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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?

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ABSTRACT

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.

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

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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.

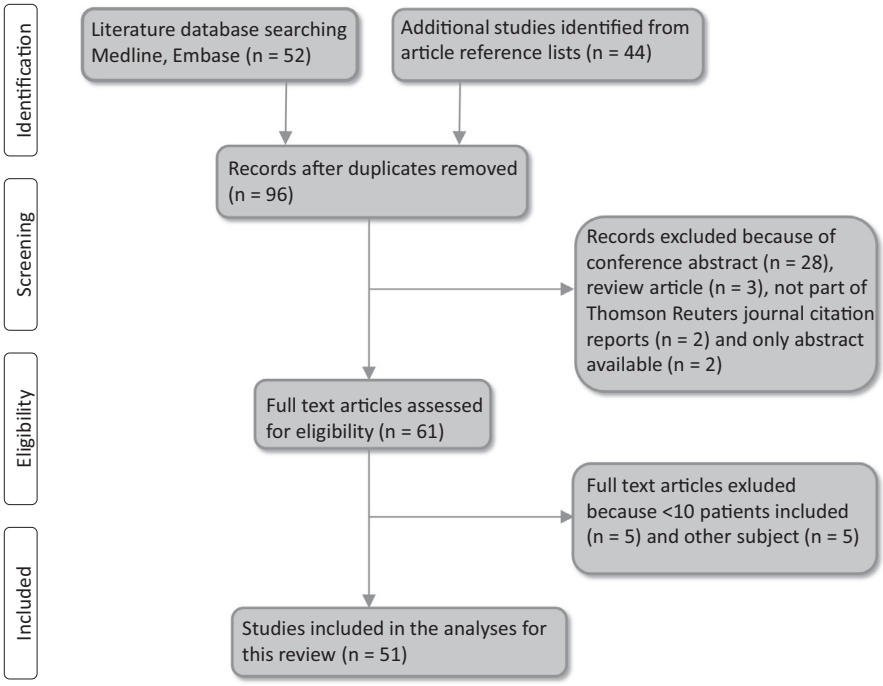

Fig. 1. PRISMA flow diagram of the literature search.

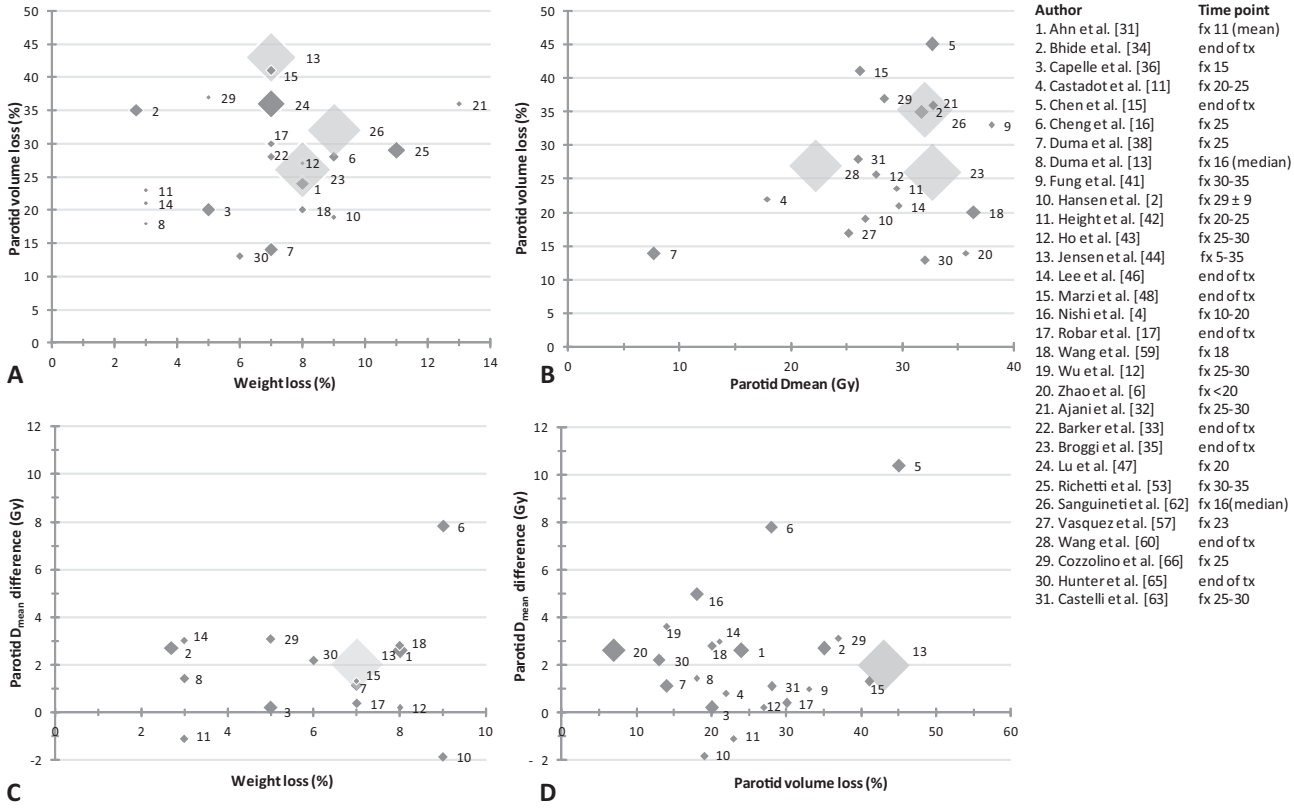

Fig. 2. (A) Parotid volume loss vs. patient's weight loss (22 studies), (B) parotid volume loss vs. planned parotid mean dose (20 studies), (C) parotid mean dose increase (repeat CT – plan CT) vs. weight loss (16 studies), and (D) parotid mean dose increase (repeat CT – plan CT) vs. parotid volume loss (23 studies) during radiotherapy. The size of the data points is proportional to the number of patients included in the study (minimum 10, maximum 87 patients). fx = fraction, tx = treatment. Time point: time of the repeat scan analysed.

Results

Literature search

Fig. 1 presents the outcome of the search strategy. Fifty-two potentially eligible records were found in MEDLINE and EMBASE, and forty-four additional papers were extracted from reference lists. We excluded twenty-eight records as they were conference abstracts, two studies because only the abstract was available [21,22], and two papers because their journal was not part of the Thomson Reuters journal citation reports® [23,24]. Furthermore, three papers were excluded as they were general reviews on image guided radiotherapy (IGRT) and ART [9,19,25]. Eventually, sixty-one full text articles were assessed for eligibility. Five of these papers did not meet the eligibility criteria since they reported on other subjects and five papers included less than ten patients [26–30]. Hence a final number of fifty-one studies could be included in the analyses for this review [2,4–7,11–18,31–68].

Reported organs at risk

In the fifty-one original studies at least one of the following organs at risk was included in the analysis: the parotid gland (PG), submandibular gland, spinal cord, spinal canal, brainstem, mandible, oral cavity, larynx, pharyngeal constrictor muscles, sternocleidomastoid muscles, masticatory muscles, masseter muscles, medial pterygoid muscles, thyroid gland, optic chiasm, optic nerve, eyeball and lens.

Timing and frequency of imaging during radiation treatment

OARs were assessed on different time points during radiotherapy (tenth fraction to end of treatment, see also Fig. 2, Table S1–S3) mainly by cone beam CT (CBCT), helical repeat CT and megavoltage CT (MVCT), but also by in-room CT [14,17,44,51] and MR imaging [52]. Two studies applied repeat MR imaging in addition to the repeat CT scans [15,16]. In most studies, the re-delineation of OARs was performed manually or automatically using deformable image registration (DIR) with visual inspection and manual corrections if needed. The frequency of imaging varied between studies. Most of the studies reported on multiple time points during radiotherapy. Fourteen studies performed at least weekly repeat imaging [7,12,17,18,37,43–46,51,53,62,63,65]. Three of these studies had daily MVCT imaging at their disposal [18,45,46], and one performed daily in-room CT imaging [7]. If results of multiple time points were reported, anatomic and dosimetric changes from the last time point were included in this review.

The authors of the different studies reported a variety of time points during treatment that could be optimal for re-scanning and re-planning. There are several indications that anatomic changes are more pronounced in the first half of treatment, and therefore repeated imaging and replanning should be performed in this first time period [34,60,62,65].

Anatomic and dosimetric changes

Twenty-six papers described both anatomic and dosimetric changes during the course of radiation [2,4,6,11–13,15–17,31,34,36,38,39,41–44,46,48,54,59,61,63,65,66]. Two studies reported on dosimetric changes without referring to anatomic changes [18,51]. Twenty studies described the relationship between several parameters and anatomic and/or dosimetric changes [4,7,11,31–33,35,36,40,43,46,48,57,59,60,62–65,68] (Table 1 and 2).

Twelve studies reported on the association between anatomic and dosimetric changes with complications and quality of life [5–7,48,50,54,55,61,63,65,67,68] (Table 3). In two of these studies, a significant reduction of side effects was found when replanning was performed vs. no replanning [5,6]. The findings of specific changes during radiotherapy and the corresponding correlations and associations are summarized per organ in the next paragraphs.

Parotid gland

The majority of the studies included anatomic and/or dosimetric changes of the parotid glands (PGs). This interest for PG changes during radiotherapy can be explained by the fact that radiation dose to the PGs was associated with reduced saliva production [69] and xerostomia [70,71].

When all studies were taken into account, the average volume decrease of the PGs during radiotherapy was 26 ± 11% (note:

Table 1
Studies reporting on parameters associated with anatomic or dosimetric changes of parotid glands during the course of radiotherapy. Only statistically significant correlations are shown. Results of Spearman correlation are denoted with ρ, Pearson correlation with R, linear regression analysis by r or r^2 and odds ratio by OR.

Study	# Pts	Parameter	Endpoint	Correlation/association	p value
Anatomic endpoints					
Ahn et al. [31]	23	Weight loss	PG volume loss	R = 0.52–0.67	n.r.
Ajani et al. [32]	13	Weight loss PG Dmean ⩾ 31 Gy vs. PG Dmean < 31 Gy	PG volume loss	ρ = 0.66	p < 0.01
Barker et al. [33]	14	Weight loss	PG centre of mass shift	ρ = 0.931, Spearman two-tailed correlation	p < 0.01
Broggi et al. [35]*	87	Weight loss	PG volume loss (cc)	OR = 0.845 (0.78–0.92), univariable analysis	p = 0.0001
		ΔBody thickness (cc)		OR = 0.181 (0.078–0.422), "	p = 0.0001
		OVP		OR = 1.191 (1.086–1.306), "	p = 0.0002
		PG V_{40}		OR = 1.038 (1.011–1.066), "	p = 0.006
		Overall treatment time		OR = 1.059 (1.018–1.100), "	p = 0.004
		Initial PG volume		OR = 1.100 (1.056–1.158), multivariable analysis	p = 0.0002
		PG Dmean		OR = 1.059 (1.003–1.118), "	p = 0.038
		PG V_{40}	PG volume loss (%)	OR = 1.034 (1.0075–1.061), multivariable analysis	p = 0.012
		ΔBody thickness (%)		OR = 0.863 (0.809–0.921), "	p < 0.00001
Fiorino et al. [40]	84	PG density decrease	PG volume loss	ρ = 0.23	p = 0.003
Ho et al. [43]	10	Weight loss	PG volume loss	ρ = 0.83	p < 0.0001
Reali et al. [64]	10	PG Dmean	PG volume loss	r^2 = 0.31, 0.41 (left, right PG)	p < 0.001
Sanguineti et al. [62]	85	Weight loss	PG volume loss	OR = 1.160 (1.04–1.29), multivariable analysis	p = 0.007
		PG Dmean		OR = 1.080 (1.01–1.17), "	p = 0.038
		Age		OR = 0.960 (0.93–0.99), "	p = 0.033
Sanguineti et al. [68]	85	Body mass index	PG volume loss	ρ = −0.234	p = 0.031
		PG Dmean		ρ = 0.258	p = 0.017
Schwartz et al. [7]	24	Weight loss	PG volume loss	n.r.	p = 0.04
Vasquez-Osorio et al. [57]	10	PG Dmean	PG volume loss	r = 0.68	p < 0.001
Wang et al. [60]	82	PG Dmean	PG volume loss	r = 0.41	p < 0.001
		SMG Dmean	SMG volume loss	r = 0.39	p < 0.001
Wang et al. [59]	15	Weight loss	PG volume loss	ρ = 0.93, 0.85 (left, right PG)	p < 0.001
Dosimetric endpoints					
Ahn et al. [31]	23	Cochlea vector increase	PG $D_{50\%}$ increase	R = 0.41	n.r.
		Mandible vector increase		R = 0.42	n.r.
		Reduction of lateral neck diameter at mandibular joint		R = 0.22–0.39	n.r.
		Reduction of lateral neck diameter at C1–C5		R = 0.17–0.28	n.r.
		Parotid volume decrease		R = 0.22	n.r.
		Weight loss		R = 0.30–0.35	n.r.
		Anatomic isocentre AP	PG $D_{50\%}$ overdose ($D_{50\%}$ > 26 Gy)	n.r.	p = 0.002
		Mandible vector, AP, SI		n.r.	p = 0.001–0.006
		Reduction of lateral neck diameter at C2–C3		n.r.	p = 0.07–0.08
Capelle et al. [36]*	20	Reduction of neck diameter mid-PTV level	Combined PG mean dose increase	ρ = 0.64	p = 0.002
Castadot et al. [11]	10	Contralateral PG shrinkage slope (cc/day)	Contralateral PG mean dose increase	0.62, correlation measure n.r.	p = 0.006
Castelli et al. [63]	15	CTV_{70} shrinkage Reduction of neck diameter	PG mean dose increase	n.r., Linear mixed effect model	p < 0.01
Hunter et al. [65]	18	PG mean dose difference first fraction (Gy)	PG mean dose difference (end of treatment)	ρ = 0.92	p < 0.001
Lee et al. [46]	10	PG COM distance decrease	PG mean dose increase	r^2 = 0.88	n.r.
		Weight loss		r^2 = 0.58	n.r.
Marzi et al. [48]	15	ΔGTV (cm^3)	PG mean dose increase	r^2 = 0.43, Stepwise multiple regression	p = 0.015
Wang et al. [59]	15	Weight loss	PG mean dose increase	ρ = 0.85	p < 0.001

Pts = patients, PG = parotid gland, ipsi = ipsilateral, contra = contralateral, n.r. = not reported, AP = anterior–posterior, SI = superior–inferior, OVP = overlap volume parotid gland and lymphnodal tumour, COM = centre of mass, OR = odds ratio (95% confidence intervals).

* Only the strongest associations were listed.

Table 2
Studies reporting on parameters associated with contour reduction (anatomic endpoints) and dosimetric changes of spinal cord and mandible (dosimetric endpoints) during the course of radiotherapy. Only statistically significant correlations are shown. Results of Spearman correlation were denoted with ρ, Pearson correlation with R.

Study	# Pts	Parameter	Endpoint	Correlation/association	p value
Anatomic endpoints					
Barker et al. [33]	14	Weight loss	External contour volume reduction at level of C2 and at base of skull	ρ = 0.917 and 0.936, respectively, Spearman two-tailed correlation	$p < 0.01$
Fiorino et al. [40]	84	PG density decrease	Absolute neck thickness reduction at C2 level	ρ = 0.27	p = 0.0005
Dosimetric endpoints					
Ahn et al. [31]	23	Mandible vector increase	Spinal cord D_{max} increase	R = 0.27	n.r.
		Reduction of lateral neck diameter at mandibular joint		R = 0.30	n.r.
		Reduction of lateral neck diameter at C4–C6		R = 0.17–0.27	n.r.
		Reduction of lateral neck diameter at mid tumor level		R = 0.18	n.r.
		ΔGTV (cm^3)	Mandible V_{60} increase	R = 0.26	n.r.
		Cochlea/incisive roll, pitch, RL, AP	Spinal cord D_{max} overdose (D_{max} > 45 Gy)	n.r.	p = 0.024–0.054
		Mandible roll, yaw		n.r.	p = 0.034
		C3–C7 vector		n.r.	p = 0.002–0.043
		C2–6 pitch		n.r.	p = 0.001–0.005
		C2–C5 AP		n.r.	p = 0.001
		Lordosis		n.r.	p = 0.001
		Anatomic isocentre vector RL	Mandible overdose	n.r.	p = 0.001–0.002
		Cochlea/incisive AP, RL, roll		n.r.	p = 0.013–0.039
		Mandible vector/yaw/roll/pitch		n.r.	p = 0.004–0.028
Capelle et al. [36]*	20	Reduction of lateral neck diameter at the level of the thyroid notch	Spinal cord D_{max} increase	ρ = 0.73	$p < 0.0001$
			Normal tissue V_{50} increase	ρ = 0.71	$p < 0.0001$
Castadot et al. [11]	10	GTV shrinkage slope (cc/day)	Spinal cord $D_{2\%}$ increase	0.75, correlation measure n.r.	p = 0.001
Nishi et al. [4]	20	ΔGTVp (cm^3)	Spinal cord $D_{2\%}$ increase	ρ = 0.91	n.r.
Wang et al. [59]	15	Weight loss	Spinal cord D_{max} increase	ρ = 0.652	$p < 0.05$

Pts = patients, PG = parotid gland, n.r. = not reported, AP = anterior–posterior, SI = superior–inferior, RL = right-left, GTVp = the volume of primary gross tumour.
* Only the most predictive parameters were listed.

volume loss reported on different time points during radiotherapy, Table S1). Some studies presented the PG shrinkage rate per treatment day or treatment week [15,33,37]. Sanguineti et al. [62] studied weekly CT scans of eighty-five patients and concluded that the PG shrinkage is not linear (PGs shrunk most during the first half of treatment).

Thirty-eight papers reported on PG anatomic changes [2,4,6,7,9,12,13,15–17,31–45,47,48,50,53,56,57,59,60,62–66]. The most common reported anatomic changes were volume loss (Table S1) and medial shifts of the PGs [17,32–34,37,42,44,45,48,51,57,59,64]. Jensen et al. [44] found a medial, cranial, and dorsal shift of the PG centre of mass from its original position. In general, a medial shift was observed of the medial and lateral aspects of both PGs [4,17,32,48,57]. Vasquez-Osorio et al. [57] reported on shape and position changes of six sub-regions of the PG. The medial translation of the inferior region of the irradiated PGs was similar to that of the lateral region (3 ± 4 mm). Fiorino et al. [40] and Belli et al. [67] found reduced PG densities during IMRT.

Twenty-four papers reported on dosimetric changes of the PGs [2,4,6,11–13,15–18,31,34,36,38,41–44,46,48,51,59,65,66]. On average, the PG mean dose increased with 2.2 ± 2.6 Gy as compared to the dose calculated on the planning CT at baseline. Not all papers reported on absolute dose values. The studies that reported the highest dose increase consisted of (a majority of) (naso)pharyngeal carcinoma patients [4,6,15,16,34,46,58]. The largest PG dose increase was found by Chen et al. [15] and Cheng et al. [16] (on average an increase of the mean dose of 10.4 Gy in the sixth week of radiotherapy, and an increase of the median dose of 7.8 Gy at the twenty fifth fraction, respectively). Both prospective studies included stage III–IV nasopharyngeal carcinoma patients.

Factors correlating with parotid gland volume loss and parotid mean dose increase. Eighteen studies reported on factors that correlated significantly with PG anatomic and/or dosimetric changes (Table 1). The most frequently reported factors were weight loss, PG dose and PG volume loss. All data available are presented in Fig. 2. On average, no clear relation between these factors and changes was found. The strongest association found was between PG dose and PG volume loss; three of the larger studies (more than eighty patients included) reported a significant correlation of PG dose with PG volume loss [35,60,62]. Still, a large variety of volume loss was observed between studies (Fig. 2B).

Details of correlations on individual study level can be found in the Supplementary Material. Table 1 includes all factors that demonstrated significant correlations ($p < 0.05$) with corresponding correlation/association measures.

Anatomic and dosimetric changes of the parotid gland and outcome. Significant associations between PG volume change and the occurrence of complications were found in five studies [7,48,55,67,68] (Table 3). In general, more PG shrinkage was associated with higher complication rates [48,67]. On the contrary,

Table 3
Studies reporting on side effects or quality of life in relation to anatomic or dosimetric alterations during radiotherapy. Only significant associations are shown. Results of Spearman correlation were denoted with ρ, linear regression analysis with r or r^2 and odds ratio by OR.

Study	# Pts	Parameter	Endpoint	Association	p-value
Anatomic parameters					
Belli et al. [67]	46	ΔPG rate (mm^3/day)	Mean xerostomia (CTC v3.0) score (treatment course) ⩾ 1.57	OR = 0.10 (0.03–0.93)	$p = 0.02$
		ΔDensity rate PG (HU/day)		OR = 0.15 (0.99–1.00), Logistic univariable analysis	$p = 0.04$
Marzi et al. [48]	15	ΔGTV (cm^3)	ΔNTCP grade 3 or higher RTOG toxicity 12 months after RT*	$r^2 = 0.609$, stepwise multiple regression	$p = 0.074$
		ΔPG (%)			$p = 0.010$
Nishimura et al. [50]	33	Initial volume of PG ΔPG (%)	Xerostomia score at 3–4 months	ρ = n.r.	$p = 0.040$
				ρ = n.r.	$p = 0.186$
Teshima et al. [55]	20	PG volume ratio post-RT/pre-RT (%)	Saliva reduction amount (g)	$\rho = -0.79$, Spearman rank correlation and Fisher exact test	$p < 0.01$
Sanguineti et al. [68]	85	ΔPG (%) mid treatment	Time to reduction of the acute xerostomia grade (CTCAE v3.0) (from ⩾grade 2 to grade 1)	HR = 1.034 (1.004–1.064), multivariable analysis	$p = 0.024$
Schwartz et al. [7]	24	PG shrinkage (%) end of treatment	Duration of PEG tube use	ρ = n.r., two-tailed nonparametric Spearman	$p = 0.025$
Senkus-Konefka et al. [54]	33	Lateral dimension changes at beam axis	Degree of mucositis	r = n.r.	$p = 0.017$
You et al. [61]	31	Weight loss >5% and/or decrease of neck diameter >10%	Acute xerostomia ⩽grade 1 vs. grade 2	n.r.	$p = 0.02$, t-test
Dosimetric parameters					
Castelli et al. [63]	15	IMRT replanning vs. no replanning in over-irradiated PG group	Xerostomia risk*	n.r.	$p < 0.01$
Hunter et al. [65]	18	PG Dmean (planned)	Stimulated selective PG salivary output 6 months post-treatment (cc/min)	$\rho = -0.55$	$p < 0.0007$
		PG Dmean (delivered)		$\rho = -0.57$	$p < 0.0004$
Yang et al. [5]	129	IMRT replanning vs. no replanning	Global quality of life**	n.r.	$p = 0.012$, ANOVA
			Speech problems	n.r.	$p = 0.000$
			Trouble with social contact	n.r.	$p = 0.000$
			Teeth	n.r.	$p = 0.031$
			Opening mouth	n.r.	$p = 0.000$
			Dry mouth	n.r.	$p = 0.000$
			Sticky saliva	n.r.	$p = 0.015$
Zhao et al. [6]	33	$T_xN_{2,3}$ replanning vs. no replanning	Mucosa	n.r.	$p = 0.05$, Mann Whitney Wilcoxon
			Xerostomia	n.r.	$p = 0.04$

* Hypothetical difference in NTCP, assessed by LKB model.
** EORTC QLQ-C30 scales role functioning, social functioning, dyspnoea, appetite loss, constipation and diarrhoea all statistically significant. PG = parotid gland, Pts = patients, n.r. = not reported, OR = odds ratio (95% confidence intervals).

Sanguineti et al. [68] observed that the patients who received mean doses over 35.7 Gy to the PG developed more physician-reported GR2+ xerostomia if the shrinkage of the combined volume of parotid glands was lower than 19.6%. Nishimura et al. [50] found out that the patients with initially small parotid glands (⩽38.8 ml) had significantly more severe xerostomia three to four months after the start of IMRT than patients with initially larger parotid glands ($p = 0.040$), while the correlation between the shrinkage of PG and the grade of xerostomia was not significant ($p = 0.186$) (Table 3). Belli et al. found that apart from volume decrease, also early density decrease was associated with significantly higher acute xerostomia scores (Table 3). Weight loss >5% and/or decrease of neck diameter >10% was associated with higher xerostomia scores in the study of You et al. [61]. Hunter et al. concluded that dosimetric changes were small relative to the standard deviations of the dose and saliva flow data [65].

Yang et al. [5] studied global quality of life in addition to the different side effects for IMRT replanning vs. no replanning, and reported better quality of life and less side effects for the IMRT replanning group (Table 3).

Submandibular glands

In contrast to the parotid glands, information on anatomic and dosimetric changes of the submandibular glands is scarce. On average, a submandibular gland volume reduction of 22% (15–32%) was found [37,57,60]. Wang et al. [60] found a significant correlation between the planned submandibular gland dose ($r = 0.389$, $p < 0.001$) and submandibular gland volume reduction, while no such correlations were found by others [57]. Irradiated submandibular glands tend to move superiorly, in particular the caudal and lateral sub-regions with displacements of on average 3–4 mm [57]. Similar results were found by Castadot et al. [11]. These authors also observed superior as well as medial shifts of the submandibular glands. In this study, the mean approximated actually delivered doses to the submandibular glands increased compared with the planned doses (52.8 vs. 51.9 Gy) (Table S3).

Brainstem and spinal cord

A number of authors reported on changes in maximum doses or $D_{1\%}$ to the brainstem [2,6,15,16,18,31,34,41–43,59] and the spinal cord [2,6,11,13,15,16,18,31,34,36,41–43,59,66] during the course of treatment (results are listed in Table S3). Zhao et al. [6] found the highest dose increase in $D_{1\%}$ of the spinal cord and the brainstem of on average 0.20 and 0.09 Gy per fraction, which would result in an accumulated excess dose of 5.6 and 2.5 Gy, respectively, for the entire treatment course. Cheng et al. [16] reported that if no replanning was performed, for 11% and 16% of the patients the tolerance dose of 54 Gy for the maximum dose to the brainstem was exceeded after 30 and 50 Gy, respectively, and for 11% of the patients the maximum dose to the spinal cord was higher than 45 Gy after both 30 and 50 Gy.

Factors correlating with brainstem and spinal cord dose increase. A number of variables correlated significantly with an increase in

dose parameters ($D_{2\%}$, D_{max}) to the spinal cord, including changes in GTV volume, weight loss, change in neck diameter at the level of the thyroid notch and a few other anatomic, CT related variables (Table 2).

Other organs at risk

The results of studies regarding anatomic and/or dosimetric changes of the larynx, masseter muscle, medial pterygoid, pharyngeal constrictor muscles, sternocleidomastoid muscles, masticatory muscles, thyroid gland, mandible, submandibular glands, oral cavity, optic chiasm, optic nerve, eyeball, lens and cochlea are listed in Tables S2 and S3, respectively [2,11,13,16,18,31,49,52,53,66]. Clear swelling of the larynx and pharyngeal constrictor muscles was found by Ricchetti et al. [53] at week seven of radiotherapy. Swelling of the larynx was also reported by Cozzolino et al. [66], five weeks after the start of radiotherapy. Popovtzer et al. [52] observed a thickness change of +111% in parts of the pharyngeal constrictors that received more than 50 Gy, three months post chemoradiation. However, the thickness and volume of the sternocleidomastoid muscles decreased [52,53].

In most publications, only small changes in the mean dose (<1 Gy) to organs at risk during the course of radiotherapy have been reported [11,13,18] (Table S3). Dosimetric changes to e.g. the mandible are more often caused by head rotation instead of anatomic changes [12]. In contrast, a rather large increase in maximum and $D_{1\%}$ was found by Cheng et al. [16] for some organs after 30 and 50 Gy, with the largest dose increase for the optic nerves after 50 Gy (D_{max} increase from 48.5 ± 4.5 to 56.3 ± 5.0 Gy (ipsilateral) and from 26.7 ± 16.1 to 36.9 ± 20.8 Gy (contralateral) (mean ± SD)) (Table S3). This means that for individual cases, the maximum dose to the optic nerve could have been >60 Gy if no replanning was performed, with a markedly increased risk of toxicity as a consequence [72].

Discussion

This is the first review that focused on anatomic and dosimetric changes of head and neck organs at risk during the course of radiotherapy and on the correlation of these changes with side effects. In total, fifty-one papers on this subject were identified according to the PRISMA methodology [20].

The parotid gland was the most studied OAR and showed the largest volume changes during radiotherapy (26% average volume decrease). The dosimetric consequences of PG shrinkage varied widely, with on average a PG mean dose increase of 2.2 ± 2.7 Gy. Only a few studies investigating volume changes of the submandibular glands were found. This could be explained by their location, encompassed by neck lymph node level IB and in close proximity to the frequently irradiated neck lymph node level II. This complicates their sparing and results in high initial submandibular gland doses, possibly less sensitive for dosimetric variations.

Introduction of adaptive radiotherapy

ART for head and neck patients is currently subject to many studies. Theoretically, ART could be performed by adapting treatment plans to the actual patient anatomy on a daily basis. Yan and Liang showed in a retrospective planning study of nineteen patients that weekly adaptive inverse planning optimization already improved the dose distribution of head and neck cancer treatment significantly [8]. Chen et al. [73] suggested from their retrospective study that for appropriately selected patients the theoretical benefits i.e. improved dose distributions of ART may be associated with actual clinical advantages. The authors also concluded that routine replanning is probably not necessary. This is confirmed by our own experience, based on weekly repeat CT scans, showing that in less than 20% of all head and neck patients replanning was needed because of target underdosage or OAR overdosage, usually during the first three weeks of treatment (personal communication).

Only limited data are published so far on the effect of dosimetric changes on the occurrence of side effects or quality of life (current review, Table 3). The optimal frequency and utilization, as well as the ultimate clinical impact of ART still remain to be determined [9,14,25]. There are several indications that anatomic changes are more pronounced in the first half of treatment, and therefore repeated imaging and replanning should be performed in this first time period [34,60,62]. Schwartz et al. [14] conducted a prospective clinical trial, and concluded that properly timed replanning could result in dosimetric improvement, but that the clinical impact of ART remains to be confirmed. Dawson and Sharpe [25] stated that increased precision and accuracy of radiotherapy are expected to augment tumour control and reduce the incidence and severity of toxic effects after radiotherapy. On the other hand, they mentioned that the desire for sub-millimetre technical precision needs to be balanced with risk of chasing only modest clinical gains and the possibility of imposing an unacceptable workload on radiotherapy planning, delivery, and review processes. There are limited resources at most radiotherapy departments, and identification of patients that benefit from ART would restrict the workload tremendously and thus would be more cost-effective. Results of future prospective clinical trials linking anatomic and dosimetric changes to outcome are needed to confirm the clinical impact of ART.

Application of selection criteria for ART

The potential selection criteria for PG volume loss identified in the current review that may improve the selection of patients for ART prior to treatment were 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 PG with lymph node metastases. PG volume loss is in this case presumed to result in higher complication rates [48,55,67] (Table 3). This could be due to an increase in PG dose, or to a direct relationship between PG volume and complications [67,68]. For the majority of patients, PG volume loss resulted in an increase of the mean dose to the PGs (Fig. 2D). However, we could not confirm a clear association between volume loss and mean dose increase (Fig. 2D). This can be explained by the fact that the treatment plan and consequential dose distribution depend on many factors such as the location of the boost volume.

Apart from selection of patients prior to treatment, selection during treatment could be performed, based on either detected changes or by parameters related to these changes. Weight loss, change in body thickness, reduction of lateral neck diameter, PG volume decrease, PG density decrease, distance between PG centres of mass and GTV volume decrease turned out to be potential selection criteria for either PG volume loss, increase of the PG dose and/or differences in the degree of side effects (Tables 1 and 3). Considering the other OARs, weight loss and GTV volume decrease during radiotherapy positively correlated with the maximum dose to the spinal cord (Table 2), and lateral dimension changes at beam axis correlated well with the degree of mucositis [54].

The difficulty with most of the potential selection criteria found in this review to select patients for ART is that although statistically significant associations were found with anatomic and/or dosimetric endpoints, these were generally weak (Tables 1 and 2). Moreover, most potential selection criteria resulted from correlation tests, although regression analysis is more suitable to investigate the

predictive power. Furthermore, some authors reported Pearson correlation coefficients, although normal distribution of the data and the linear relationship between variables was not proven. If a non-linear but monotonic relationship between variables is observed, the Spearman correlation should be used.

To enable proper selection of patients for re-planning, multivariable prediction models are needed, derived from sufficiently powered prospective study populations. Most studies in this review consisted of limited patient populations and were therefore not suitable for model development. The performance of such models should be sufficient to identify patients that need ART with high sensitivity and specificity.

Bias in individual studies

It is likely that the large heterogeneity in results as depicted in Fig. 2 can be explained by differences between study designs, such as different patient and tumour characteristics (localization, staging), differences in timing of repeated imaging, treatment (combination with surgery/chemotherapy), treatment technique (IMRT or tomotherapy), margins, specific settings of the radiotherapy treatment planning, and patients' nutritional status.

Another problem in the comparison of the results of the different studies is that different types of analysis were used, and results were reported in different quantities (e.g. volume changes in % or cm^3, dose changes in % of prescribed dose or in Gy). Also, individual patient data and standard deviations of the differences were often lacking. These aforementioned differences in study design and the variation in methods of analysis and reported quantities are one of the most common problems in systematic reviews of prognostic studies [74]. It is therefore not possible to perform a meta-analysis, but it is a strong argument in favour of systematic reviews [74]. On the individual study level, random allocation of patients is seldom performed. Often, detailed study inclusion criteria are lacking, and some of the studies are retrospective, most likely selecting patients that suffer most from anatomic and dosimetric changes during treatment. Two studies from China investigated the effect of replanning on quality of life [5,6] (Table 3). In both studies, significant lower incidences of side effects were found in the replanning group with respect to the no replanning group. Conversely, patients were not randomly allocated to the different treatment groups, and therefore differences in these specific studies might be explained by other factors such as differences in socioeconomic status between the two populations [75].

Inaccuracies in the calculation of dosimetric changes

Two factors of inaccuracy in the ART chain that influence the accuracy of the calculation of dose on repeat imaging are contouring variability and the dose recalculation procedure on (MV)CBCT. Earlier studies showed that the coefficients of variance for contouring OARs varied between 12% and 16% [76] resulting in dose differences of on average 3.5 Gy [77]. Automatic contouring on MVCBCT was found to be comparable to inter-observer uncertainty in delineating parotid glands on CT [78]. Morin et al. [79] showed that dose calculation on MVCBCT could be performed within a 3% / 3 mm accuracy. In kV-CBCT imaging the dosimetric error depends on the HU adjustment technique and imaging artefacts. For the spinal cord D_{max} the error could be >5% [80]. Some dose differences found in this review are thus in the same order of magnitude as differences that could be introduced because of contouring variability or dose calculation inaccuracy. For instance given a mean dose of 30 Gy to the PG, a deviation of 3% would result in a deviation of 0.9 Gy. We should therefore pay attention to select the most accurate and reproducible segmentation and dose calculation procedures to most accurately predict actual given doses.

Conclusions

Despite the relatively large number of studies published so far, the heterogeneity between studies prevented unambiguous conclusions on how to select patients for adaptive radiotherapy in head and neck cancer. Still, a number of potential selection criteria for anatomic and dosimetric changes were identified that could be included in well-designed and well-powered studies on anatomic and dosimetric changes during radiotherapy, including 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. There is a need for larger prospective studies including assessment of anatomic and dosimetric changes, and to identify possible relationships between these changes and outcome. Moreover, we hope to draw attention to the paucity of good quality data on this subject so far, and therewith improve the quality of future research.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2015.05.018.

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