (3%)	4 (9%)	5 (6%)
	2	30 (86%)	33 (70%)	63 (77%)
	3	2 (6%)	3 (7%)	5 (6%)
	4	0	0	0
	5	0	0	0
RTPN[$]	**0**	11 (31%)	24 (51%)	35 (43%)
	1	12 (34%)	10 (21%)	22 (27%)
	2	10 (29%)	12 (26%)	22 (27%)
	3	2 (6%)	1 (2%)	3 (4%)
	4	0	0	0
	5	0	0	0
All toxicities grades ≥ 3		**25 (71%)**	**36 (77%)**	**61 (74%)**
	3	20 (57%)	26 (55%)	46 (56%)
	4	3 (9%)	8 (17%)	11 (13%)
	5[†]	2 (6%)	2 (4%)	4 (5%)
Grade ≥ 3[%††] Hematological				
White Blood Cell Decreased		2 (6%)	9 (19%)	11 (13%)
Lymphocyte Decreased		1 (3%)	8 (17%)	9 (11%)
Neutrophil Decreased		4 (11%)	8 (17%)	12 (15%)
Grade ≥ 3 Other				
Lung Infection		9 (26%)	9 (19%)	18 (22%)
FEV Decreased		5 (14%)	7 (15%)	12 (15%)

[$] RTPN = radiotherapy pneumonitis. Two patients received higher lung doses than allowed in the protocol. Both received prescribed tumor doses of 63Gy, one with a lung V_{20} of 46.5% and one with 40.7%. Neither experienced RTPN.

[†] Four patients had grade 5 events: In Group 1, one patient experienced esophageal perforation and one hemoptysis. Two Group 2 patients experienced hemoptysis.

[††] There were no relevant hemoglobin-related events.

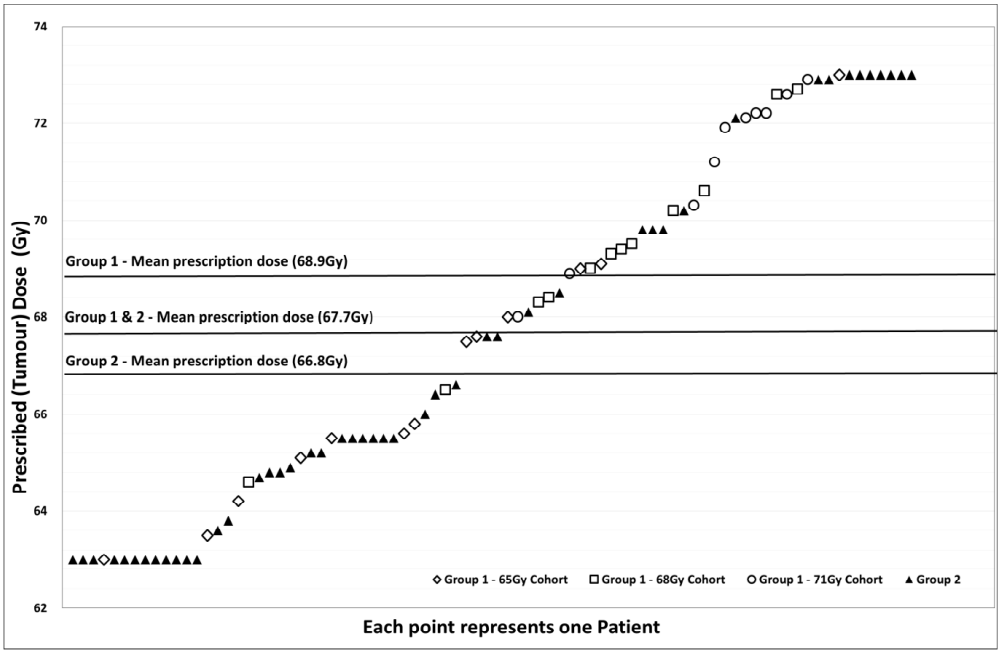
Figure 1: CONSORT diagram.



* Two patients did not start chemotherapy or RT (one patient deteriorated before start of treatment and one had collapsed lung).

†† Patients were evaluable for safety and efficacy analysis if they received one dose of either chemotherapy or RT.

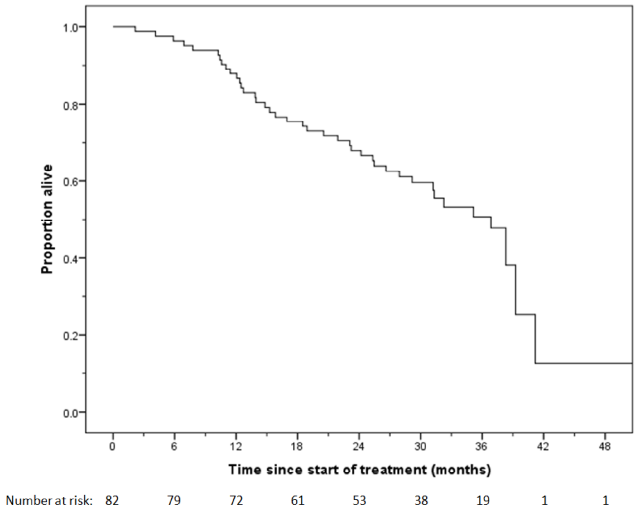
Figure 2: RT tumor doses delivered to the ICRU reference-point.



Horizontal lines show the 68.9, 66.8 and 67.7Gy mean prescribed dose-levels in Groups 1 and 2 and overall.

Figure 3: Overall and progression-free survival.

a) **Overall survival: median 36.9 months (95% CI: 31.7-42.1 months); 1 and 2 year rates are 87.8% (80.7-94.9%) and 68.0% (57.8- 78.1%); 40 events.**



b) **Overall survival by tumor stage.**