



# Treatment of locally advanced, unresectable or medically inoperable stage III non-small-cell lung cancer; the past, present and future of chemoradiotherapy

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## ABSTRACT

We aimed to review the development of the chemoradiotherapy options used in the treatment of locally advanced, unresectable or medically inoperable Stage III non-small-cell lung cancer (NSCLC) patients with this review. There are many differences about extent and localization of disease for locally advanced stage NSCLC. The optimal management depends upon multiple factors, including the specific combination of tumor (T) and node (N) staging parameters, the potential to achieve a complete surgical resection of all disease if indicated, and the patient's overall condition and preferences. Chemoradiotherapy has always been the cornerstone of treatment of locally advanced NSCLC and techniques have significantly advanced over this time. Radiation oncology needs to develop the new techniques to improve their survival and the toxicity associated with treatment.

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## 1. Introduction

Locally advanced Non-Small-Cell Lung Cancer (NSCLC) accounts for approximately one fourth of all new lung cancer cases. Locally advanced NSCLC remains a complex and heterogeneous disease with evolving treatment approaches. Concurrent chemoradiotherapy (CCRT) has been the standard treatment for patients with unresectable stage III NSCLC.<sup>1–3</sup> The addition of chemotherapy to thoracic radiation improves overall survival (OS), and CCRT appears to offer superior outcomes when compared to sequential therapy. In patients who received cisplatin-based chemotherapy with radiation, there was a 30% reduction in 2-year mortality compared to radiation alone. Using standard traditional radiation doses and techniques, survival rates of 40%, 15%, and 5% were achieved at 1, 2, and 5 years, respectively.<sup>4–6</sup> Recent technological advances in RT and novel chemotherapeutic approaches have provided preliminary data for further improving clinical outcome while minimizing the morbidity associated with the therapy.<sup>5</sup> We reviewed the recent development of chemoradiotherapy in the treatment of stage III NSCLC in this review.

## 2. The past

Before 1990s, definitive radiotherapy (RT) alone was the mainstay of treatment of the locally advanced, unresectable or medically inoperable NSCLC. RTOG 7301 phase III randomized study found that 60 Gy is the most tolerable and optimal dose with better tumor response offering a better intrathoracic control as well as survival.<sup>7</sup> During the early 1990s, however, as the deaths from distant metastasis were still high, the quest of multiple randomized phase III studies shifted from the standard radiotherapy alone to adding systemic therapies to the radiation. CCRT became as standard.<sup>2–6</sup>

In the 1990s, the predominant RT technique for treating locally advanced lung cancer was two-dimensional. Progress in technology in imaging especially with modern multisliced computerized tomography has led to three-dimensional conformal RT (3DCRT) approach. The widespread use of 3DCRT provides a significant advantage over two dimensional radiation: conformal beam design and the ability to manipulate beam geometry and weighting through the planning process improves coverage of the tumor target, and decreases the dose to normal tissue.

Cooperative group studies dating back as far as 25 years established that sequential chemotherapy and radiation therapy modestly improved survival over radiation therapy alone. With the better treatment planning systems and developments in the image guidance during radiotherapy, the use of intensity-modulated RT (IMRT) has been increasing in frequency over the past two decades.

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In contrast to 3DCRT, IMRT is inverse planned. The use of IMRT results in a more conformal plan than 3DCRT, thus reducing the exposure of surrounding normal tissue to high doses of radiation.<sup>8,9</sup>

### 3. The present

Despite multimodality treatment, the prognosis for unresectable stage III NSCLC remains poor, with five-year OS rates of approximately 15%.<sup>10,11</sup> Therefore interest exists in developing newer treatment paradigms such as radiation dose escalation and integrating newer systemic therapies to radiotherapy.

#### 3.1. Concurrent chemoradiotherapy

The addition of chemotherapy to radiation has been the subject of many prospective trials and several meta-analyses. 1995 meta-analysis of stage III NSCLC examined 1887 patients from 14 trials, found that there was a significant reduction in mortality rates with the addition of chemotherapy to radiation. Combined therapy with both cisplatin-based and noncisplatin-based groups were better than radiotherapy alone. For cisplatin-based group, 1 and 2-years reduction in mortality was 24% and 30%, respectively whereas it was 5% and 18% for the noncisplatin-based group.<sup>12</sup> The first large-scale trial to demonstrate a survival benefit with sequential chemoradiation therapy compared with standard RT alone was conducted by the CALGB.<sup>13</sup>

After the trials supporting survival advantage with sequential chemotherapy, CCRT was also questioned under the knowledge of chemosensitization. RTOG 9410 trial was the key study showing higher survival and higher response rate with CCRT.<sup>14</sup> Several trials clearly demonstrate an OS advantage for the use of CCRT as opposed to the sequential use of chemotherapy followed by thoracic RT.<sup>15</sup> The absolute survival benefit was 4.5% at 5-years with the concurrent approach.<sup>11</sup> The use of concurrent, rather than sequential, chemotherapy with thoracic RT appears to improve OS, at the cost of increased acute toxicity. So, induction chemotherapy should be used for bulky diseases which is the issue for radiation portals in terms of protecting normal tissues.<sup>16</sup>

Although CCRT is the standard, the best chemotherapy regimen in CCRT is not well defined. The two chemotherapy regimens that have been most commonly used in the United States are the cisplatin-etoposide and carboplatin-paclitaxel regimens during CCRT.<sup>17</sup> Cisplatin regimens found to be better than carboplatin regimens and offer a higher response rate.<sup>18–20</sup> But grade 3 or higher adverse effects were less with paclitaxel-carboplatin regimen. Third generation chemotherapy regimens were mostly found to be non-inferior but generally more toxic.<sup>21,22</sup>

The choice of a particular regimen is often made on the basis of secondary factors, such as cost, logistical convenience, ease of administration, toxicity profile, patient preference, and physician experience. Induction chemotherapy appears to reduce the number of distant relapses, which translates into a modest benefit in survival. Further studies are necessary to fully define the optimal administration of current chemoradiation with or without induction or consolidation chemotherapy.

#### 3.2. Molecular-targeted combined modality therapy

Molecular-targeted therapy is a novel strategy born from our increasing understanding of the underlying pathways and key molecules. The addition of antiangiogenics has not improved outcomes. The RTOG phase II trial (RTOG 0324) administered weekly cetuximab with carboplatin and paclitaxel to patients with stage III disease who were receiving concurrent chemoradiation therapy and reported a response rate of 62% and a 24-month OS of 49.3%.<sup>23</sup>

A randomized trial conducted by the Eastern Cooperative Oncology Group added thalidomide to concurrent or sequential chemoradiation did not show any benefit.

Bevacizumab, the monoclonal antibody to the vascular endothelial growth factor receptor was also used with chemoradiation. It provided longer overall and progression free survival (PFS) with higher response rates but grade 3 or worse toxicity was more frequent and tracheoesophageal fistula formation was the major problem. So, routine concurrent clinical use of Bevacizumab with radiation is not recommended.<sup>24,25</sup> Bevacizumab, has also been added to chemoradiation in a phase 2 study that also incorporated an EGFR TKI and escalated radiation dose.<sup>26</sup> There was no improvement over standard therapy.

#### 3.3. Immunotherapy and chemoradiotherapy

Given preclinical evidence suggests that chemotherapy and radiotherapy may up-regulate PD-L1 expression in tumor cells.<sup>27–29</sup> Low doses of fractionated radiotherapy led to PD-L1 upregulation on tumor cells in a variety of syngeneic mouse models of cancer. Mechanistic investigations showed that IFN $\gamma$  produced by CD8<sup>+</sup> T cells was responsible for mediating PD-L1 upregulation on tumor cells after delivery of fractionated radiotherapy. In a phase III trial, over 700 patients with unresectable stage III NSCLC without progression after at least two cycles of platinum-based chemoradiotherapy were randomly assigned to the programmed death ligand 1 (PD-L1) antibody durvalumab or placebo in a 2:1 ratio.<sup>30</sup> The benefit in PFS with durvalumab was observed irrespective of PD-L1 expression before chemoradiotherapy. The results demonstrate efficacy and tolerability of durvalumab for treatment of unresectable stage III NSCLC in patients who experience an objective response or stable disease following completion of chemoradiotherapy.

#### 3.4. Other treatment approaches

Multiple image guided ablative techniques are being developed for use in patients with primary nonsmall cell lung cancer (NSCLC) or oligometastatic pulmonary lesions in whom surgery is not an option. Radiofrequency ablation is the most studied technique, but other approaches under development include microwave ablation, laser ablation, cryoablation, and irreversible electroporation.

#### 3.5. Improving the radiation

The standard dose and fractionation regimen of RT with chemotherapy for stage III NSCLC remains 60 Gy in 30 daily fractions over 6 weeks. Retrospective analysis of 7 prospective RTOG trials showed higher biologically effective dose (BED) results better outcomes. Increasing dose intensity turns out increased local control and better survival.<sup>31</sup> Phase I-II dose escalating studies demonstrated 74 Gy as the maximum tolerated dose.<sup>32</sup> But RTOG 0617 Phase III trial comparing high dose 74 Gy with standard dose 60 Gy in the modern radiation technique era, found 74 Gy was worse than 60 Gy in terms of overall survival and toxicity. And also Cetuximab did not effect survival.<sup>33</sup> Mature 5-year follow up data of this trial supported the same results.<sup>34</sup>

Hyperfractionated radiotherapy is the way to give higher radiation doses over the same period of time. Radiation is given 2 times per day with 6 h intervals. Results of RTOG 8808 and RTOG 9410 trials showed no advantage of hyperfractionated regimens over the standard courses.<sup>35</sup> Continuous hyperfractionated accelerated radiotherapy (CHART) is applied in 12 consecutive days, 1.5 Gy per fractions, three times per day to a total dose of 54 Gy.<sup>36</sup> CHART significantly improves overall survival at 2-years, but the largest

benefit is seen among squamous-cell histology. CHARTWEL study is a modification of CHART where therapy is not given during weekends.<sup>37</sup> Unlike CHART, just an improvement in the local control was seen with CHARTWEL. An individual patient data meta-analysis reviewing hyperfractionated or accelerated RT presented that hyperfractionated regimens significantly prolong survival with an increased 5-year overall survival by 2.5% and decreased the risk of death by 12%.<sup>38</sup> But acute toxicity and logistics of the department are the main issues for hyperfractionated regimens.

Hypofractionation gives higher dose per fraction, total dose is lower than the conventional therapy. There are a number of phase I-II studies. EORTC 08972-22973 Phase III trial tested hypofractionation.<sup>39</sup> As a result of hypofractionation studies, there is no survival advantage and local control and response rates were similar to the conventional radiation.

IMRT and proton therapy are new techniques. Image-guided RT (IGRT) implies the presence of radiographic imaging incorporated into the radiation treatment device. The use of IGRT allows the reduction of the expansion margin around the clinical target volume, since interfraction variations in patient positioning are reduced.<sup>40</sup> After abandonment of elective irradiation of the nodal areas<sup>41</sup> and widely usage of FDG-PET/CT and endobronchial ultrasound (EBUS) for disease staging, radiation treatment portals became smaller. Auditing target volumes during treatment with such devices like respiratory/tumor gating has led IMRT more compatible for lung cancer treatment.<sup>42</sup>

The use of charged particle therapy such as protons is an area of active investigation in lung cancer. Protons have distinct physical characteristics that suggest they can be used to deliver thoracic radiation with a lower risk of side effects, when compared to standard photon therapy. Phase 2 trials of fractionated proton therapy with concurrent chemotherapy in locally advanced lung cancer have demonstrated excellent median survival, with relatively low toxicity.<sup>43,44</sup>

#### 4. The future

When the mechanisms of action of immunotherapy and radiotherapy are examined, information is increasing with their relationship and coexistence. Drugs targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1/programmed death ligand 1 (PD1/PDL1) have shown significant early promise in a range of cancer types. Studies will show new modalities to evaluate the options of immuno-checkpoint inhibitors and chemoradiotherapy in the treatment of locally advanced NSCLC patients in the future.

#### 5. Conclusion

The chemoradiotherapy approaches in the treatment of locally advanced NSCLC has advanced since the 1990s. Uncertainty about the potential mechanisms driving the interaction between immunotherapy and chemoradiotherapy warrants further investigation. The identification and inhibition of key drivers of immunosuppression may augment antitumor immune responses with the potential to improve patient outcome.

#### References

1. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med*. 1985;312:1604.
2. Furuse K, Fukuoka M, Kawahara M, 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;17:2692–2699.
3. Curran WJ, Paulus R, Langer CJ, 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;103:1452–1460.
4. Mohiuddin MM, Choi NC. The role of radiation therapy in non-small cell lung cancer. *Semin Respir Crit Care Med*. 2005;26(3):278–288.
5. Rigas JR, Lara Jr PN. Current perspectives on treatment strategies for locally advanced, unresectable stage III non-small cell lung cancer. *Lung Canc*. 2005;50(Suppl 2):S17–S24.
6. Stinchcombe TE, Fried D, Morris DE, Socinskia MA. Combined modality therapy for stage III non-small cell lung cancer. *Oncologist*. 2006;11(7):809–823.
7. Perez CA, Stanley K, Rubin P, et al. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung. Preliminary report by the Radiation Therapy Oncology Group. *Cancer*. 1980;45:2744–2753.
8. Grills IS, Yan D, Martinez AA, et al. Potential for reduced toxicity and dose escalation in the treatment of inoperable non-small-cell lung cancer: a comparison of intensity-modulated radiation therapy (IMRT), 3D conformal radiation, and elective nodal irradiation. *Int J Radiat Oncol Biol Phys*. 2003;57:875–890.
9. Liu HH, Wang X, Dong L, et al. Feasibility of sparing lung and other thoracic structures with intensity-modulated radiotherapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2004;58:1268–1279.
10. Ahn JS, Ahn YC, Kim JH, et al. Multinational randomized phase III trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III non-small-cell lung cancer: KCSG-LU05-04. *J Clin Oncol*. 2015;33:2660.
11. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol*. 2010;28:2181.
12. Marino P, Preatoni A, Cantoni A. Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIb non-small cell lung cancer. A meta-analysis. *Cancer*. 1995;76:593–601.
13. Dillman RO, Seagren SL, Propert KJ, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. *N Engl J Med*. 1990;323(14):940–945.
14. Curran WJ, Paulus R, Langer CJ, 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;103:1452–1460.
15. Zatloukal P, Petruzzelka L, Zemanova M, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. *Lung Canc*. 2004;46(1):87–98.
16. Rodrigues G, Choy H, Bradley J, et al. Definitive radiation therapy in locally advanced non-small cell lung cancer: executive summary of an American Society for Radiation Oncology (ASTRO) evidence based clinical practice guideline. *Pract Radiat Oncol*. 2015;5:141–148.
17. Liang J, Bi N, Wu S, et al. Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: a multicenter randomized phase III trial. *Ann Oncol*. 2017;28:777.
18. Wang L, Wu S, Ou G, et al. Randomized phase II study of concurrent cisplatin/etoposide or paclitaxel/carboplatin and thoracic radiotherapy in patients with stage III non-small cell lung cancer. *Lung Canc*. 2012;77:89–96.
19. Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M, Tanimoto M. Meta-analysis of randomized clinical trials comparing Cisplatin to Carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol*. 2004;22:3852–3859.
20. Ardizzoni A, Boni L, Tiseo M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. *J Natl Cancer Inst*. 2007;99:847–857.
21. Yamamoto N, Nakagawa K, Nishimura Y, et al. Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan Thoracic Oncology Group WJTOG0105. *J Clin Oncol*. 2010;28:3739–3745.
22. Senan S, Brade A, Wang LH, et al. Proclaim: randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2016;34:953–962.
23. Blumenschein Jr GR, Paulus R, Curran WJ, et al. Phase II study of cetuximab in combination with chemoradiation in patients with stage IIIA/B non-small-cell lung cancer: RTOG 0324. *J Clin Oncol*. 2011;29(17):2312–2318.
24. Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for non-squamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). *Ann Oncol*. 2010;21:1804–1809.
25. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355:2542–2550.
26. Socinski MA, Stinchcombe TE, Moore DT, et al. Incorporating bevacizumab and erlotinib in the combined-modality treatment of stage III non-small-cell lung cancer: results of a phase I/II trial. *J Clin Oncol*. 2012;30:3953–3959.
27. Zhang P, Su DM, Liang M, Fu J. Chemopreventive agents induce programmed death-1-ligand 1 (PD-L1) surface expression in breast cancer cells and promote PD-L1-mediated T cell apoptosis. *Mol Immunol*. 2008;45:1470–1476.
28. Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest*. 2014;124:687–695.
29. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, et al. Acquired resistance to

- fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Canc Res.* 2014;74:5458–5468.
30. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med.* 2017;377(20):1919–1929.
  31. Machtay M, Bae K, Movsas B, 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;82:425–434.
  32. Socinski MA, Rosenman JC, Halle J, et al. Dose-escalating conformal thoracic radiation therapy with induction and concurrent carboplatin/paclitaxel in unresectable stage IIIA/B non-small cell lung carcinoma: a modified phase I/II trial. *Cancer.* 2001;92:1213–1223.
  33. Bradley JD, Paulus R, Komaki R, 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;16:187–199.
  34. Bradley JD, Hu C, Komaki RU, et al. Long-term results of RTOG 0617: a randomized phase 3 comparison of standard dose versus high dose conformal chemoradiation therapy +/- cetuximab for stage III NSCLC. *Int J Radiat Oncol Biol Phys.* 2017;99(2):S105.
  35. Sause W, Kolesar P, Taylor SIV, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: radiation therapy oncology group, Eastern cooperative oncology group, and Southwest oncology group. *Chest.* 2000;117:358–364.
  36. Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Palmar M. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee. *Radiother Oncol.* 1999;52:137–148.
  37. Baumann M, Herrmann T, Matthiessen W, Koch R, Strelocke K, Paul U. CHARTWEL-Bronchus (ARO 97-1): a randomized multicenter trial to compare conventional fractionated radiotherapy with CHARTWEL radiotherapy in inoperable non-small-cell bronchial carcinoma. *Strahlenther Onkol.* 1997;173:663–667.
  38. Mauguen A, Le Péchoux C, Saunders MI, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. *J Clin Oncol.* 2012;30:2788–2797.
  39. Belderbos J, Uitterhoeve L, van Zandwijk N, et al. Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972-22973). *Eur J Canc.* 2007;43:114–121.
  40. Grills IS, Hugo G, Kestin LL, et al. Image-guided radiotherapy via daily online cone-beam CT substantially reduces margin requirements for stereotactic lung radiotherapy. *Int J Radiat Oncol Biol Phys.* 2008;70:1045–1056.
  41. Yuan S, Sun X, Li M, et al. A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III non-small cell lung cancer. *Am J Clin Oncol.* 2007;30:239–244.
  42. Chun SG, Hu C, Choy H, et al. Comparison of 3-D conformal and intensity modulated radiation therapy outcomes for locally advanced non-small cell lung cancer in nrg oncology/RTOG 0617. *Int J Radiat Oncol Biol Phys.* 2015;93: S1–S2.
  43. Chang JY, Komaki R, Lu C, et al. Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III non-small cell lung cancer. *Cancer.* 2011;117:4707–4713.
  44. Oshiro Y, Mizumoto M, Okumura T, et al. Results of proton beam therapy without concurrent chemotherapy for patients with unresectable stage III non-small cell lung cancer. *J Thorac Oncol.* 2012;7:370–375.