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Overview

The Current Role of Radiotherapy in the Treatment of Small Cell Lung Cancer

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Abstract

Radiotherapy has been shown to play a key role in the management of small cell lung cancer. There are well-established data in the literature for the use of concurrent chemoradiotherapy for stage I–III disease, although key questions remain over the timing of radiation, the optimal dose/fractionation and particularly once versus twice daily treatment, the use of elective nodal irradiation and drug combinations. Data for the use of thoracic radiation in stage IV disease, after chemotherapy, have recently become available and are leading to a change in practice. Prophylactic cranial irradiation has been shown to be of use in both stage I–III and stage IV disease, although uncertainties surround its use in the elderly population and the use of brain imaging before treatment. This overview will address the current available evidence and focus on areas for future research.

Key words: Advances; lung cancer; radiotherapy; small cell

Statement of Search Strategies Used and Sources of Information

Searches were made on PubMed in November 2015 using the key words: small cell lung cancer, radiotherapy, chemoradiotherapy, chemotherapy, palliative, cranial irradiation, prophylactic. In addition, references from relevant articles and publications that the authors are aware of were included.

Introduction

Small cell lung cancer (SCLC) accounts for 13% of lung cancers in the developed world and almost all patients have been exposed to tobacco, so this is a highly preventable malignancy [1]. The incidence of SCLC is declining mainly due to a reduction in smoking rates and changes in cigarette composition [1]. However, SCLC remains a significant public health issue as about 6500 new patients are diagnosed each year with this disease in the UK. Most patients (57%) present with stage IV disease (extensive stage) [1] as opposed to stage I–III disease (limited stage) and the recommendation is that SCLC should now be staged with the primary tumour, lymph node metastasis, distant metastasis (TNM) system [2,3]. For those who are felt to have curable disease, brain imaging, preferably with a magnetic resonance imaging scan, as well as 18F-fluorodeoxyglucose positron emission tomography imaging, should be considered to evaluate for distant disease [4], alongside histological confirmation of any distant site if needed. These investigations may upstage up to 15% of stage I–III SCLC [5–7] and this recent change in practice is an important consideration when reviewing earlier studies that did not have the benefits of these investigations.

Chemotherapy was considered the mainstay of treatment until the 1980s when the role of radiotherapy in addition to systemic treatment was shown [8]. In the last two decades most of the advances in the management of all

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stages of disease have been due to improvements in radiotherapy. These include improvements in radiotherapy techniques, better integration of chemotherapy and radiotherapy and the use of prophylactic cranial irradiation (PCI). Here we review the current evidence supporting the use of radiotherapy in the treatment of SCLC, focusing specifically on areas of controversy, and discuss areas of research needs and future developments.

Management of Stage I–III Small Cell Lung Cancer

Stage I–III SCLC is primarily managed with concurrent chemotherapy and radiotherapy followed by PCI, which confers a high response rate, but also a significant risk of local relapse and distant metastases, including brain metastases. Five year overall survival in clinical trials ranges between 11 and 30% [9]. There is therefore potential to improve both radiotherapy treatment and systemic therapy to impact on survival rates.

Radical Thoracic Chemoradiotherapy

The standard of care for stage I–III SCLC that can be encompassed in a radiotherapy treatment plan that does not exceed normal tissue tolerance is thoracic radiotherapy given with concurrent chemotherapy. The role of thoracic radiotherapy in the management of limited stage SCLC was established by two meta-analyses published in 1992 investigating the addition of thoracic radiotherapy to chemotherapy. These showed an absolute survival benefit of 5.4% at 3 years and an improvement in local control at 2 years from 24% to 47% [8,10]. However, it should be noted that the chemotherapy agents and radiotherapy dose fractionations in the studies were heterogeneous, and responses to treatment were mainly assessed by chest X-ray. This improvement in survival with concurrent treatment was also observed in a retrospective review from the USA of the National Cancer Data Base [11].

Despite these benefits, a number of questions remain over the optimal treatment with concurrent chemoradiotherapy. These are, what chemotherapy agents are best used and how should they be delivered in conjunction with radiotherapy, what is the ideal dose fractionation schedule, what are the most appropriate radiotherapy treatment volumes and how should the elderly best be managed?

Timing of Radiotherapy

A key question regarding the use of chemotherapy and radiotherapy for stage I–III SCLC is whether a sequential or concurrent approach is superior and what the optimal timing of radiation should be? A meta-analysis conducted by Fried *et al.* [12] in 2004 included seven trials and 1524 patients and evaluated early versus late thoracic radiotherapy. Early radiotherapy was defined as beginning within 9 weeks of the initiation of chemotherapy (i.e. before the third cycle of chemotherapy). Two year overall survival was found to favour early radiotherapy, with a risk ratio of 1.17 (95% confidence interval 1.02–1.35, $P = 0.03$). Subgroup analysis showed a greater magnitude of benefit for early radiotherapy with the use of hyperfractionation and platinum-based chemotherapy regimens.

A systematic overview by De Ruysscher [13] has shown that time from the start of chemotherapy to the completion of radiotherapy (SER) is a key variable in predicting outcome. With an SER less than 30 days, the 5 year overall survival rate was more than 20% and significantly higher than with a longer SER (relative risk = 0.62; 95% confidence interval 0.49–0.80; $P = 0.0003$). However, a lower SER was also associated with a higher incidence of severe oesophagitis (relative risk 0.55; 95% confidence interval 0.42–0.73; $P < 0.0001$). These findings support the use of a radiotherapy regimen given concurrently with the first cycle of chemotherapy and administered twice daily as both overall treatment time and early radiotherapy are important in improving outcomes. They also support the concept that accelerated tumour cell repopulation is an important cause of treatment failure in SCLC and delivering an intensive chemoradiotherapy regimen upfront, before the process of accelerated tumour cell proliferation starts, may overcome this phenomenon.

Dose Fractionation

A number of studies have shown that increased dose is associated with improved outcomes. An early retrospective study showed that as the total dose increases from 30 to 50 Gy the local control also improves [14] and subsequent prospective studies suggest that dose escalation beyond 50 Gy results in better outcomes [15,16]. A phase I study published in 1998 showed that it was feasible to deliver 70 Gy in 35 fractions with oesophagitis being the dose-limiting toxicity [17]. A further study conducted by the Cancer and Leukemia Group B (CALGB) showed that 70 Gy in 35 fractions concurrently with chemotherapy was well tolerated and safe, suggesting that dose escalation up to and possibly beyond 70 Gy may be achievable [18]. The optimal dose for standard fractionation (1.8–2 Gy per fraction given daily, 5 times per week) has therefore not been defined, although there has been a trend to give higher doses despite limited data to support this [19].

As well as increasing the total dose, given in 2 Gy per fraction, there has been significant work investigating either or both hyperfractionated or an accelerated fractionation approach to stage I–III SCLC, which confers radiobiological advantages such as a reduction in overall treatment time leading to reduced tumour repopulation. A number of studies have shown that hyperfractionated radiotherapy was associated with promising results [20,21]. Subsequently a seminal study (Intergroup 0096) showed that 45 Gy given in 1.5 Gy fractions, twice daily over 3 weeks with concurrent cisplatin-etoposide was superior to 45 Gy given in 1.8 Gy fraction, once a day over 5 weeks [22]. Twice daily radiotherapy improved 5 year survival from 16 to 26% at the expense of an increase in grade 3–4 oesophagitis from 16 to 32%. The main criticism of this study was the use of low dose radiotherapy in the control arm considered to be suboptimal. This consideration alongside concerns regarding logistics

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