

Challenges in optimizing chemoradiation in locally advanced non small-cell lung cancers in India

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Abstract

Data supporting use of concurrent chemoradiation in locally advanced lung cancers comes from clinical trials from developed countries. Applicability and outcomes of such schedules in developing countries is not widely reported. There are various challenges in delivering chemoradiation in locally advanced non small cell lung cancer in developing countries which is highlighted by an audit of patients treated with chemoradiation in our center. This article deals with the challenges in the context of a developing country. We conclude that sequential chemoradiotherapy is better tolerated than concurrent chemoradiation in Indian patients with locally advanced non-small cell lung cancers. Patients with stage IIIa, normal weight or overweight, and adequate baseline pulmonary function should be offered concurrent chemoradiation.

Key words: Locally advanced non-small cell Lung cancer; concurrent chemoradiation, developing countries, non-small-cell lung cancer; chemoradiation

Introduction

Lung cancer remains a major cause of death worldwide with more than 1.1 million deaths per year.^[1] Non-small-cell lung cancer (NSCLC) represents more than 80% of all lung tumors, and approximately 35% of patients with NSCLC in developed countries present with locally advanced non-metastatic disease. The incidence of lung cancer in developing countries has risen from 31% in 1980 to 50% in 2002.^[2] In India, it is the second commonest cancer in urban males.^[3] Most patients present in advanced stages and the intent of treatment is palliative.^[4] Since the mid-1990s, the standard treatment for patients with locally advanced non metastatic disease was thoracic radiotherapy and then combined radiochemotherapy. The NSCLC Collaborative Group meta-analysis and the meta-analysis of platin-based concomitant chemotherapy in NSCLC demonstrated that adding sequential or concomitant chemotherapy to radical radiotherapy improved survival in locally advanced NSCLC.^[5,6] The hazard ratio (HR) for survival resulting from the addition of sequential chemotherapy to radiotherapy was 0.88 (95% CI, 0.81-0.96). The HR resulting from the addition of platin-based concomitant chemotherapy to radiotherapy was 0.89 (95% CI, 0.81-0.98). Several NSCLC trials and

meta-analysis have compared sequential and concomitant combinations directly, almost all of which showed a trend in favor of concomitant radiochemotherapy.^[5,6] However, some authors still believe that more evidence is required to prove the superiority of concurrent chemoradiation due to heterogeneity of the included trials in the meta-analysis, low patient numbers and lack of statistical power.^[7] Most of the data supporting this observation comes from the developed world and rarely have good-quality clinical trials been carried out in developing countries. Applicability of the results of randomized studies in clinical practice in developing countries is not known. It is, therefore, of paramount importance to put the experience of the developed world into the context of the limited resources and other health care problems of developing countries.^[8] Outcomes with chemoradiotherapy in Indian patients with locally advanced lung cancer have been rarely reported.^[9]

There are various challenges in treatment of locally advanced lung cancer especially in the context of developing countries. Hence the purpose of this review is to highlight the various challenges in optimizing chemoradiation in locally advanced NSCLC and evaluate its applicability in developing countries based on our audit of outcomes with chemoradiation in patients with locally advanced lung cancer over 5 years.

Tumor and patient heterogeneity

Locally advanced NSCLC is a heterogeneous disease which explains the large differences in treatment outcome between patients. The stage subdivision in IIIA and IIIB varies considerably depending on tumor size, location and nodal involvement. A large number of patients with more advanced or metastatic disease may be included in this subset based on CT scan findings, if not ruled out as metastatic disease by PETCT.^[10] PETCT is still available in only select metropolitan cities in such a vast country and hence accurate staging of these patients is a challenge in our country. Positivity of radiologically

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enlarged mediastinal lymph nodes should be proven by endobronchial ultrasound guided or transbronchial cytology. Availability of endobronchial ultrasound-guided cytology is also a challenge in our country. Out of 495 patients registered in our department over 5 years (2007-2011), only 55 (11%) patients with stage III disease were suitable for radical chemoradiation (based on radiological staging with CT scan and excluding patients with frank pleural effusion). Among these only 16 (29%) had stage IIIA disease and 39 (71%) had stage IIIB disease. Based on the guidelines for eligibility for chemoradiation in developing countries only those with IIIA should be offered concurrent chemoradiation, but since the superiority of concurrent chemoradiation over sequential chemoradiation were preliminary at the time when we embarked on concurrent chemoradiation, 63% patients were treated with concurrent chemoradiation with an intent to offer superior treatment.^[11] Those with poor performance status, greater weight loss and bulkier disease were treated with sequential chemoradiation.^[11] This data reflects that the majority of patients of NSCLC (89%) present in advanced stages and are unfit for any radical treatment at the time of presentation, which can be attributed to illiteracy, lack of awareness and resources for early detection of lung cancers in our country.

Clinical factors

Clinical factors such as weight loss, performance status, comorbidity and cardiopulmonary reserves will influence tolerance to treatment and outcome in NSCLC. Comorbidity is frequently observed in elderly patients and in smokers, two groups with a high incidence of lung cancer. These patients often receive less aggressive treatment.^[12,13] More than half of the patients with stage III are currently thought to be ineligible for concurrent regimens, if inclusion is restricted to patients less than 75 years and those with less than two serious comorbidities.^[14] However, comorbidity does not correlate *per se* with treatment outcome in patients fit enough for chemoradiation therapy (CRT).^[15] In a prospective study of 203 patients with locally advanced NSCLC, prognostic factors like age, sex, ethnicity, smoking status, performance status, body mass index (BMI), forced expiratory volume in 1 minute (FEV₁), use of FDG-PET scan, stage (IIIA versus IIIB) and baseline hemoglobin were analyzed to find out factors associated with better outcomes. On multivariate analysis, baseline hemoglobin (>12 g/dl) and FEV₁ more than 2 lt predicted favorable outcomes in patients treated with chemoradiation.^[16] The median age of our patients was 62 years and the median survival of patients less than 65 years age was 12 months as compared to 10 months with more than 65 years age. On multivariate analysis FEV₁ more than 2 lt, BMI and radiotherapy dose predicted favorable outcomes. Those with FEV₁ more than 2 lt had a median survival of 36 months versus 12 months for FEV₁ less than 2 lt, BMI overweight had median survival of 24 months versus 12 and 6 months

with normal and underweight and radiotherapy dose more than 50 Gy predicted better survival than that with less than 50 Gy. Patients with stage IIIA had a median survival of 23 months as compared to 12 months with Stage IIIB. Performance status, weight loss and stage did not show prognostic significance.

Chemotherapy schedule

There is still no consensus on which cytotoxic drug combinations are the standard of care for sequential chemotherapy. No two studies included in various meta-analyses on outcomes of concurrent versus sequential chemoradiotherapy have similar drug combinations in the sequential arm. For sequential chemotherapy poor patients received cisplatin etoposide combination, patients coming from far places were offered carboplatin paclitaxel combination and those who had to travel shorter distance were offered cisplatin gemcitabine combination. However, all the above mentioned cytotoxic drugs were well-tolerated by Indian patients. Another challenge in developing countries is lack of health insurance policy for the vast population, resulting in difficulty in delivering similar cytotoxic drugs across the population which in turn leads to difficulty in interpretation of outcome. Also the government funding agencies for research as a policy do not support costs of chemotherapy drugs required for conducting clinical trials for cancer care, where the same regimen can be given to all the patients for ensuring uniform treatment and meaningful interpretation of outcomes.

Choice of concomitant drugs

There is still no consensus on which cytotoxic drug combinations and schedule of drug delivery are the standard of care for concomitant chemoradiotherapy. At present platinum-based polychemotherapy is considered the standard. Apart from the radio-sensitizing effects, cytotoxic agents may influence cell cycle synchronization, prevent tumor cell repopulation and inhibit DNA repair to hypoxic cell sensitization. Drugs such as cisplatin and carboplatin are frequently used in combination CRT. Cisplatin can be given in low daily dose or in higher doses in a weekly or three weekly regimen. Cisplatin is active as a radio sensitizer but this has not been shown clearly for carboplatin.^[17,18] For practical reasons, however, carboplatin-based doublets are often used. The second agent varies and its choice should be based on its toxicity profile. Etoposide, vinorelbine and taxanes do not show any unexpected toxicity in studies reported so far and are thus good candidates to be added to the platinum compound. Incorporation of newer cytotoxic drugs and targeted agents are being explored for their potential role in the treatment of locally advanced NSCLC. In a JCOG study evaluating induction chemotherapy followed by gefitinib and concurrent thoracic radiotherapy for unresectable locally advanced adenocarcinoma of the lung, toxicity was acceptable and the median survival time was 28.5 months.^[19] In another study where patients were stratified based on risk categories into good risk and

poor risk groups. Patients with good risk were treated with concurrent gefitinib 250 mg daily and weekly paclitaxel 50 mg/m² plus carboplatin AUC 2 and those with poor risk with concurrent gefitinib 250 mg daily along with RT (66 Gy). Survival of poor-risk patients with wild type or mutated EGFR receiving sequential CRT with gefitinib was promising. Survival for good-risk patients receiving concurrent CRT plus gefitinib was disappointing even for tumors with activating EGFR mutations.^[20] Although this strategy is less toxic, only data of feasibility studies are available. This strategy is attractive for our population because of higher incidence of EGFR mutation status in Asians but availability of EGFR mutation status is a challenge in our country and hence outcomes with concurrent EGFR tyrosine kinase inhibitors are not available for our population.

In our patients concurrent chemotherapy with cisplatin etoposide combination as per the SWOG protocol showed 80% compliance and hence can be safely delivered.^[21] The popularity of carboplatin paclitaxel combination in US, when tested in two of our patients resulted in fungal pneumonia leading to death. Therefore, this regimen has been further abandoned in our setup but is being used in some centres in our country. Literature on radiation pneumonitis also suggests that this combination results in higher incidence of radiation pneumonitis.^[22] Hence use of this combination is advisable in centers with resources to tackle these complications.

Radiotherapy

Thoracic radiotherapy is an integral component of treatment in locally advanced NSCLC as it is responsible for local disease control and contributes to improved survival. In the Radiation Therapy Oncology Group (RTOG73-01) study using two-dimensional treatment techniques, 376 patients were randomized between a radiation dose of 40 Gy split course and a continuous fractionation schedule of 40, 50, or 60 Gy.^[23] The intrathoracic failure rates at 3 years in these arms were 44, 52, 42, and 33%. A higher dose resulted in a greater proportion of complete responses, resulting in a higher tumor control. Dose escalation using conventional fractionation schedules has the disadvantage that the overall treatment time will increase considerably. However, dose escalation can be performed using hyperfractionation. This approach was tested by the RTOG 83-11 study when fractions of 1.2 Gy were given twice daily.^[24] Patients were randomized to receive a total dose of 60, 64.8, 69.6, 74.4, and 79.2 Gy. Survival improved in patients irradiated with 69.6 Gy compared with lower doses but no improvement was seen with doses above 69.6 Gy. This unexpected effect in the highest dose groups could be due to the higher number of delays in treatment in the highest dose groups. In a large phase III trial, using two-dimensional radiotherapy, 563 patients were randomized between standard radiotherapy of 60 Gy/6 weeks and continuous hyperfractionated accelerated radiotherapy or CHART (54 Gy given in 36 fractions, three fractions daily,

of 1.5 Gy with an overall treatment time of 12 days).^[25] A significant improvement of 2-year survival was seen in the CHART regimen (29%) compared to the conventional arm (20%). In addition, a significant reduction in local tumor progression was seen in the CHART arm. This trial illustrated that a reduction in overall treatment time increased the tumor control probability and survival in lung cancer patients but at the cost of higher esophagitis.

The outcome of radiotherapy treatment is dependent on accurate delineation of the tumor area and all involved lymph nodes and adequate treatment planning strategies. The radiation dose has remained the same for many years due to technical factors, normal tissue complications and recent RTOG results of dose escalation showing no improvement in outcomes beyond 66 Gy. The preliminary results of a phase III trial that compared conventionally fractionated standard-dose TRT (60 Gy) with high-dose TRT (74 Gy) revealed an inferior survival outcome among patients assigned to the high-dose arm.^[26] Innovations such as the introduction of three-dimensional conformal planning, the use of multileaf collimators, four-dimensional planning CT scans, intensity modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) techniques have improved targeting of the tumor volume. This allows the administration of higher radiation doses while reducing the exposure of healthy tissues and thus the risk of normal organ damage.^[27,28] The organs at risk during radiation therapy are the lungs, the heart, the spinal cord and the esophagus. The above-mentioned new techniques allows the use of (boost) doses of radiation up to 74-94 Gy, depending on generally accepted dose constraints, such as the mean lung dose.^[27,29,30] Radiotherapy dosimetric parameters are the most effective tools for predicting radiation-related lung damage (V20 and mean lung dose).^[31,32] For those patients who are considered to be at a high risk for side-effects, a sequential approach of induction chemotherapy followed by radiation therapy is recommended. At present, patients with stage III disease, who present with large tumor volumes, are precluded from high-dose concurrent CRT. These patients can roughly be divided into those presenting with bulky mediastinal disease and/or multilevel lymph node (N3) involvement and patients in whom the primary tumor is located in the periphery of the lung with extended involvement of mediastinal lymph nodes.^[33] There is a high chance of distant metastasis at presentation in these patients. In patients with significant weight loss or abnormal serum biochemistry, and those with poor lung function, treatment is aimed at achieving local control until subclinical metastases become obvious, but the tumors are often so large that local control is unlikely and growth delay is the only realistic aim. Tumors 3.5 cm in diameter have a local control rate of 50% after radical radiotherapy (wvy in 20-30 fractions) and 50% of patients with tumors of this size subsequently develop metastases.^[34] Larger tumors are associated with significantly poorer results. The

mean tumor size of patients treated with chemoradiation in our setup was 7 cm and hence the median survival was poor (12 months). The median survival of patients with comorbidities with concurrent chemoradiation with IMRT and IGRT is 19 months.^[15] In our country the above-mentioned innovations are available only in select metropolitan cities, while 75% of our population is rural. Secondly as per our audit only one third of patients with locally advanced non-small cell lung cancers present as stage IIIA (which comprises only 3.2% of all lung cancer patients presenting to us in the clinic), who are ideal candidates for such radical radiotherapy with 3DCRT, IMRT, and IGRT. Hence lack of such facilities hardly impacts on the overall outcomes of all lung cancer patients, though presence of such facilities is required to cater to the select few suitable for such treatment. Hyperfractionated treatment is not advisable in countries with limited resources as these patients require intensive care to deal with side-effects.

Patients who already have or are likely to develop significant thoracic symptoms should be treated with local palliative radiotherapy. A recently updated Cochrane review has shown that for good performance status patients higher doses of local radiotherapy appear to be associated with longer survival.^[35] The largest trial that only recruited good PS patients showed a 2-month improvement in median survival and a 5% increase in 1-year survival (36% vs. 31%) for patients treated with 39 Gy in 13 fractions compared to those treated with 17 Gy in 2 fractions.^[36,37]

Compliance and toxicity

In a Czech study comparing sequential versus concurrent chemoradiation in locally advanced NSCLC, 64% of patients in the sequential arm actually received radiotherapy because 30% patients developed progression of disease on chemotherapy.^[38] Furuse, in a similar comparison reported only 25% compliance with cisplatin, mitomycin, and vindesine combination as sequential treatment.^[39] In our patients treatment compliance was 80% for both sequential as well as concurrent chemoradiation. The incidence of severe granulocytopenia (grade 3) with sequential chemotherapy was 15% which is similar to 17% reported in the EORTC study.^[40] These toxicities can be easily managed in countries with limited resources.

Concurrent chemoradiation has been reported to result in higher rates of esophagitis (19%). Use of concurrent chemoradiation resulted in 37% incidence of esophagitis (grades 2 and 3) in our patients. Recognition and admission of such patients for symptomatic management is important, as out-patient management of such patients may lead to noncompliance to feeding instructions and further morbidity. The incidence of symptomatic pneumonitis (requiring steroids) was 38% in our patients which is similar (35%) to that reported by the RTOG.^[41] The higher incidence of pneumonitis observed in RTOG study has been attributed to carboplatin paclitaxel combination.^[22] The higher incidence of pneumonitis

observed in our patients can be explained by the inclusion of 36% patients with FEV₁ 1-2 lt and 14% with FEV₁ less than 1 lt. Only 25% of patients receiving concurrent chemoradiation had FEV₁ >2 lt and FEV₁ was unknown in 25% patients. Adequacy of FEV₁ (>2 lt) is an essential criterion for including patients for concurrent chemoradiation. Patients with inadequate FEV₁ 1-2 lt should be treated with sequential chemoradiotherapy in developing countries. Palliative radiotherapy regimes should be offered to patients with stage IIIB, FEV₁ <1 lt, poor performance status and in those with chest symptoms in developing countries.

Sequence of treatment

Several meta-analyses have concluded that concurrent chemoradiation is superior to sequential chemoradiotherapy at the cost of increased toxicity. But the criticism of these meta-analyses is the heterogeneity of treatment protocols across these trials, the low patient numbers and the lack of statistical power which limits the interpretation of the results. Even though the median survival reported for the concurrent treatment schedules was uniform across all studies at 16-17 months, with survival ranging from 13 to 15 months in the sequential arms, some authors are of the opinion that concurrent chemoradiation should not be accepted as the standard of care based on the available evidence.^[7,42]

Our audit on outcomes with chemoradiation revealed that the median survival was 12 months with both sequential and concurrent treatment. This was because of inclusion of patients with poorer FEV₁, normal weight BMI, stage IIIB patients, and few elderly patients (age 70-75 yrs) for concurrent chemoradiation. Timely management of grade 3 esophagitis, pneumonitis and better resources could have salvaged few patients on concurrent chemoradiation. Lack of endobronchial cytology facility for histopathological confirmation of radiologically enlarged mediastinal nodes and of PET-CT facility in our centre could be other reason for poor survival. Also in patients with superior sulcus tumors, surgical resection after radical chemoradiotherapy could have led to better outcomes.^[43] The only reported randomized Indian study by Dasgupta which compared outcomes with radical radiotherapy versus sequential chemoradiotherapy versus concurrent chemoradiotherapy had 75% patients with stage III A and the reported progression free survival of 21 months is the highest survival with concurrent chemoradiation reported in the world.^[8] Additionally the pertinent toxicities like esophagitis and radiation pneumonitis have not been mentioned.

Chemoradiotherapy followed by surgery

Chemoradiotherapy has been used as induction therapy, although most often with modest radiation doses in patients with superior sulcus tumours. A subset of patients might be identified who benefit from surgery after CRT.^[44,45] Patients who present with vertebra, subclavian vessel or brachial plexus involvement are unsuitable for such treatment. Surgical resection should be considered for patients who

become resectable or have downstaging of N2 mediastinal disease after sequential or concurrent chemoradiotherapy, both from a curative and palliative perspective. Thirty percent of patients presenting with superior sulcus tumors are fit to receive combined modality treatment, out of which 50% of patients are technically resectable. Patients with comorbidity, poor cardiopulmonary reserve and poor performance status do not tolerate concurrent chemoradiotherapy. Pathological complete response after CRT varies from 31 to 47%. Higher radiotherapy dose of 66 Gy has shown higher pathological response. There is improvement in local disease control (77% at 2 years) and survival (70% at 2 years) after surgical resection.^[46]

Surgical resection after chemoradiotherapy requires a dedicated thoracic surgery team, which is available only in few centers in our country. The outcomes with surgical resection after chemoradiotherapy in superior sulcus tumors are not available in our country. There is need for optimization of surgery after chemoradiotherapy in our setup.

Locally advanced lung cancer in elderly

Thirty to 40% of cases are diagnosed in patients aged more than 70 years. Data from the Surveillance, Epidemiology, and End Results (SEER) registry indicate that the median age at diagnosis in NSCLC patients is 69 years.^[47] Age 70 years is considered a cutoff point for elderly in clinical trials in oncology. Data from the SEER database show that most elderly patients did not receive combined modality treatment.^[48] This reflects the uncertainty about concurrent chemoradiation as a treatment of choice for elderly patients with locally advanced NSCLC.

One phase III elderly-specific trial has evaluated chemoradiation versus RT alone.^[49] Patients were randomly assigned to RT (60 Gy) alone or to the chemoradiation arm (same RT with concurrent use of carboplatin 30 mg/m²). This trial was closed early because of deaths in combined modality arm. The Radiation Therapy Oncology Group (RTOG) pooled together the results of 749 NSCLC patients participating on three separate RTOG trials. These patients had received RT alone; hyperfractionated RT (hRT); induction platinum-based therapy, followed by either RT alone or concurrent CMRT or concurrent CMRT with hRT. One hundred and fourteen patients (15%) were more than 70 years of age. The authors reported that as therapy intensified, the incidence of grades 3-5 toxic effects increased in elderly population. They found no significant difference in survival between treatment arms in these elderly patients. The conclusion was that unlike the overall patient population, elderly patients did not benefit from increased therapeutic intensity and that sequential or concurrent CRT showed less, if any, benefit over RT alone for elderly patients.^[50] According to the EORTC Elderly Task Force and Lung Cancer Group and International Society for Geriatric Oncology (SIOG) experts' opinion for the treatment of NSCLC in an elderly population concurrent CRT approach should be offered to elderly

patients with locally advanced NSCLC. But because of lack of evidence of randomized trials and higher risk of toxicity in elderly patients, treatment decision should be based on PS, absence of significant comorbid diseases and patient life expectancy.^[51]

In our center 10% of locally advanced lung cancer patients were elderly, out of which few were treated with chemoradiation and few with radiotherapy alone. The median survival was 14 months with radiotherapy as well as chemoradiation. Chemotherapy was poorly tolerated in this group.

Conclusions

Sequential chemoradiotherapy is better tolerated than concurrent chemoradiation in Indian patients with locally advanced NSCLC. Patients with stage IIIA, normal weight or overweight, and adequate baseline pulmonary function should be offered concurrent chemoradiation.

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