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Overview

Improving Therapeutic Outcomes in Non-small Cell Lung Cancer not Suitable for Curative Intent Therapy — A Review of the Role of Radiation Therapy in an Era of Increasing Systemic Therapy Options

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Abstract

Lung cancer is the highest cause of mortality from cancer worldwide. Most patients present with disease not suitable for curative therapeutic options. In these patients, radiation therapy provides durable palliation of symptoms due to intrathoracic disease, whereas systemic chemotherapy improves survival compared with best supportive care. Over recent years the systemic therapeutic options available for the non-curative management of advanced lung cancer, particularly non-small cell lung cancer, have expanded to include molecularly targeted agents and immune modulating agents. The aim of this overview is to review the role and future of radiation therapy in this era of increasing systemic therapy options with particular emphasis on how radiation therapy can be used to improve therapeutic outcomes.

Key words: Chemotherapy; immunotherapy; lung cancer; non-curative therapy; radiation therapy; targeted agents

Statement of Search Strategies Used and Sources of Information

This review is based on a search of peer-reviewed articles found on Pubmed and Google Scholar databases. Search terms included 'lung cancer', 'radiation therapy', 'molecularly targeted agents', 'immunotherapy', 'immune modulating agents', 'palliation'. Individual bibliographies were reviewed for additional relevant references. Information on relevant clinical trials was obtained from the International Clinical Trials Registry.

Introduction

Lung cancer is the most common malignancy and the highest cause of mortality from cancer worldwide [1]. Most lung cancers are of the non-small cell (NSCLC) histological subtype [2] and will therefore be the main focus of this review. In the vast majority of patients, curative treatment options are not possible either because the disease is too advanced at presentation or because patient or tumour factors make radical options not possible. Even for those patients who are treated with curative intent, most will recur either locally or distantly at some months or some years after the completion of therapy. Median and 5 year survival figures for all stages of NSCLC and small cell lung cancer (SCLC) are poor and, compared with progress made in other tumour sites, improvements in survival over recent years have been marginal at best [3].

Whereas for patients with locally advanced, incurable lung cancer who have a poor performance status the most appropriate therapy may be best supportive care, for those patients with incurable lung cancer who are suitable for treatment the aims of therapy are: to relieve symptoms, maintain quality of life, prolong survival and minimise treatment-related side-effects. In NSCLC, the efficacy of radiation therapy in providing durable palliation of common symptoms due to intrathoracic disease has been shown in

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multiple randomised trials and two systematic reviews [4–17]. Likewise, platinum-based chemotherapy has been found to improve survival, relieve symptoms and maintain quality of life compared with best supportive care [18].

Over recent years, there has been increasing awareness of the molecular pathways that drive malignancy particularly in lung adenocarcinoma and the development of agents that target and negate those pathways. The best studied of these are the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs), although many other agents targeted at specific genetic alterations are under investigation. Randomised studies have shown that first-line EGFR or ALK TKI use in appropriately molecularly selected patients with advanced NSCLC provides benefit in progression-free survival, symptom relief, quality of life and side-effect profile compared with traditional platinum-based chemotherapy [19,20]. Although an overall survival benefit has not been found, a pre-planned analysis of the Lux-Lung 3 and 6 trials showed an overall survival benefit for afatanib compared with chemotherapy for patients with del 19-positive tumours [21]. A more recent addition to the available systemic options is nivolumab [a programmed death-1 (PD-1) inhibitor] following the early release of the CheckMate017 trial results showing an improvement in median overall survival for patients with advanced squamous cell carcinoma progressing on platinum-based chemotherapy who received nivolumab compared with docetaxel. These results prompted the Food and Drug Administration to extend the approved use of nivolumab to the second-line therapy of advanced squamous cell carcinomas [22].

In an era of molecularly targeted agents and immunotherapy, the role and future of radiation therapy needs to be defined. It is important to remember that although the availability of new systemic therapy options represents a significant advance, they are not a cure-all. In a large proportion of lung cancers, a driver mutation has not been detected. The most common mutation (KRAS) does not have an identifiable target. There is considerable genetic heterogeneity in the worldwide incidence of EGFR mutations [23–27] and durable response rates are not seen, with resistance and progression occurring often within months [28]. Radiation therapy, on the other hand, provides effective, durable and cost-effective palliation of symptoms irrespective of tumour type or genetic profile. However, the therapeutic benefit of radiation therapy as a sole modality in the non-curative setting has arguably plateaued. The potential for improving therapeutic outcomes in patients with advanced lung cancer not suitable for curative therapy is being explored, with the strategies under investigation including:

Combined modality therapy – either the combination of conventional radiation therapy with conventional chemotherapy or molecularly targeted agents or

The incorporation of newer methods of radiation therapy delivery into therapeutic strategies. For example, ablative radiation therapy delivered to oligometastatic or oligoprogressive disease or in combination with immune modulating agents.

These areas are discussed in the following below.

Combined Modality Therapy

Conventional Radiation Therapy and Conventional Chemotherapy

Traditionally, there has been a reluctance to combine systemic chemotherapy with radiation therapy due to concerns about increasing side-effects in a cohort of patients with a limited life span. The 2012 ASTRO consensus statement on palliative lung radiation therapy concluded that there was no evidence for the administration of concurrent chemotherapy and palliative lung radiation therapy [29]. At that stage, the only phase III evidence was from a randomised study in which infusional fluorouracil given concurrently with 20 Gy/five fractions was associated with significant side-effects and no survival benefit [30].

However, uncontrolled local disease constitutes a major cause of morbidity and mortality in this cohort of patients. It is not an uncommon clinical scenario for patients receiving systemic chemotherapy to be referred for radiation therapy to palliate intrathoracic symptoms. In a population-based cohort study of >1500 patients with advanced NSCLC receiving systemic therapy, 80% received radiation therapy at some point in the time course of their treatment, with 20–25% receiving radiation therapy to the chest to palliate symptoms [31]. Evidence that uncontrolled local disease can lead to pulmonary deterioration and death comes from a pooled analysis of data from single institution phase II/III studies of systemic chemotherapy in which patients with bulky central disease, disease causing bronchial or vascular compression or presenting with pulmonary symptoms had worse overall survival. The authors concluded that although these patients may have distant disease, there was a subset of patients who would benefit from planned local therapy in addition to systemic therapy [32].

There is a precedent for the benefit of improved local control on survival. In stage III NSCLC treated with curative intent, level one evidence supports a survival benefit for the concurrent administration of chemotherapy and radiation therapy over the sequential administration, largely due to improved locoregional control [33].

Similarly in limited stage SCLC, the addition of radiation therapy to systemic chemotherapy improves survival and reduces locoregional failure [34,35].

Evidence for the benefit of improved locoregional control in stage III NSCLC patients not suitable for curative therapy was shown in a study conducted by the Norwegian Lung Cancer Study group [36]. This study, which closed before reaching target accrual, randomised 195 patients to either chemotherapy (four cycles of carboplatin day 1, oral vinorelbin day 1 and 8) or chemotherapy + radiation therapy (CTRT; 42 Gy/15 fractions given concurrently with the same chemotherapy regimen). Eighty per cent of enrolled patients had performance status 0–1, 42% were aged 70 years

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