Clinical Oncology 27 (2015) 290–297

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Stereotactic Body Radiotherapy for Oligometastatic Disease

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Received 2 January 2015; received in revised form 14 January 2015; accepted 5 February 2015

Abstract

Stereotactic body radiotherapy (SBRT) is now an established therapy in stage I lung cancer with comparable local control rates to surgical resection. Owing to the conformity of treatment dose delivery and with appropriate fractionation considerations, minimal side-effects to surrounding normal tissues are observed in most patients. SBRT is now being used in the treatment of oligometastatic disease, alone or alongside systemic therapy. At present there is a paucity of evidence available showing a clinical benefit, but several international studies are being set-up or have started recruitment. This overview considers the clinical entity of an oligometastatic state, discusses the role of SBRT in the management of oligometastatic disease and discusses potential novel therapy combinations with SBRT.

Key words: Oligometastases; SABR; SBRT; stereotactic

Statement of Search Strategies Used and Sources of Information

The terms 'stereotactic body radiotherapy', 'stereotactic ablative radiotherapy' and 'oligometastases', together with their derivatives, were used to search PubMed. All studies relating to stereotactic body radiotherapy in the treatment of oligometastatic disease and of relevance to this overview were included in the preparation of the review. No limitations were placed on language or year of publication.

Introduction

Stereotactic body radiotherapy (SBRT), or stereotactic ablative radiotherapy, has become more practical over the last decade owing to seismic technical advances in both imaged-guided radiotherapy and with advances in the precision of radiotherapy delivery with the various forms of intensity-modulated radiotherapy currently available [1]. However, the term stereotactic is perhaps misleading in so far that stereotaxis, as used in the neurosurgical sense, is not used. SBRT is used to denote the precise and accurate delivery of high-dose, hypofractionated radiotherapy to targets generally less than 5 cm in maximum diameter, with relative sparing of surrounding normal tissues [2]. SBRT is now an established therapy in stage I lung cancer, with comparable local control rates to surgical resection and the role of SBRT is under investigation in a number of primary tumour sites, such as prostate carcinoma [3–5].

There is increasing use of SBRT for the treatment of oligometastatic disease, but the evidence of clinical benefit is not as strong as the evidence supporting its use in stage I lung cancer [6]. Owing to the conformity of treatment dose delivery and with appropriate fractionation considerations, side-effects to surrounding normal tissues are frequently minimal [7]. Also, for most primary tumour sites and treatment locations, local control after SBRT treatment is high. Thus, it follows that SBRT may have a role in the treatment of oligometastatic disease to provide long-term control or even cure if the metastatic sites treated represent the only sites of residual disease. In the oligometastatic setting, SBRT has been delivered alone or in conjunction with systemic therapy. At present there is a paucity of evidence available showing a clinical benefit, but several international studies are being set-up or have started recruitment. However, the trials under development now

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http://dx.doi.org/10.1016/j.clon.2015.02.003

need to be put in context for the reader so that the results that will soon start coming through thick and fast can be reviewed. This overview seeks to do this and does not seek to be a systematic review of the area. Using non-small cell lung cancer (NSCLC) as an exemplar, this overview considers the clinical entity of an oligometastatic state, discusses the role of SBRT in the management of oligometastatic disease and discusses potential novel therapy combinations with SBRT.

The Concept of Oligometastatic Disease

The term oligometastatic, posited by Hellman and Weichselman [8], describes the presence of a limited number of metastatic sites of disease, usually less than six in number and in some descriptions less than four. The potential existence of this clinical entity implies that cure may be possible because there are no viable micrometatases and that all the metastases that are present have declared themselves [9]. Hence, the oligometastases present are simply an extension of locally advanced disease and, as Hellman and Weichselman [8] suggest, are an intermediate state between locoregional and widespread metastatic disease. At the time this theory was proposed, all that was missing were potentially curative or ablative techniques to deal with most metastases not amenable to low-morbidity surgery. Where surgery is possible the results are encouraging and in patients with complete resection of lung metastases overall survival at 5 years of 46% has been reported [10]. With the availability of SBRT, at least as a research tool in this context, testing of the oligometastasis hypothesis may occur. According to this theory, the addition of local ablative treatment to the metastases may increase cure rates. Logically, therefore, the correct trial design to test the theory is to concentrate on these local therapies in addition to the local therapies for the primary tumours and the end point should be cure rate and not overall survival: tail on the overall survival curve rather than the median.

Using the number of long-term survivors as the end point for any oligometastatic study might be logically correct, but does not address some important patient and disease variables. First, the advocates of the oligometastatic state agree that patient cure can only be reliably identified retrospectively [11]. It is hoped that the current round of randomised trials will generate translational research, one outcome being to be able to identify upfront patients with very low further metastatic potential. This will probably be a function of both tumour genetics and host environmental factors. For now, though, the oligometastatic patient group contains a mixture of patients with and without potential for further metastases. These patients cannot be forgotten in a trial design that includes or replaces the standard treatment of this patient group. For these patients, in whom there seems to be general agreement that with current systemic therapies there is no chance of cure for most primary tumour types, a median overall survival end point is surely more relevant than cure rate.

Second is the assumption that patients who do have further metastatic potential will not benefit from ablative treatment of the metastases. If a drug was shown to act with such high complete remission rates as SBRT, even though it was only to act on visible disease, trials would undoubtedly be undertaken to investigate its role alongside standard systemic therapy. We do not as a rule in clinical oncology blindly follow the drug development pathway with all of its quirks. Nevertheless, there is a logic that says that a highly effective boost treatment to well over 90% of malignant disease (i.e. all that is visible in oligometastatic patients) might give additional value to standard systemic therapy. This value, if present, is likely to be measured in metastatic disease-free and overall survival. A number of prospective randomised trials designed to show a survival advantage with ablative treatment of oligometastatic disease are either recruiting or in planning. One of the first is the recently completed UK PulMicc trial, testing surgical metastasectomy for colorectal cancer patients with oligometastases to the lung [12]. In the planned UK NSCLC SARON trial, the control arm will be four cycles of platinum-based doublet chemotherapy followed by maintenance systemic therapy according to local guidelines.

Finally the issue of the definition of oligometastases requires consideration. What is ‘a few metastases’? At present no standard definition is agreed and it remains for those researchers designing clinical trials to define the maximum number of sites of metastatic disease that may be considered as oligometastatic. Therefore, only by conducting well-designed prospective trials that compare the outcomes in the oligometastatic state to the general metastatic population of each tumour type will we ever get close to an answer as to the true definition of oligometastases, if indeed an over-arching definition exists.

Patients with molecular alterations that significantly alter their outcome with systemic therapy only, such as sensitising EGFR mutations and Alk-fusion or ROS-1 rearrangements, have a different natural history and outcome to those without [13–15]. Although the general cancer biology principles of oligometastatic disease might apply equally to this group in order to maintain as homogeneous a population, it is imperative that any trial of ablative interventions has clearly defined inclusion criteria based on molecular disease classifications in addition to the standard disease and patient criterion.

A number of other points in the 1995 editorial are directly relevant to clinical trial design. Hellman and Weichselbaum [8] argued that tumours that have only single organ metastases might be less likely to be harbouring further metastases in other organs. Furthermore, patients with more sites of disease and overall greater tumour burden were hypothesised to have a higher rate of microscopic metastases. To address these points, trials in this area should stratify patients by the number of organs involved and should collect data on the overall volume of disease present to correlate with clinical outcomes. These factors may form the basis of future selection criteria for the use of SBRT in oligometastatic disease.