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Review

New radiotherapy approaches in locally advanced non-small cell lung cancer

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Abstract Radiotherapy plays a major role in the treatment of patients with locally advanced non-small cell lung cancer (NSCLC), particularly since most patients are not suitable for surgery due to the extent of their disease, advanced age and multiple co-morbidities. Despite advances in local and systemic therapies local control and survival remain poor and there is a sense that a therapeutic plateau has been reached with conventional approaches. Strategies for the intensification of radiotherapy such as dose escalation have shown encouraging results in phase I–II trials, but the outcome of the phase III Radiation Therapy Oncology Group 0617 trial was surprisingly disappointing. Hyperfractionated and/or accelerated fractionating schedules have demonstrated superior survival compared to conventional fractionation at the expense of greater oesophageal toxicity. Modern radiotherapy techniques such as the integration of 4-dimensional computed tomography for planning, intensity modulated radiotherapy and image-guided radiotherapy have substantially enhanced the accuracy of the radiotherapy delivery through improved target conformality and incorporation of tumour respiratory motion. A number of studies are evaluating personalised radiation treatment including the concept of isotoxic radiotherapy and the boosting of the primary tumour based on functional imaging. Proton beam therapy is currently under investigation in locally advanced NSCLC. These approaches, either alone or in combination could potentially allow for further dose escalation and improvement of the therapeutic ratio and survival for patients with NSCLC.

1. Introduction

Radiotherapy, either alone or combined with chemotherapy, plays a major role in the treatment of patients

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with locally advanced (stage III) non-small cell lung cancer (NSCLC). The standard of care for patients with good performance status (PS) is concurrent platinum-based chemo-radiotherapy [1,2]. However, in Europe less than 40% of patients are deemed suitable for concurrent treatment due to advanced age and multiple co-morbidities, these patients will therefore receive sequential chemo-radiotherapy [3,4]. Despite treatment with curative intent, survival remains poor due to both local and distant relapse and a 2-year loco-regional control rate of 20–44% has been reported [5–7]. We have learnt from the field of stereotactic ablative body radiotherapy (SABR) that doses in excess of 100 Gy biologically equivalent dose (BED) are needed to achieve local control of ~90% in NSCLC [8]. Furthermore, we now have a much better understanding of the importance of local control and its impact on survival in patients with NSCLC. An individual patient data meta-analysis of concurrent versus sequential chemo-radiotherapy demonstrated a significant decrease in loco-regional progression with concurrent treatment translating into an absolute 5-year survival benefit of 4.5% (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.74–0.95; $p = 0.004$) [6]. Similarly, a recent retrospective analysis of seven chemo-radiotherapy trials undertaken by the Radiation Therapy Oncology Group (RTOG) demonstrated a significant association between loco-regional progression and decreased survival rates (HR, 1.42; 95% CI, 1.26–1.60; $p < 0.0001$) [7]. The consistently poor outcomes seen in patients with locally advanced disease over the last 30 years cannot be solely attributed to advanced stage at presentation and thus it is likely that a therapeutic plateau has been reached with conventional radiotherapy approaches [9].

This review will discuss new radiotherapy approaches including dose escalation, modified fractionation, individualised radiotherapy administration and advanced modern radiotherapy techniques that aim to improve outcomes in locally advanced NSCLC. These strategies can be combined with the aim to improve local control and survival.

2. Dose escalation

Martel et al. showed that a dose of 84 Gy with conventional fractionation is required to achieve a significant tumour control probability (>50%), demonstrating a clear radiation dose–response relationship in locally advanced NSCLC [10]. The RTOG meta-analysis reported that BED was significantly associated with local control ($p < 0.0001$) and subsequently survival ($p < 0.001$) [7]. The relationship between local control and BED is further suggested by data from SABR studies [8]. It is worth noting that this relationship was demonstrated with SABR which typically involves irradiation of small tumours. After the introduction of 3-dimensional conformal radiotherapy (3DCRT) in the late 1990s, the RTOG conducted a series of phase I–II dose escalation studies (Table 1) demonstrating that radiation doses of 74 Gy in 37 fractions could be delivered concurrently with chemotherapy using strict dose-volume constraints for the organs at risk (OARs) [11–15]. However, it should be noted that these studies recruited a small number of select patients from leading academic centres. Notably, none of these studies provided data on the gross tumour volume (GTV). The percent volume of total lung receiving at least 20 Gy (V_{20}) is considered one of the most important predictors for radiation-induced lung toxicity and has been commonly used as a constraint for dose escalation. In the RTOG dose escalation studies, median V_{20} ranged from 24% to 32% [11–15].

The encouraging results of the phase I/II dose escalation studies, particularly those suggesting the safety and efficacy of 74 Gy in 37 fractions with concurrent chemo-radiotherapy regimens formed the basis for the recent RTOG 0617 phase III randomised controlled trial (RCT). In this 2×2 factorial design study, patients with stage III NSCLC were randomised to receive high-dose (74 Gy in 37 fractions) or standard dose (60 Gy in 30 fractions) 3DCRT in 2 Gy fractions concurrently with weekly paclitaxel/carboplatin with or without cetuximab [15]. Following the completion of radiotherapy, all patients were treated with consolidation chemotherapy. In a planned interim analysis after 90 events, the high-dose arms were closed for futility suggesting a low likelihood of any survival benefit from high-dose radiotherapy with further accrual or follow-up. At a median follow-up time of 17.2 months, survival of 419 eligible patients was significantly inferior with high-dose compared to standard dose radiotherapy (median overall survival (OS) 19.5 versus 28.7 months and 18-month OS, 53.9% versus 66.9% respectively; $p = 0.0007$). Surprisingly, local and loco-regional failure rates were worse in the high-dose compared to standard dose arms (local failure rates 34.3% versus 25.1%; $p = 0.03$ and loco-regional failure rates 44% versus 35.3%; $p = 0.04$ respectively). Treatment-related severe ($\geqslant$Grade 3) toxicity was not significantly different in the high and standard dose arms respectively (78.2% versus 74.2%; $p = 0.34$). Grade 5 adverse events occurred more frequently in the high-dose arm but the difference was not statistically significant.

At the time of writing there are no clear reasons to explain the poor results of the high-dose arms [16]. Possible explanations include unreported toxicities,