

Review Article

Increasing frequency of reirradiation studies in radiation oncology: systematic review of highly cited articles

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Abstract: Objectives: Identification of the most influential scientific publications and directions of mainstream reirradiation research. Methods: A systematic search of the database Scopus (Elsevier B.V., www.scopus.com) was performed, which focused on the time period 1998-2010. Patterns of citation were analysed (total number of citations accumulated independently of their origin and proportion of highly cited articles, arbitrarily defined as those with ≥ 50 citations). Results: Up to 64 articles were published each year. Numbers increased over time, especially after the year 2007. Among all 76 articles with at least 50 citations, 28 (37%) focused on head and neck cancer, 27 (36%) on brain tumours including metastases, and 5 (7%) on bone metastases. Most articles evaluated external beam approaches while 10 (13%) focused on brachytherapy. Many of the often quoted publications reported on stereotactic and/or intensity-modulated radiotherapy. Two (3%) reported on randomised clinical studies and 10 (13%) on non-randomised prospective clinical studies (single institution or cooperative group). Only two articles (3%) reported on experimental animal studies. Conclusions: The number of published reirradiation studies has increased in recent years. Many studies examined highly conformal and precise radiotherapy, in particular of brain and head and neck tumours. Given that few randomised clinical trials were published, efforts to increase this type of research activity are warranted.

Keywords: Radiotherapy, radiation oncology, radiation retreatment, reirradiation, citation, research evaluation

Introduction

For several decades, radiation oncologists have administered a repeat course of radiotherapy to a previously irradiated volume (reirradiation) in selected patients because such treatment might provide worthwhile clinical benefit in terms of palliation or sometimes even cure to patients who develop locoregional relapse or second primary tumours [1-3]. A previous audit showed that 10% of all palliative radiotherapy courses in a Norwegian health care region consisted of reirradiation [4]. Given the potentially serious consequences of normal tissue damage from high cumulative doses, intense research activity is directed towards harnessing highly conformal reirradiation techniques [5, 6]. The purpose of our study was to identify the most influential scientific publications and directions of mainstream reirradiation

research. For several reasons including but not limited to tenure track or likelihood of future funding, researchers attempt to publish their results in a way that ensures high visibility and allows for broad adoption of the progress achieved. Successful publication might be defined by various measures. Impact factor of journals is a two-edged sword, e.g. regarding the publication bias that strikes negative or inconclusive studies [7-9]. Article download rates might provide some indication for visibility and impact, but will depend on presence and quantity of fees charged by the publisher. Another potential measure of quality and impact of research is the citation rate [10, 11]. Landmark or practice-changing research is likely to be cited by successor trials, editorials and review articles. For the purpose of this review, we focused mainly on citation rates of articles published between 1998 and 2010. Information

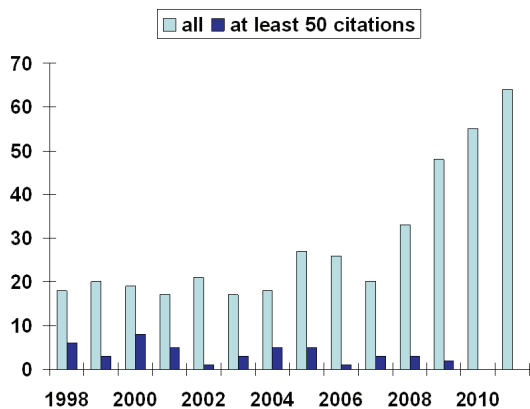


Figure 1. Number of articles and highly cited articles published per year.

about highly cited article types can be useful for preparation of future research projects. Moreover, identification of underrepresented areas might facilitate efforts to increase their visibility.

Methods

A systematic search of the database Scopus (Elsevier B.V., www.scopus.com) by use of the key words 'reirradiation', 're-irradiation', 'repeat radiotherapy', 'radiation retreatment' and 'recurrent AND radiotherapy' was performed on 3rd September 2012. Articles were selected irrespective of language and article type (review, clinical study, experimental study etc.). Patterns of citation (field 'times cited' in the Scopus citation database) were analysed as described in a previous study [12]. We evaluated total number of citations accumulated independently of their origin, and proportion of highly cited articles, arbitrarily defined as those with ≥ 50 citations. A complete list of articles cited at least 50 times can be requested from the corresponding author. While focusing on the time period 1998-2010, both younger and older publications were included for selected end points.

Results

Up to 64 articles were published each year. **Figure 1** shows the number of publications per year, which has increased over time (especially after the year 2007). References [13-51] represent the 3 most frequently cited articles per year. After 2008, more and more of these often quoted studies reported on highly conformal

irradiation techniques such as stereotactic and frameless robotic radiotherapy [13, 15, 16, 18]. However, it becomes clear from earlier studies that new technological developments always were utilised for the purpose of reirradiation early after commercial availability [44, 52]. Experimental technology such as carbon ion radiotherapy or boron neutron capture therapy also was harnessed [31, 32, 35]. Many studies incorporated strategies of radiosensitisation, e.g. by chemotherapy [23, 27, 40, 41], which in theory might broaden the therapeutic window of reirradiation. **Table 1** shows the 10 most frequently cited articles overall. Most of these were clinical studies related to head and neck or brain tumours. All of them were published before 2005. Since articles published for example in 2000 are more likely to have accumulated a large number of citations than articles published in 2010, the average of the annual numbers of citations was also calculated. For this purpose, 2012 was defined as 0.67 years (January 01st - September 02nd). **Table 2** shows the 10 articles with most citations per year (in fact 12 articles because some had equal citation counts). The table contains articles published between 2000 and 2009. This distribution suggests that citation of older articles declines after 10-12 years. Again, most of the articles were clinical studies related to head and neck or brain tumours. Many of them reported on stereotactic and/or intensity-modulated radiotherapy.

As shown in **Figure 1**, variable numbers of articles acquired at least 50 citations. With one exception (the year 2000 where 42% of all articles were cited at least 50 times) less than one third of articles were cited at least 50 times. Among all 76 articles with at least 50 citations (1998-2010), 28 (37%) focused on head and neck cancer, 27 (36%) on brain tumours including metastases, and 5 (7%) on bone metastases. Other types of cancer were represented less frequently. Most articles evaluated external beam approaches while 10 (13%) focused on brachytherapy. Only two articles (3%) reported on experimental animal studies [42, 58], and one (1%) was a review paper [59]. Two (3%) reported on randomised clinical studies [21, 60], and 10 (13%) on non-randomised prospective clinical studies (single institution or cooperative group). These 76 articles were published in 15 different scientific journals. Twenty

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Table 1. Ten articles with most citations (absolute count)

Authors and year of publication	Short title	Absolute citation count	Citations per year
Shaw et al. 2000 [43]	RTOG 90-05 radiosurgery study	312	27
Schulz-Ertner et al. 2004 [31]	Carbon ion radiotherapy	149	19
Chao et al. 2000 [44]	IMRT for head and neck cancer	144	12
De Crevoisier et al. 1998 [49]	Head and neck cancer	136	10
Loeffler et al. 1990 [52]	Radiosurgery for brain metastases	135	6
Catton et al. 1996 [53]	Chordoma	133	8
Castro et al. 1994 [54]	Charged particle skull base irradiation	133	8
Wang 1987 [55]	Nasopharynx cancer	133	5
Grado et al. 1999 [46]	Prostate cancer brachytherapy	127	10
Lee et al. 1993 [56]	Nasopharynx cancer	119	6

RTOG: Radiation Therapy Oncology Group, IMRT: intensity modulated radiotherapy.

Table 2. Articles with most citations per year

Authors and year of publication	Short title	Citations per year	Absolute citation count
Gutin et al. 2009 [16]	SFRT for glioma	31	83
Shaw et al. 2000 [43]	RTOG 90-05 radiosurgery study	27	312
Iwamoto et al. 2009 [17]	Glioblastoma	26	70
Maier-Hauff et al. 2007 [22]	Glioblastoma	24	111
Schulz-Ertner et al. 2004 [31]	Carbon ion radiotherapy	19	149
Grosu et al. 2005 [28]	SFRT for glioma	17	112
Sterzing et al. 2008 [19]	Helical tomotherapy	17	64
Seiwert et al. 2008 [20]	Head and neck cancer	17	61
Sulman et al. 2009 [18]	IMRT for head and neck cancer	17	46
Salama et al. 2006 [25]	Head and neck cancer	14	77
Janot et al. 2008 [21]	Head and neck cancer	14	52
Sahgal et al. 2009 [57]	SBRT for spinal metastases	14	38

SFRT: stereotactic fractionated radiotherapy, RTOG: Radiation Therapy Oncology Group, IMRT: intensity modulated radiotherapy, SBRT: stereotactic body radiotherapy.

articles (26%) were published in the International Journal of Radiation Oncology Biology and Physics, 5 (7%) in the Journal of Clinical Oncology, 4 (5%) in Cancer, and 2 each (3%) in Radiotherapy and Oncology, Neurosurgery, Journal of Neurosurgery and Journal of Neuro-Oncology.

Discussion

The objective of this review was to identify influential, highly cited scientific publications and thereby research mainstreams related to reirradiation. After arbitrary decisions about which database to search and which keywords to use, we performed a systematic literature search and applied a broad definition of reirradiation related publication. For example, articles which reported on salvage treatment of a certain type of cancer where subgroups received reirradiation were included. Citation rate of published

articles was evaluated. Articles with high numbers of citations are likely those that impressed other clinicians/scientists and had profound influence on clinical practice or future developments in the field. Besides absolute number of citations, we also evaluated average annual citation rate because the exact time course or kinetics of citation is hard to predict and varies with topic and journal [61]. Both accumulation of citations of recently published articles and reduced interest in older articles over time pose challenges if reliable quantitative analysis is attempted. We did not account for date of publication, i.e. whether an article was published earlier or later during a given year. For the purpose of this overview, the chosen methods are sufficient even if more detailed and quantitative analyses can be performed with the internet based tools available. It should be noticed that searches in different databases or with different key words will result in more or

less variable citation counts and that the present results therefore provide only a snapshot. Self citation is likely to influence the final citation count of sparsely cited articles, whereas its impact on highly cited articles might be less pronounced. It was recently estimated that 6.4% of all citations per article (interquartile range 2.8–11.3, mean 8.4) were self citations [62]. Studies most vulnerable to this effect were those with more authors and small sample size.

Reirradiation research activity has increased in the time period studied here. Our results are consistent with the assumption that citation rate is gradually increasing for several years after publication. However, the purpose of this overview was not to explore dynamics of citation count. Given the fact that most scientific radiation oncology journals had steady increases in the number of published issues and articles, and that each article contains a certain number of references, the increase in total numbers of publications over time is expected to lead to a parallel increase in citation rates. It is also interesting to note that highly cited research was published in a large number of different scientific journals with or without high impact factor, but always in the English language.

During the time period between 1998 and 2010, major progress has been achieved in the areas of combined modality treatment and implementation of highly conformal radiotherapy techniques. Several articles on these subjects were among those with the highest numbers of citations. Despite overrepresentation of head and neck and brain tumour studies, reirradiation is administered to targets throughout the body [34, 37, 39, 46]. The small number of published randomised clinical trials is noteworthy. In order to establish regimens, which are based on the highest level of evidence, more randomised studies and metaanalyses are necessary. In contrast to general radiation oncology publications [63], reirradiation studies did not achieve more than 40 citations per year (average number). Given that randomised trials and metaanalyses are the most frequently cited study types [10, 63] their scarcity explains the observed difference in citation pattern. The limited preclinical research activity during recent years [42, 58], addressing for example reirradiation tolerance of normal tis-

ues, was also surprising. Prospective clinical research in related areas of toxicity prevention and mitigation by use of radioprotectors and response modifiers was not among the highly cited studies reviewed here. Efforts to support randomised prospective trials and normal tissue research might be warranted.

Conclusions

The number of published reirradiation studies has increased in recent years. Many studies examined highly conformal and precise radiotherapy and combined modality treatment, in particular of brain and head and neck tumours. Few randomised clinical trials were published.

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