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Systematic review

Identifying patients who may benefit from adaptive radiotherapy: Does the literature on anatomic and dosimetric changes in head and neck organs at risk during radiotherapy provide information to help?

Charlotte L. Brouwer, Roel J.H.M. Steenbakkers, Johannes A. Langendijk, Nanna M. Sijtsema *

University of Groningen, University Medical Center Groningen, Department of Radiation Oncology, The Netherlands

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A B S T R A C T

In the last decade, many efforts have been made to characterize anatomic changes of head and neck organs at risk (OARs) and the dosimetric consequences during radiotherapy. This review was undertaken to provide an overview of the magnitude and frequency of these effects, and to investigate whether we could find criteria to identify head and neck cancer patients who may benefit from adaptive radiotherapy (ART). Possible relationships between anatomic and dosimetric changes and outcome were explicitly considered. A literature search according to PRISMA guidelines was performed in MEDLINE and EMBASE for studies concerning anatomic or dosimetric changes of head and neck OARs during radiotherapy. Fifty-one eligible studies were found. The majority of papers reported on parotid gland (PG) anatomic and dosimetric changes. In some patients, PG mean dose differences between planning CT and repeat CT scans up to 10 Gy were reported. In other studies, only minor dosimetric effects (i.e. <1 Gy difference in PG mean dose) were observed as a result of significant anatomic changes. Only a few studies reported on the clinical relevance of anatomic and dosimetric changes in terms of complications or quality of life. Numerous potential selection criteria for anatomic and dosimetric changes during radiotherapy were found and listed. The heterogeneity between studies prevented unambiguous conclusions on how to identify patients who may benefit from ART in head and neck cancer. Potential pre-treatment selection criteria identified from this review include tumour location (nasopharyngeal carcinoma), age, body mass index, planned dose to the parotid glands, the initial parotid gland volume, and the overlap volume of the parotid glands with the target volume. These criteria should be further explored in well-designed and well-powered prospective studies, in which possible relationships between anatomic and dosimetric changes and outcome need to be established.

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Radiotherapy is a commonly applied treatment modality in head and neck cancer patients. Intensity modulated radiotherapy treatment plans with steep dose gradients are currently considered standard. These treatment plans are constructed on planning CT images, acquired prior to the start of radiotherapy. To account for patient positioning errors relative to these planning CT images, position verification procedures are generally applied. However, because of different patient postures and anatomic changes during the course of radiotherapy, the dose actually given to the patient can deviate from the planned dose [1]. These dose differences may lead to underdosage to target volumes and/or overdosage to organs at risk (OARs) [2].

Radiation-induced complications have a significant adverse impact on health-related quality of life [3]. Hence, it is important to monitor radiation doses to OARs during treatment. This is particularly salient in the head and neck area, where OARs are in close proximity to target volumes. However, at present, verification of the dose actually given to the patient is not considered routine clinical practice. Adaptive radiotherapy (ART) could be applied to reduce dose to OARs and eventually to improve quality of life [4–8]. ART is a formal approach to correct for daily tumour and normal tissue variations through streamlined online or offline modification of original target volumes and plans [9,10]. Implementation of ART is challenging both from clinical and logistic points of view and generally requires many resources. Clear guidelines are needed on the timing of rescanning and replanning, and an increasing amount of data needs to be acquainted, handled, transferred and stored. It is unlikely that every patient will benefit from ART and therefore tools

* Corresponding author at: Department of Radiation Oncology, University Medical Center Groningen, P.O. Box 30001, 9300 RB Groningen, The Netherlands.

E-mail addresses: c.l.brouwer@umcg.nl (C.L. Brouwer), n.m.sijtsema@umcg.nl (N.M. Sijtsema).

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to select patients who are expected to benefit most from plan adaptation during treatment become increasingly important [11].

In previous studies, it was shown that anatomic changes cause more dose deviations in OARs than in target volumes [12–15]. Clinical target volume (CTV) coverage is usually more robust to changes because of the use of the planning target volume (PTV) concept, while planning volumes at risk (PRV) margins are generally applied for the spinal cord and brain stem, but are not common practice for all OARs. Only 13% of the studies in this review reported PRV margins around the spinal cord and/or the brainstem [4,5,11,16–18], and 4% of the studies reported on PRV margins for all OARs [5,16]. In addition, position verification mainly focuses on correcting for set-up errors of targets, and for that reason might lead to increased doses to distant OARs. Therefore, it is expected that the largest gain of ART would be the monitoring and reduction of the dose to OARs.

For a strategic selection of patients who may benefit from ART, identification of selection criteria that are associated with dosimetric changes and resulting complications is necessary. Patient selection for ART can be realized by selection prior to treatment, i.e. based on pre-treatment characteristics, and by selection during treatment based on geometric and/or dosimetric changes early in treatment, either by non-imaging related factors (e.g. weight loss) or by imaging related factors (e.g. density changes).

Castadot et al. [19] have summarized the results of seven studies reporting on anatomic modifications of head and neck target volumes and OARs during radiotherapy in 2010. The authors concluded that radiotherapy induces major volumetric and positional changes in CTVs and OARs during treatment. Parotid glands tend to shrink and to shift medially towards the high dose region, potentially jeopardizing parotid sparing [19]. Not all of these studies reported to what extent these anatomic changes actually translate into dosimetric changes. Furthermore, no unambiguous effect of anatomic changes on dose has been found. Since 2010, the amount of studies reporting on anatomic and dosimetric changes has increased dramatically.

The main objective of this review was to evaluate the current literature on anatomic and dosimetric changes of head and neck OARs during radiotherapy. Furthermore, implications of these changes for the rate and severity of complications and quality of life were reported. In addition, we tried to identify selection criteria for changes during radiotherapy and recommended on the conduction of further studies on this subject. Results of this review could provide useful information for the development of strategies for patient selection in ART.

Methods

We performed a literature search in MEDLINE and EMBASE according to PRISMA guidelines [20] using the following keywords: ((synonyms for anatomic changes) OR (synonyms for dosimetric changes)) AND (synonyms for organs at risk) AND (synonyms for head and neck radiotherapy). The search was completed by March 1, 2015.

In addition, reference lists of papers were screened in order to retrieve additional relevant papers. Both prospective and retrospective studies published in journals part of the Thomson Reuters journal citation reports® were included. Studies in languages other than English, and studies only available in abstract form were excluded from this review.

Studies had to fulfil the following eligibility criteria to be selected for this review:

- report on anatomic and/or dosimetric changes of adult head and neck organs at risk during the course of photon radiotherapy, and
- at least ten patients included.

We present overviews of anatomic changes, dosimetric changes, and report potential selection criteria of either one. In addition, we report on studies describing the effects of anatomic and dosimetric changes during radiotherapy on side effects and quality of life. The results are presented by volume changes in percentages and dose changes in Gray in order to make comparisons across studies easier to interpret. Associations are presented in five ways; by the Pearson correlation coefficient (R), the coefficient of determination (R^2), the Spearman's rank correlation coefficient (ρ), linear regression analysis (r or r^2), and by the odds ratio (OR), according to the study methodology.

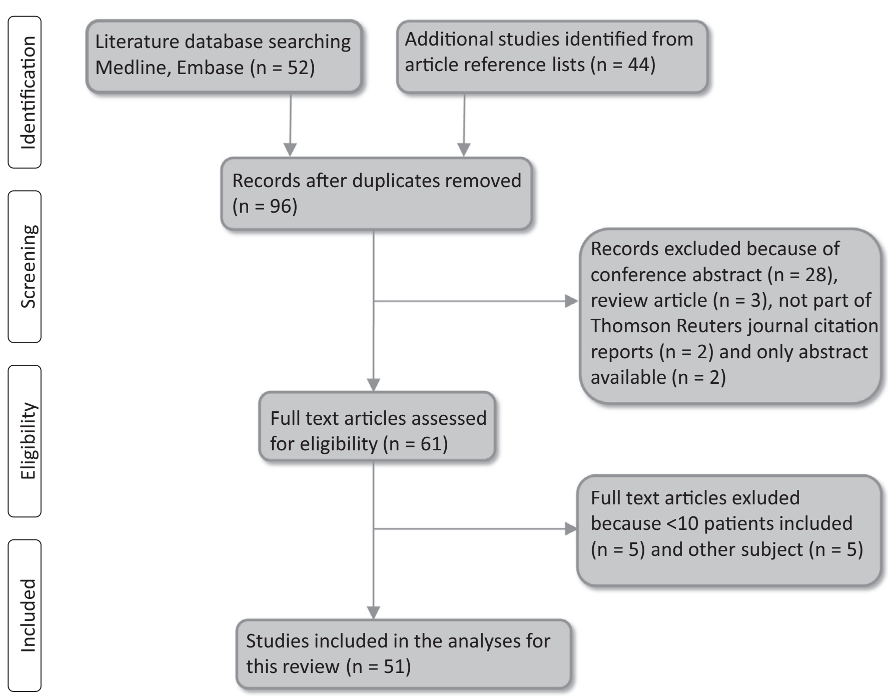

Fig. 1. PRISMA flow diagram of the literature search.

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