

INVITED REVIEW

Radiation dose escalation with modified fractionation schedules for locally advanced NSCLC: A systematic review

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Keywords

Acute esophagitis; EQD_{2,T}; modified fractionation; radiation dose escalation; systematic review.

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Abstract

Concomitant chemo-radiotherapy (cCRT) with 60 Gy in 30 fractions is the standard of care for stage 111 non-small cell lung cancer (NSCLC). With a median overall survival of 28.7 months at best and maximum locoregional control rates of 70% at two years, the prognosis for these patients is still dismal. This systematic review summarizes data on dose escalation by alternative fractionation, which has been explored as a primary strategy to improve both local control and overall survival over the past three decades. A Pubmed literature search was performed according to the PRISMA guidelines. Because of the large variety of radiation regimens total doses were converted to EQD_{2,T}. Only studies using an EQD_{2,T} of at least 49.5 Gy, which corresponds to the conventional 60 Gy in six weeks, were included. In a total of 3256 patients, the median OS was 17 months (range 7.4–30 months). While OS was better for patients treated after the year 2000 ($P = 0.003$) or with a mandatory ¹⁸F-FDG-PET-CT in the diagnostic work-up ($P = 0.001$), treatment sequence did not make a difference ($P = 0.106$). The most commonly reported toxicity was acute esophagitis (AE) with a median rate of 24% (range 0%–84%). AE increased at a rate of 0.5% per Gy increment in EQD_{2,T} ($P = 0.016$). Dose escalation above the conventional 60 Gy using modified radiation fractionation schedules and shortened OTT yield similar mOS and LRC regardless of treatment sequence with a significant EQD_{2,T} dependent increase in AE.

Key points

Significant findings

- Modified radiation dose escalation sequentially combined with chemotherapy yields similar outcome as concomitant treatment.
- OS is better with the mandatory inclusion of FDG-PET-CT in the diagnostic work-up.
- The risk of acute esophagitis increases with higher EQD_{2,T}.

What this study adds

- Chemo-radiotherapy (CRT) with modified dose escalation regimens yields OS and LC rates in the range of standard therapy regardless of treatment sequence. This broadens the database of curative options in patients who are not eligible concomitant CRT.

Introduction

Approximately 80% of all patients with pulmonary malignancies present with non-small cell lung cancer (NSCLC),

of which 35% are locally advanced at the time of diagnosis.^{1,2} As for pathological discrimination, 70% are non-squamous, ie, adeno- or large cell carcinomas.³ In the Europe-wide estimation for 2019, NSCLC will account for

Table 1 Selected studies

Study	Year	PET-CT	RT	SD (Gy)	TD (Gy) (5)	OTT (days)	EQD _{2,T}	N	mOS (months)	LRC (%)	AP (%) (3)	AE (%) (3)
Concomitant CRT												
Wada et al. (1)	2018	No	3D	2 + 1.2	64	28	58.9	163	23.1	60	n.s.	n.s.
Walraven et al.	2016	Yes	3D/IMRT	2.75	66	32	64.6	92	30	n.s.	n.s.	n.s.
Kerner et al.	2014	Yes	3D	2.40	60	35	55.0	284	24.6	n.s.	20.8	23.6
Maguire et al. SOCCAR	2014	No	3D	2.75	55	28	54.9	62	24.3	47	3.1	8.8
Donato et al.	2013	No	Tomotherapy	2.28	67.95	42	59.0	29	24.1	74	10	7
Bearz et al. (2)	2013	Yes	n.s.	2.40	60	35	55.0	33	24	n.s.	0	24
Chen et al. (12)	2013	Yes	IMRT	2.75	66	32	64.6	171	n.r.	n.s.	n.s.	29
de Ruysscher et al. INDAR	2012	Yes	n.s.	1.80	64.8	24	62.2	66	n.r.	n.s.	n.s.	n.s.
Casas et al. (2)	2011	No	3D	2.68	61.6	31	60.1	30	16.9	35	12.5	34.3
Curran et al.	2011	No	n.s.	1.20	69.6	41	55.0	187	15.6	71	3	45
Nyman et al. (2)	2009	No	3D	1.70	64.6	27	60.0	40	19.6	n.s.	0	20
Jitterhoeve	2007	No	3D	2.75	66	32	64.6	56	16	56	27	
Belderbos et al.	2007	No	n.s.	2.75	66	32	64.6	66	16.5	n.s.	9	17
Chen et al.	2004	No	3D	1.2 to 1.5	66	35	55.3	73	13	35	8	15
Ball et al.	1999	No	3D	2.00	60	21	60.0	41	15	75	n.s.	80
Schuster-Uitterhoeve et al.	1996	No	2D	2.75	55	28	54.9	38	16	n.s.	39.5 (4)	31.6 (4)
Cagney et al.	2018	No	3D	3.00	72	35	71.0	48	13.6	48	12.2	22.4
Sequential CRT or RT alone												
Wurstbauer et al. DART-bid*	2013 / 2017†	Yes	3D	1.80	79.2	30	73.4	116	26.3	70	11.3	33.3
Maguire et al. SOCCAR	2014	No	3D	2.75	55	28	54.9	45	18.4	45	5.2	8.5
Cannon et al.	2013	No	IMRT	2.28	57	35	51.3	37	16	61	21	48
Donato et al.	2013	No	Tomotherapy	2.28	67.95	42	59.0	32	18.6	74	10	0
Din et al.	2013	Yes	2D/3D	2.75	55	28	54.9	139	21	63	n.s.	n.s.
McPartlin et al.	2013 (13)	No	n.s.	2.75	55	28	54.9	45	7.4	n.s.	n.s.	n.s.
de Ruysscher et al. INDAR	2012	Yes	n.s.	1.80	64.8	24	62.2	129	23.6	n.s.	n.s.	n.s.
Hatton et al. INCH	2011	No	n.s.	1.50	54	12	51.8	20	25	n.s.	35 (7)	15
Jenkins et al. INCH	2011	No	3D	1.50	54	12	51.8	33	15.7	51	32.5	10
Zhu et al. (8)	2011	No	3D	2.5 + 3	68	36	64.0	34	19	61	28.4	20.6
Baumann et al. CHARTWEL	2011	No	3D	1.50	60.00	17	57.5	187	15	31	7.2	43.5
Hatton et al. INCH	2011	No	n.s.	1.50	54	12	51.8	23	17	n.s.	17 (7)	13
van Baardwijk et al.	2010 (9)	Yes	3D	1.80	61.2	23	59.2	99	16.2-17.2	67	28.3 (10)	26.5 (11)
Kepka et al.	2009	No	3D	2.80	58.8	27	59.7	173	17	40	7	7
Uitterhoeve et al.	2007	No	3D	2.75	66	32	64.6	26	16	56	23	
Belderbos et al.	2007	No	n.s.	2.75	66	32	64.6	76	16.2	n.s.	8	5
Uitterhoeve et al.	2007	No	3D	2.75	66	32	64.6	49	12	56	8.2	
Ishikura et al. ‡	2005	No	n.s.	1.80	57.6	12	56.6	29	24	57	27.5	62
Belani et al.	2005	No	3D	1.5 + 1.8 + 1.5	57.6	17	54.6	56	20.3	n.s.	23.2	73.2
Marks et al.	2004	No	3D	1.60	80.8	37	70.1	36	18	82.1	9	39
Herskovic et al.	2000	No	3D	1.10	79.2	34	66.8	32	10.5	n.s.	10.3	35.9

Table 1 Continued

Study	Year	PET-CT	RT	SD (Gy)	TD (Gy) (5)	OTT (days)	EQD _{2,T}	N	mOS (months)	LRC (%)	AP (%) (3)	AE (%) (3)
Sause et al.	2000	No	n.s.	1.20	69.6	41	55.0	154	12	n.s.	n.s.	n.s.
Saunders et al. CHART	1999	No	3D	1.50	54	12	56.3	309	16.5	23	10	19
Ball et al.	1999	No	3D	2.00	60	21	60.0	36	14.4	75	n.s.	84
King et al.	1996	No	2D	1.60	73.6	31	66.1	49	15.3	64	0	61

AE, acute esophagitis; AP, acute pneumonitis; EQD_{2,T}, biologically equivalent dose in 2 Gy fractions with an assumed start of repopulation at 21 days; IMRT, intensity modulated RT; LRC, locoregional control; mOS, median overall survival; N, number of evaluable patients per study and treatment arm; n.r., not reached; n.s., not stated; OTT, overall treatment time; RT, radiation technique; SD, single dose per fraction; TD, total dose.

Studies with different treatment arms are listed separately in the Table.

*Median total dose: 79.2 Gy (range 73.8–90 Gy). †Final toxicity data published 2017. ‡Highest single dose given. (1) "Daily concomitant boost". (2) Induction chemotherapy followed by cCRT. (3) Toxicity grade 2 or higher according to CTC if not otherwise specified. (4) WHO toxicity criteria. (5) If various dose levels were tested in the study, the median total dose was taken for this review. (6) Alternating treatment schedule: chemotherapy in week 1 and 4, radiotherapy in week 2, 3 and 6, 7. (7) The term "breathlessness" was used instead of "pneumonitis". (8) The first 19 patients were treated to a total dose of 65 Gy, the remaining 15 patients received 68 Gy. (9) The average total dose was 61.2 Gy, 13.8% of the stage III patients received the maximum dose of 79.2 Gy. (10) Dyspnea. (11) Dysphagia. (12) Total of 26 patients were also included in the Walraven analysis. (13) Minimum age 80 years, range: 80.0–94.8.

23% and 15% of all cancer deaths in men and women, respectively.⁴ According to the eighth edition of the TNM classification stage III NSCLC summarizes a scope of diverse subentities.

Thoracic radiotherapy (RT) combined with chemotherapy (CT) is the cornerstone in the treatment of stage III NSCLC. Historically sequential chemo-radiotherapy (sCRT) was the first treatment strategy in the field.⁵ During the following 1.5 decades prospective randomized control trials showed better outcome with concomitant chemo-radiotherapy (cCRT) compared to the sequential mode.^{6–9} This result was corroborated by an individual patient data meta-analysis.¹ Although cCRT with 60 Gy is regarded as the standard of care (SOC), a substantial number of patients are still treated sequentially. The majority of prospectively randomized control trials^{6–9} were performed before the routine use of ¹⁸F-FDG PET-CT.

With median overall survival (mOS) of 28.7 months and 65% locoregional control (LRC) in the conventional treatment arm clinical outcome has certainly improved over the past three decades. Nevertheless, a further improvement of survival by both better local and systemic control remains challenging.¹⁰ Better LC and OS by cCRT go hand in hand with potentially higher toxicity, which is one of the reasons why not all patients may be regarded as fit enough for the concurrent approach by the treating physician.¹¹ The second reason are comorbid conditions, which allow for the inclusion of only 30% of the patient population with stage III NSCLC in concomitant treatment regimens.⁸ While guidelines generally propose concurrent treatment some of them, such as The National Institute for Health and Care Excellence (NICE), recommend alternative fractionation schedules (eg, CHART) for patients who are not eligible for the concurrent approach.¹¹

Dose escalation by modified fractionation as the primary strategy to increase LC has been explored in several phase I and II studies.^{8,12–45} In 2015 the RTOG 0617 trial, which applied conventional dose escalation, was negative for the experimental arm in terms of LC and OS.⁴⁶ The increase of the number of fractions entails prolonged OTT, which leads to accelerated repopulation and may therefore not yield the best possible results.^{11,47,48} A meta-analysis by Mauguen *et al.* revealed an OS benefit for patients treated with alternative fractionation as opposed to conventional therapy⁴⁸ Both hyperfractionation and hypofractionation may contribute to an increase in biologically effective total dose. The latter is especially promising since it saves radiation resources and is potentially more convenient for the patient.¹⁰

Since the majority of patients die from distant metastases, an improvement in systemic treatment is necessary.³ In recent years, new systemic agents such as immune checkpoint inhibitors (ICI) have come into play. One of

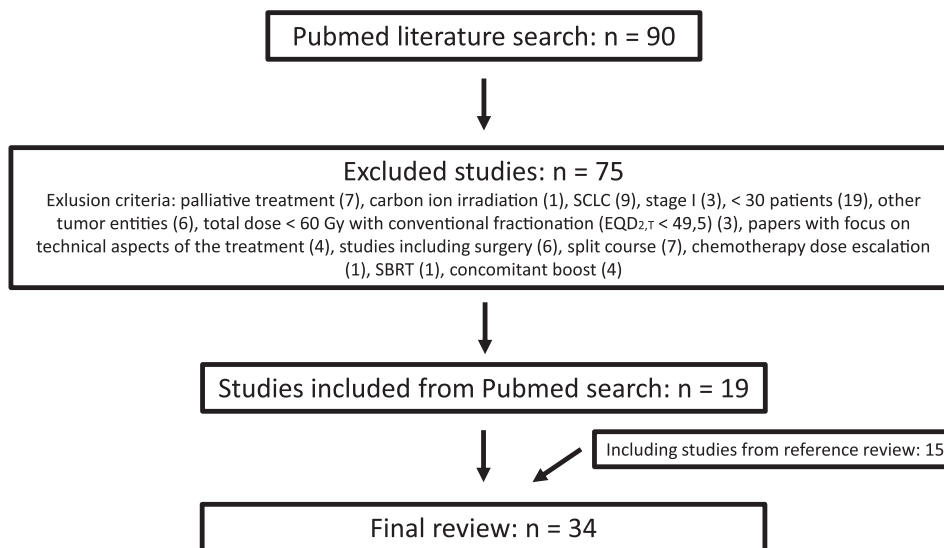


Figure 1 Selection process according to the PRISMA statement.

the underlying mechanisms of action is assumed to be radiogenic DNA damage, which activates the immune system. In addition, RT promotes PD-L1 upregulation, which is blocked by ICI.³ With the results of the PACIFIC trial, durvalumab maintenance therapy for one year after completion of CRT is regarded as the new standard regimen.^{49,50}

The aim of the current review was to summarize data accumulated in the past three decades on dose escalation by alternative fractionation with a focus on treatment sequence.

Methods

Literature search

Based on the PRISMA guidelines⁵¹ a Pubmed literature search with the following terms was performed: “(lung cancer) AND (stage III) AND (radiotherapy OR irradiation OR radiation therapy OR radiation treatment) AND (hypofract* OR accelerated) AND (clinical trial) NOT (review OR case report)”. Publications before 1990, including less than 30 patients, available in abstract only as well as in languages other than English and German, were excluded. Primarily, papers were selected by title and abstract. In a second step, the references in full papers were screened and – if suitable – included in this review. The selection process is summarized in Figure 1 and the included studies are listed in Table 1.

Studies were included if they used alternative fractionation in at least one treatment arm throughout the radiation therapy course. Alternative fractionation was defined as hypofractionated irradiation with daily doses of >2 Gy per fraction or more than one fraction per day either normofractionated, i.e. 1.8–2 Gy, or hyperfractionated

(< 1.8 Gy per fraction). For the purpose of this review, dose escalation was defined as $EQD_{2,T} > 49.5$ Gy, which equals a total dose of 60 Gy in 30 fractions given within six weeks. In accordance with the ESMO guidelines concomitant chemo-radiotherapy (cCRT) was defined as at least one cycle of systemic treatment parallel to RT.⁵² If a study compared several treatment schedules, only those using alternative fractionation either with or without systemic treatment were considered for this review.

EQD_{2,T}

Because of the wide variety of radiation regimens total doses were converted to $EQD_{2,T}$ assuming an $\alpha/\beta = 10$ for tumor as well as acute effects and a T_{ref} of 21 days as the starting point for accelerated repopulation.^{53,54} D , d and D_{prolif} are defined as total physical dose, dose per fraction and time loss factor (= 0.6 Gy per day), respectively.

$$EQD_{2,T} = D \cdot \frac{d + \alpha/\beta}{2 + \alpha/\beta} - \text{MAX}(0, T - T_{ref}) \cdot D_{prolif}$$

If various single doses were used, subtotals were calculated and finally added up to one total $EQD_{2,T}$.

Toxicity

For the purpose of this analysis, toxicities were only considered clinically relevant as of grade 2 according to the CTCAE versions available at the time the study was published. If the authors used a different scoring system, this is explicitly specified.

Statistical analysis

Clinical outcome parameters such as mOS, LRC and AE were plotted as a function of EQD_{2,T} either based on the numbers stated in the publications or derived from the respective Kaplan-Meier-plots therein. In order to detect differences between cCRT and sCRT the nonparametric Mann-Whitney-U test was used. The correlations between EQD_{2,T} and mOS, LRC and AE were calculated with the Pearson test.

Results

Literature search

The Pubmed literature search with the above-mentioned terminology yielded 90 items. Papers were excluded on the basis of the following criteria: palliative treatment (7), carbon ion irradiation (1), SCLC (9), stage I (3), < 30 patients (19), other tumor entities (6), total dose < 60 Gy with conventional fractionation (EQD_{2,T} < 49.5) (3), papers with focus on technical aspects of the treatment (4), studies including surgery (6), split course (7), chemotherapy dose escalation (1), stereotactic ablative body radiotherapy (SABR) (1) and late concomitant boost (4). In total, 34 studies (42 treatment arms altogether) were included either as a result of the search strategy or as the review of the references in selected publications (Table 1). These studies encompass the time span between 1996 and 2018, which marks the transition from early 3D planning to modern treatment planning with IMRT/VMAT and IGRT. A total of 16 studies used cCRT (table). In six of these,^{18,20,24,29,30,32} one treatment arm was either sCRT or RT alone. A total of 18 applied nonconcomitant treatment, ie, sCRT or RT alone (Table 1). In 22 treatment arms, the daily dose was applied in one fraction of more than the conventional 2 Gy, whereas in 20 treatment arms at least two daily fractions were used. The median total EQD_{2,T} in all studies was 59.1 Gy (range 51.3–73.4 Gy). The total number of evaluable patients was 3256 with a median of 49 (range 20–309) per treatment arm.

Overall survival

The mOS for all studies was 17 months (range 7.4–30 months, see Table 1). In two treatment arms, the median was not reached.^{18,26} The correlation between EQD_{2,T} and mOS was not significant (Pearson test P -value = 0.437). The mOS for patients treated with cCRT was 18.3 months (range: 13–30 months), which did not differ significantly from the 16.7 months (range: 7.4–26.3 months) achieved with sCRT (Mann-Whitney-U test: P -value = 0.106; Fig 2a,b). The mOS was significantly

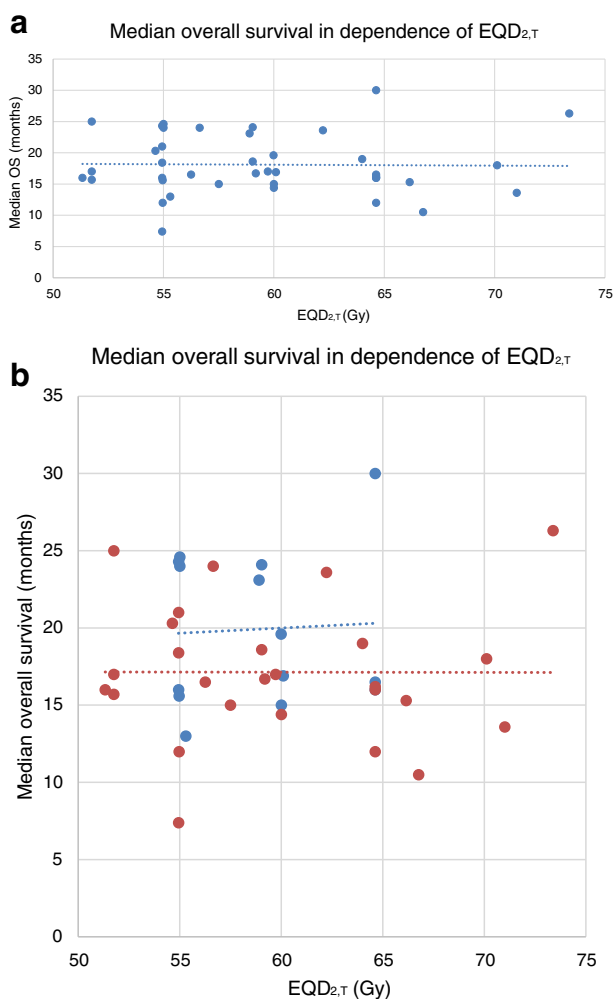


Figure 2 (a) Median overall survival. The correlation between EQD_{2,T} and mOS was not significant (Pearson test P -value = 0.437). (b) Median overall survival for patients treated with concomitant (cCRT) versus sequential chemo-radiotherapy (sCRT) did not differ significantly (Mann-Whitney-U test: P -value = 0.106). (●) cCRT, (●) sCRT or RT alone, (.....) Linear (cCRT), (.....) Linear (sCRT or RT alone)

better for patients treated after the year 2000 (Mann-Whitney-U test: P -value = 0.003). In the eight studies which included a mandatory ¹⁸F-FDG-PET-CT scan in the diagnostic work-up, the patients survived significantly longer than in those without (Mann-Whitney-U test: P -value = 0.001; see Table 1).

Locoregional control

For 26 treatment arms, the median LRC was available. The overall median LRC at two years was 59% (range: 23%–82.1%, see Table 1). The correlation between EQD_{2,T} and LRC was not significant (Pearson test P -value = 0.371). Furthermore, no significant differences could be detected

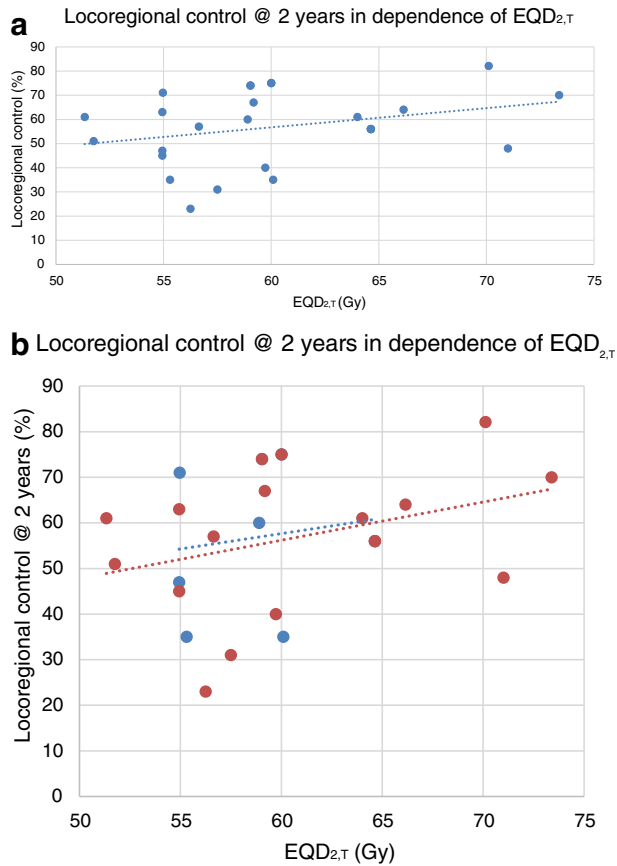


Figure 3 Locoregional control after two years. (a) The correlation between EQD_{2,T} and LRC was not significant (Pearson test *P*-value = 0.371). (b) Locoregional control after two years for patients treated with concomitant (cCRT) versus sequential chemo-radiotherapy (sCRT) did not differ significantly (Mann-Whitney-U test: *P*-value = 0.651). (●) cCRT, (●) sCRT or RT alone, (-----) Linear (cCRT), (-----) Linear (sCRT or RT alone)

between cCRT (median: 56%, range 35%–75%) and sCRT (median: 59%; range: 23%–82.1%; Mann-Whitney-U test: *P*-value = 0.651; Fig 3a,b). We also compared cCRT to sCRT in studies published after the year 2000 and found no differences in LRC (Mann-Whitney-U test: *P*-value = 0.352). A comparison of the two treatment modalities in those studies with mandatory ¹⁸F-FDG-PET-CT in the diagnostic work-up revealed a similar result (Mann-Whitney-U test: *P*-value = 0.242).

Acute esophagitis

The most common toxicity was acute esophagitis (AE), which was reported in 32 treatment arms with an overall median rate of 24% (range: 0%–84%). In three study arms AE was summarized with AP under “treatment toxicity” and was not assessed in seven treatment schedules

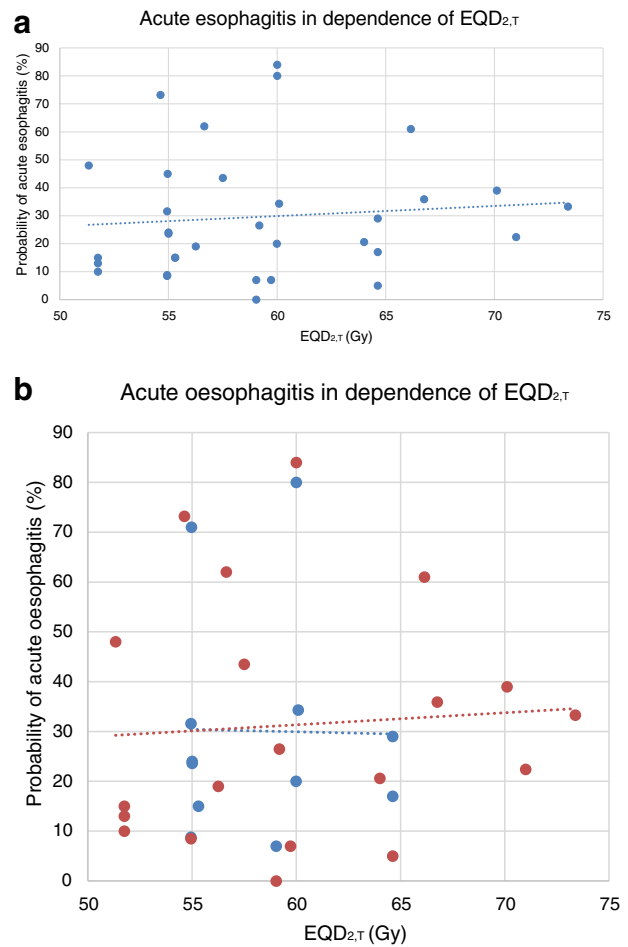


Figure 4 (a) Acute esophagitis (AE). The occurrence of AE depended on EQD_{2,T} (Pearson correlation: *P* = 0.016). (b) Acute esophagitis in patients treated with concomitant (cCRT) versus sequential chemo-radiotherapy (sCRT) did not differ significantly (Mann-Whitney-U test: *P*-value = 0.640). (●) cCRT, (●) sCRT or RT alone, (-----) Linear (cCRT), (-----) Linear (sCRT or RT alone)

(Table 1). While the incidence of AE was not correlated with the sequence of CRT (Fig. 4,b) a significant correlation with EQD_{2,T} could be detected. In treatment arms with EQD_{2,T} above median (= 59.11 Gy) patients had a significantly higher incidence of AE (Pearson test *P*-value = 0.016). The probability of AE increased at a rate of 0.5% per Gy increment in EQD_{2,T}.

Discussion

This systematic review demonstrated that cCRT and sCRT are equally effective in terms of mOS and LRC if alternative radiation schedules are used. OS was significantly better if patients were treated after the year 2000 with

compulsory inclusion of ^{18}F -FDG-PET-CT in the diagnostic work-up. The risk of AE increased with higher EQD_{2,T}.

The standard of care for stage III NSCLC is cCRT with 60 Gy combined with two cycles of platinum-based chemotherapy. Four prospectively randomized control trials published between 1999 and 2011 demonstrated the superiority of this treatment mode compared to sCRT.^{6–9} The highest mOS and LRC rates were 17 months⁸ and 72%,⁶ respectively. As for toxicity, 18%⁹ to 32%⁷ AE and 4%^{6,8,9} to 5%⁷ AP were reported. A meta-analysis based on individualized patient data showed that higher LRC achieved by cCRT translates into better OS.¹ In fact, radiation dose escalation is a strategy to improve the dismal prognosis for patients with stage III NSCLC since it harbors the potential to increase LRC, which may – combined with effective systemic treatment – prolong survival.

The latest prospectively randomized phase III trial on dose escalation was the four-armed RTOG 0617 study.⁴⁶ In this randomized trial, 544 patients received platinum-based chemotherapy concurrently with a total dose of 60 Gy or 74 Gy with or without the addition of cetuximab.⁴⁶ LC at two years ranged between 61.4% and 69.3%. The mOS in the standard treatment arm with 60 Gy was 28.7 months compared to 20.3 months with dose escalation. The AP and AE rates were 7% and 44%. One of the major reasons for the unexpected outcome was the prolonged OTT of 7.5 weeks in the experimental arm.⁴⁶ It also appears that enrollment policy has influenced OS in as far as patients treated in high volume centers had easier access to advanced treatment modalities, which resulted in better OS⁵⁵ because of lower doses to OARs.^{55,56} Although RTOG 0617 provides evidence that there is no gain in conventional dose escalation, alternative radiation fractionation schemes may achieve better OS by biological dose escalation compared to conventional RT.⁴⁸

A meta-analysis by Manguen *et al.* revealed a significant absolute OS benefit of 2.5% with alternatively fractionated RT compared to the conventional 60 Gy.⁴⁸ No difference between the two treatment approaches could be detected for LRC control. The pre-requisite for inclusion in this meta-analysis was that the patients in the included studies received a minimum total dose of 60 Gy. In terms of toxicity, the authors publish robust data only on AE, with a two-fold increase in the experimental arms up to an average of 19% clinically relevant esophagitis. In summary, they conclude that their OS data support the rationale for increasingly aggressive radiation schedules.⁴⁸ Our systematic review including more than 3200 patients in 42 treatment arms^{8,12–45} partly revealed comparable results for mOS, LRC and AE. Since the results of the meta-analysis by Manguen *et al.* are mainly driven by one study, ie, CHART, the authors' conclusion that alternative fractionation as such leads to better mOS could be mitigated in the

sense that alternative dose escalation with shortened OTT is successful.

As mentioned in the context of the RTOG 0617 trial, prolonged OTT triggers accelerated repopulation.^{57,58} This is why conventional dose escalation may not be the best possible option to improve mOS and LRC. This idea is supported by Kaster *et al.* who found a relationship between biologically effective dose including a time factor and OS.¹⁰ The results of the current study corroborate such a correlation between EQD_{2,T} and AE (Fig 4) with a toxicity increase of 0.5% per 1 Gy increment in total dose. This is important since toxicity is of major concern with any dose escalation strategy.^{10,59} While in a substantial part of the reports radiation techniques were not explicitly mentioned, most studies used 3D used conformal RT. Based on the given data it was not possible to draw any conclusions with respect to OS and AE (see Table 1). Nevertheless, it is not counterintuitive that with modern radiation technologies such as IMRT/VMAT, protons and SABR, radiation doses to the OARs can be kept low thereby allowing for safe treatment delivery presumably with less toxicity increase per Gy dose escalation.

In recent years, immune checkpoint inhibitors (ICI) have shown their efficacy in the treatment of stage III NSCLC.^{49,50} Currently, four ICIs are available for the treatment of unresectable stage III NSCLC. A clinicaltrials.gov search revealed 28 studies worldwide investigating the combination of radiation and ICIs. (accessed on 10 September 2019). In light of the promising results of the PACIFIC trial,^{49,50} which have made CRT followed by durvalumab maintenance therapy the new SOC, its efficacy and toxicity profile in combination with alternative fractionation remains an unresolved issue. The total doses in the PACIFIC trial ranged from 54 to 66 Gy delivered in conventional fractionation. Unfortunately, details on radiation therapy were not described, which could have been rewarding since the underlying mechanism of action is – putatively to a large extent – based on radiogenic stimulation of the immune system potentiated by PD-L1 blockage. Thus far no integration of ICI in alternative fractionation regimens has been reported. Nevertheless, this could be an interesting treatment approach since higher total radiation doses could – at least theoretically – stimulate the immune system in a more effective way. What this means in terms of toxicity, especially for AP, is yet to be resolved. Since checkpoint inhibitors themselves have a considerable pneumonitis potential, the question of supra-additive effects of high dose irradiation combined with ICIs is of special interest to the radio-oncological community.

This systematic review has several limitations. We had no access to individualized patient data, so the numbers were either taken directly from the publications or extracted from the graphs in the respective results sections.

The current analysis is potentially not very reliable with respect to LRC as it was reported in only 62% (26/42) of the treatment arms. Toxicities are only partially comparable among studies since the CTC versions changed over time and some studies used different scoring systems. Finally, with systematic reviews like this, nomenclature is a problem in the sense that some publications might not have been considered simply because they were registered with keywords that were not included in our search terms.

In summary, it seems that the question of the best possible treatment strategy for stage III patients is a matter of ongoing debate, which can only be resolved by direct comparison of modified fractionation schedules to SOC within a prospective randomized control trial.^{2,10,59,60} Such a study must include ¹⁸F-FDG-PET-CT in the diagnostic work-up and use modern radiation techniques to escalate the dose to the tumor while sparing OARs.

In conclusion, dose escalation above the conventional 60 Gy using modified radiation fractionation schedules and shortened OTT yield similar mOS and LRC regardless of treatment sequence with a significant EQD_{2,T} dependent increase in AE. In order to counterbalance toxicity the use of modern irradiation techniques is mandatory.

Disclosure

All authors declare that they have no conflict of interest.

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