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Overview

Continuous Hyperfractionated Accelerated Radiotherapy (CHART) and Non-conventionally Fractionated Radiotherapy in the Treatment of Non-small Cell Lung Cancer: a Review and Consideration of Future Directions

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Abstract

There is a well-established role for radiation treatment in the management of non-small cell lung cancer. As a single modality, it is indicated as a radical treatment option for patients deemed unsuitable for chemotherapy with inoperable locoregional disease or who decline surgery. In this patient group, the evidence shows advantages for accelerated treatment regimes, e.g. continuous hyperfractionated accelerated radiotherapy (CHART). Research efforts should be directed towards dose escalation with the application of the new technologies available. The multi-modality approach of chemoradiotherapy is established in the radical treatment of non-small cell lung cancer in those who are inoperable, radically treatable and fit enough to receive chemotherapy. How best these two modalities are combined remains unclear, and the combination of CHART and other non-conventionally fractionated radiotherapy schedules with chemotherapy and targeted agents is another potentially productive research area.
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Key words: Accelerated radiotherapy; CHART; chemoradiotherapy; non-small cell lung cancer

Statement of Search Strategies Used and Sources of Information

The search strategies used were the online Medline Library Resource www.nlm.nih.gov using the key words ‘accelerated’, ‘CHART’, ‘CHARTWEL’, ‘chemoradiotherapy’, ‘chemotherapy’, ‘dose escalation’, ‘fractionation’, ‘non-small cell lung cancer’, ‘radiotherapy’.

Introduction

Radiotherapy plays a major role in the management of non-small cell lung cancer (NSCLC), which accounts for over 80% of all diagnosed lung cancers in the UK. Radiation treatment has an established curative role in early stage disease when complete surgical resection cannot be carried out; in advanced disease, its role is palliation of symptoms and maintenance of a patient’s quality of life. About 70% of patients receive radiation therapy as part of their cancer treatment [1].

The early development of radiation treatment showed that one large radiation dose had profound effects on tumours, but the equally profound effects on normal tissues limited clinical usefulness. This limitation led to the development of fractionated treatments, using the radiobiological principles of repair, redistribution, resistance, repopulation and reoxygenation to enhance the radiation effects on rapidly dividing tumour cells in comparison with the more slowly dividing, normal tissues. Both normal and malignant tissues have sigmoid dose-response relationships. Therefore, a certain radiation dose must be given before a response is seen. The outcome of treatment will depend on the total dose delivered. These factors have led to the classical radiation schedule, delivering one fraction per day (usually 1.8–2 Gy per fraction), 5 days per week, over 5–7 weeks. In the 1970s, these schedules became widespread practice and evidence started to confirm that the total dose is important in the treatment of NSCLC [2].

Increasing the radiation doses is a challenge for the radiotherapist due to the tolerance of several vital normal tissues (lung, heart and spinal cord) that must be taken into

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account. Most side-effects are predictable and it is the irreversible late treatment effects causing significant morbidity, i.e. pulmonary fibrosis, radiation myelitis, that cause most concern. This risk of late effects limits the dose delivered in lung cancer treatments. Although the total dose is the main determinant of the risk of late effects, these risks are made greater by increasing the treatment volume and the fraction size.

Progress in radiation treatment has centred on a reduction of the risk of late effects, primarily with new technologies to reduce the volume of normal tissue being treated and novel fractionations to maintain (or increase) the biological tumour dose. These non-conventional fractionation schedules have been developed on an empirical basis, or more recently to take advantage of different radiobiological properties of tumour and normal tissues. Altered fractionation schedules (Table 1) aims to improve the local control rates leading to a reduction in distant metastasis and an improvement in survival.

This article reviews non-conventional fractionation in the light of the realistic expectation of future improved outcomes for curative lung radiotherapy treatment, as a result of increasing use of combination treatment with chemotherapy and/or surgery and the technical advances in imaging, radiotherapy planning and treatment delivery.

Radical Radiotherapy in Non-small Cell Lung Cancer

Surgery remains the cornerstone of curative treatment, with high-dose radiotherapy the treatment of choice for the radically treatable, but inoperable, patients with NSCLC. One randomised trial showed a small survival advantage for radical radiotherapy; however, this was carried out in 1968 with doses and techniques that now would be considered suboptimal [3]. In the 1970s, a Radiation Therapy Oncology Group trial showed improved 3 year survival rates with increasing radiation doses (9, 10 and 15% after doses of 40, 50 and 60 Gy, respectively). This set the standard of 60 Gy in 30 fractions over 6 weeks [2].

There have been no randomised trials addressing the benefit of radical radiotherapy in early stage disease. Series published in the 1980s and 1990s report wide ranges of median and 5 year survivals (16–36 months and 6–50%, respectively). The retrospective Surveillance Epidemiology

Table 1
Fractionation schedules used in radiotherapy practice

Treatment week	1 2 3 4 5 6 7	x size Gy	x/day	week
Conventional	xxxxxooxxxxxooxxxxxooxxxxxooxxxxxooxxxxxooxx	2	1	6–7
Split course	xxxxxooxxxxxooooooooooooooooxxxxxooxxxxx	>2	1	>5
Hypofractionated	xxxxxooxxxxxooxxxxxooxxxxx	>2	1	<5
Hyperfractionated	xxxxxooxxxxxooxxxxxooxxxxxooxxxxxooxxxxx xxxxxooxxxxxooxxxxxooxxxxxooxxxxxooxxxxx	1–1.3	2	6
CHART	xxxxxxxxxxxx xxxxxxxxxxxx xxxxxxxxxxxx	1.5	3	2
HART	xxxxxooxxxxxooxx xxxxxooxxxxxooxx xxxxxooxxxxxooxx	1.6	3	2.5

Fractionation schedules used in radiotherapy practice

x Radiotherapy fraction

o Non treatment day

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