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review

A current review of dose-escalated radiotherapy in locally advanced non-small cell lung cancer

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Background. The mainstay therapy for locally advanced non-small cell lung cancer is concurrent chemoradiotherapy. Loco-regional recurrence constitutes the predominant failure patterns. Previous studies confirmed the relationship between increased biological equivalent doses and improved overall survival. However, the large randomized phase III study, RTOG 0617, failed to demonstrate the benefit of dose-escalation to 74 Gy compared with 60 Gy by simply increasing fraction numbers.

Conclusions. Though effective dose-escalation methods have been explored, including altered fractionation, adapting individualized increments for different patients, and adopting new technologies and new equipment such as new radiation therapy, no consensus has been achieved yet.

Key words: non-small cell lung cancer; dose escalation; hyperfractionation; hypofractionation; adaptive radiotherapy; proton radiotherapy; carbon ion radiotherapy

Introduction

Conventionally fractionated (1.8–2.0 Gy/day) radiotherapy to a dose of 60–70 Gy with concurrent chemotherapy has long been established as the standard care for locally advanced non-small cell lung cancer (LANSCLC). However, the outcomes remain poor with a 5-year overall survival (OS) less than 20%.[1] Local-regional recurrence is the main challenge for long-term survival. Efforts have been made to explore the safe and effective methods to improve loco-regional control (LRC). Of them, dose escalation shows promising prospects.

Materials and methods

PubMed and EMBASE were searched using the following keywords: locally advanced non-small cell lung cancer, unresectable non-small cell lung cancer, radiotherapy, radiation therapy, dose escalation, hyperfractionation, hypofractionation, adaptive radiotherapy, proton radiotherapy, carbon ion radiotherapy. Clinical studies, clinical trials, meta-analysis, reviews and references from the articles were selected and further classified into altered radiotherapy delivery regimens, personalized radiotherapy regimen and new techniques: proton and heavy ion radiotherapy.

Results and discussion

Current status and problems of traditional dose escalation

Machtay *et al.* conducted a retrospective analysis of 1356 LANSCLC patients from seven prospective clinical trials of the Radiation Therapy Oncology Group (RTOG).[2] Biologically equivalent dose (BED) and time-adjusted BED were calculated for each patient. The study revealed that BED was highly correlated with OS and loco-regional relapse-free survival ($p < 0.0001$). Increase of 1 Gy in BED was related with a 3% (HR = 0.97) improvement in local control and a 4% (HR = 0.96) relative improvement in survival. It is noteworthy that accompanied with escalated dose, treatment related-toxicity may be increased. In several randomized trials, a median survival of 15–20.6 months was observed in LANSCLC patients treated with a radiation dose of 60–66 Gy and concurrent chemotherapy.[3-8] A serial phase I and II trials explored the efficacy of dose escalation to 74 Gy radiotherapy concurrent with chemotherapy and showed an improved median OS of 21.6–37 months with acceptable toxicity.[9-12] Motivated by these results, RTOG launched a large randomized phase III study 0617, trying to find out whether a 74 Gy radiotherapy was superior to a 60 Gy radiotherapy administered with concurrent chemotherapy followed by consolidative chemotherapy. The result suggested that compared with 60 Gy radiotherapy, neither overall survival nor local control improved in high-dose radiotherapy arm (median OS time: 28.7 *vs*. 20.3 months, p = 0.004; 2-year local failure rate: 30.7% *vs*. 38.6%, p = 0.13).[13] The prolongation of overall treatment time (7.5 weeks) and the associated tumor repopulation may be the contributing factors to this unsatisfactory outcome.[14] Radiobiology and clinical trials have confirmed that the doubling time of most tumors is less than one week.[15,16] Dose escalation by simply increasing fraction numbers results in lengthened overall treatment, which has proven to have a negative impact on tumor control. Worse overall survival was observed when the treatment course exceeded 6 weeks.[17, 18] In addition, results of RTOG 0617 showed that the exposure of lung, esophagus, and heart were significantly higher in high-dose radiotherapy arm; greater toxicity may be another possible explanation.[13,14] Brower *et al*. analyzed 33566 patients with stage III NSCLC who underwent concurrent chemoradiation and found that dose escalation above 60 Gy was associated with improved OS.[19] But an OS plateau was also found when radiation dose prescribed was greater than 70 Gy. It is suggested that dose escalation should be limited in a specified range.

Recent meta-analysis demonstrated a survival benefit of dose escalation in patients treated with sequential chemoradiotherapy. However, in concurrent chemoradiotherapy group, increased dose was related to poorer survival.[20,21] One possible explanation is that the underlying toxicity accompanied with concurrent chemoradiotherapy compromises the survival benefits of dose escalation in tumor control.

Therefore, in the era of concurrent chemotherapy, applying traditional approaches of dose escalation in unselected patients could lead to extra toxicity and impaired survival. There is a need to explore safe, efficacious and feasible dose escalation methods for LANSCLC.

Recent progress in dose escalation

Altered radiotherapy delivery regimens

Two feasible approaches enable the delivery of an increased BED without prolonging treatment time, hyperfractionation (reduced fraction size, two times or more per day) and hypofractionation (fewer fractions, larger dose-per-fraction). [22]

Hyperfractionated radiotherapy

Hyperfractionated radiotherapy demonstrated to have a survival benefit over conventional radiotherapy in NSCLC patients. In the continuous hyperfractionated accelerated radiotherapy (CHART) trial, 563 NSCLC patients were randomized at a 3:2 ratio into CHART and conventional group. Compared with conventional regimen (once daily fraction of 2 Gy to a total of 60 Gy/30 d), CHART (three times per day fraction of 1.5 Gy to a total of 54 Gy/12 d) group appeared to have a significant survival benefit with a 2-year OS rate increased by 9% (20% *vs*. 29%, p = 0.004). [23] However, CHART regimen is hard to implement for institutions due to its additional weekend treatment. Therefore, Baumann *et al.* proposed a modified CHARTWEL (CHART weekend less) trial in which the same schedule as CHART was applied except that it omitted the weekend treatment.[24] CHARTWEL group was treated with three times per day fraction of 1.5 Gy to a total dose of 54 Gy in 36 fractions. The conventional group escalated to 66 Gy (2 Gy per fraction). CHARTWEL group showed no significant survival benefit (2-year OS rate: 32% *vs*. 31% at 2 years, p = 0.43). One reasonable explanation was that escalated dose in conventional

TABLE 1. Researches on altered fractionation in NSCLC

Author	Regimen	No.	Stage	Treatment outcome	p value	RE	p value	RP	p value
Saunders[23]	Conventional radiotherapy: 60Gy/2Gy/30f	225	-	20%(2-year OS)	0.004	acute: 7%; late: 5%	-	acute: 19%; late: 4%(symptomatic)	-
	CHART: 1.5Gy tid, 7 days/week, a total of 54Gy	339		29%(2-year OS)		acute: 9%; late: 7%	-	acute: 10%; late: 16%(symptomatic)	-
Baumann[24]	conventional radiotherapy: 66Gy/2Gy/33f	203	inoperable	31%(2-year OS)	0.43	acute: 2.2%; late;: 0.7%(≥G2)	acute: 0.17; late: 0.62	acute: 9.5%; late:11%(≥G2 symptomatic)	acute: 0.32; late: 0.59
	CHART: 1.5Gy tid, 5 days/week, a total of 54Gy	203		32%(2-year OS)		acute: 5%l late: 1.9%(≥G2)		acute: 6.6%; late:9.2%(≥G2 symptomatic)	
Mauguen[25]	Conventional radiotherapy	2000	-	15.9%(3-yearOS), 8.3%(5-year OS)	<0.04	9%	<0.001	-	-
	CHART			19.7%(3-yearOS), 10.8%(5-year OS)		19%			
Din[26]	55Gy/2.67Gy/20f	609	III	50%(2-year OS)	-	-	-	15.1%(G1-2 symptomatic)	-
Sun[27]	conventional radiotherapy: 70.8Gy/1.86Gy/38f	54	inoperable stage III	48.1%(RR)	0.032	33.3%(G2)	-	42.6% (≥G2)	-
	hypofractionated radiotherapy: 65Gy/2.5Gy/26f	43		69.8%(RR)		25.6%(G2)		34.9%(≥G2)	
Cannon[29]	57-85.5Gy/2.28-3.42Gy/25f	79	LANSCLC	29%(3-year OS)	-	acute: 48%(G2); late: 28%(G2)	-	16%(G2)7.6%(G4-5)	-
Feddock[32]	A month after standard radiotherapy to 60Gy with concurrent chemotherapy, an SBRT boost was given in ≤5cm residual primary tumors: 10Gy×2f for peripheral lesions, 6.5Gy×3f for central lesions	61	II/III	82.9%(primary tumor control with a median follow-up of 13 months)	-	1.6%(G2)	-	acute:17.1%; late: 9.4%(≥G2)	-
Karam[33]	An SBRT boost with 20-30Gy over 5 fractions was prescribed after conventional CCRT to a median dose of 50.4Gy	16	LANSCLC	78%(1-yearOS) ,76%(1-yearLRC)	-	18% (G2)	-	25% (G2)	-
Higgins[34]	Standard radiotherapy to 44Gy with concurrent chemotherapy, followed by an SBRT boost in the lung and nodal residuals in four groups: 9Gy×2f, 10Gy×2f, 6Gy×5f and 7Gy×5f	19	stageIII(N1/N2) with primary tumors ≤8cm and lymph nodes ≤5cm	39%(3-yearOS) ,59%(3-yearLRC)	-	-	-	-	-
Hepel[35]	Standard radiotherapy to 50.4Gy with concurrent chemotherapy, followed by an SBRT boost in the lung and nodal residuals in four groups: 8Gy×2f, 10Gy×2f, 12Gy×2f and 14Gy×2f	12	Stage II/III with primary tumor ≤120cc and lymph node volume ≤ 60cc	78%(1-yearLRC)	-	0(≥G3)	-	acute: 0(≥G3); late: 8.33%(G5)	-

f = fraction(s); LANSCLC = locally advanced non-small cell lung cancer; LRC = loco-regional control; OS = overall survival; RE = radiation esophagitis; RP = radiation pneumonitis; SBRT = stereotactic body radiation therapy; tid = three-fractions-per-day

treatment group compensated for the adverse effect of longer treatment time. A meta-analysis by Mauguen *et al.* identified 10 clinical trials describing 2000 NSCLC patients treated with hyperfractionated radiotherapy.[25] An increased risk of acute radiation esophagitis (19% *vs*. 9%, p <0.001) was found in the hyperfractionation group. However, the compliableness was good, over 90% of patients completed the prescribed radiotherapy. The result showed that hyperfractionation significantly improved survival with a 12% reduction in the risk of death (HR = 0.88, p = 0.009). The 3-year and 5-year OS rates were improved by 3.8% (19.7% *vs*. 15.9%) and 2.5% (10.8% *vs*. 8.3%), respectively.

Hypofractionated radiotherapy

It has been well established that the delivery of larger dose-per-fraction in fewer fractions could significantly improve BED, represented by stereotactic body radiation therapy (SBRT). However, SBRT is treatment of choice only for early lung cancer without affected lymph nodes. The delivery of SBRT is limited by the large tumor size and the proximity of normal tissues such as major vessels, esophagus, heart and other important organs. Some studies explored a moderate hypofractionated escalation schedule of 2–4 Gy per fraction dose radiotherapy. With this delivery, treatment time has been significantly shortened without provid-

TABLE 2. Researches on personalized dose escalation radiotherapy in NSCLC

Author	Regimen	No.	Stage	Treatment outcome	p value	RE	p value	RP	p value
Van Baardwijk[36]	Initially 1.5Gy bid to 45Gy, then 2Gy per fraction daily increments until reaching the limit dose of normal tissue	137	III	52.4% (2-year OS)	-	acute: 25.5% (G3); late: 4.6% (G3)	-	late: 3% (≥G3)	-
Van Elmpt[38]	Initially 2.75Gy to 66Gy,then boost to the entire primary tumor	15	I- III	-	-	-	-	-	-
	Initially 2.75Gy to 66Gy,then boost in the high FDG uptake area	15							
Vera[40]	^{18}F-FMISO PET-CT (-): 66Gy CCRT	20	LANSCLC	95% (1-year OS) 85% (1-year DFS)	p=0.10 (1-year OS)	acute: 75% (G1-3)	-	acute: 15% (G1-2) late: 5% (G1-2)	-
	^{18}F-FMISO PET-CT (-): 68-86Gy CCRT	24		81% (1-year OS) 50% (1-year DFS)	p=0.01 (1-year DFS)	acute: 75% (G1-3)		acute: 12.5% (≥G3)	
	^{18}F-FMISO PET-CT (+): 66GyCCRT	10		50% (1-year DFS)		acute: 100% (G1-5)		acute: 0	
Kong[41]	Initially 50Gy, then adapt target basing on midtreatment PET-CT and escalate dose to the constraints of normal tissue concurrent with chemotherapy	42	Inoperable stage I- III	2-year LRC: 62%; median OS: 25 months	-	12% (G3)	-	7% (G3)	-

CCRT = concurrent chemoradiotherapy; DFS = disease free survival; LANSCLC = locally advanced non-small cell lung cancer; LRC = loco-regional control; RE = radiation esophagitis; RP = radiation pneumonitis; OS = overall survival

TABLE 3. Researches on proton and heavy ion radiotherapy in NSCLC

Author	Regimen	No.	Stage	Treatment outcome	p value	RE	p value	RP	p value
Higgins[47]	Median dose of photon radiotherapy: 59.4Gy	243474	I- IV	13.5% (5-year OS)	0.01	-	-	-	-
	Median dose of PSPT: 60Gy (RBE)	348		23.1% (5-year OS)					
Chung[48]	74Gy (RBE) PSPT concurrent with chemotherapy	64	III	26.5 months (median OS)	-	8% (G3)	-	14% (G3-4)	-
Liao[49]	IMRT: 66-74Gy	92	LANSCLC	10.9% (LRF)	0.86	-	-	6.5%	0.40
	PSPT: 74Gy (RBE)	57		10.5% (LRF)				10.5%	
Takahashi[50]	68-76Gy (RBE) carbon ion radiotherapy	72	LANSCLC	93.1% (2-year LRC), 51.9% (2-year OS)	-	1.4% (G3)	-	1.4% (G3)	-
Karube[51]	52.8-72Gy (RBE) carbon ion radiotherapy	64	II- III	81.8% (2-year LRC), 62.2% (2 -year OS)	-	0 (≥G2)	-	0 (≥G2)	-
Shirai[52]	52.8-70.4Gy (RBE)/4-16f carbon ion radiotherapy	23	T2b-4N0M0	81% (2-yearLRC), 70% (2-year OS)	-	0 (≥G3)	-	0 (≥G3)	-

CCRT = concurrent chemoradiotherapy; DFS = disease free survival; IMRT = intensity modulated radiation therapy; LANSCLC = locally advanced non-small cell lung cancer; LRC = loco-regional control; OS = overall survival; PSPT = passive scattered proton therapy; RBE = relative biologic equivalent; RE = radiation esophagitis; RP = radiation pneumonitis

ing additive toxicity. Also, a positive relationship between OS and BED was found.

A retrospective study of four UK centers evaluated 609 NSCLC patients treated with accelerated hypofractionated radiotherapy. Ninety-eight percent of them received the radiotherapy scheme of 2.67 Gy per fraction to a total dose of 55 Gy in 20 fractions. The 2-year OS of stage III NSCLC patients approximates 50% with comparable side effects to previous data.[26] Sun *et al.* conducted a prospective clinical study comparing hypofractioned schedule (2.5 Gy per fraction to 65 Gy) with conventional radiotherapy (1.86 Gy per fraction to 70.8 Gy) in patients with stage III inoperable NSCLC.[27] Hypofractioned schedule had significantly better response rate (p = 0.032) over conventional regimen with comparable treatment-related toxicity. A systematic review by Tyler *et al.* gathered data from 33 articles identifying LANSCLC patients treated with radical hypofractionated radiotherapy between 1990 and 2014, of which, 15 studies included concurrent chemotherapy.[28] A fractionation schedule of 45-85.5 Gy at 2.3-3.5 Gy/fraction daily was administered. The study reported an OS benefit of increased BED (p = 0.001): every 1 Gy increase in BED resulted in an absolute OS benefit ranging from 0.36% to 0.7%. Acute radiation esophagitis was the most obvious toxicity with an incidence of 14.9%. However, the incidence of late toxicity had no relationship with BED.

Inconsistent with the above study, the prospective single-center phase I trial of dose-escalated hypofractionated radiotherapy without concurrent chemotherapy still showed that severe toxicity was related to the total dose. Escalation of per dose fraction ranging from 2.28 Gy to 3.42 Gy to a total dose of 57–85.5 Gy in 25 fractions was prescribed to 79 NSCLC patients. They reported a maximum tolerable dose (MTD) of 2.53 Gy in 25 fractions (63.25 Gy total). Grade 4 to 5 pneumonitis occurred in 6 patients, which was strongly correlated with the total dose ($p = 0.004$).[29] These data confirmed that dose escalation in either hypofractioned or conventional radiotherapy warrants caution and should be in a certain range. The benefit of hypofractionation requires further validation.

SBRT boost for residual disease

An excellent control rate in NSCLC could be achieved when BED exceeds 100 Gy demonstrated by several studies.[30, 31] Recently, a novel technique has been proposed to improve BED. SBRT boost for residual disease after concurrent chemoradiotherapy in NSCLC patients have effectively escalated BED and showed an encouraging loco regional control (LRC) without increased toxicity.

The study of Feddock *et al.* enrolled 61 patients with stage II/III NSCLC. After conventional radiotherapy to a dose of 60 Gy combined with concurrent chemotherapy, remaining lesions were evaluated.[32] Patients who had no evidence of mediastinum progression and ≤ 5 cm residual primary tumors identified by positron emission tomography/computed tomography (PET-CT), were further treated with a SBRT boost. Two different prescriptions were delivered based on tumor locations: 10 Gy × 2 fractions (cumulative BED: 110 Gy) for peripheral lesions, and 6.5 Gy × 3 fractions (cumulative BED: 102 Gy) for central lesions. After a median follow-up of 13 months, a favorable outcome was reached with a primary tumor control rate of 82.9%. The incidence of radiation pneumonitis was comparable to standard radiotherapy. Similar findings were achieved in Karam's study, in which 16 LANSCLC patients were included.[33] SBRT boost with 20–30 Gy over 5 fractions was boosted after conventional concurrent chemotherapy to a median dose of 50.4 Gy. The result showed that the 1-year OS and LRC rates were 78% and 76%, respectively. Three patients (18%) underwent grade 2 esophagitis and 4 (25%) developed grade 2 pneumonitis. Dose escalation studies for SBRT boost technique to define the MTD were also explored. Nineteen stage III (N1/N2) NSCLC patients with primary tumors ≤ 8 cm and lymph nodes ≤ 5cm were analyzed by Higgins *et al.*[34] In this study, patients were treated with standard radiotherapy to 44 Gy with concurrent chemotherapy, followed by a SBRT boost to the lung and nodal residuals. Four SBRT boost regimens were tested: 9 Gy × 2 fractions (cumulative BED: 87 Gy), 10 Gy × 2 fractions (cumulative BED: 92.8 Gy), 6 Gy × 5 fractions (cumulative BED: 100.8 Gy) and 7 Gy × 5 fractions (cumulative BED: 112.3 Gy). The study confirmed a maximum tolerable boost dose of 6 Gy × 5 fractions, and a safe dose prescription of 10 Gy × 2 fractions with no grade 3 or more toxicity. Hepel *et al.* came to a similar conclusion.[35] The trial included 12 stage II/III NSCLC patients with primary tumor and lymph node volume limited within 120 cc and 60 cc, respectively. The SBRT boost to both primary and nodal disease was delivered after 28 fractions of radiotherapy (50.4 Gy) with concurrent chemotherapy. Patients were assigned to four boost dose arms escalating from 16 Gy to 28 Gy: 8 Gy × 2 fractions (accumulated BED: 88.3 Gy), 10 Gy × 2 fractions (accumulated BED: 99.5 Gy), 12 Gy × 2 fractions (accumulated BED: 112.3 Gy) and 14 Gy × 2 fractions (accumulated BED: 126.7 Gy). The results revealed that the utilization of SBRT boost technique was well tolerated. There was only one patient that experienced grade 5 adverse effect (fatal bleeding). Also, a favorable outcome with a 1-year LRC of 78% was reported; LRC was 100% in patients with a boost dose over 24 Gy.

It should be noted that patients included in these studies were all required to have tumors with limited size/volume. The prescription of dose should also take into account the location. Furthermore, all these data were from studies with small sample size, the potential benefits should be validated in a larger randomized controlled study.[32, 34, 35]

Personalized radiotherapy

Fixed dose radiotherapy has been long used in dose dose-escalation studies. However, with varied tumor volumes, the tolerance of normal tissue would be different and dose delivery could be personalized accordingly. Several recent studies explored the feasibility of personalized radiotherapy. The phase II trial of van Baardwijk *et al.* evaluated dose intensification based on normal tissues concurrent with chemotherapy for patients with LANSCLC.[36] After completing concurrent chemoradiotherapy to 45 Gy in 1.5 Gy bid fractions, boost dose was escalated 2 Gy per fraction in daily increments until reaching the limit dose of organ at risk (OARs). A total of 137 patients were included, 27% of them received a maximal allowed dose of 69 Gy. The median radiotherapy dose was 65 Gy. They reported a

2-year OS rate of 52.4% and an acceptable adverse effects (G3 esophagitis: 30.1%, ≥ G3 pneumonitis: 3%).

Selective dose escalation according to tumor activity and radiosensitivity has also been tested. High fludeoxyglucose (FDG) uptake prior to treatment has been demonstrated as a negative indicator for local recurrence.[37] Based on this, a phase II randomized clinical trial evaluated the role of dose escalation in high FDG uptake area. Patients who completed an initial radiotherapy of 66 Gy in 24 fractions were then assigned either to receive a boost in the entire primary tumor (group A) or in the high FDG uptake area (> 50% maximum standardized uptake values (SUVmax) (group B). Similar with the previous study, maximal boost dose was delivered within the constraints of normal tissue. The results showed that average doses of primary tumors in groups A and B were 77.3 ± 7.9 Gy and 77.5 ± 10.1 Gy, respectively. For group B, the average dose in boost area reached 86.9 ± 14.9 Gy. Organs in the mediastinum were thought to be the major dose-limiting organs, such as great vessels, trachea etc. However, the local control and survival data was not provided.[38] The existence of hypoxia is strongly associated with radioresistance and unfavorable prognosis.[39] Vera *et al.* carried out a prospective phase II clinical trial to investigate the efficacy of selectively dose increase in hypoxic zones.[40] ^{18}F-misonidazole (^{18}F-FMISO) PET-CT was used to detect hypoxic areas and to guide the delineation of boost volumes. Boost dose was prescribed as high as possible within the tolerated dose of lung and spinal cord. A total of 54 LANSCLC patients treated with concurrent chemoradiotherapy were enrolled and 34 patients were ^{18}F-FMISO positive, of whom, 24 had a dose escalation up to 86 Gy, 10 received a standard radiotherapy of 66 Gy. In ^{18}F-FMISO positive patients, dose escalation showed no improvement in progression-free survival and OS. It suggests that with dose of hypoxic region escalated up to 86 Gy, the survival still cannot be improved.

Dynamic changes in tumor volume during radiotherapy lead to the idea of adaptive radiotherapy. Kong et al. [41] found that tumor volume was significantly shrunk when radiation dose reached 45 Gy, which offers opportunity to adapt target area in the middle of treatment. The reduction in target volume allows delivering higher radiotherapy dose. They then conducted a Phase II clinical trial to test the efficiency of adapting target volume based on midtreatment PET-CT. Forty-two inoperable patients with stage I–III NSCLC were analyzed. Patients had their target volume re-planned according to midtreatment PET-CT and received a maximally escalated dose without increasing radiation induced lung toxicity. The median dose was 83 Gy. They provided a promising 2-year LRC approximately 62%.[42] The randomized RTOG 1106 trial (NCT01507428) is currently ongoing attempting to verify this finding. The control group was designed to give 60 Gy in 30 fractions. In the adaptive group, the target was redefined on the midtreatment PET-CT after an initial 46.2 Gy in 21 fractions delivered. An individualized escalated dose ranged from 19.8–34.2 Gy/9 fractions with a total dose up to 80.4 Gy. This result would offer us more information.

Furthermore, individualized radiotherapy based on molecular biological information (sensitivity and risk of injury) has also been investigated. Recently, Scott *et al.* proposed a genome-based model to identify tumor radiosensitivity, genomic-adjusted radiotherapy dose (GARD), which was calculated by gene-expression-based radiosensitivity index and the linear quadratic model.[34] Lower tumor GARD score predicts radiation resistance, thus higher radiation doses could be administered. The analysis confirmed that GARD was highest in head and neck cancers and cervical cancers, while the lowest in gliomas, which could be used to guide individualized escalated dose prescription. Another novel idea proposed by MD Anderson Cancer Center is that escalated tumor dose could be delivered according to the risk of radiation pneumonitis estimated by dose-volume histograms and single-nucleotide polymorphism information.[44] Although the above studies are not yet mature enough to guide clinical practice, it may be a development trend in the future.

New techniques: proton and heavy ion radiotherapy

A lesson from RTOG 0617 is that normal tissue exposure should be fully considered while escalating doses. Previous studies have shown that protons and heavy ions have unique characteristic known as Bragg peak, which offers the possibility to increase tumor dose while sparing normal tissues.[45,46]

Higgins *et al.* retrospectively analyzed 243,822 patients with stage I- IV NSCLC in the National Cancer Database; 243,474 of them were treated with photon radiotherapy and 348 were treated with proton radiotherapy.[47] The analysis indicates that low-income groups tend to choose non-proton therapy ($p < 0.011$). After propensity matching analysis, a significant superior 5-year survival rate of stage II–III patients was found in the proton therapy group (23.1% *vs*. 13.5%; $p<0.01$). The prospective single-arm phase II clinical trial conducted by Chung *et al.* also confirmed the safety and efficacy of proton radiotherapy.[48] A total of 64 patients with stage III NSCLC were enrolled in the trial; all patients received 74 Gy (relative biologic equivalent, RBE) proton radiotherapy combined with concurrent chemotherapy. They reported a median OS of 26.5 months. The incidence of grade 3 or greater toxicity including esophagitis and radiation pneumonitis was 8% and 14%, respectively. Contradicts to these findings, the more recent results of phase II randomized trials published by Liao *et al.* failed to show the superiority of proton radiotherapy.[49] This trial compared the local control and toxicity of intensity modulated radiation therapy (IMRT) and proton radiotherapy of 66–74 Gy (RBE) combined with concurrent chemotherapy in NSCLC patients. Although there was no significant difference in the incidence of radiation pneumonitis ($p = 0.40$) and local control ($p = 0.86$) in both groups, proton radiotherapy significantly reduced heart exposure ($p = 0.002$). However, OS was not the endpoint for this study, the effect of reduced heart dose on OS is still unknown. The ongoing Phase III prospective clinical trial RTOG 1308 (NCT01993810) which compares the OS between proton radiotherapy and IMRT may bring some insight into this issue. Patients with inoperable stage II–III NSCLC were randomized to proton radiotherapy versus IMRT photon arm. Patients in the proton radiotherapy arm received 2 Gy (RBE) daily to 70 Gy (RBE) course, whereas, those patients on the IMRT arm received 2 Gy to 60 Gy course, concurrent with weekly platinum-based chemotherapy followed by 2 cycles of consolidation chemotherapy.

Heavy ion beams possess the physical advantages of proton beams, also better biological effects, which seemed to be more suitable for dose escalation studies. Takahashi *et al.* performed phase I/ II non-randomized prospective clinical study to test carbon ion radiotherapy in LANSCLC.[50] Phase I trial included a total of 36 patients with escalated dose from 68 Gy (RBE) to 76 Gy (RBE) in 16 fractions. The MTD was 76 Gy (RBE) with 2 patients developed G3 toxicity including pneumonitis and tracheo-esophageal fistula. In the phase II trial, 22 patients were analyzed; all of them received a regimen of 72 Gy (RBE) in 16 fractions. No grade 3 or higher toxicity was found. The 2-year LRC and OS of 72 patients were 93.1% and 51.9%, respectively. This outcome data are in keeping with the multicenter retrospective analysis reported by Karube *et al.* [51] The median dose prescribed for 64 stage II–III NSCLC patients was 72 Gy (RBE) in 16 fractions. The 2-year LRC and OS rate were 81.8% and 62.2%, respectively. No grade 2 or greater toxicity occurred. Shirai *et al.* conducted a retrospective analysis of 23 patients with T2b–4N0M0 stage NSCLC treated with carbon ion radiotherapy. [52] Sixty-five percent of patients received a total dose of 52.8–60 Gy (RBE) in 4 fractions and 35% of patients were treated with 64–70.5 Gy (RBE) in 16 fractions. The 2-year LRC and OS rates were 81% and 70%, respectively, and no person experienced ≥ 2 degree radiation pneumonitis. The above studies showed that hypofractionation carbon ion radiotherapy could be safely and efficiently used in LANSCLC. However, the conclusion still needs to be validated by larger prospective studies. Combined modality such as chemotherapy and immunotherapy could be further explored. In addition, cost-effectiveness of proton and heavy ion radiotherapy should also be considered.

Conclusions

Local recurrence remains the major failure pattern after concurrent chemoradiotherapy of LANSCLC. Although increasing doses can theoretically improve outcome, the negative results of RTOG 0617 suggested that the traditional one dose fits all modes could not improve survival. Though effective dose-escalation methods have been explored, including altered fractionation, adapting individualized increments for different patients, and adopting new technologies and new equipment such as new radiation therapy, no consensus has been achieved yet. It is expected that the ongoing clinical trials and explorations for increasing doses of radiotherapy can further improve control rate survival in LANSCLC.

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References

1. Auperin A, Le Pechoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010; **28:** 2181-90. doi: 10.1200/JCO.2009.26.2543
2. Machtay M, Bae K, Movsas B, Paulus R, Gore EM, Komaki R, et al. Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with chemoradiation: an analysis of the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 2012; **82:** 425-44. doi: 10.1016/j.ijrobp.2010.09.004
3. Schild SE, Stella PJ, Geyer SM, Bonner JA, Marks RS, McGinnis WL, et al. Phase III trial comparing chemotherapy plus once-daily or twice-daily radiotherapy in Stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2002; **54:** 370-8. doi: 10.1016/S0360-3016(02)02930-9
4. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999; **17:** 2692-99. doi: 10.1200/JCO.1999.17.9.2692
5. Fournel P, Robinet G, Thomas P, Souquet PJ, Lena H, Vergnenegre A, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Francais de Pneumo-Cancerologie NPC 95-01 Study. *J Clin Oncol* 2005; **23:** 5910-7. doi: 10.1200/JCO.2005.03.070
6. Zatloukal P, Petruzelka L, Zemanova M, Havel L, Janku F, Judas L, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. *Lung Cancer* 2004; **46:** 87-98. doi: 10.1016/j.lungcan.2004.03.004
7. Belani CP, Choy H, Bonomi P, Scott C, Travis P, Haluschak J, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol* 2005; **23:** 5883-91. doi: 10.1200/JCO.2005.55.405
8. Curran WJ Jr, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst* 2011; **103:** 1452-60. doi: 10.1093/jnci/djr325
9. Bradley JD, Bae K, Graham MV, Byhardt R, Govindan R, Fowler J, et al. Primary analysis of the phase II component of a phase I/II dose intensification study using three-dimensional conformal radiation therapy and concurrent chemotherapy for patients with inoperable non-small-cell lung cancer: RTOG 0117. *J Clin Oncol* 2010; **28:** 2475-80. doi: 10.1200/JCO.2009.27.1205
10. Schild SE, McGinnis WL, Graham D, Hillman S, Fitch TR, Northfelt D, et al. Results of a Phase I trial of concurrent chemotherapy and escalating doses of radiation for unresectable non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006; **65:** 1106-11. doi: 10.1016/j.ijrobp.2006.02.046
11. Lee CB, Stinchcombe TE, Moore DT, Morris DE, Hayes DN, Halle J, et al. Late complications of high-dose (>/=66 Gy) thoracic conformal radiation therapy in combined modality trials in unresectable stage III non-small cell lung cancer. *J Thorac Oncol* 2009; **4:** 74-9. doi: 10.1097/JTO.0b013e3181915028
12. Blackstock AW, Ho C, Butler J, Fletcher-Steede J, Case LD, Hinson W, et al. Phase Ia/Ib chemo-radiation trial of gemcitabine and dose-escalated thoracic radiation in patients with stage III A/B non-small cell lung cancer. *J Thorac Oncol* 2006; **1:** 434-40. doi: 10.1016/S1556-0864(15)31608-7
13. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015; **16:** 187-99. doi: 10.1016/S1470-2045(14)71207-0
14. Belderbos J, Walraven I, van Diessen J, Verheij M, de Ruysscher D. Radiotherapy dose and fractionation for stage III NSCLC. *Lancet Oncol* 2015; **16:** e156-7. doi: 10.1016/S1470-2045(15)70121-X
15. Kerr KM, Lamb D. Actual growth rate and tumour cell proliferation in human pulmonary neoplasms. *Br J Cancer* 1984; **50:** 343-9. PMID: 6087867
16. Trott KR. Cell repopulation and overall treatment time. *Int J Radiat Oncol Biol Phys* 1990; **19:** 1071-5. doi: 10.1016/0360-3016(90)90036-J
17. Machtay M, Hsu C, Komaki R, Sause WT, Swann RS, Langer CJ, et al. Effect of overall treatment time on outcomes after concurrent chemoradiation for locally advanced non-small-cell lung carcinoma: analysis of the Radiation Therapy Oncology Group (RTOG) experience. *Int J Radiat Oncol Biol Phys* 2005; **63:** 667-71. doi: 10.1016/j.ijrobp.2005.03.037
18. Fowler JF, Chappell R. Non-small cell lung tumors repopulate rapidly during radiation therapy. *Int J Radiat Oncol Biol Phys* 2000; **46:** 516-7. doi: 10.1016/S0360-3016(99)00364-8
19. Brower JV, Amini A, Chen S, Hullett CR, Kimple RJ, Wojcieszynski AP, et al. Improved survival with dose-escalated radiotherapy in stage III non-small-cell lung cancer: analysis of the National Cancer Database. *Ann Oncol.* 2016; **27:** 1887-94. doi: 10.1093/annonc/mdw276
20. Yamoah K, Showalter TN, Ohri N. Radiation therapy intensification for solid tumors: a systematic review of randomized trials. *Int J Radiat Oncol Biol Phys* 2015; **93:** 737-45. doi:10.1016/j.ijrobp.2015.07.2284
21. Ramroth J, Cutter DJ, Darby SC, Higgins GS, McGale P, Partridge M, et al. Dose and fractionation in radiation therapy of curative intent for non-small cell lung cancer: meta-analysis of randomized trials. *Int J Radiat Oncol Biol Phys* 2016; **96:** 736-47. doi: 10.1016/j.ijrobp.2016.07.022
22. Mehta M, Scrimger R, Mackie R, Paliwal B, Chappell R, Fowler J. A new approach to dose escalation in non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2001; **49:** 23-33. doi: 10.1016/S0360-3016(00)01374-2
23. Saunders M, Dische S, Barrett A, Harvey A, Gibson D, Parmar M. Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial. CHART Steering Committee. *Lancet* 1997; **350:** 161-5. doi: 10.1016/S0140-6736(97)06305-8
24. Baumann M, Herrmann T, Koch R, Matthiessen W, Appold S, Wahlers B, et al. Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC). *Radiother Oncol* 2011; **100:** 76-85. doi: 10.1016/j.radonc.2011.06.031
25. Mauguen A, Le Pechoux C, Saunders MI, Schild SE, Turrisi AT, Baumann M, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. *J Clin Oncol* 2012; **30:** 2788-97. doi: 10.1200/JCO.2012.41.6677
26. Din OS, Harden SV, Hudson E, Mohammed N, Pemberton LS, Lester JF, et al. Accelerated hypo-fractionated radiotherapy for non small cell lung cancer: results from 4 UK centres. *Radiother Oncol* 2013; **109:** 8-12. doi: 10.1016/j.radonc.2013.07.014
27. Sun LM, Leung SW, Wang CJ, Chen HC, Fang FM, Huang EY, et al. Concomitant boost radiation therapy for inoperable non-small-cell lung cancer: preliminary report of a prospective randomized study. *Int J Radiat Oncol Biol Phys* 2000; **47:** 413-8. doi: 10.1016/S0360-3016(00)00429-6
28. Kaster TS, Yaremko B, Palma DA, Rodrigues GB. Radical-intent hypofractionated radiotherapy for locally advanced non-small-cell lung cancer: a systematic review of the literature. *Clin Lung Cancer* 2015; **16:** 71-9. doi: 10.1016/j.cllc.2014.08.002
29. Cannon DM, Mehta MP, Adkison JB, Khuntia D, Traynor AM, Tome WA, et al. Dose-limiting toxicity after hypofractionated dose-escalated radiotherapy in non-small-cell lung cancer. *J Clin Oncol* 2013; **31:** 4343-8. doi: 10.1200/JCO.2013.51.5353
30. Grills IS, Hope AJ, Guckenberger M, Kestin LL, Werner-Wasik M, Yan D, et al. A collaborative analysis of stereotactic lung radiotherapy outcomes for early-stage non-small-cell lung cancer using daily online cone-beam computed tomography image-guided radiotherapy. *J Thorac Oncol* 2012; **7:** 1382-93. doi: 10.1097/JTO.0b013e318260e00d
31. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007; **2:** S94-100. doi: 10.1097/JTO.0b013e318074de34
32. Feddock J, Arnold SM, Shelton BJ, Sinha P, Conrad G, Chen L, et al. Stereotactic body radiation therapy can be used safely to boost residual disease in locally advanced non-small cell lung cancer: a prospective study. *Int J Radiat Oncol Biol Phys* 2013; **85:** 1325-31. doi: 10.1016/j.ijrobp.2012.11.011
33. Karam SD, Horne ZD, Hong RL, McRae D, Duhamel D, Nasr NM. Dose escalation with stereotactic body radiation therapy boost for locally advanced non small cell lung cancer. *Radiat Oncol* 2013; **8:** 179. doi: 10.1186/1748-717X-8-179

34. Higgins KA, Pillai RN, Chen Z, Tian S, Zhang C, Patel P, et al. Concomitant chemotherapy and radiotherapy with SBRT boost for unresectable stage III non-small cell lung cancer: a phase I study. *J Thorac Oncol* 2017; **12:** 1687-95. doi: 10.1016/j.jtho.2017.07.036

35. **35.** Hepel JT, Leonard KL, Safran H, Ng T, Taber A, Khurshid H, et al. Stereotactic body radiation therapy boost after concurrent chemoradiation for locally advanced non-small cell lung cancer: a phase 1 dose escalation study. *Int J Radiat Oncol Biol Phys* 2016; **96:** 1021-7. doi: 10.1016/j.ijrobp.2016.08.032

36. van Baardwijk A, Reymen B, Wanders S, Borger J, Ollers M, Dingemans AM, et al. Mature results of a phase II trial on individualised accelerated radiotherapy based on normal tissue constraints in concurrent chemo-radiation for stage III non-small cell lung cancer. *Eur J Cancer* 2012; **48:** 2339-46. doi: 10.1016/j.ejca.2012.04.014

37. Abramyuk A, Tokalov S, Zophel K, Koch A, Szluha Lazanyi K, Gillham C, et al. Is pre-therapeutical FDG-PET/CT capable to detect high risk tumor subvolumes responsible for local failure in non-small cell lung cancer? *Radiother Oncol* 2009; **91:** 399-404. doi: 10.1016/j.radonc.2009.01.003

38. van Elmpt W, De Ruysscher D, van der Salm A, Lakeman A, van der Stoep J, Emans D, et al. The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer. *Radiother Oncol* 2012; **104:** 67-71. doi: 10.1016/j.radonc.2012.03.005

39. Salem A, Asselin MC, Reymen B, Jackson A, Lambin P, West CML, et al. Targeting hypoxia to improve non-small cell lung cancer outcome. *J Natl Cancer Inst* 2018; **110:** 14-30. doi: 10.1093/jnci/djx160

40. Vera P, Thureau S, Chaumet-Riffaud P, Modzelewski R, Bohn P, Vermandel M, et al. Phase II study of a radiotherapy total dose increase in hypoxic lesions identified by (18)F-misonidazole PET/CT in patients with non-small cell lung carcinoma (RTEP5 Study). *J Nucl Med* 2017; **58:** 1045-53. doi: 10.2967/jnumed.116.188367

41. Kong FM, Frey KA, Quint LE, Ten Haken RK, Hayman JA, Kessler M, et al. A pilot study of [18F]fluorodeoxyglucose positron emission tomography scans during and after radiation-based therapy in patients with non small-cell lung cancer. *J Clin Oncol* 2007; **25:** 3116-23. doi: 10.1200/JCO.2006.10.3747

42. Kong FM, Ten Haken RK, Schipper M, Frey KA, Hayman J, Gross M, et al. Effect of midtreatment PET/CT-adapted radiation therapy with concurrent chemotherapy in patients with locally advanced non-small-cell lung cancer: a phase 2 clinical trial. *JAMA Oncol* 2017; **3:** 1358-65. doi: 10.1001/jamaoncol.2017.0982

43. Scott JG, Berglund A, Schell MJ, Mihaylov I, Fulp WJ, Yue B, et al. A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study. *Lancet Oncol* 2017; **18:** 202-11. doi: 10.1016/S1470-2045(16)30648-9

44. Vinogradskiy Y, Tucker SL, Bluett JB, Wages CA, Liao Z, Martel MK. Prescribing radiation dose to lung cancer patients based on personalized toxicity estimates. *J Thorac Oncol* 2012; **7:** 1676-82. doi: 10.1097/JTO.0b013e318269410a

45. Chang JY, Zhang X, Wang X, Kang Y, Riley B, Bilton S, et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in Stage I or Stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006; **65:** 1087-96. doi: 10.1016/j.ijrobp.2006.01.052

46. Kanai T, Endo M, Minohara S, Miyahara N, Koyama-ito H, Tomura H, et al. Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. *Int J Radiat Oncol Biol Phys* 1999; **44:** 201-10. doi: 10.1016/S0360-3016(98)00544-6

47. Higgins KA, O'Connell K, Liu Y, Gillespie TW, McDonald MW, Pillai RN, et al. National Cancer Database analysis of proton versus photon radiation therapy in non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2017; **97:** 128-37. doi: 0.1016/j.ijrobp.2016.10.001

48. Chang JY, Verma V, Li M, Zhang W, Komaki R, Lu C, et al. Proton beam radiotherapy and concurrent chemotherapy for unresectable stage III non-small cell lung cancer: final results of a phase 2 study. *JAMA Oncol* 2017; **3:** e172032. doi: 10.1001/jamaoncol.2017.2032

49. Liao Z, Lee JJ, Komaki R, Gomez DR, O'Reilly MS, Fossella FV, et al. Bayesian adaptive randomization trial of passive scattering proton therapy and intensity-modulated photon radiotherapy for locally advanced non-small-cell lung cancer. *J Clin Oncol* 2018; **36:** 1813-22. doi: 10.1200/JCO.2017.74.0720

50. Takahashi W, Nakajima M, Yamamoto N, Yamashita H, Nakagawa K, Miyamoto T, et al. A prospective nonrandomized phase I/II study of carbon ion radiotherapy in a favorable subset of locally advanced non-small cell lung cancer (NSCLC). *Cancer* 2015; **121:** 1321-7. doi: 10.1002/cncr.29195

51. Karube M, Yamamoto N, Shioyama Y, Saito J, Matsunobu A, Okimoto T, et al. Carbon-ion radiotherapy for patients with advanced stage non-small-cell lung cancer at multicenters. *J Radiat Res* 2017; **58:** 761-4. doi: 10.1093/jrr/rrx037

52. Shirai K, Kawashima M, Saitoh JI, Abe T, Fukata K, Shigeta Y, et al. Clinical outcomes using carbon-ion radiotherapy and dose-volume histogram comparison between carbon-ion radiotherapy and photon therapy for T2b-4N0M0 non-small cell lung cancer - a pilot study. *PLoS One.* 2017; **12:** e0175589. doi: 10.1371/journal.pone.0175589