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REVIEW

Adaptive radiation therapy in head and neck cancer for clinical practice: state of the art and practical challenges

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Abstract Modern radiation therapy techniques are characterized by high conformality to tumor volumes and steep dose gradients to spare normal organs. These techniques require accurate clinical target volume definitions and rigorous assessment of set up uncertainties using image guidance, a concept called image-guided radiation therapy. Due to alteration of patient anatomy, changes in tissue density/volumes and tumor shrinkage over the course of treatment, treatment accuracy may be challenged. This may result in excessive irradiation of organs at risk/healthy tissues and undercoverage of target volumes with a significant risk of locoregional failure. Adaptive radiation therapy (ART) is a concept allowing the clinician to reconsider the planned dose based on potential changes to accurately delivering the remaining radiation dose to the tumor while optimally minimizing irradiation of healthy tissues. There is little consensus on how to apply this concept in clinical practice. The current review investigates the current ART issues, including patient selection, clinical/dosimetric criteria and timing for re-planning, and practical technical issues. A practical algorithm is proposed for patient management in cases where ART is required.

Keywords Adaptive radiation therapy · Head and neck squamous cell cancer · Anatomy · Dose · Image guided radiotherapy (IGRT) · Replanning

Introduction

Recent advances in radiation therapy technologies, such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT), allow accurate radiation delivery to the tumor. However, the steep dose gradients

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achieved with highly conformal techniques may be a double-edged sword as any change in patient anatomy and/or tumor volume may result in an excessive radiation dose to the normal organs and decreased dose to the tumor. Several factors may result in set-up uncertainties and a potentially decreased therapeutic ratio such as patient repositioning on the treatment table, weight loss, tumor and lymph node shrinkage, tissue swelling and lymphedema, and alteration of fat distribution. When such changes are considered dosimetrically and clinically significant, the radiotherapy plan should be quickly adapted during the course of treatment (with treatment interruption as short as possible to avoid tumor repopulation). Replanning then aims at avoiding potential tumor undercoverage induced by tumor shifting outside of the high dose area and/or an excessive radiation dose to the organs at risk (OAR) that may lead to long-term complications.

As imaging has been improving, a more accurate delineation of clinical target volumes based on CT scanners, magnetic resonance imaging (MRI) and/or positron emission tomography (PET) scans has been achieved. One might be tempted to reduce the "security margins" applied around the clinical target volumes to create smaller planning target volumes (PTVs) to decrease treatment toxicity. However, this must not be considered without adequate repeated in-room imaging procedures to verify that the dose is correctly delivered spatially (IGRT) and also over time from the start to the end of the radiotherapy course (ART). Adaptive radiation therapy (ART) may be viewed as an evolution of IGRT that accounts for the time dimension in addition to spatial dose delivery assessed and corrected by IGRT.

The concept of ART was introduced in the era of two-dimensional (2D) radiotherapy when clinicians were adjusting radiation fields based on clinically observed tumor and/or nodal shrinkage [1, 2]. Daily (or at least once weekly after three correct daily set-ups) imaging with either a megavoltage CT scan (MVCT) or kilovoltage CT scan (kVCT) or cone beam CT (CBCT) enables visualization of the tumor volume, adjacent OAR and patient contours, thus alerting the clinician about the need for re-planning. However, even though the concept of ART is appealing, a consensus is still lacking as for decision thresholds, technical means and practical limitations in head and neck squamous cell carcinomas (HNSCC). In addition, identification of patients who may benefit the most from ART may be expensive. Thus, the clinician should be aware of the limitations of ART in order to tailor an individual approach depending on the tumor response to treatment.

The aim of this review of the literature is to present ART in HNSCC and to propose an algorithm for patient management in clinical practice.

Adaptive radiation therapy in head and neck cancers

IGRT modalities

ART relies on the daily detection of tumor volume reduction and normal tissue changes throughout the treatment course in order to undertake corrective measures, when necessary. Many imaging systems have been introduced for head and neck cancers as such changes are quite frequent in head and neck tumors.

Verification of patient setup may be performed by kV or MV 2D or 3D imaging systems. Two-dimensional portal images allow identification and fusion of bony structures, which accurately verify the patient treatment position. However, with this technique, tumor volume and soft tissue changes cannot be visualized. This limitation inherent to the technology represents a challenge to the implementation of ART. A diagnostic CT scan for re-planning during treatment may be performed to overcome the lack of daily tumor and soft tissue visualization. Three-dimensional IGRT allows the visualization of soft tissues and direct registration of bony and/or soft tissue structures. IGRT can be performed with in-room kVCT, MVCT or CBCT. The daily pre-treatment CT scan can be compared to the planning CT scan to assess variations of the external contours, target volumes or OAR. The magnitude of the structure changes can be assessed by the clinician who determines whether re-planning is needed to avoid excessive irradiation to critical OAR or undercoverage of target volumes.

Although the quality of MVCT images is generally inferior to kVCT images, both modalities provide adequate soft tissue resolution for ART. In patients with dental fillings, MVCT produces fewer dental artifacts that may obscure the adjacent tumor volume than kVCT.

Setup errors may be corrected on-line (in real time IGRT while the patient is on the couch, without postponing the treatment) with correction of systematic and random errors. However, delineation and dosimetry times do not allow on-line re-planning. Offline strategies (between fractions) are more practical, e.g., less time consuming on the treatment couch, in clinical practice but only correct for systematic errors (and not random ones). Clinical implementation of on-line ART is time consuming and would require that the patients wait for their treatment replanning to have their fraction on the very same day. However, the current treatment planning processes, which include region-of-interest (ROI) delineation either manually or on an atlas-based image segmentation basis, followed by remaining dose recalculation and total dose sum-up, still takes a few hours. It is thus rarely feasible in the busy clinics. It is possible for clinical volumes to be mapped on daily on-line images

Table 1 Reduction of target volumes and dose changes associated with volume reduction during head and neck cancer irradiation

Study	Target volume reduction	Doses changes
Barker et al. [5]	Mean GTV *T*: 1.7% (0.8–3.1%)/day	Not specified
	N: 1.7% (0.2–2.7%)/day	
	Median GTV reduction: 70% (10–92%)	
Loo et al. [6]	Mean CTV 54 reduction: 10.7% (5.5–18.4%)	Increase in CTV 54 dose: 1.9%
	Mean CTV 60 reduction: 7.1% (0–22%)	Increase in CTV 60 dose: 2.4%
	Mean CTV 68 reduction: 5.8%	Increase in CTV 68 dose: 1.3%
Castadot et al. [7]	Mean GTV *T*: 3.2%/day	Not specified
	Mean GTV *N*: 2.2%/day	
	Mean CTV *T*: 2.6%/day	
	Mean CTV *N*: 1.5%/day	
Yang et al. [8]	Mean GTV reduction rate	Not specified
	Oropharyngeal cancer: 43% (1.4–73%)	
	Hypopharyngeal cancer: 33% (1.1–79%)	
Hansen et al. [9]	Mean PTV (CTV): 7.5%	Decrease in D95 PTV(GTV): 7%
		D95 PTV(CTV): 1%
Bhide et al. [10]	Mean CTV1: 3.2%	Increase in CTV1 dose: 35%
	Mean CTV2: 10.5%	Increase in CTV2 dose: 42%
Mechalakos et al. [11]	Mean PTV: 45%	No significant change
Bando et al. [12]	Mean GTV: 28%	Not specified
Chen et al. [13]	Not investigated	Increase in PTV dose: 1.9–2.9%
		Increase in CTV dose: 1.8–2.9%
Duma et al. [14]	Mean PTV: 4%	Increase in PTV dose: 3%
Chen et al. [15]	Mean GTV: 14.7%	No significant change

CTV clinical target volume, *CTV1* clinical target volume covering gross tumor volume and lymph node, *CTV2* clinical target volume covering microscopic disease, *CTV 68* clinical target volume covering gross tumor and high-risk areas, *CTV 60* clinical target volume covering intermediate-risk areas, *CTV 54* clinical target volume covering low-risk areas, *GTV* gross tumor volume, *PTV* planning target volume, *PTV* (*CTV*) planning target volume of clinical target volume, *PTV* (*GTV*) planning target volume of gross tumor volume, *T* tumor; lymph node

using automatic deformable image registration [3, 4], and calculation times will make such procedures feasible in the near future.

Determination of anatomic modifications during radiation therapy

Significant dose modifications are suspected when patients present with weight loss of 10% or more compared to their baseline weight and/or with significant reduction of the tumor volume (Table 1). Radiation therapists may also notice that the immobilization mask no longer fits the patient's face because of weight loss and/or tumor shrinkage. When these situations arise, it is usually necessary to request a new planning CT scan.

When the planning CT scan is repeated, the patient must be in an identical position to the one performed at the initial planning CT. A new thermoplastic head and neck mask is made to fit the patient's skin and avoid movements within the mask in case of weight loss, for example. The new CT scan is transferred to the treatment planning system for re-planning. However, there is controversy on how to delineate target volumes on the new CT scan: some advocate only adjusting tumor contours on air without shrinking the initial tumor volume, while others advocate accounting for tumor shrinkage. Analysis of the patterns of failure following re-planning may help define future recommendations.

Analysis of anatomic changes and subsequent dose modifications of target volumes and OAR in the literature

Target volumes

Most authors reported a reduction of tumor and lymph nodes volumes during radiation therapy [5–15] (Table 2). Barker et al. reported that gross tumor volumes (GTVs) decreased throughout the course of fractionated radiation therapy at a median rate of 0.2 cm^3 per treatment day in 14 patients. This led to a median total relative loss of 69.5% of the initial GTV (range 10–92%) (Fig. 1). Figure 1 shows target volumes as defined by the ICRU (International

Table 2 Modifications of the volume and dose of the organs at risk during head and neck cancer irradiation

Study	Organs	Volume changes	Dose changes
Barker et al. [5]	Parotid	Median reduction: 0.19 cm^3/day	Not specified
Loo et al. [6]	Parotid	Mean volume reduction	Mean dose increase
		Ipsilateral: 30.2%	Ipsilateral: 8.9%
		Contralateral: 17.5%	Contralateral: 19.3%
	Spinal cord	No change	Mean dose increase: 0.5%
	Patient contour	Mean volume reduction: 350 ml	Not specified
Castadot et al. [7]	Parotid	Not specified	Not specified
	Submandilular gland	Ipsilateral: 1.5%/day	Not specified
		Contralateral: 1.3%/day	
Hansen et al. [9]	Parotid	Mean volume reduction:	Mean dose increase:
		Right: 15.6%	Significant only for right
		Left: 21.5%	Parotid
	Spinal cord	Not specified	Mean maximum dose increase: 4.5 Gy
	Brain stem	Not specified	Mean maximum dose increase: 3.1 Gy
Bhide et al. [10]	Parotids	Mean volume reduction: 14.7%	Ipsilateral: 2.7 Gy increase
			Contralateral: not significant
Bando et al. [12]	Submandibular glands	Mean volume reduction:	Not specified
		Right: 30%	
		Left: 27%	
	Neck	7% volume loss	Not specified
Duma et al. [14]	Parotid	Mean volume reduction:	Median dose increase
		Right; 17%	Right: 9%
		Left: 2%	Left: 4%
	Spinal cord	Not specified	Maximum dose increase: 1%
	Larynx	Not specified	Median dose increase: 2%
	Oral cavity	Not specified	Median dose increase: 2%
Chen et al. [15]	Parotid	Mean volume reduction:	Mean dose increase:
		Right: 6.7%/week	Right: 11 Gy
		Left: 6.5%/week	Left: 9.8 Gy
Robar et al. [16]	Parotid	Mean volume reduction	Mean dose:
		Right: 5%/week	Reduction: 5.6% (right)
		Left: 4.7%/week	Increase: 6.4% (left)
Wang et al. [17]	Parotids	Mean volume reduction: 20%	Not specified
	Submandibular glands	Mean volume reduction: 11.4%	Not specified
Lee et al. [18]	Parotids	Median volume loss: 21%	Not specified
Wu et al. [19]	Parotid	Mean volume reduction:	Mean increase:
		Right: 14%	Right: 10%
		Left: 12%	Left: 10%
	Spinal cord	Not specified	No change
	Brain Stem	Not specified	No change
	Mandible	Not specified	No change
Vasquez Osorio et al. [20]	Parotid	Mean volume reduction:	Not specified
		Ipsilateral: 17%	
		contralateral: 5%	
	Submandibular gland	Mean volume reduction:	Not specified
		Ipsilateral: 20%	
		Contralateral: 11%	

Table 2 continued

Study	Organs	Volume changes	Dose changes
Ballivy et al. [21]	Parotid	Not specified	Mean dose increase: Ipsilateral: 2–3 Gy Contralateral: 1–1.5 Gy
	Spinal cord	Not specified	Maximum dose increase: 2 Gy
	Brain stem	Not specified	Maximum dose increase: 2 Gy
	Larynx	Not specified	Mean dose increase: 2.8 Gy
	Mandible	Not specified	Maximum dose increase: 1 Gy
Cazoulat et al. [22]	Parotids	Not specified	Mean dose increase: 12%
Ricchetti et al. [23]	Parotids	Mean volume reduction Ipsilateral: 31.9% Contralateral: 26.4%	Not specified
	Submandibular glands	Mean volume reduction: Ipsilateral: 26.9% Contralateral: 19.7%	Not specified
	Larynx	Mean volume increase: 15.7%	Not specified
	Constrictor muscles	Mean volume increase: 16.9%	Not specified
	SCM	Mean volume reduction: Ipsilateral: 8.4% Contralateral: 7.8%	Not specified
	Masticator muscles	Mean volume reduction: Ipsilateral: 5.9% Contralateral: 8.2%	Not specified
	Thyroid	Mean volume reduction: 8.7%	Not specified

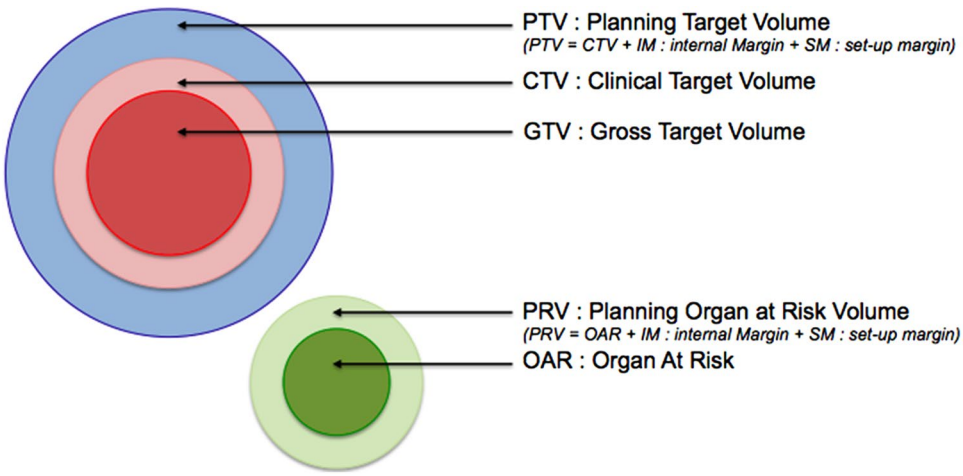

Fig. 1 Volume is defined by the International Commission on Radiation Units and Measurements (ICRU)

Commission on Radiation Units and Measurements). In studies where CT scans were performed weekly during treatment, changes in tumor volumes were observed across the entire treatment period. Barker et al. [5] reported that these changes were more significant in the second half of the treatment (after weeks 3–4). However, Hansen et al. [9] observed major modifications within the 2nd week of treatment. Bando et al. [12] also reported that the GTV was reduced to 28% of its initial size within the first 3 weeks of chemoradiation.

In patients with weight loss, the dose to the GTV and planning target volume (PTV) surrounding the GTV may change significantly [13]. Duma et al. [14] reported an increase in dose within the PTV induced by soft tissue change of more than 5 mm. A PTV dose increase was also reported in other studies during head and neck radiation

therapy [6, 10]. However, Hansen et al. [9] observed lower dose and decreased PTV coverage during treatment. Another study did not report a correlation between tumor shrinkage and PTV dose change [15]. Thus, ART should be individualized for each patient. The dose to the neck target volumes may also change during radiation therapy [15].

Organs at risk

Table 2 summarizes OAR volume modifications during head and neck cancer radiation therapy and their impact on the cumulative received dose [5–23].

Salivary glands Parotid and submandibular gland volume frequently decreased during treatment. The parotid volume shrinkage may reach its maximum during the 2nd week and tends to stabilize after the 5th week [10]. At the end of the treatment, the parotid volume loss is estimated to be 26–30% [5, 6, 17, 18, 23] (Table 2). The parotid glands tend to retract and deform, and the parotid center migrates toward the mid line [5, 16, 18]. The parotid gland volume reduction is more important on the side ipsilateral to the tumor [6, 20]. Because of limited patient numbers in these studies, definite conclusions cannot be drawn as to whether the relative sparing of the contralateral parotid gland may be related to a lower dose [10, 21]. Parotid gland displacement is correlated with weight loss, mean parotid dose and regression of lymph node volumes, which push the parotids into the high dose area [5, 20, 24]. Radiation dose to the parotid glands increases significantly during the treatment course, thus emphasizing that re-planning may lead to reduction of normal salivary gland irradiation and potentially improving patient quality of life [6, 9, 10, 14–17, 21, 22]. Whether ART corrects xerostomia remains to be assessed as only patients with a significant increase of mean parotid gland dose (>4 Gy) are likely to benefit from re-planning [25].

During radiation therapy, the submandibular glands also decrease in size and change in shape [7, 12, 17, 20, 23]. The ipsilateral submandibular gland frequently receives a higher dose because of its close proximity to the tumor and moved upwards [7, 20]. Submandibular volume reduction ranges from 11 to 30% [12, 20].

Spinal cord and brainstem The spinal cord and the brainstem volumes do not change during irradiation, but their position may shift in relation to the external contour because of weight loss [6]. As a result, the radiation dose to the spinal cord may increase [6, 9, 14, 21]. The dose increase is usually minor, but in case of severe weight loss and/or major tumor shrinkage, it may become significant and require re-planning [9].

Little or no significant dose variation has been reported during treatment on other normal organs such as the larynx, mandible and oral cavity [14, 19, 21]. The larynx and constrictor muscle volumes increase slightly during radiation therapy in relation with edema. Other muscles such as the masticator and sternocleidomastoid decrease in volume most likely because of weight loss [23]. However, such changes were not found to mandate replanning.

External contours HNSCC radiation therapy quite often induces severe mucositis resulting in significant weight loss. Patient external contour may change because of weight loss and reduction of the subcutaneous fat [6, 12]. The dose change observed in the OAR may result from patient external contour changes. More prospective studies are mandatory for accurate quantification.

Optimal timing for adaptive therapy

Most conventional head and neck radiation therapy schemes occur over 7 weeks. Optimal time for ART aims at maintaining proper target volume coverage as initially prescribed while ensuring the dose to the OAR below that associated with a probability of complication. This assumption requires that the tumor and OAR volumes decrease at the same pace during treatment. Ricchetti et al. reported a significant reduction of OAR volume after the 1st treatment week, while the largest average tumor volume reduction occurred after the 5th week in patients with oropharyngeal cancer undergoing IMRT with concurrent chemotherapy [23]. Wang et al. [17] also noticed that the average rates of volume reduction of the parotid and submandibular glands in the first 3 weeks of radiation therapy were larger (20 and 11.4%, respectively) than within the last 3 weeks of treatment (8.5 and 6%, respectively). Bhide et al. [10] observed a significant reduction of CTV volume at week 2 but the largest parotid gland volume reduction occurred at week 4. Barker et al. [5] also reported significant reduction of the parotid and submandibular gland volumes after 3 or 4 weeks of treatment. These conflicting reports suggest that the decision to re-plan should be based on clinical judgment. Tumor response to treatment and the radiosensitivity of normal tissues may vary from one patient to another. During the treatment, daily or weekly CT scans may identify patients who require re-planning, but it is time-consuming and increases the radiation dose received by the patients.

Identification of patients who benefit from ART

Capelle et al. [26] assessed the benefit of routine re-planning in 20 HNSCC patients who had either definitive or postoperative chemoradiation. Patients with severe weight loss, significant reduction of the neck volume and advanced T stage were more likely to benefit from ART

because of the increased radiation dose to the normal tissues. Jensen et al. [27] also reported a benefit of ART in patients with severe weight loss during head and neck radiotherapy. In a study including 31 patients who underwent radiation therapy with daily MVCT, a benefit of ART to reduce the rate of grade 2 xerostomia was shown in those who had more than 5% weight loss and/or more than 10% of neck diameter decrease [28]. As the patients who developed weight loss and neck volume reduction may also experience set-up uncertainties, they are at risk for a further increased radiation dose to the spinal cord; these criteria may serve as guidelines for clinicians to develop an algorithm for ART [29].

Definition of volumes on re-planning CT scan

The soft tissue resolution of in-room MVCT, CBCT or kVCT is inferior to a diagnostic CT scan. In addition, the lack of contrast agent makes it difficult to delineate the GTV and lymph nodes for re-planning. As an illustration, Mencarelli et al. [30] reported that the deformable image registration (DIR) process to outline the GTV during treatment is less precise than delineating the borders of the tumor with gold markers before treatment. The precision of DIR also deteriorated significantly during treatment. The limitations of DIR to outline precisely the GTV were also reported in another study where two methods of DIR were compared to physician's delineations on repeat diagnostic CT scans during treatment [31]. Dosimetric coverage of the GTV by DIR was inferior to manual delineation and may lead to local recurrence [32]. Thus, given the uncertainty of outlining the GTV by DIR, a new planning CT scan is required if ART is necessary. However, even when there is significant GTV reduction during treatment, there are no data about the microscopic extension of the tumor within the previous pre-treatment GTV. Expert physicians recommend that the GTV and CTV should not be changed regardless of tumor response (NCT01874587). These precautions may be necessary to avoid in-field failures secondary to marginal miss. Prospective studies should be done in the future to assess the impact of tumor volume reduction on ART.

The major advantage of DIR over manual contouring is the time efficiency to outline the OAR and the reduction of inter- and intra-observer variability of manual contouring [33]. However, DIR may overestimate OAR volume changes during treatment and may lead to unnecessary ART [34]. In addition, even though the automatic contouring workflow is shorter than the manual contouring process, manual correction of the volumes of interest is frequently required [35].

There is currently no consensus on the optimal method of DIR for ART. Many algorithms have been introduced and have their own limitations. Atlas-based segmentation

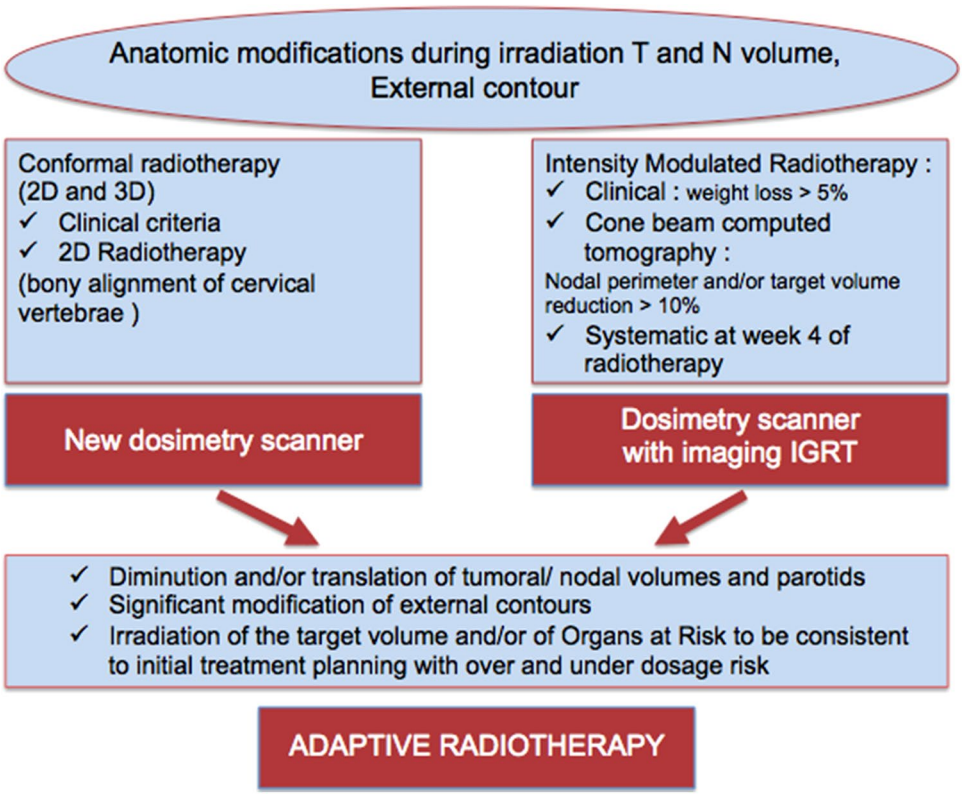

Fig. 2 Conditions of adaptive radiation therapy. *IGRT* image-guided radiation therapy

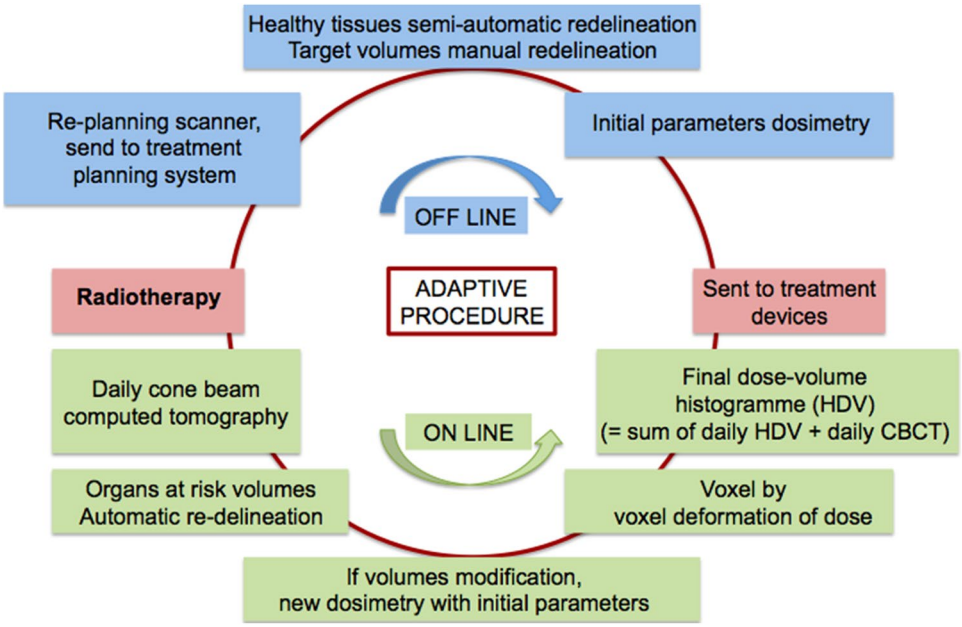

Fig. 3 Procedures for an offline adaptive radiation therapy (currently applicable) and on-line (to be made available in the near future). *CBCT* cone beam computed tomography

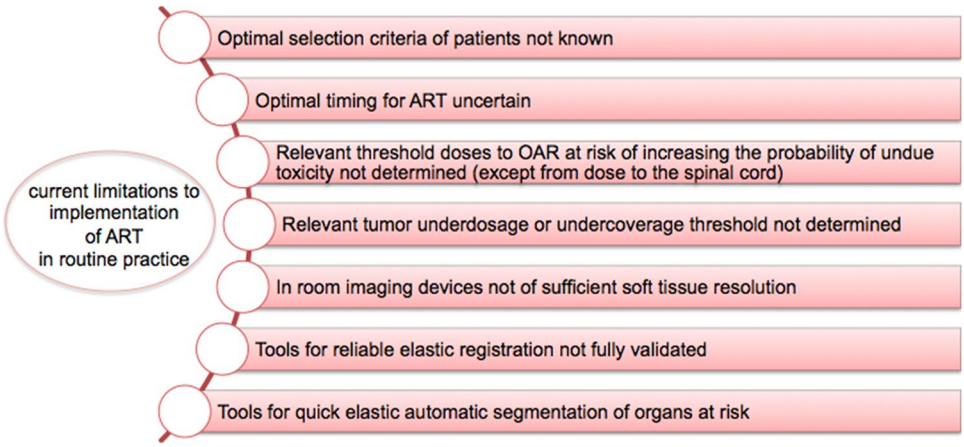

Fig. 4 Current limitations to implementation of adaptative radiation therapy in routine practice. *OAR* organs at risk, *ART* adaptative radiation therapy

has been frequently applied in medical image analysis. By establishing one-to-one correspondence between an atlas image and target image (mapping corresponding landmarks for example), the segmentation label can be transferred to the target image from the atlas [36, 37]. However, registration errors may occur and produce segmentation errors. [38]. Another potential limitation to atlas segmentation is the difference in soft tissue contrast resolution between atlas-based diagnostic CT scans and CBCT [4, 5]. Despite these limitations, atlas-based segmentation accuracy is comparable to manual delineations of OAR [39]. Even though editing of contours is inevitable, auto-segmentation of the OAR allows substantial time saving for the clinicians [40]. Another validated option is to use the patient diagnostic planning CT for segmentation to CBCT [34].

A different set of algorithms such as the Demon algorithm uses a regular grid of forces to deform an image to a target image based on matching intensity values between these two images [41]. Regardless of the algorithm chosen, quality assurance procedures such as digital phantoms should be performed to quantify intrinsic errors of DIR [42].

Proposed algorithm

Given the current technical and cost limitations for systematic ART in head and neck cancers, a practical algorithm may be proposed for select patients as follows: patients with more than 5% weight loss and/or more than 10% decrease in neck thickness during treatment should undergo a new planning CT scan with IV contrast at the 3rd or 4th week of treatment or even earlier if clinically noticed and dosimetrically relevant. The OAR may be delineated either manually or with DIR if available for re-planning. The

GTV and CTV should be delineated manually based on the institution protocol as DIR is not reliable for tumor delineation. The use of CBCT for tumor delineation is not reliable with the current available technology. However, as technology evolves, CBCT may become more accurate for tumor delineation and avoid the need for a new planning CT scan (Figs. 2, 3). Figure 2 shows the main steps and possibilities of adaptive radiation therapy. Figure 3 shows the various procedures for an offline adaptive radiation therapy (done a posteriori after treatment fractions) or online (to be made available in the near future once time issues in radiotherapy have been solved with more sophisticated and quicker on-board imaging technologies with approval by RTT or physicians).

Conclusions

Significant variations of the volume, shape and position of tumors and OAR are frequently observed during the course of radiation therapy for HNSCC. When these alterations produce significant dose changes resulting in potential excessive dose to OAR or decrease the dose to PTV, ART becomes necessary. However, despite advances in imaging technology, ART has many limitations that the clinician should be aware of to avoid the pitfalls of its application (Fig. 4). Figure 4 shows the current limitations to implementation of adaptative radiation therapy in routine practice. Future prospective studies may resolve current ART limitations and allow its routine adaptation in the clinic.

Compliance with ethical standards

Conflict of interest The authors have no financial conflict of interest and hereby waive their copyright.

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