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Overview

Radical Radiotherapy for Locally Advanced Non-small Cell Lung Cancer: When Should Concurrent Chemoradiotherapy Not Be Used?

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Abstract

Concurrent chemotherapy and radiotherapy confers a significant, but small, benefit for overall survival compared with sequential chemoradiotherapy. The improvement of about 4% with a hazard ratio of 0.85 has only been proven for fit patients with a good organ function. From non-randomised trials, there are no indications that concurrent chemoradiotherapy is clearly superior to the sequential approach in other patients. Moreover, radiotherapy alone can lead to 5 year survival rates of 20%. As the differences in long-term survival between the treatment options are small, even fit patients should be offered, via a shared decision process, the choice between concurrent and non-concurrent chemotherapy and radiotherapy. In less fit patients, sequential chemoradiotherapy offers a chance for long-term survival and cure with less toxicity than the concurrent approach.

Key words: Combined modality treatment; concurrent; elderly; frail; non-small cell lung cancer; sequential

Statement of Search Strategies Used and Sources of Information

PubMed was searched using the following terms: non-small cell lung cancer; chemotherapy; radiotherapy; radiation; combined modality treatment; randomised; phase III; phase II; prospective; meta-analysis; elderly; concurrent; sequential; co-morbidity; toxicity.

Introduction

Locally advanced non-small cell lung cancer (NSCLC) is a heterogeneous disease. This not only relates to its anatomical presentation, but also to the diverse biology of the tumour and the very frequently occurring co-morbidities in this patient population [1,2].

Locally advanced NSCLC, which is often used for stage III disease, can be treated with curative intent by the administration of chemotherapy with or without radiotherapy or surgery or both [1]. Data from many phase III trials and meta-analyses showed a clear benefit in overall survival when chemotherapy was added to either radiotherapy or to surgery, when chemotherapy is delivered concurrently with radiotherapy instead of sequentially, or when radiotherapy is given with accelerated schedules [1,3,4]. Tri-modality treatment that combines chemotherapy, surgery and radiotherapy has not shown to lead to a better overall survival, although some subgroups may benefit from this approach, such as patients with so-called 'Pancoast' tumours, some borderline resectable cancers or tumours that have a high likelihood to cause important local complications, such as tumours with central necrosis with or without air-fluid levels on computed tomography scan [5]. It should be acknowledged though that most of the randomised trials were massively underpowered to detect small differences in overall survival between the different variations of surgery and radiotherapy as local treatments [5].

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As most patients with locally advanced NSCLC have unresectable disease, concurrent chemoradiotherapy is considered to be the first choice therapy for most of them [1].

However, when examining the inclusion criteria of the phase III trials used to derive the guidelines as well as the risk/benefit ratio of the different non-surgical treatment options and the absolute benefit, a more balanced view may arise. We therefore searched PubMed using the following terms: non-small cell lung cancer, chemotherapy, radiotherapy, radiation, combined modality treatment, randomised, phase III, phase II, prospective, meta-analysis, elderly, concurrent, sequential, co-morbidity and toxicity in order to address this question.

What is the Absolute Survival Benefit of Concurrent Chemoradiotherapy versus Sequential Chemoradiation or Radiotherapy Alone?

The addition of chemotherapy to radiotherapy has been investigated in several phase III studies [1,3,6]. Both induction and adjuvant chemotherapy have been studied. In a meta-analysis, the hazard ratio for overall survival was 0.88 favouring the addition of chemotherapy to radiotherapy. This corresponded to an absolute gain in 5 year survival of about 4%. Sequential chemotherapy and radiotherapy therefore became the first choice approach.

Thereafter, randomised trials compared sequential chemotherapy and radiotherapy with concurrent chemoradiotherapy. In a meta-analysis based on individual patient data, the concurrent administration led to an overall survival benefit of 4.5% after 5 years with a hazard ratio of 0.85 [3].

Finally, in patients treated without concurrent chemotherapy and radiotherapy, accelerated radiotherapy led to an improved 5 year survival with a hazard ratio of 0.88 and an absolute benefit of 3.5% [4].

From non-randomised studies, there is no indication that accelerated radiotherapy, when given concurrently with chemotherapy improves overall survival [7,8]. It is also unclear if accelerated radiation given after chemotherapy would result in a similar overall survival than concurrent chemoradiation, but possibly with fewer side-effects.

It is therefore clear that even in selected patients in phase III trials, all incremental steps in improving the outcome of locally advanced NSCLC patients are small, with at the very best an overall gain with a hazard ratio of $0.88 \times 0.85 = 0.75$ (hazard ratio of adding chemotherapy to radiotherapy multiplied by the hazard ratio of sequential chemoradiation versus concurrent) or an approximate 7% 5 year overall survival gain between the two most extreme scenarios, conventionally fractionated radiotherapy alone or concurrent chemoradiotherapy. Because accelerated radiotherapy alone also improved survival, it may well be that the absolute 5 year overall survival increase comparing accelerated radiation with concurrent chemoradiotherapy is lower than 7%.

It is nevertheless clear that the answer to the question who should not receive concurrent chemoradiotherapy should take into account these small, though significant, improvements.

Can the Results Obtained from Phase III Trials be Extrapolated to the Common Lung Cancer Patient?

The small gains in overall survival were obtained in phase III trials in which patients are by definition selected. Less than 10% of the patients were older than 75 years and virtually none had a World Health Organisation performance status greater than 1 [3]. All had to have an adequate organ function and major co-morbidities were excluded [3].

Two prospective trials specifically reporting on concurrent chemoradiotherapy in elderly NSCLC patients have been published. The first study was a phase II study evaluating accelerated radiotherapy (51 Gy in 34 fractions of 1.5 Gy twice daily) with concurrent carboplatin/etoposide in patients $\geq$ 70 years [9]. The median overall survival was 10 months, with a 2 and 5 year overall survival of 24 and 9%, respectively. Acute and late toxicity were considered acceptable with acute haematological, oesophageal and pulmonary toxicity $\geq$ grade 3 in 22, 7 and 4%, respectively, and no late toxicity of grade 3 or higher. The second trial was a randomised study from Japan, in which 200 patients were enrolled [10]. Radiotherapy alone was compared with radiation plus weekly low dose carboplatin in elderly patients with stage III NSCLC. The median overall survival for the chemoradiotherapy and radiotherapy alone groups were 22.4 months and 16.9 months, respectively ($P = 0.0179$). More patients had grade 3–4 haematological side-effects in the chemoradiotherapy group than in the radiotherapy alone group, including leucopenia (63.5% versus none), neutropenia (57.3% versus none) and thrombocytopenia (29.2% versus 2.0%). Grade 3 infection was more common with chemoradiotherapy (12.5%) than with radiotherapy (4.1%). The incidence of grade 3–4 pneumonitis and late lung toxicity was similar between groups. There were seven treatment-related deaths: 3.0% in the chemoradiotherapy group and 4.0% in the radiotherapy group.

Subgroup analyses of randomised trials comparing concurrent versus sequential chemotherapy and radiotherapy or radical radiotherapy alone in stage III NSCLC showed inconsistent results regarding the influence of age. Subgroup analyses of several Radiation Therapy Oncology Group (RTOG) trials showed no improved outcome for concurrent chemoradiation for elderly patients compared with sequential chemotherapy and radiotherapy or radiotherapy only [11], whereas the subgroup analysis of the most recent RTOG 94-10 trial did show a survival advantage for this group [12]. The meta-analysis of Aupérin *et al.* [3] did not find a significant difference in treatment effect between different age groups. It should be emphasised, however, that in these trials, only the 'very fit' older NSCLC patients have been selected to participate.

Studies that are specifically designed for elderly patients and/or individuals with important co-morbidities are therefore needed.

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