review

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

Li Ma1, Yu Men2, Lingling Feng1, Jingjing Kang3, Xin Sun3, Meng Yuan3, Wei Jiang1, Zhouguang Hui2,3

1 Department of Radiation Oncology, National Cancer Center/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, 518116, China
2 Department of VIP Medical Services, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100021, China
3 Department of Radiation Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100021, China

Radiol Oncol 2019; 53(1): 6-14. Received 31 August 2018 Accepted 5 January 2019

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). 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. 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. The prolongation of overall treatment time (7.5 weeks) and the associated tumor repopulation may be the contributing factors to this unsatisfactory outcome. Radiobiology and clinical trials have confirmed that the doubling time of most tumors is less than one week. 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.

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. 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. 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. 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).

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 survival benefit over conventional radiotherapy, 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.
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 1. Researches on altered fractionation in NSCLC**

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>No.</th>
<th>Stage</th>
<th>Treatment outcome</th>
<th>p value</th>
<th>RE</th>
<th>p value</th>
<th>RP</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saunders23</td>
<td>Conventional radiotherapy: 60Gy/2Gy/30f</td>
<td>225</td>
<td>-</td>
<td>20%(2-year OS)</td>
<td>0.004</td>
<td>acute: 7%; late: 5%</td>
<td>-</td>
<td>acute: 19%; late: 4%(symptomatic)</td>
<td>-</td>
</tr>
<tr>
<td>CHART: 1.5Gy tid, 7 days/week, a total of 54Gy</td>
<td>339</td>
<td>-</td>
<td>29%(2-year OS)</td>
<td>-</td>
<td>acute: 9%; late: 7%</td>
<td>-</td>
<td>acute: 10%; late: 16%(symptomatic)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Baumann24</td>
<td>Conventional radiotherapy: 66Gy/2Gy/33f</td>
<td>203</td>
<td>Inoperable</td>
<td>31%(2-year OS)</td>
<td>0.43</td>
<td>acute: 2.2%; late: 0.7%(pG2)</td>
<td>acute: 0.17; late: 0.62</td>
<td>acute: 0.9%; late: 11%(pG2)</td>
<td>acute: 0.32; late: 0.59</td>
</tr>
<tr>
<td>CHART: 1.5Gy tid, 5 days/week, a total of 54Gy</td>
<td>203</td>
<td>-</td>
<td>32%(2-year OS)</td>
<td>-</td>
<td>acute: 9.5%; late: 11%(≥G2 symptomatic)</td>
<td>-</td>
<td>acute: 6.4%; late: 9.2%(pG2)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Mauguen25</td>
<td>Conventional radiotherapy</td>
<td>2000</td>
<td>-</td>
<td>15.9%(3-year OS), 8.3%(5-year OS)</td>
<td>0.04</td>
<td>acute: 9%</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CHART</td>
<td>-</td>
<td>-</td>
<td>19.7%(3-year OS), 10.9%(5-year OS)</td>
<td>-</td>
<td>acute: 6.6%; late: 9.2%(≥G2 symptomatic)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Dinn26</td>
<td>55Gy/2.67Gy/20f</td>
<td>609</td>
<td>II</td>
<td>50%(2-year OS)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>15.1%(G1-2 symptomatic)</td>
<td>-</td>
</tr>
<tr>
<td>Sun27</td>
<td>conventional radiotherapy: 70.8Gy/1.86Gy/38f</td>
<td>54</td>
<td>Inoperable stage III</td>
<td>48.1%(RR)</td>
<td>0.032</td>
<td>33.3%(G2)</td>
<td>-</td>
<td>42.6%(G2)</td>
<td>-</td>
</tr>
<tr>
<td>hypofractionated radiotherapy: 55Gy/2.5Gy/26f</td>
<td>43</td>
<td>-</td>
<td>61.5%(RR)</td>
<td>25.5%(G2)</td>
<td>-</td>
<td>54.9%(G2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cannon29</td>
<td>57.5Gy/2.3Gy/25f</td>
<td>79</td>
<td>LANSCLC</td>
<td>25%(3-year OS)</td>
<td>-</td>
<td>acute: 48%(G2); late: 28%(G2)</td>
<td>-</td>
<td>16%(G2); 6.5%(G4-5)</td>
<td>-</td>
</tr>
<tr>
<td>Feddock32</td>
<td>A month after standard radiotherapy to 60Gy with concurrent chemotherapy, an SBRT boost was given in 5ccm residual primary tumors: 10Gy×2f for peripheral lesions, 6.5Gy×3f for central lesions</td>
<td>61</td>
<td>III/IV</td>
<td>82.9%(primary tumor control with a median follow-up of 13 months)</td>
<td>-</td>
<td>1.6%(G2)</td>
<td>-</td>
<td>acute: 17.1%; late: 9.4%(≥G2)</td>
<td>-</td>
</tr>
<tr>
<td>Karam30</td>
<td>An SBRT boost with 20-30Gy over 5 fractions was prescribed after conventional CCRT to a median dose of 50Gy</td>
<td>16</td>
<td>LANSCLC</td>
<td>78%(1-year OS), 59%(3-year LC)</td>
<td>-</td>
<td>18%(G2)</td>
<td>-</td>
<td>25%(G2)</td>
<td>-</td>
</tr>
<tr>
<td>Higgins31</td>
<td>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×3f and 7Gy×3f for central lesions</td>
<td>19</td>
<td>stage(IIN1/ N2) with primary tumor ±3cm and lymph nodes ≤5ccm</td>
<td>39%(3-year OS), 39%(3-year LC)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Heipel32</td>
<td>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×3f and 14Gy×2f</td>
<td>12</td>
<td>Stage (III) with primary tumor ±30cc and lymph node volume ≤60cc</td>
<td>78%(1-year LC)</td>
<td>-</td>
<td>0(G3)</td>
<td>-</td>
<td>acute: 0(G3); late: 8.3%(G5)</td>
<td>-</td>
</tr>
</tbody>
</table>

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
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. Sun et al. conducted a prospective clinical study comparing hypofractionated 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. Hypofractionated 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.26 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

### TABLE 2. Researches on personalized dose escalation radiotherapy in NSCLC

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>No.</th>
<th>Stage</th>
<th>Treatment outcome</th>
<th>p value RE</th>
<th>p value RP</th>
<th>p value OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Baardwijk³⁶</td>
<td>Initially 1.5Gy bid to 45Gy, then 2Gy per fraction daily increments until reaching the limit dose of normal tissue</td>
<td>137</td>
<td>II</td>
<td>52.4% (2-year OS)</td>
<td>-</td>
<td>acute: 25.9% [G3]; late: 4.6% [G3]</td>
<td>-</td>
</tr>
<tr>
<td>Van Emfert³⁸</td>
<td>Initially 2.75Gy to 66Gy, then boost to the entire primary tumor</td>
<td>15</td>
<td>I-III</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>late: 3% [G3]</td>
</tr>
<tr>
<td>Vera²⁶</td>
<td>1F-FMISO PET-CT (i): 66Gy CCRT</td>
<td>20</td>
<td>LANSCLC</td>
<td>95% (1-year OS)</td>
<td>p=0.10</td>
<td>acute: 75% [G1-3]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1F-FMISO PET-CT (i): 68-86Gy CCRT</td>
<td>24</td>
<td>II</td>
<td>81% (1-year OS)</td>
<td>p=0.01</td>
<td>acute: 75% [G1-3]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1F-FMISO PET-CT (i): 66Gy CCRT</td>
<td>10</td>
<td>I-III</td>
<td>51% (1-year OS)</td>
<td></td>
<td>acute: 100% [G1-3]</td>
<td></td>
</tr>
<tr>
<td>Kong²⁷</td>
<td>Initially 50Gy, then adapt target basing on midtreatment PET-CT and escalate dose to the constraints of normal tissue concurrent with chemotherapy</td>
<td>42</td>
<td>Inoperable stage I-III</td>
<td>2-year LRC: 42%; median OS: 25 months</td>
<td>12% [G3]</td>
<td>-</td>
<td>7% [G3]</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>No.</th>
<th>Stage</th>
<th>Treatment outcome</th>
<th>p value RE</th>
<th>p value RP</th>
<th>p value OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higgins³³</td>
<td>Median dose of photon radiotherapy: 59.4Gy</td>
<td>243474</td>
<td>I-IV</td>
<td>13.5% (5-year OS)</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Median dose of PSPT: 60Gy [RBE]</td>
<td>348</td>
<td>I</td>
<td>23.1% (5-year OS)</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chung³³</td>
<td>74Gy [RBE] PSPT concurrent with chemotherapy</td>
<td>64</td>
<td>II</td>
<td>26.5 months (median OS)</td>
<td>-</td>
<td>8% [G3]</td>
<td>14% [G3-4]</td>
</tr>
<tr>
<td>Liao³³</td>
<td>IMRT: 66-74Gy</td>
<td>92</td>
<td>LANSCLC</td>
<td>10.9% (5FR)</td>
<td>0.86</td>
<td>-</td>
<td>6.5% 0.40</td>
</tr>
<tr>
<td></td>
<td>PSPT: 74Gy [RBE]</td>
<td>57</td>
<td></td>
<td>10.5% (5FR)</td>
<td></td>
<td>-</td>
<td>10.5%</td>
</tr>
<tr>
<td>Takahashi³³</td>
<td>68-74Gy [RBE] carbon ion radiotherapy</td>
<td>72</td>
<td>LANSCLC</td>
<td>93.1% (2-year LRC), 51.9% (2-year OS)</td>
<td>-</td>
<td>1.4% [G3]</td>
<td>1.4% [G3]</td>
</tr>
<tr>
<td>Karube³³</td>
<td>52.8-70.4Gy [RBE] carbon ion radiotherapy</td>
<td>64</td>
<td>II-III</td>
<td>81.8% (2-year LRC), 62.2% (2-year OS)</td>
<td>-</td>
<td>0 [G2]</td>
<td>0 [G2]</td>
</tr>
<tr>
<td>Shira³³</td>
<td>52.9-70.4Gy [RBE] (4+16) carbon ion radiotherapy</td>
<td>23</td>
<td>IIb-IV</td>
<td>81% (2-year LRC), 70% (2-year OS)</td>
<td>-</td>
<td>0 [G3]</td>
<td>0 [G3]</td>
</tr>
</tbody>
</table>

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
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). 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 achieved when BED exceeds 100 Gy demonstrated an excellent control rate in NSCLC could be achieved. This 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

**Personalized radiotherapy**

Fixed dose radiotherapy has been long used in 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. 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. The existence of hypoxia is strongly associated with radioresistance and unfavorable prognosis. Vera et al. carried out a prospective phase II clinical trial to investigate the efficacy of selectively dose increase in hypoxic zones. 18F-misonidazole (18F-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 18F-FMISO positive, of whom, 24 had a dose escalation up to 86 Gy, 10 received a standard radiotherapy of 66 Gy. In 18F-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. 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%. 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 mid-treatment 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. 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. 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. 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. The analysis indicates that low-income groups tend to choose non-pro-
ton 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. 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. 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 chemotherapry 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 proton 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. 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 multi-center retrospective analysis reported by Karube et al. 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. 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.

Acknowledgements

This study was supported by National key research and development program (2017YFC1311000), Beijing Hope Run Special Fund of Cancer Foundation of China (No.LC2016L03), CAMS Innovation Fund (No.2016-I2M-1-011), Clinical Application Project of Beijing Municipal Commission of Science and Technology (Z17110001017114).
References


