Radical-Intent Hypofractionated Radiotherapy for Locally Advanced Non–Small-Cell Lung Cancer: A Systematic Review of the Literature

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Abstract

Purpose: To identify survival and toxicity characteristics associated with radical-intent hypofractionated radiotherapy for the treatment of stage III non–small-cell lung cancer (NSCLC). **Materials and Methods:** Relevant studies were identified from a systematic PubMed search of articles published between January 1990 and January 2014. All studies were peer reviewed and included both retrospective and prospective studies of NSCLC patients being treated with radical hypofractionated radiotherapy. Data on overall survival (OS) and toxicity were extracted from each of the studies where available. **Results:** Of 685 studies initially identified by the search, a total of 33 studies were found to be relevant and were included in this systematic review. The number of fractions ranged from 15 to 35, the dose per fraction ranged from 2.3 to 3.5 Gy, and the delivered dose ranged from 45.0 to 85.5 Gy. Fifteen of the studies included concurrent chemotherapy, while 18 did not. OS was found to be associated with tumor biological effective dose, with the Pearson correlation coefficient ranging from 0.34 to 0.48. For both concurrent and nonconcurrent chemoradiotherapy acute pulmonary, late esophageal and late pulmonary incidences of toxicity ranged from 1.2% to 12.2%, but had 95% confidence intervals that included zero. The greatest incidence of toxicity was acute esophageal toxicity at 14.9% (95% confidence interval, 0.7%, 29.1%). **Conclusions:** There is a moderate linear relationship between biological effective dose and OS, and greater acute esophageal toxicity with concurrent chemotherapy. Improving outcomes in stage III NSCLC may involve some form of hypofractionation in the context of systemic concurrent therapy.

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Introduction

Lung cancer is the leading cause of cancer-related mortality, representing just over one quarter of all deaths.[1] Approximately 80% of lung cancer patients have non–small-cell lung cancer (NSCLC), and most present with advanced stage at diagnosis.[2] The mainstay of curative-intent treatment for such patients is chemoradiation (CRT) provided either concurrently or sequentially with chemotherapy, using conventionally fractionated radiation doses in the range of 60 to 66 Gy in 30 to 33 fractions.[3] In general, the 5-year survival for these patients remains a dismal 13% to 16%.[4] Even more recently, the Radiation Therapy Oncology Group (RTOG) 0617 study demonstrated a median survival of 28 months for patients with stage III disease treated with concurrent chemoradiotherapy.[5]

Improving outcomes for patients with stage III disease remains a challenge despite multiple decades of clinical trials. In order to improve survival, both better local control[6] and systemic control are required. The traditional approach to improving local control is to increase the number of fractions to increase the overall dose. Preliminary evidence suggested that this approach could provide an overall survival benefit.[7] However, the RTOG 0617 trial, a randomized controlled trial testing this hypothesis, found that patients who received higher doses delivered via additional fractions of 2 Gy per day resulted in worse survival and reduced patient-reported quality of life.[5,8]

There are likely multiple contributing factors to this counterintuitive result,[9] but the lengthier overall treatment time (OTT) may

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have played a significant role. Previous work has demonstrated that lengthening treatment time beyond 6 weeks has a negative impact on overall survival,[10] likely due to accelerated repopulation of tumor cells.

In general, there are 2 approaches whereby the deleterious effect of an extended OTT might be mitigated in clinical practice while still enabling delivery of an increased biological effective dose (BED): hyperfractionation and hypofractionation. Hyperfractionation represents an increase in the total number of delivered fractions, at a reduced dose per fraction, with treatment delivered twice (or more) per day. Although hyperfractionation has been associated with a significant survival benefit over conventional fractionation,[11] there are several barriers to the widespread implementation of this approach, including the complicated logistics and increased resources required to deliver these dose schedules, as well as the fact that it is not entirely clear how to optimize the integration of such treatment with chemotherapy.[12,13]

On the other hand, hypofractionation represents the delivery of fewer fractions at an increased dose per fraction, typically only once per day. Until recently, hypofractionation was not possible because of the concern about severe adverse effects on the lung and soft tissues of chest wall,[14] particularly in the context of concurrent CRT.[15] However, advanced technologies such as intensity-modulated radiotherapy, image-guided radiotherapy, treatment gating, and positron emission tomography—computed tomography imaging have made this approach more feasible, to the point where a hypofractionated regimen of 55 Gy in 20 fractions is now the most common fractionation schedule in the United Kingdom.[16] There are now ongoing prospective trials evaluating the efficacy and safety of hypofractionated radiotherapy including a randomized phase III trial (NCT01459497).[17,18]

Although each approach holds promise, the logistical benefit inherent in a smaller number of fractions is particularly attractive, especially in the setting of a busy radiation treatment center. Therefore, the goal of this review was to determine the state of the current literature regarding curative-intent hypofractionated radiotherapy, with or without chemotherapy, for locally advanced NSCLC.

Methods

Research Question

What are the survival and toxicity characteristics associated with hypofractionated radiotherapy with radical intent for treatment of stage III NSCLC?

Search Strategy

PubMed was searched using the following concepts: (1) synonyms for nonmetastatic NSCLC; (2) synonyms for radiotherapy (3) synonyms/related terms for hypofractionation (dose escalation, accelerated, concomitant boost, simultaneous infield boost); (4) concepts 1, 2, and 3 were combined with a boolean operator; and (5) references from the articles identified using the above strategy were also searched for relevant articles.

The following search strategy was performed on January 17, 2014, of the PubMed database: (lung AND (non small cell OR NSCLC) NOT metast*[TI]) AND (radiation therapy OR radiotherapy) AND (hypofract* OR concomitant boost OR dose-per fraction escalation OR dose escalation OR accelerated OR simultaneous infield boost) NOT case reports[Publication Type].

Study Criteria

Studies were considered for inclusion (by T.K. and G.R.) if they met the following criteria: adult patients with stage III NSCLC; retrospective or prospective study design; consistent hypofractionated regimen (ie, $>$ 2 Gy per fraction); once-daily treatment; high total delivered dose ($\geq$ 45 Gy); external beam radiation with photons; and English language.

Data Extraction

Relevant information regarding dose schedule, treatment planning, systemic therapy use, trial design, and outcome (overall survival, observed toxicity) was extracted into a database. Studies were further subdivided into concurrent chemotherapy versus no concurrent chemotherapy groups. Survival data were extracted (by T.K. and reviewed by G.R.) from the text where possible. When survival data were depicted only in a figure, the results were estimated manually from that figure. For dose-escalation trials, the mean of all doses delivered was used to define the relevant reference dose for our study. Esophageal toxicity was defined as esophagitis, and lung toxicity was defined as radiation pneumonitis. Relevant toxicities were defined as events that could be scored as grade 3 or higher according to the toxicity scale used in the individual study. Timing of any observed toxicity (acute or late) was based on the study definition. For trials with both a concurrent and nonconcurrent chemotherapy arm, each arm of the trial was recorded in the appropriate table.

Data Analysis

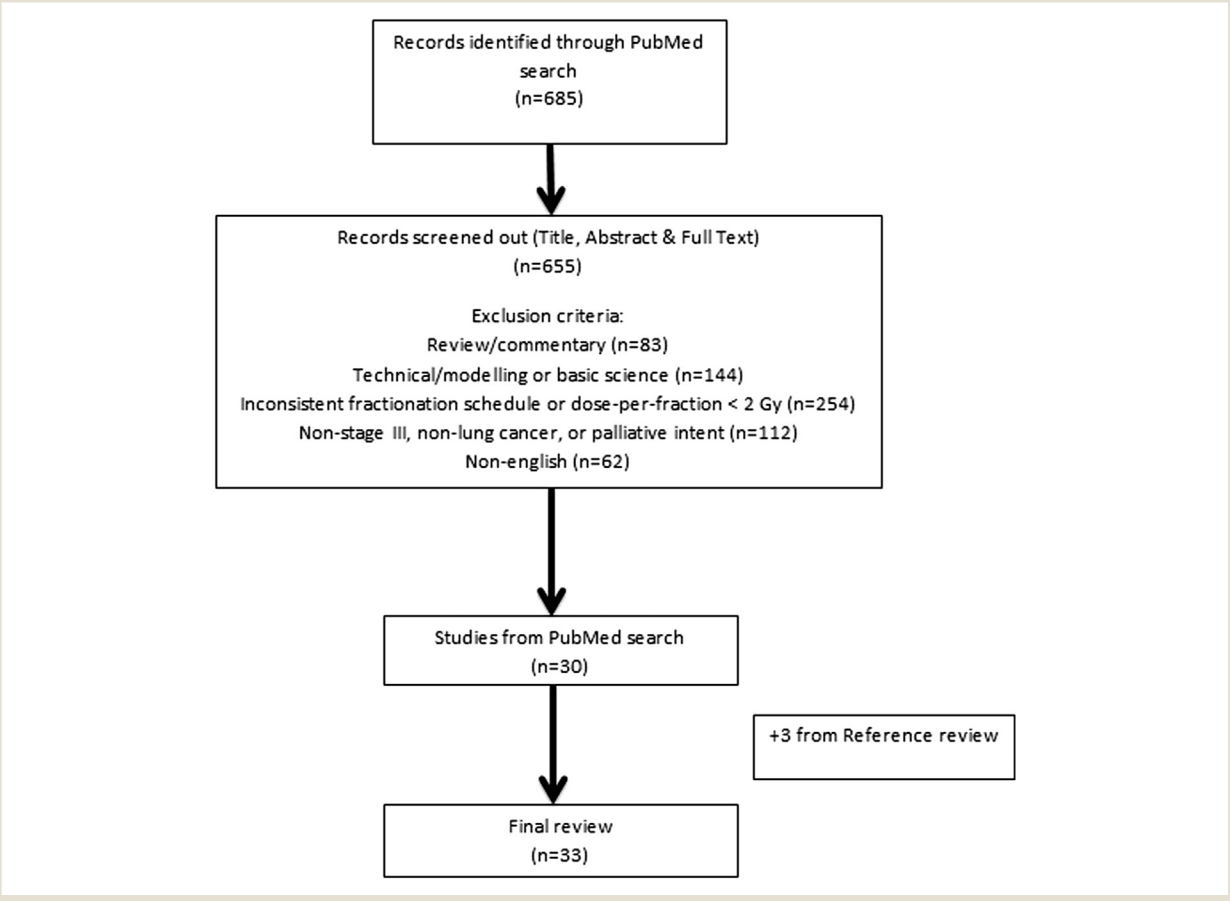
BED for late ($\alpha/\beta = 3$) and early ($\alpha/\beta = 10$) effects were calculated for the dose fractionation schedules, as well as an adjustment for time factors for acute effects.[19] Overall survival as a function of BED was plotted for studies within the past 15 years that enrolled at least 30 patients with stage III NSCLC, and a linear regression was performed in Excel 2007 (Microsoft, Redmond, WA), with Pearson correlation coefficient and line of best fit reported. Toxicity as a function of BED was plotted for all studies that reported esophageal and pulmonary toxicity. The Pearson correlation coefficient for BED versus toxicity was calculated, and a 2-sided Student t distribution was used to determine statistical significance. The weighted mean incidence of toxicity (acute and late, lung and esophagus) of concurrent and nonconcurrent CRT was calculated, along with its 95% confidence interval. Similar analyses between OTT and overall survival/toxicity was performed as well.

Results

Search Results

Our search strategy initially identified 685 articles, of which 655 were excluded for several reasons (Figure 1). We eventually identified a total of 33 relevant articles (30 from the systematic search, and 3 from the references within those 30 articles) describing the use of hypofractionated radiotherapy with radical intent in stage III NSCLC. This represented a total of 1902 patients (Table 1, Table 2, Supplementary Appendix A). The number of fractions ranged from 15 to 35, with delivered doses

Figure 1 Flow Diagram Related to Electronic Search Strategy



ranging from 45 to 85.5 Gy, and dose per fraction ranging from 2.25 to 3.5 Gy. The acute time-unadjusted BED ranged from 58.5 to 114.7 Gy, while the time-adjusted BED ranged from 55.7 to 106.4 Gy, and the late BED ranged from 90.0 to 183.0 Gy. Ten studies were retrospective, while the remainder were prospective, which included dose-escalation trials (n = 3), feasibility studies (n = 5), cohort studies (n = 3), and phase I/II and III trials (n = 12).

Concurrent Chemotherapy

Fifteen studies were identified that included concurrent chemotherapy (Table 1). Of these, 4 compared concurrent chemotherapy with sequential chemotherapy. The most common forms of concurrent chemotherapy were cisplatin (8 studies), vinorelbine (6 studies), carboplatin (3 studies), and paclitaxel (3 studies). Other forms of concurrent systemic therapy included cetuximab, docetaxel, carboplatin, and doxorubicin.

The number of fractions ranged from 15 to 30, with delivered doses ranging from 52.5 to 75 Gy, and dose per fraction ranging from 2.24 to 3.5 Gy. The acute time-unadjusted BED ranged from 70.9 to 97.5 Gy, while the acute time-adjusted BED ranged from 64.6 to 89.2 Gy, and the late BED ranged from 108.8 to 150.0 Gy. The median survival ranged from 8 months to 29.5 months. Actuarial overall survival was reported for 1-year (46% to 80%), 2-year (24% to 58%), 3-year (24% to 44%), and 5-year (15% to 33.6%) time points.

Acute esophageal toxicity occurred in 0% to 22% of patients, and acute pulmonary toxicity occurred in 0% to 10% of patients. Late esophageal toxicity occurred in 0% to 25% of patients, and late pulmonary toxicity occurred in 0% to 25% of patients. The weighted mean incidences of acute and late toxicities (including 95% confidence intervals) are displayed in Table 3.

Nonconcurrent Chemotherapy

Twenty-two studies and treatment arms were identified that did not use concurrent chemotherapy. These studies included a variety of systemic approaches, which included neoadjuvant chemotherapy, adjuvant chemotherapy, biologics, nontraditional agents, or no chemotherapy at all (Table 2).

The number of fractions ranged from 15 to 35, with delivered doses ranging from 45 to 85.5 Gy, and dose per fraction ranging from 2.25 to 3.42 Gy. The acute time-unadjusted BED ranged from 58.5 to 114.7 Gy, while the time-adjusted BED ranged from 55.7 to 106.4 Gy, and the late BED ranged from 90.0 to 183.0 Gy. The median survival ranged from 7.4 months to 21.4 months. Actuarial overall survival was reported for 1-year (41% to 75%), 2-year (18% to 42%), 3-year (7% to 32%), and 5-year (0% to 7.4%) time points.

Table 1 Studies With Concurrent Chemoradiotherapy

Study	Dose	Fraction	Dose/fx	Acute BED	Late BED	3 Year OS (%)	1 Year OS (%)	AE (%)	AP (%)	LE (%)	LP (%)
Machtay (2005)[21]	60	20	3	78.0	120.0			0	0	0	25
Belderbos (2007)[22]	66	24	2.75	84.2	126.5	29	56	17	9	5	18
Uitterhoeve (2007)[23]	66	24	2.75	84.2	126.5	31	57	NR	NR	5[a]	18[a]
Tsoutsou (2008)[24]	52.5	15	3.5	70.9	113.8		28	0	0	NR	NR
Bral (2010)[25]	67.2	30	2.24	82.3	117.4			NR	NR	NR	NR
Matsuura (2009)[26]	65	26	2.5	81.3	119.2	44	90	0	0	0	0
Casas (2011)[27]	61.6	23	2.68	78.2	116.7	34	59	6.	3	0	0
Carruthers (2011)[28]	55	20	2.75	70.1	105.4			13	3	NR	NR
Maguire (2012)[17]	55	20	2.75	70.1	105.4	38	73	NR	NR	NR	NR
Lin (2013)[29]	69	22-24	3	85.8	132.0			15	8	NR	NR
Liu (2013)[30]	75	25	3	78.0	120.0		61	15	8	8	0
Chen (2013)[31]	55	20	2.75	70.1	105.4		69	22	NR	11	NR
Donato (2013)[32]	68.4	30	2.28	82.7	118.1		77[a]	7	10[a]	0[a]	5[a]
van Den Heuvel (2013)[33]	66	24	2.75	84.2	126.5		80	NR	NR	NR	NR
Bearz (2013)[34]	60	25	2.4	74.4	108.0	24	80	3	0	0	0

Abbreviations: AE = acute esophagitis; AP = acute pneumonitis; LE = acute esophagitis; LP = late pneumonitis; NR = not reported; OS = overall survival for stage III non–small-cell lung cancer.
[a]Toxicity data reported for both concurrent and nonconcurrent chemoradiotherapy.

Acute esophageal toxicity occurred in 0% to 8% of patients, and acute pulmonary toxicity occurred in 0% to 10% of patients. Late esophageal toxicity occurred in 0% to 5% of patients, and late pulmonary toxicity occurred in 0% to 18% of patients. The weighted mean incidences of acute and late toxicities (including 95% confidence intervals) are displayed in Table 4.

Table 2 Studies With Nonconcurrent Chemoradiotherapy

Study	Dose	Fraction	Dose/fx	Acute BED	Late BED	3 Year OS (%)	1 Year OS (%)	AE (%)	AP (%)	LE (%)	LP (%)
Schuster-Uitterhoeve (1993)[35]	60	20	3	78.0	120.0		57	0	6	NR	NR
Graham (1995)[36]	75	28	2.68	95.2	142.1	18	41	5	0	NR	NR
Bernier (1999)[37]	55	20	2.75	70.1	105.4			6	9	3	6
Nguyen (1999)[38]	45	15	3	58.5	90.0			NR	NR	NR	NR
Sun (2000)[39]	65	26	2.5	81.3	119.2			0	0	NR	NR
Holloway (2004)[40]	84	35	2.4	104.2	151.2			NR	NR	NR	NR
Lester (2004)[41]	55	20	2.75	70.1	105.4	22	57	0	0	0	0
Thirion (2004)[42]	72	24	3	93.6	144.0		68	8	4	0	0
Kepka (2009)[43]	56.7-60.9	21	2.7-2.9	72.0-78.5	107.7-119.8	19	69	7	0	0	6
Pemberton (2009)[12]	55	20	2.75	70.1	105.4	7	65	NR	NR	NR	NR
Bral (2010)[44]	70.5	30	2.35	87.1	125.7	18	65	NR	NR	0	16
Zhu (2011)[45]	65-68	25-26	2.6	81.9-85.8	121.3-127.3	32	68	6	3	NR	NR
Monaco (2012)[46]	67.5	30	2.25	82.7	118.1			0	0	NR	NR
Amini (2012)[47]	45	15	3	58.5	90.0	12	53	NR	NR	NR	NR
Din (2013)[13]	55	20	2.75	70.1	105.4			0	0	NR	NR
McPartlin (2013)[48]	55	20	2.75	70.1	105.4			NR	NR	NR	NR
Osti (2013)[49]	60	20	3	78.0	120.0		75	7	3	3	7
Cannon (2013)[18]	57-85.5	25	2.28-3.42	70.0-114.7	100.3-183.0	29		0	0	0	0
Belderbos (2007)[22,b]	66	24	2.75	84.2	126.5	22	69	5	8	4	13
Uitterhoeve (2007)[23,b]	66	24	2.75	84.2	126.5	19	53	NR	NR	5[a]	18[a]
Donato (2013)[32,b]	68.4	30	2.28	82.7	118.1		77[a]	0	10[a]	0[a]	5[a]
Maguire (2012)[17,b]	55	20	2.75	70.1	105.4	27	83	NR	NR	NR	NR

Abbreviations: AE = acute esophagitis; AP = acute pneumonitis; LE = acute esophagitis; LP = late pneumonitis; NR = not reported; OS = overall survival for stage III non–small-cell lung cancer.
[a]Toxicity data reported for both concurrent and nonconcurrent chemoradiotherapy.
[b]Study with concurrent and nonconcurrent chemoradiotherapy arms, with the nonconcurrent arm reported here.

Table 3 Reported Weighted Toxicity for Studies With Concurrent Chemoradiotherapy

Site	Acute, Mean (95% CI)	Late, Mean (95% CI)
Esophagus	14.9% (0.7%, 29.1%)	6.6% (−1.9%, 4.0%)
Lung	7.9% (−9.8%, 20.9%)	12.2% (−3.8%, 8.1%)

Abbreviation: CI = confidence interval.

Lesional BED/OTT: Overall Survival and Toxicity

One-, 2-, and 3-year overall survival versus acute effects BED lesional dose (BED10), including both time-adjusted and time-unadjusted BEDs, as well as late-effects BED lesional dose (BED3), are depicted in Figure 2. The Pearson correlation coefficient ranged from 0.34 to 0.48 (Figure 2). None of these correlation coefficients reached statistical significance (ie, all $P > .05$). The slope of the line of best fit ranged from 0.0036 to 0.007. The various toxicities versus lesional BED are depicted in Figure 3. The correlation between lesional BED and acute and late toxicity for both esophagus and lung was not statistically significant ($P > .05$). There was a positive relationship between overall survival and OTT (not statistically significant, but similar r values to the BED−overall survival [OS] relationships; Supplementary Appendix B). There was also a negative relationship between toxicity (exception: late pneumonitis) and OTT (not statistically significant, but similar r values to the BED−toxicity relationships).

Discussion

This systematic literature review identified 33 articles describing more than 1900 patients with stage III NSCLC treated with radical intent with a dose per fraction greater than the conventional 2 Gy per fraction. The published literature is heterogenous, with a wide variety of dose prescriptions (ranging from 45 Gy in 15 fractions to 75 Gy in 28 fractions), and a correspondingly wide range of survivals and toxicities. However, the analysis demonstrated a moderate linear relationship between lesional BED and overall survival: for every 1 Gy increase in BED, there was an absolute overall survival benefit ranging from 0.36% to 0.7%.

This positive relationship between BED and overall survival is consistent with recent work by Machtay et al[20] examining the relationship between BED and survival in conventionally fractionated and hyperfractionated regimens, where a 1 Gy increase in BED resulted in a 4% (95% confidence interval 3%, 5%) relative improvement in survival. In the context of 15% long-term survival, a 4% relative improvement in survival, as found by Machtay et al, corresponds to an absolute improvement of 0.6%, which is similar to the results from our literature review.

Table 4 Reported Weighted Mean Toxicity Mean With 95% Confidence Intervals for Studies With No Concurrent Chemoradiotherapy

Site	Acute, Mean (95% CI)	Late, Mean (95% CI)
Esophagus	1.9% (−3.84%, 7.74%)	1.4% (−2.5%, 5.4%)
Lung	1.2% (−4.2%, 6.7%)	6.9% (−5.6%, 19.5%)

Abbreviation: CI = confidence interval.

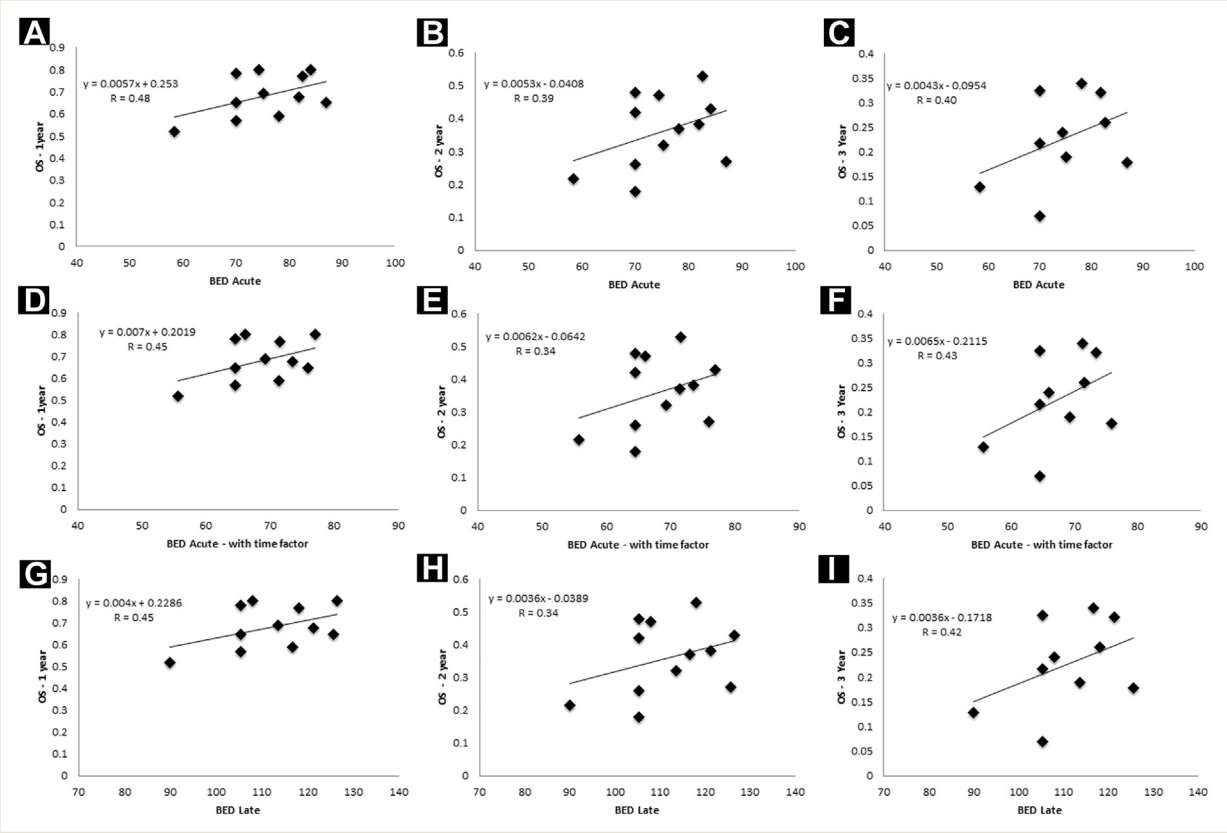
This relationship between BED and survival is only moderately strong, as there are multiple other factors contributing to OS in stage III NSCLC, including performance status, age, stage (IIIA vs. IIIB), weight loss, and the high systemic relapse risk associated with locally advanced NSCLC.[50] One of the most important factors imperfectly captured by BED is the OTT. It has been demonstrated that there is an a loss of absolute 3-year survival rate of 1.6% per day OTT prolongation beyond 6 weeks due to rapid tumour repopulation in NSCLC.[10] This repopulation may be one of the factors contributing to the disappointing results of RTOG 0617 in which higher doses of radiation did not improve survival. RTOG 0617 demonstrated an 18-month OS of 66.9% versus 53.9% ($P = .0007$) for 60 Gy versus 74 Gy.[5] In order to deliver this higher dose, the dose per fraction was maintained at 2 Gy and the OTT was extended from 6 weeks to 7.5 weeks.

Hypo- and hyperfractionation also achieve an increased BED but without lengthening OTT. A common hyperfractionation regimen involves the delivery of 54 Gy provided in 12 consecutive days (including weekends) with 1.5 Gy provided 3 times per day.[11] This approach was shown by the CHART trial to be significantly better than the conventional 60 Gy in 30 fractions, as there was a 24% reduction in the relative risk of death, or a 9% absolute improvement in 2-year survival.[11] This survival benefit was also seen in a recent meta-analysis, which demonstrated a 2.5% absolute overall survival benefit at 5 years over conventional fractionation.[51]

However, despite the apparent advantages of hyperfractionation, there are also significant disadvantages, both to the patient and to the health care system. For the patient, hyperfractionation can be extremely inconvenient compared to conventional fractionation regimens, as it is often delivered on an inpatient basis and occurs several times per day, possibly including weekends.[13] Hyperfractionation is also extremely resource intensive, with the result that it is subject to limited availability, as seen by a major UK cancer center that only had the capacity to offer continuous hyperfractionated accelerated radiotherapy (CHART) to 3 patients per month.[12] In an attempt to make the treatment more logistically feasible, this hyperfractionation approach was modified to exclude weekends, an approach that was analyzed in 2 independent approaches, (1) continuous hyperfractionated accelerated radiotherapy weekend less (CHARTWEL) and (2) hyperfractionated accelerated radiotherapy (HART). However, neither study demonstrated a statistically significant improvement in overall survival compared to conventional fractionation.[52,53]

Hypofractionation may also allow for improved local control by increasing BED without lengthening OTT, but with a more favorable impact on both patients and health care systems; this approach suggested by Mehta et al,[6] and a recent review by Partridge et al[54] came to a similar conclusion. This latter review used an informal search technique to identify clinical trials with dose-escalated techniques, including both hypo- and hyperfractionated approaches, for patients with stage I to III NSCLC. They then compared the observed disease-free survival of these trials with the models of Martel et al[55] and Fenwick et al[56] to determine the tumor dose−response relationship. The authors concluded that hypofractionated schedules with OTT of ≤ 6 weeks are predicted to be more beneficial than short hyperfractionated schedules or prolonged conventionally fractionated treatments.

Figure 2 Scatter Plot of (A-C) Acute BED Versus 1-, 2-, and 3-Year Overall Survival (OS), (D-F) Acute Time-Adjusted BED Versus 1-, 2-, and 3-year OS, and (G-I) Late BED Versus 1-, 2-, and 3-Year OS. Line of Best Fit and Pearson Correlation Coefficient Are Displayed



The traditional concern with hypofractionated radiotherapy is that it may be too toxic for patients.[14,21,40] Our review did not suggest a significant correlation between lesional BED and acute or late toxicity. Therefore, the major cause of patient toxicity was not simply lesional BED but rather correlated more closely with the dose delivered to normal tissues. This supposition has been supported by a phase I study of hypofractionated radiotherapy for locally advanced NSCLC reported by Cannon et al.[18] They demonstrated a significant relationship between maximum dose to the proximal bronchial tree and severe late toxicity. Although this is a significant concern, similar results that occurred with stereotactic ablative radiotherapy[57] were mitigated with protocol adjustments based on tumor location.[58]

Furthermore, 3 studies comparing standard fractionation to a hypofractionated scheme did not report any significant differences in toxicity between the regimens.[38,39,47] Another study, comparing

Figure 3 Scatter Plot of BED Versus Percentage Incidence of (A) Acute and (B) Late Toxicity

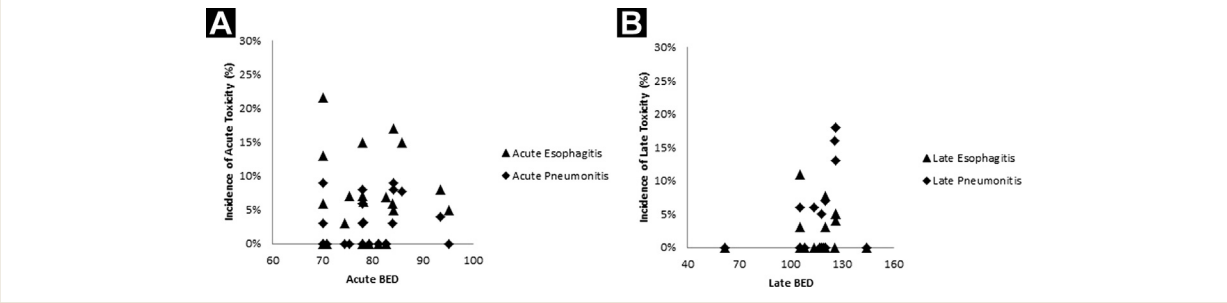


CHART to hypofractionated therapy, did not find any significant difference in toxicities between the treatment approaches.[12] However, careful selection of dose, concurrent chemotherapy agents, and robust quality assurance is needed, as 2 studies were stopped early due to toxicity.[21,40] In one of these,[40] the reported dose was later determined to be an error in calculation.[59] In the other, a high dose per fraction (3 Gy) was used with 2 concurrent chemotherapeutic agents (carboplatin and paclitaxel). In this latter study, one patient developed a tracheoesophageal fistula, and another patient developed late grade 3 radiation pneumonopathy.[21]

The concern with respect to toxicity in the treatment of stage III NSCLC becomes more prominent in the setting of concurrent chemoradiotherapy.[60,61] Although the survival benefit is well established, a recent meta-analysis found that concurrent chemotherapy confers a 16% relative survival benefit over sequential chemotherapy, although its toxicity is well known.[62] This same meta-analysis found that concurrent chemotherapy increased the incidence of acute esophageal toxicity from 4% to 18% (relative risk of 4.9) but with no impact on acute pulmonary toxicity. This is similar to the result of the RTOG 9410 study with standard fractionation and concurrent chemotherapy, where concurrent CRT had statistically significant higher rates of acute esophagitis. However, in that study, acute pulmonary toxicity was higher for sequential rather than concurrent chemotherapy.[4] This is consistent with the data reported herein, as the greatest toxicity was found to be with acute esophagitis in the setting of concurrent chemotherapy. All other reported toxicity measures had a 95% confidence interval that included zero. However, there was still a trend toward greater toxicity with concurrent CRT in all other measures (acute pneumonitis, late esophagitis, pneumonitis). The lack of statistical significance may be due to the small sample size rather than a true lack of effect.

Two major issues to be resolved in the treatment of stage III NSCLC: (1) improving local control by increasing the lesional BED with dose per fraction escalation, and (2) incorporating concurrent systemic therapy without excessive toxicity. For the first issue, one of the most promising is the use of stereotactic ablative radiotherapy (SABR) as a boost after standard (or hypofractionated) external beam radiation.[63-65] In the study by Feddock et al,[63] 2 patients with large cavitary recurrences had grade 5 toxicity (fatal hemoptysis), which resulted in the fractionation scheme for medial tumors being adjusted partway through the trial. This is similar to previous trials with SABR for early-stage NSCLC that required fractionation scheme adjustments based on tumor location because of toxicity from radiation dose to central structures.[58] However, the authors of this recent study concluded that the use of SABR did not increase the risk of acute toxicities any more than would be expected from a standard radiation treatment course.[63]

An alternative approach is the use of adaptive radiotherapy, which is the focus of the RTOG 1106 randomized study (NCT01507428). In this study, conventional radiotherapy is used up to 46.2 Gy in 21 fractions, at which point, if randomized to the adaptive arm, the patient is provided an adaptive radiotherapy boost of 19.8 to 34.2 Gy in 9 fractions based on ^{18}F-fluorodeoxyglucose positron emission tomography uptake. There is also a role for evaluating commonly used hypofractionated regimens, such as the 55 Gy in 20 fractions commonly used in the United Kingdom.[16] This is the goal of the SOCCAR trial (NCT00309972), which is a randomized phase III trial comparing induction chemotherapy plus radiation with concurrent CRT and consolidation chemotherapy. This study reported extremely promising results, with 2-year OS of 54% in the concurrent arm and similar toxicity in this arm to the sequential arm.[17] Whichever hypofractionated treatment schedule is studied, it should eventually be directly compared to the conventional treatment of 60 Gy in 30 fractions in a well-designed prospective randomized trial.

To address the second issue, if we accept that concurrent CRT is the standard of care for such patients, it is not entirely clear at this point how exactly chemotherapy should best be delivered concurrently with hypofractionated radiotherapy. Our review suggests that hypofractionated radiotherapy can be delivered safely with concurrent chemotherapy, with acute esophageal toxicity being the most negative impact. Novel targeted agents could represent another promising approach by improving systemic control without significantly increasing toxicity. Unfortunately, preliminary results of one of these agents, cetuximab, are not promising. Two independent groups, including RTOG 0617, have published results in which no survival benefit of cetuximab was found.[33,66] One of the studies actually had increased toxicity.[33] The use of personalized targeted agents is the goal of the recently initiated RTOG 1306 study (NCT01822496), in which patients are separated into cohorts based on the *EGFR TK* mutation or the ALK Tran L arrangement and will receive erlotinib or crizotinib, respectively, with conventional fractionation of 60 Gy in 30 fractions. The use of proton therapy is also under active investigation, with a favorable toxicity profile.[67]

There are inherent limitations to this systematic review. The first limitation is that there may have been some articles that were missed, simply because of how they were indexed or recorded. In particular, a challenge with the hypofractionation literature is that the terminology is not consistent, as it includes multiple synonyms, most of which we tried to capture in our search strategy. As well, in our list of reviewed articles, one of them[22] did not even describe the approach as hypofractionated despite using $>$ 2 Gy per fraction. Additionally, significant stage-migration effects were likely to have occurred during the time frame of the articles assessed in this review as a result of changes in tumor, node, metastasis classification system staging rules, treatment planning approaches (ie, the use of 3-D and 4-D computed tomography imaging) and the increasing prevalence of positron emission tomographic staging for locally advanced NSCLC. There were also limitations with the data extraction from the studies. We did not acquire individual patient data, and we were limited to using only the data that were reported in the articles. Specifically, the toxicity end points were not always consistent, and each article reported data slightly differently. We attempted to extract standardized data from the articles as much as possible. In some cases, estimates of point survival were required. However, despite these limitations, our results are comparable to previously reported publications of toxicity[4,60] and OS.[20]

Conclusions

Locally advanced NSCLC remains a significant contributor to cancer mortality, and efforts to improve outcomes have been only modestly successful. Dose per fraction escalation made possible by advanced technology, such as SABR, may be beneficial and should be the subject of future randomized controlled trials. Concurrent CRT offers the best survival, but toxicity, especially at higher radiotherapy doses, can be problematic. There are ongoing trials (eg, NCT01459497) evaluating currently used hypofractionated regimens and novel systemic agents that will provide important information regarding the appropriateness of this treatment approach. However, further clinical trials need to be performed using novel hypofractionated regimens with increased lesional BED, such as SABR or adaptive radiotherapy.

Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental appendices accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.cllc.2014.08.002.

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