Clinical Oncology xxx (2017) 1–9

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Re-irradiation for Locally Recurrent Lung Cancer: Evidence, Risks and Benefits

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Received 25 July 2017; received in revised form 16 October 2017; accepted 26 October 2017

Abstract

In spite of recent improvements in both the technical delivery of radiotherapy and systemic therapy in the treatment of non-small cell lung cancer, local recurrence rates after radiotherapy remain a significant challenge. In the setting of local relapse after radiotherapy, treatments such as surgical resection or radiofrequency ablation are often not appropriate owing to disease and patient factors. Re-irradiation may be a potential treatment option. This overview considers the published evidence and potential treatment strategies.

Key words: Lung cancer; radiotherapy; re-irradiation; retreatment

Statement of Search Strategies Used and Sources of Information

A Pubmed search was conducted on 20 May 2017 using the search terms: 'lung cancer' AND 're-irradiation' OR 're-irradiated'. Of the 149 papers found, the search was limited to papers written in English and studies in humans. Articles were discarded if the primary tumour was not lung cancer, if the study included brachytherapy or was published in abstract form. Twenty-three articles were identified, two of which were review articles, 16 were retrospective observational studies (including a toxicity update of one study), one phase I–II prospective study and one prospective palliative study. Three studies were included for dosimetric information on thoracic re-irradiation.

Introduction

Lung cancer remains the most lethal cancer in the UK, with over 45 000 new patients diagnosed each year and over 39 000 deaths [1]. It is estimated that half of all patients will have radiotherapy as part of their initial treatment, and a further 15% will have further palliative radiotherapy [2,3]. Using radiotherapy as the sole modality has both poor 2 year local control and overall survival rates of about 16–23% and 21–30%, respectively [4]. The use of concurrent chemoradiotherapy improves survival but still has a locoregional recurrence rate of 28.9% at 5 years [5,6].

For those patients who relapse locally after curative intent or 'radical' radiotherapy, the treatment options are limited. Radical surgery is often precluded due to comorbidities and the increased intraoperative risks. Palliative chemotherapy in patients without an activating mutation has a response rate between 20 and 35% with significant toxicities [7].

The technical capability to treat locally relapsed disease has increased with recent advances in highly conformal

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https://doi.org/10.1016/j.clon.2017.11.003
0936-6555/

radiotherapy, such as volumetric arc therapy and stereotactic ablative radiotherapy (SABR) [8], better image guidance (cone-beam computed tomography) and more accurate dose prediction algorithms, which all allow for greater sparing of normal tissue. Moreover, with SABR, the dose per fraction to the tumour is large, which may overcome radioresistance to a degree. The clinical evidence for re-irradiation is limited to small retrospective studies and one early phase prospective trial. These studies often describe single-centre experiences over several years, combining small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and a variety of different radiotherapy doses and fractionations, with or without chemotherapy, both as initial treatment and for retreatment. The rationale of re-irradiation with further radical doses of radiotherapy requires consideration and has not been explored in any randomised clinical trial. Therefore, three important considerations are:

- Is a second radical treatment deliverable safely without causing unacceptable increased normal tissue toxicity
- Will further radical radiotherapy be effective, given that the recurrent tumour may have an intrinsic radioresistance
- What is the role of palliative radiotherapy in the context of prior chest radiotherapy?

This overview will analyse the published evidence for radical re-irradiation, with either conventionally fractionated treatment, or SABR, and the efficacy and risks of palliative re-irradiation, with the goal of identifying features that are useful to consider when planning re-irradiation.

Search Strategy

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Radical Conventional Re-irradiation

The goal of any radical dose is to eliminate the tumour and, if this is not achieved, to provide local control for as long as possible. In the setting of chest re-irradiation the goal of radical treatment must be balanced against the potential toxicities (which are more likely with re-irradiation), such as radiation pneumonitis, bronchial fistulation, myelitis and oesophageal perforation. In terms of the re-irradiation technique used, both fractionated re-irradiation and SABR have been used [9]. For the purposes of this review, a radical treatment was defined as an administered dose over 50 Gy for NSCLC and over 40 Gy for SCLC. Table 1 summarises the treatment and outcome measures for the relevant fractionation re-irradiation studies.

All of the studies described had heterogeneous cohorts of patients in terms of previous treatment, histology and baseline characteristics. The only prospective phase I/II study by Wu *et al.* [10] took 23 patients, of whom 13 had radical radiotherapy, six had palliative and four had post-operative radiotherapy as their initial treatment. Seven patients had a diagnosis of SCLC and 16 had NSCLC. The inclusion criteria were recurrence greater than 6 months from initial treatment, a Karnofsky performance status (KPS) $\geq$ 70 and a forced expiratory volume in the first second of forced breath (FEV_1) $>$ 1 l. Re-irradiation was delivered with sequential chemotherapy in most patients and the authors reported a median gross tumour volume of 80 cm^3. One strength of this study was that in patients with recurrence, histological confirmation was achieved in 65% of the patients. The overall 2 year survival rate was 21% and the local control rate was 42%, which is comparable with that achieved by radical radiotherapy alone [4]. Although the rate of grade 1–2 pneumonitis and oesophagitis was high (96% and 40%, respectively), there were no grade 3 or 4 toxicities reported.

Tada *et al.* [11] reported a retrospective study in which patients with NSCLC received radical intent re-irradiation. In the analysis of the patients treated, they reported a significant difference in survival according to performance status, with patients with a performance status of 3 often unable to complete treatment, having a median survival of 1.1. months, whereas patients with a performance status of 0–1 had a median survival of 12.6 months. Moreover, the longer the time since initial irradiation, the better the survival, with patients relapsing within 12 months having a median survival of 2.1 months compared with 11.5 months if the interval was greater than 18 months. Kruser *et al.* [12] also reported better survival in patients with a KPS $\geq$ 80, but found that the rate of grade 2 or worse pneumonitis was higher in those receiving retreatment with radical intent (38.5% as opposed to 11.4% in those treated with palliative intent). In the published retrospective series available, the highest recorded median overall survival was reported by Sumita *et al.* [13], with a median of 31.4 months, but importantly, this study reported the survival time from the initial diagnosis, whereas the other studies reported the time from re-irradiation. The local control rate at 2 years was similar to other studies at 34% and they noted that smaller planning target volumes (PTV) and receiving $\geq 60Gy_{10}$ (equivalent dose in 2 Gy fractions [EQD2], using an α/β ratio of 10 for the tumour) at re-irradiation were associated with better survival.

Griffioen *et al.* [14] reported on a mixed group of locally recurrent patients (54%) and new lung primaries (46%), with all but one having central tumours. Again, they found a significant association between better survival and a PTV

Please cite this article in press as: Rulach R, et al., Re-irradiation for Locally Recurrent Lung Cancer: Evidence, Risks and Benefits, Clinical Oncology (2017), https://doi.org/10.1016/j.clon.2017.11.003