Review Article

Chemoradiotherapy for stage III non-small cell lung cancer: have we reached the limit?

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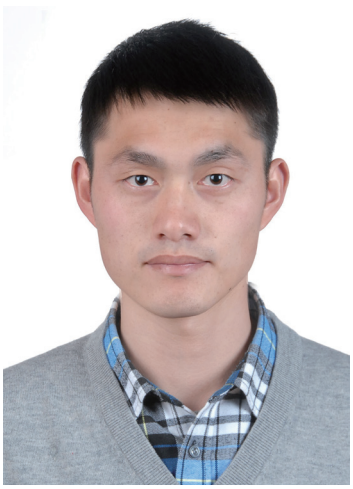

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Abstract: Lung cancer is the leading cause of cancer-related mortality in men and the second leading cause in women. Approximately 85% of lung cancer patients have non-small cell lung cancer (NSCLC), and most present with advanced stage at diagnosis. The current treatment for such patients is chemoradiation (CRT) provided concurrently preferably or sequentially with chemotherapy, using conventionally fractionated radiation doses in the range of 60 to 66 Gy in 30 to 33 fractions. An individual patient data based meta-analysis has shown that in good performance status (PS), concomitant CRT was associated to improved survival by 4.5% compared to sequential combination (5-year survival rate of 15.1% and 10.6% respectively). In the recent years, improvement of modern technique of radiotherapy (RT) and new chemotherapy drugs may be favorable for the patients. Furthermore, the positron emission tomography-computed tomography (PET-CT) contributes to improved delineation of RT especially in terms of nodal involvement. Improving outcomes for patients with stage III disease remains a challenge, this review will address the questions that are considered fundamental to improving outcome in patients with stage III NSCLC.

Keywords: Lung cancer; non-small cell lung cancer (NSCLC); locally advanced inoperable; combined chemoradiotherapy (combined cRT)

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Worldwide, lung cancer is the leading cause of cancer deaths in men and the second leading cause of cancer deaths in women. Based on the GLOBOCAN 2012 estimates, about 1.9 million new lung cancer cases and 1.6 million deaths expected to occur (1). Approximately 85% of lung cancers are non-small cell lung cancers (NSCLC) and only 25-30% of these are eventually suitable for surgical resection with a curative intent (2). At present, the 5-year survival of resected patients ranges between 75% for stage IA and 25% for stage IIIA (2). The current treatment strategy for NSCLC depends on clinical staging. Surgical resection is generally considered the treatment of choice in operable patients with stage I and II disease (3,4). Conversely the role of surgery for stage III NSCLC patients continues to be debated (5-7).

Treatment decisions concerning patients with stage III disease, have to be taken upfront; ideally within a multidisciplinary thoracic tumour board to decide the optimal strategy taking into consideration the anatomical characteristics of the tumour as well as performance status (PS) and ability to undergo surgery, high-dose radiotherapy (RT) and chemotherapy (8,9). The first decision is usually to decide whether the patient is potentially operable, and surgery will be discussed for most stage IIIA patients and some selected stage IIIB patients, whereas most stage IIIB patients will be eligible for combined chemoradiation (CRT) (9). Thus most patients with inoperable stage III disease will be candidates for combined modality chemotherapy and RT. While concomitant administration improves survival compared to sequential combination as shown in several meta-analyses, there is a higher rate of acute toxicities, especially esophageal toxicities (9-13). While the randomized trials have provided evidence in favor of concurrent chemoradiotherapy (cCTRT), there is place for improvement for future research and protocols to optimize chemoradiotherapy. The 5-year survival with concomitant platin based CRT is 15.1% in the meta-analysis and 16% in the largest randomized trial included, the Radiation Therapy Oncology Group (RTOG 9410) with median survival rate of 17 months whereas the 5-year survival in the sequential CRT arm is 10.6% in the meta-analysis and 10% in the RTOG trial (11,14). It should be outlined that the patients included in the trials included in the meta-analysis were treated between 1988 and 2003, before the positron emission tomography-computed tomography (PET-CT) era. It is superior to CT to rule out detectable extrathoracic extracranial metastasis and to assess potential mediastinal lymph node involvement. More recently, a randomized trial (RTOG 0617) evaluating both dose escalation from 60 to 74 Gy as well as the addition of cetuximab to concomitant CRT was published. The median survival in the control arm was 28.7 months for patients with stage III disease treated with cCTRT at the dose of 60 Gy (15). It should be outlined that 90% of patients were selected with PET-CT,

and improved survival compared to previous studies is partly due to better selection. Part of the improvement may also be explained by more modern technique of RT and more conformal RT as indirectly shown in retrospective studies (16,17).

Improving outcomes for patients with stage III disease remains a challenge, this review will address the questions that are considered fundamental to improving outcome in patients with stage III NSCLC.

Radiotherapy (RT)

Changes in radiotherapy (RT) technology

Historically, thoracic RT planning has been complicated by difficult target delineation, unquantifiable tumor motion, all issues that may have led to geographic miss using conventional RT. There have been major changes in the past 15 years due also to the systematic implementation of PET-CT into radiation treatment planning (18,19). PET CT contributes to improved delineation especially in terms of nodal involvement, as well as difficult situations such as tumor with atelectasis. It should be performed ideally within 4 weeks before the start of treatment. We have no randomized data to support that contemporary conformal RT with the implementation of PET-CT increases local control and potentially survival. There are however retrospective studies that seemed to show a beneficial effect of the use of more modern RT techniques in stage III NSCLC patients (16,17).

Compared with 3D-CRT, intensity-modulated radiation therapy (IMRT) enables even tighter sculpting of high-dose regions around the tumor volume, creates steep dose gradients and thus reduces radiation dose to surrounding normal tissues, ultimately facilitating dose-escalation (20). The University of Texas M.D. Anderson Cancer Center investigated the rate of high-grade treatment-related pneumonitis in patients with advanced NSCLC treated with concurrent chemotherapy and IMRT. Toxicity rates were compared with a similar cohort of patients treated with 3D-CRT (median radiation dose 63 Gy for both treatment modalities). The levels of grade ≥3 radiation pneumonitis at 12 months according to RTOG toxicity scoring were significantly (P=0.002) lower for IMRT than for 3D-CRT, being 8% [95% confidence interval (CI), 4-19%] and 32% (95% CI, 26-40%), respectively (21). This initial evaluation is consistent with the conclusion of a subsequent study, including more patients and with longer follow-up times (17). Out of 496 NSCLC patients, 318 were treated with CT/3D-CRT and 91 with 4DCT/IMRT. The hazard ratio (HR) for 4DCT/IMRT was 0.33 (95% CI, 0.13-0.82; P=0.017) for grade ≥3 radiation pneumonitis, indicating lower toxicity rates were associated with 4DCT/IMRT. These findings were confirmed by other studies (22,23). Furthermore, IMRT reduces radiation doses to the esophagus, heart and spinal cord (23,24).

The following solutions could be considered to allow using IMRT to both primary and lymph node areas. A reduction in the planning target volume (PTV) margin may allow for dose escalation for more patients using IMRT. We could use 4DCT for getting the data on systematic and random movements of the proximal bronchial tree and great vessels, and generate the most appropriate margin (25); use of daily online cone-beam CT to decrease CTV to PTV margins (26).

Changes in radiation dose

Dose-escalation studies of three-dimensional conformal RT seem to show that in a 63-103 Gy range, a higher radiation dose increased local control of the tumor and OS (27). However other studies did not result in better outcome. The clinical practice of stereotactic body irradiation for NSCLC comfort this hypothesis that higher doses of RT may result in better outcome: the survival of patients who received RT at a BED ≥100 Gy was significantly better than those who received a BED of less than 100 Gy (28).

Although phase I/II dose-escalation studies of conventional fractionated RT with concurrent chemotherapy reported encouraging survival outcomes obtained with the high dose of 74 Gy (29,30), the results of the subsequent phase III randomized did not confirm these results (15). In the latter study, 166 patients were randomly assigned to receive carboplatin-paclitaxel based chemoradiotherapy with 60 Gy considered as the standard RT dose, 121 to high-dose chemoradiotherapy (same regimen with RT at the dose of 74 Gy), 147 to standard-dose chemoradiotherapy and cetuximab, and 110 to high-dose chemoradiotherapy and cetuximab. Median follow-up for the RT comparison was 22.9 months (IQR, 27.5-33.3). Median overall survival was 28.7 months (95% CI, 24.1-36.9) for patients who received standard-dose RT and 20.3 months (17.7-25.0) for those who received high-dose RT (HR 1.38, 95% CI, 1.09-1.76; P=0.004). Both the radiation-dose and cetuximab results crossed protocol specified futility boundaries. The authors recorded no statistical differences in grade 3 or worse toxic effects between RT groups. There were no differences in severe pulmonary events between

treatment groups. Severe esophagitis was more common in patients who received high-dose chemoradiotherapy than in those who received standard-dose treatment [43 (21%) of 207 patients *vs.* 16 (7%) of 217 patients; P<0.0001] (19). The authors have concluded that dose escalation for all patients at the dose of 74 Gy could be harmful. There are ongoing studies exploring a more selective dose escalation.

NSCLC is a rapidly proliferating cancer, and accelerated repopulation occurs during RT. Thus another area of possible RT intensification is altered fractionation. An individual data based meta-analysis showed that modified fractionation (hyperfractionated and/or accelerated RT) improved survival as compared with conventional schedules resulting in an absolute benefit of 2.5% (8.3% to 10.8%) at 5 years (P=0.009). In a RTOG retrospective study evaluating treatment duration in several CTRT prospective studies, overall treatment time exceeding by over 5 days the theoretical duration, was associated with a 2% increase in the risk of death for each day of prolongation in therapy (31). Prolonged overall treatment time may be one of the reasons why high-dose RT in the RTOG 0617 study failed to produce any survival benefit as treatment time was 7.4 weeks long (32).

Changes in radiation fractionation

Several studies have shown that higher biologically effective doses (BEDs) of RT in cancer treatments could improve local control and survival (32-34). An 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% (35). Because dose escalation with conventional fractionation requires a significant increase in treatment time, two methods to improve BED that maintain or reduce treatment time have been explored: hyperfractionation and hypofractionation.

Accelerated hypofractionated irradiation (AHRT) is infrequently used for the treatment of locally advanced NSCLC. Several studies have explored AHRT combined with chemotherapy with some interesting results (36-44). However hypofractionation particularly in the context of concurrent CRT may cause severe adverse effects on the lung and soft tissues of chest wall, so that it cannot be recommended outside a clinical trial (45). A randomised phase II trial comparing sequential versus concurrent chemotherapy and radical hypofractionated RT at the dose of 55 Gy in 20 fractions of 2.75 was recently published and showed similar survival rates at 2 years of 50% and 46%. Hypofractionated dose-escalated RT with IMRT at doses from 57 to 85.5 Gy in 25 daily fractions over 5 weeks was explored in a phase I study. The maximum tolerated dose was 63.5 Gy; late toxicity was dominated by late radiation toxicity involving central and perihilar structures (45). It should be outlined that no concomitant chemotherapy was administered in this study.

Recently, high-precision RT such as intensity-modulated RT, image-guided RT, treatment gating, have made this approach more feasible. Compared to prior RT approaches, IMRT can significantly lower the doses of radiation to normal tissues, allowing for the administration of larger doses per fraction on tumors. The hypofractionated regimen of 55 Gy in 20 fractions is one of the most common fractionation schedules in the United Kingdom (44).

In the UK, a very dose intense approach, a continuous hyperfractionated accelerated radiotherapy (CHART) was evaluated in NSCLC (32). Patients were randomly assigned to receive the dose of 54 Gy provided in 12 consecutive days (including weekends) with 1.5 Gy administered 3 times per day, or 60 Gy in conventional fractionation. This trial showed a significant benefit in favor of the investigational arm as there was a 24% reduction in the relative risk of death, a 9% absolute improvement in 2-year survival. However these results were not confirmed in the CHARTWEL-trial whether patients were randomly assigned to the CHART week-end less regimen (60 Gy/40 fractions/2.5 weeks) or to control arm (66 Gy/33 fractions/6.5 weeks) (46). Overall, outcome was not different in both arms with 2- and 5 year-survival respectively 31% and 11% in the CHARTWELL arm and 32% and 7% in the control arm (P=0.43). There was a trend for higher efficacy in higher stages and after induction chemotherapy. Both trials were included in the meta-analysis exploring the role of altered fractionation in lung cancer; it demonstrated a 2.5% absolute overall survival benefit at 5 years over conventional fractionation (33).

However, such accelerated treatment may induce more acute toxicity (especially esophagitis) But a further study of cost effectiveness of altered fractionation schedules compared to standard regimen seems to show that accelerated RT may be more efficient and should be recommended as standard RT for the curative treatment of unresected NSCLC patients not receiving concurrent chemo-radiotherapy (33,47).

One could expect less toxicity with newer RT techniques such as IMRT. In the study of Yom *et al.* (21), where 4D IMRT enabled less high grade pneumonitis than it was observed with 3DRT (8% *vs.* 32 % at 12 months,

respectively). More clinical research is needed in this field to provide deeper insight into the problem of high-grade toxicity of hyperfractionated RT with concurrent CT. In the meta analysis exploring for predictive factors of pneumonitis, after combined CRT using either 3-D conformal RT or IMRT, older age, use of carboplatin and paclitaxel concomitant chemotherapy as well as dosimetric parameters were predictive of symptomatic pneumonitis (48). Based on this study, the rate of pneumonitis (≥ grade 2) was 29.8%; only 1.9% was fatal. Daily doses over 2 Gy (7% if >2 Gy *vs.* 1.5% if ≤2 Gy; P=0.01), V20 (OR, 1.09 per 1% increase, P=0.044), and tumor location (1% for upper lobe, 0% for middle lobe, and 5% for lower lobe, P=0.007) were found to be associated with fatal pneumonitis in this meta-analysis. The same group performed another individual data based meta-analysis to explore to determine factors predictive of clinically significant radiation esophagitis. Based on the data of over 1,000 patients, the risk of grade 2, grade 3 and grade 4 esophagitis was respectively 32.2%, 17.1%, and 0.9%. The value of V60 was the best predictor for radiation esophagitis (49).

Chemotherapy

Changes of chemotherapy timing

cCTRT is widely used throughout the world as standard of care for inoperable stage III NSCLC patients with good PS and limited co-morbidities (6,9,11,12,50-57). Concurrent CRT may be offered to selected elderly patients, but it should be outlined that there is a higher risk for toxicity reported in the elderly population (57). In a large meta-analysis (N=1,205) of chemotherapy in locally advanced NSCLC, concomitant chemoradiotherapy, as compared with sequential chemoradiotherapy, produced significant improvements in overall survival (HR, 0.84; 95% CI, 0.74-0.95), 3-year survival (absolute benefit of 5.7%), and 5-year survival (absolute benefit of 4.5%) (11), while the advances have been made in improving survival from stage III NSCLC by optimizing local control, latest evidence suggests that cc CTRT does not reduce the risk of distant relapse. But randomized trials having evaluated induction or consolidation chemotherapy added to concomitant CRT do not seem to improve survival (9,58-60). The phase III trial which evaluated consolidation CT after treatment with cCTRT compared consolidation docetaxel (75 mg/m^2 every 21 days) for three cycles *vs.* observation (58). The trial was terminated early after planned interim analysis on the basis of futility. No significant difference in median survival between the docetaxel and observation arms was observed (21.2 *vs.* 23.2 months, P=0.883). There were higher rates of grade 3-5 pneumonitis in the docetaxel arm compared to the observation arm (9.6% *vs.* 1.4%, P<0.001) and a subsequent analysis of the data confirmed that treatment with consolidation docetaxel was a predictive factor for radiation pneumonitis following cCTRT (61). A recent pooled analysis of 41 phase II/III trials has confirmed that there is no evidence to suggest that consolidation chemotherapy after cCTRT improves survival for stage patients with III NSCLC (60).

In general, the highest incidence of NSCLC is observed in patients older than 65 years. As a consequence, a considerable percentage of patients with newly diagnosed NSCLC are frail and unfit for concurrent RCT treatments. More than half of patients are theoretically not eligible for concurrent RCT in a population-based study (61). Intensification of both RT and concurrent chemotherapy may result also into excessive toxicity or incomplete treatment (57,61). Less toxic alternatives are needed for these patients.

Changes in the chemotherapy drugs

The current standard for locally advanced NSCLC is conformal RT administered at the dose of 60-66 Gy combined with concurrent platinum-based regimen (9,11,49,50,52,53). Etoposide-cisplatin, cisplatin-vinorelbine as well as paclitaxel-carboplatin are commonly used with concurrent radiation therapy in locally advanced NSCLC.

The broadest evidence concerning this issue comes from trials that have included cisplatin based doublets, particularly, cisplatin and etoposide or cisplatin and vinorelbine (9). Despite this accepted evidence, there has been a strong trend in North America and even in parts of Europe to prefer outpatient administration of weekly low-dose carboplatin and paclitaxel combination schedules that are simultaneously administered with outpatient RT, on the basis of the assumption that this is more convenient and possibly just as effective as cisplatin-based doublets (9). It should be outlined that the concomitant administration of carboplatin-taxol as well as docetaxel administered concomitantly or as consolidation treatment seems to increase the rate of pneumonitis (48,54,55).

Santana-Davila *et al.* (62) tried to evaluate the optimal CRT regimen, in a large retrospective study from the Veterans Health Administration (VHA) database of 1,842 patients treated over a 10-year period (2001 to 2011). They compared

patient groups receiving either cisplatin and etoposide, or a combination of carboplatin and paclitaxel, administered concurrently with curative doses of radiation. The aim of their study was to compare the two chemotherapy protocols with respect to the survival outcome. They concluded that carboplatin and paclitaxel, when administered concurrently with RT, resulted in survival outcomes that were comparable to cisplatin and etoposide in a comparable clinical setting. However one should always be cautious with such a posteriori comparisons. This cannot be considered as robust evidence in favour of one treatment modality. It should be outlined that carboplatin may also not be as effective as cisplatin against micro metastases in lung cancer, as we have learned a meta-analysis on metastatic NSCLC which showed that cisplatin-based chemotherapy was slightly superior to carboplatin-based chemotherapy in terms of response rate and, in certain subgroups, in prolonging survival without being associated with an increase in severe toxic effects (63). A subsequent meta-analysis comparing cisplatin doublets to carboplatin doublets combined to third generation drugs in metastatic NSCLC did not show any difference in survival but a better response rate with cisplatin doublets (64). It should be recalled that all trials that have evaluated carboplatin alone with RT were negative (65). On the basis of the published evidence from the meta-analysis that used individual patient data (48), it was found that carboplatin/paclitaxel might be even more toxic than the cisplatin/etoposide combination with respect to the development of pneumonitis. Pulmonary toxicity remains a sensitive issue for such a curative treatment. It also has clinically relevant implications for quality of life and well-being of patients, based on the development of late effects from chemoradiotherapy (48).

A number of other drugs have been investigated for combined modality treatment and the development of newer chemotherapeutic agents with activity in NSCLC provides the opportunity to explore novel approaches in the treatment of stage III disease, as pemetrexed which has become one of the major drugs in metastatic adenocarcinoma. According to a current review of the literature of phase I and phase II studies (66), it seems pemetrexed can be administered safely at full systemic doses with cisplatin concomitantly with radical doses of thoracic RT. Of the six phase II trials with mature data available, median overall survival ranged from 18.7 to 34 months. However, we should wait for the results of the phase III trial PROCLAIM which has not been published yet. The trial has been presented at the ASCO meeting 2015 (67). It shows that pemetrexed and cisplatin may be safely administered, but is not superior in terms of efficacy to cisplatin and etoposide in the concurrent setting. Median survival, 2- and 3-year survival rate was respectively 26.8 months, 52% and 40% in the pemetrexed-cisplatin based CTRT arm and 25 months, 52% and 37% in the control arm combing RT at the dose of 66 Gy with etoposide and cisplatin.

In conclusion, it is clear that cCTRT is the current standard of care for inoperable stage III NSCLC patients with good PS and minimal co-morbidities. However, a survival plateau has been reached, with disappointing results from dose escalation studies using conventional fractionation and studies investigating the addition of systemic doses of chemotherapy delivered before or after concurrent CRT. Further improvement such as IMRT/IGRT utilized for more selective dose escalation and to reduce dose to critical structures will be determined by better local control and by reducing the risk of distant recurrence. The benefits of newer chemotherapeutic agents will reduce both the risk of local and distant relapse. Collaborative efforts are now needed to these advances for optimal treatment and improved outcomes of locally advanced NSCLC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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