Clinical Oncology xxx (2017) 1–6

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

The Principles and Practice of Re-irradiation in Clinical Oncology: An Overview

W. Dörr *, D. Gabryś †

* *ATRAB – Applied and Translational Radiobiology, Department of Radiotherapy, Medical University of Vienna, Vienna, Austria*

† *Radiotherapy Department, Maria Sklodowska – Curie Memorial Cancer Center and Institute of Oncology Gliwice Branch, Gliwice, Poland*

Received 10 November 2017; received in revised form 20 November 2017; accepted 22 November 2017

Abstract

Long-term cancer survivors are at risk of the development of recurrence or a new primary cancer that requires a second (or third) radio-oncological treatment. Publications on re-irradiation have been followed and are summarised in this overview. Information from clinical and experimental animal studies suggests that specific normal tissues can tolerate a considerable retreatment radiation dose. However, the risk of normal tissue damage and the impact on the quality of life must be considered. If a second course of radiotherapy needs to be administered, this should be done with maximum care and accuracy. Optimum conformation of the dose to the planning target volume is required. For radiobiological reasons – in order to reduce the risk of late effects – hyperfractionation protocols should be applied for curative treatments. Alternatively, small volume exposure may be considered in a highly conformal, image-guided stereotactic approach.

Key words: Complications; normal tissue; radiotherapy; re-irradiation; tissue tolerance

Statement of Search Strategies Used and Sources of Information

Publications related to studies of re-irradiation, both preclinical and clinical, have been followed over the last decades and are summarised in this overview, which is based on a recent chapter in Joiner M, van der Kogel A. Basic clinical radiobiology. 5th ed. London: Hodder Arnold; in press.

Introduction

Optimisation of radiotherapy over the last few decades, due to technological advances and exploitation of radiobiological principles, has resulted in a significant increase in the survival rates for a variety of malignancies. This has led to significant attention being paid to cancer survivorship [1]. Long-term surviving cancer patients obviously have an increased risk of developing a recurrence as well as a secondary cancer, as they are still subject to the normal age-related risk of cancer. Moreover, compared with the general population, the risk of developing a second tumour is higher in cancer survivors than in other comparable persons. This relates to familiar predisposition, aetiological factors associated with the first tumour (lung/head and neck tumours – smoking) or the primary cancer therapy (chemotherapeutics, biologically targeted agents, radiation). The latter is of particular importance for children; childhood cancer survivors have an up to a 19-fold increased risk of developing secondary cancers [2].

A decision on re-irradiation needs to consider:

- the localisation of the second tumour in relation to the initial radiation treatment volumes, and thus the previous exposure of organs at risk [3];
- parameters of the initial radiotherapy: dose, fractionation and volume;

Author for correspondence: D. Gabryś, Radiotherapy Department, Maria Sklodowska - Curie Memorial Cancer Center and Institute of Oncology Gliwice Branch, Wybrzeze Armii Krajowej 15, 44-101 Gliwice, Poland. Tel: +48-784-067-548; Fax: +48-32-278-80-01.

E-mail address: dorota.gabrys@io.gliwice.pl (D. Gabryś).

https://doi.org/10.1016/j.clon.2017.11.014

Please cite this article in press as: Dörr W, Gabryś D, The Principles and Practice of Re-irradiation in Clinical Oncology: An Overview, Clinical Oncology (2017), https://doi.org/10.1016/j.clon.2017.11.014

- combination therapy for the first tumour (chemotherapy, 'biologicals');
- time interval from the treatment of the first tumour with regard to potential tissue-specific morbidity after re-irradiation and its impact on the patient's quality of life.

A detailed summary of the current knowledge of radiobiological aspects of re-irradiation strategies is summarised elsewhere [4].

In this overview, the tolerance doses for organs at risk above which specific grades of morbidity are observed at a specified incidence rate, are referred to as the equivalent dose in 2 Gy fractions – $EQD2_{tol}$ [4]. The contribution of both the initial treatment and the re-irradiation can thus be specified as a percentage of the $EQD2_{tol}$.

It should be mentioned that the vast majority of clinical reports on re-irradiation do not include data from simultaneous control groups with primary irradiation of the same site. In the following sections, the current knowledge – from clinical and preclinical studies – regarding re-irradiation tolerance of specific tissues – head and neck and breast, where the most reliable information is available – are briefly summarised.

Head and Neck Tissues

Re-irradiation has been increasingly applied to patients with a primary tumour in the head and neck region. Therefore, the greatest number of research publications is dedicated to experience in this region.

The major organ at risk that needs to be considered with regard to head and neck re-irradiation is the carotid artery. For the end point of carotid rupture, aggressive re-irradiation (accelerated treatment) [5], vessel encasement by the tumour and presence of ulceration and irradiation to lymph nodes by stereotactic re-irradiation [6,7] seem to be associated with a higher risk, compared with conventionally fractionated re-irradiation. Further complications after re-irradiation are fibrosis, mucosal ulceration/necrosis, fistula osteoradionecrosis, eye morbidity/blindness and skin ulcerations [8,9]. Temporal lobe necrosis, hearing loss, dysphagia and trismus are also seen in variable tumour localisations, but more often in patients with nasopharyngeal carcinoma [10–12]. Re-irradiation-induced mucosal reactions, 2–3 years after first radiotherapy, may be more severe (confluent: grade 3) at earlier time points. This may be a consequence of the presence of chronic mucosal atrophy, related to the decreased cell numbers, causing an increased vulnerability and a reduction in the time required for total cell depletion [4]. Furthermore, there is a wide range in the rate of severe mucositis (11–52%) and/or dysphagia/pharyngitis in postoperative head and neck re-irradiation (grade 3–4 according RTOG or CTCAE 2.0), as reviewed in [13].

Much effort has been put into the identification of predictors for developing long-term morbidity. Shorter intervals to re-irradiation and larger re-irradiated volumes were significant predictors of the risk of developing severe late toxicity [14,15]. Moreover, in patients with smaller tumour volumes, tumour progression, especially locoregional failure, was the leading cause of death. By contrast, in patients with larger tumours, radiation-induced injuries, including mucosal necrosis or massive haemorrhage, radiation encephalopathy, eating difficulties and other radiation injuries, became more frequent and caused half of deaths in this group [14]. Before selecting the appropriate re-irradiation method, it is necessary to consider the location of the recurrence, because it has been shown that those treated for a recurrence in the larynx/hypopharynx experienced significantly more severe late morbidity compared with other primary tumour sites or nodal recurrence [16]. In addition, a significantly lower retreatment tolerance for late morbidity may be related to primary combined treatment with chemotherapy [17]. Radio-chemotherapy induces more severe reactions than radiotherapy alone, which may be associated with a reduced re-irradiation tolerance.

Despite the occurrence of a spectrum of morbidity caused by irradiation, a large study describing re-irradiation for nasopharyngeal carcinoma described lower than expected normal tissue injury (excluding xerostomia), based on the sum of the initial and retreatment doses. This indicated partial long-term recovery of the head and neck tissues, particularly after intervals of $\geq$2 years [10].

There has been a tendency for the use of hyperfractionated regimens, for which safety and usability was illustrated by the results of two prospective phase II trials, RTOG 9610 and RTOG 9911 [11,12]. In both studies, patients received re-irradiation to a total dose 60 Gy (1.5 Gy per fraction bid, 5 days/week) in combination with chemotherapy: 5-fluorouracil and hydroxyurea [12] or cisplatinum and paclitaxel [12]. In RTOG 9610, treatment was delivered with three-dimensional conformal radiotherapy; early morbidity grade $\geq$4 occurred in 25.3%, late adverse events grade $\geq$3 in 22.4% of the patients. Six patients died of early treatment-related causes, but no late grade 5 toxicity was reported [11]. In RTOG 9911, treatment was delivered with three-dimensional conformal radiotherapy or intensity-modulated radiation therapy techniques; grade $\geq$4 general early complications occurred in 28% and grade $\geq$4 early haematological toxicity in 21% of the patients. Eight treatment-related deaths (8%) occurred: five associated with early effects, three in the late phase (including two carotid haemorrhages) [12]. For patients with recurrent or second primary head and neck tumours whose disease is not surgically resectable, salvage treatments are needed. Concurrent chemotherapy with re-irradiation has a high risk for complications and treatment-related death. Therefore, appropriate patient selection restricting this approach to patients with excellent performance status could improve on this, as the majority of severe morbidities appeared in the early phase.

In the case of postoperative treatment, re-irradiation with chemotherapy should only be introduced very carefully. Disease-free survival was found to be improved, but no difference was observed in overall survival. Despite this there was increased morbidity; 28% and 39% of patients

Please cite this article in press as: Dörr W, Gabryś D, The Principles and Practice of Re-irradiation in Clinical Oncology: An Overview, Clinical Oncology (2017), https://doi.org/10.1016/j.clon.2017.11.014