

Concurrent Chemoradiation in Inoperable, Locally Advanced Non-small Cell Lung Cancer – Comparison of Efficacy and Toxicity in the Elderly

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Abstract

Clinicians are faced with the challenge of treating increasing numbers of elderly patients with locally advanced non-small cell lung cancer (LA-NSCLC) and co-morbid conditions. The benefit of combined chemoradiation in the younger patient using the concurrent modality compared with the sequential administration of both modalities has been established in several randomised trials and recent meta-analyses. Because of the underrepresentation of elderly patients in clinical trials on concurrent chemoradiation (CCRT) in LA-NSCLC, treatment guidelines for this age group are not well established. The objective of this report is to summarise the data on efficacy and toxicity of CCRT in the elderly.

Keywords

Locally advanced non-small cell lung cancer, concurrent chemoradiation, elderly, efficacy, toxicity

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The incidence of lung cancer diagnosed in the elderly population is rising as a result of increasing life expectancy. Patients aged over 65 years at diagnosis represent half of the population of newly diagnosed non-small cell lung cancer (NSCLC), while 30–40 % of cases are diagnosed in patients older than 70 years.¹ As reported by Balducci et al., the cut-off point at which an adult is considered 'elderly' has not been well defined, but commonly 70 years is considered to be the reference point in clinical trials. The age-related physiological changes that increase the risk of toxicity related to systemic therapy occur around 70 years of age.²

Extermann et al. have defined the geriatric oncology group of patients as "when the health status of a patient population begins to interfere with oncological decision-making guidelines".³ Within clinical trials, this is defined by exclusion criteria and as pointed out in the review by Pallis et al., a number of barriers, other than co-morbid conditions, to the recruitment of older patients to cancer clinical trials were revealed,⁴ such as difficulty in accessing university hospitals, lack of adequate information about the availability of clinical trials and perception of the individual physician that the patient would not be able to tolerate treatment. The conclusion of a prospective, population-based trial by De Ruyscher et al. on eligibility for concurrent chemoradiation (CCRT) concluded that more than half of patients with LA-NSCLC were theoretically not eligible because they had one or more important co-morbid conditions or were 75 years or older.⁵

Consequently, prospective elderly-specific trials are lacking and treatment recommendations are made on the basis of retrospective data. These might suffer from selection bias, since elderly patients that meet protocol eligibility criteria often do not present with co-morbid conditions or organ function failures, present in the

real-life situation. Because of the rising incidence of NSCLC in the elderly population, biological age rather than chronological age should guide clinicians in deciding on treatment strategy. Geriatric scoring systems can be implemented in an attempt to better define the role of co-morbid disease in the elderly population. In addition, technological advances in the field of radiotherapy could contribute to increased efficacy⁶ and reduced side effects⁷ of treatment in the LA-NSCLC patient population.

Available Evidence Supporting Concurrent Chemoradiation in the Elderly Population

Regarding the use of radiotherapy in elderly patients, it has been reported that elderly patients are not at risk for increased acute or late toxicity after radiotherapy with curative doses.^{8,9} The addition of chemotherapy to radiation has an additional effect on survival in LA-NSCLC at a price of increased toxicity.¹⁰ Concurrent chemoradiation (CCRT) has a temporary impact on quality of life, primarily because of fatigue and oesophagitis during and shortly after treatment. However, the quality of life usually recovers to baseline values within three months.¹¹ The recent meta-analysis of concurrent versus sequential chemoradiation by Aupérin et al.¹² demonstrated the improved overall survival of the concurrent approach with an absolute benefit of 5.7 % at three years and 4.5 % at five years, as compared with sequential chemoradiation, primarily because of a better locoregional control. The effect of CCRT on distant progression was not different from that of the sequential approach. Acute grade 3–4 oesophageal toxicity was increased from 4 % to 18 %, but manageable. Since CCRT leads to significantly higher side effects, it is often reserved for younger patients with few co-morbid conditions.^{4,13} This underrepresentation of elderly patients in clinical trials restricts the available clinical trial data

Table 1: Retrospective Subgroup Analyses of Chemoradiation Trials for Non-small Cell Lung Cancer Comparing Treatment Outcomes between Elderly and Younger Patients

Study	Trials	No. of Patients	Efficacy	Toxicity	MST
Langer et al. ¹⁸	Phase III trial CCRT (qd or bid) versus SCRT	<70 y: 491 ≥70 y: 104	In favour of CCRT for >70 y	Short-term toxicities (G>3) more neutropenia and oesophagitis pronounced in elderly, long-term toxicities similar	≥70 y: 10.8 months (SCRT) versus 16.4 months (CCRTbid) versus 22.4 months (CCRTqd)
Schild et al. ¹⁹	Phase III trial: CCRTbid versus CCRTqd	<70 y: 181 ≥70 y: 63	Survival not age-related	More myelosuppression and pneumonitis in elderly	<70 y: 5-y survival rate = 18 % ≥70 y: 5-y survival rate = 13 %
Rocha-Lima et al. ¹⁴	Two CALGB Phase III trials: SCRT versus CCRT	<70 y: 222 ≥70 y: 31	Survival not age-related	More haematologic toxicity in elderly	<70 y: 11–15 months ≥70 y: 13 months
Werner-Wasik et al. ¹⁶	Nine Phase I–III trials: RT, SCRT or CCRT	<70 y: 1,565 ≥70 y: 429	Survival age-related	NR	<70 y: 10–16 months ≥70 y: 3–6 months
Movsas et al. ¹⁷	Six Phase II and III trials: RT, SCRT or CCRT	<70 y: 835 ≥70 y: 144	<70 y: improved survival with CMT >70 y: best quality-adjusted survival with RT alone	NR	<70 y: 12–14 months ≥70 y: 11 months

CCRT = concurrent chemoradiation; CCRTbid = concurrent chemoradiation twice a day; CCRTqd = concurrent chemoradiation daily; CMT = combined modality treatment; G = grade; LA-NSCLC = locally advanced non-small cell lung cancer; MST = median survival time in months; NR = not reported; RT=radiotherapy; SCRT = sequential chemoradiation; y = years.
Source: Table modified from Gridelli C. et al.²⁷

to guide physicians in treatment decisions for elderly patients. Controlled clinical trials especially designed toward the elderly, including geriatric evaluations, are indicated.¹⁴

Only one prospective elderly-specific Phase III trial has evaluated CCRT versus radiotherapy (RT) alone.¹⁵ Patients were randomly assigned to RT alone (60 Gy) or to CCRT (same RT with concurrent administration of carboplatin 30 mg/m²). The trial was prematurely closed for accrual after the occurrence of four treatment-related deaths, of which three occurred in the CCRT arm. For the 46 patients treated at that time, the median survival time was not significantly different between both arms (14.3 months with RT alone compared with 18.5 months in the CCRT arm). Because of the small number of patients included and protocol violations concerning the radiation field that might have influenced half of the treatment-related deaths attributed to pneumonitis, the investigators concluded that the efficacy of concurrent carboplatin plus radiotherapy in elderly patients remains unclear and no definitive conclusions can be drawn from this trial.

When looking at retrospective subgroup analyses of randomised chemoradiation trials comparing treatment outcomes between elderly and younger patients, results are inconsistent (see *Table 1*). For example, secondary analysis of a Radiation Therapy Oncology Group (RTOG) study demonstrated inferior outcomes of chemoradiation in the elderly and those with poorer performance status.¹⁶ Movsas et al. reported that the best quality-adjusted survival in older patients was achieved with RT alone.¹⁷ In contrast, subset analyses of several other trials^{14,18–20} and the NSCLC Collaborative Group meta-analysis²¹ concluded that the survival advantage of chemoradiation was not related to age.

Valuable information can be obtained from population-based studies that examined the effects of combined modality treatment in the elderly population. These are treatment results obtained in the heterogeneous population of older patients with co-morbid conditions and poorer performance status (PS) that are not treated in

a clinical trial setting. Davidoff and colleagues²² investigated the effects of combined modality treatment in elderly LA-NSCLC patients using Surveillance, Epidemiology and End Results – Medicare data and concluded that survival benefits associated with combined modality treatment in clinical trials can be extended to the elderly population in routine daily practice. The absolute survival duration observed is shorter than that reported in clinical trials, reflecting the higher co-morbid conditions or poorer PS of the elderly patients treated outside the clinical trial setting.

Concurrent Chemoradiation in the Frail Elderly

We could only identify one institutional report, by Semrau et al., on CCRT in elderly LA-NSCLC patients presenting with multiple morbidities. They reported their six-year experience of CCRT with vinorelbine plus a platinum compound. The frail elderly population was defined as patients with an increased risk profile of treatment side effects due to World Health Organization (WHO) performance status 2–3, cardiac, renal or pulmonary failure, extensive weight loss before treatment or age 71–78 years. A total of 66 patients received CCRT, with manageable toxicity. The dose intensity of chemotherapy and radiotherapy was 62 % and 94 %, respectively. In this population with poor prognostic factors, dose-adjusted chemotherapy and radiotherapy was feasible, and the survival rates of 25 % at two years and 8 % at five years were comparable to those achieved in other studies.²³

Technological Advances in the Field of Radiotherapy

Technological advances in radiotherapy treatment planning and delivery have occurred in the past five years, including incorporation of functional imaging by [18F]deoxyglucose-positron emission tomography (PET) scan in the planning process,⁵ three-dimensional conformal radiotherapy, respiratory gating, four-dimensional computed tomography,⁷ intensity-modulated radiotherapy, helical tomotherapy and image-guided radiotherapy. These newer radiation techniques significantly reduce toxicity by limiting the volume of irradiated lung tissue.⁷

Irrespective of age, the acute and late toxicity profile after high-dose radiotherapy is related to the extent of the radiation field. Only in the most recent studies on combined modality treatment has conformal radiotherapy been introduced. Most studies used two-dimensional large radiation fields that included elective nodal areas. Systematic integration of three-dimensional conformal radiotherapy and target delineation based on functional imaging will undoubtedly influence the oesophageal and pulmonary toxicity after chemoradiation.

Our group has engaged in a Phase I/II radiation dose escalation trial using helical tomotherapy with a fixed dose of weekly low-dose chemotherapy consisting of cisplatin and docetaxel at a dose of 20 mg/m² each. The toxicity profile of this approach was published earlier.²⁴ We thereafter compared treatment-related toxicity, impact of treatment on quality of life and differences in outcome between younger (<70 years, n=42) and older (≥70 years, n=17) patients. Besides an increased rate of neutropenia, elderly patients did not experience increased toxicity or decreased quality of life after concurrent chemoradiation. A comparable survival was achieved with median survival time of 18.5 months in younger versus 17.9 months in the older patient group (p=0.6105).

Comprehensive Geriatric Assessment-based Approach

The current standard of functional status assessment using Eastern Cooperative Oncology Group (ECOG) or Karnofsky scales poorly predicts functional impairment in the elderly.²⁵ A comprehensive

geriatric assessment (CGA) is a multidisciplinary evaluation, by oncologists and geriatricians, in which the multiple problems of older patients are uncovered, described and explained. It typically consists of evaluation of an older individual's functional status, co-morbid conditions, cognition, psychological state, social support and nutritional status and a review of the patient's medications.²⁶ There is strong evidence that a CGA detects problems that may have been missed by a regular clinical evaluation. Accumulating data show the benefit of incorporating a CGA in the initial evaluation of older patients with cancer because it uncovers problems relevant to cancer care that would otherwise go unrecognised and a CGA can predict morbidity and mortality in older patients with cancer. Pre-treatment values of instrumental activities of daily living (IADL) correlate with survival.³ Therefore, the integration of geriatric assessment into studies with a high proportion of older patients needs to be encouraged.

Conclusions

Concurrent chemoradiation should be offered to elderly patients suffering from LA-NSCLC since a survival benefit can be achieved. Even in the absence of prospective elderly-specific data, authors encourage treatment of older patients with CCRT since elderly patients treated with CCRT outside the clinical trial setting experience the same survival benefit albeit with a shorter survival duration. Elderly-specific CCRT trials incorporating modern radiation techniques and geriatric assessment should be encouraged to truly establish the place of CCRT in the older patient with LA-NSCLC. ■

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