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Head and Neck Cancer Adaptive Radiation Therapy (ART): Conceptual Considerations for the Informed Clinician

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For nearly 2 decades, adaptive radiation therapy (ART) has been proposed as a method to account for changes in head and neck tumor and normal tissue to enhance therapeutic ratios. While technical advances in imaging, planning and delivery have allowed greater capacity for ART delivery, and a series of dosimetric explorations have consistently shown capacity for improvement, there remains a paucity of clinical trials demonstrating the utility of ART. Furthermore, while ad hoc implementation of head and neck ART is reported, systematic full-scale head and neck ART remains an as yet unreached reality. To some degree, this lack of scalability may be related to not only the complexity of ART, but also variability in the nomenclature and descriptions of what is encompassed by ART. Consequently, we present an overview of the history, current status, and recommendations for the future of ART, with an eye toward improving the clarity and description of head and neck ART for interested clinicians, noting practical considerations for implementation of an ART program or clinical trial. Process level considerations for ART are noted, reminding the reader that, paraphrasing the writer Elbert Hubbard, "Art is not a thing, it is a way."

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"When an artist uses a conceptual form of art, it means that all of the planning and decisions are made beforehand and the execution is a perfunctory affair. The idea becomes a machine that makes the art. "- Sol LeWitt[1]

ART 101

The concept of "adaptive radiation therapy" (ART) has been widely praised, serially modeled in silico, and heavily discussed, but to date, at a practical level, remains rarely implemented in vivo outside the research setting. We aim to discuss the "state of the ART" in head and neck therapy, with an emphasis on specification of the intent with which ART is performed; the terms of ART used, or a disambiguation of the nomenclature; technical aspects considered at the implementation of ART; and, importantly, rigorous and standardized means of reporting.

The standard of care for locoregionally involved organ-sparing therapy of squamous cell carcinoma in the head and neck is chemoradiotherapy, consisting of systemic administration of

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cisplatin in combination with fractionated radiotherapy to a dose of 63-70 Gy. The effects of chemoradiotherapy for 7 weeks of treatment for head and neck cancer are substantial. Patients suffer from general side-effects, such as weight loss and distress, as well as acute and late toxicities induced by chemotherapy, radiotherapy or a combination of the two. Important acute radiation induced toxicities include severe mucositis, dermatitis, xerostomia and the need for a feeding tube. Important late or chronic toxicities include xerostomia, dysphagia, and fatigue, which have been shown to influence quality of life for years after treatment.[2,3] Although weight loss or reduction of nodular volume might be apparent by physical examination, anatomical changes that occur during treatment have been shown to result in unintended (or, at least, unmonitored) deviation from the initial planning geometry. Sometimes it deviates to such a degree that inadvertent clinical target volume (CTV) undercoverage and/or organ at risk (OAR) overdosage occurs,[4-6] even when isocentric image-guided alignment is applied.

ART History

Modern head and neck ART can be conceptually traced to the seminal work by Yan et al,[7] who proposed a method for offline assessment of 3D-conformal RT head and neck cancer set-up error, using planar imaging in 3 cardinal axes with electronic portal imaging devices. Their proposal included replanning when sufficient deviation from the planned dose was observed.

Shortly thereafter, in-room imaging improved with the introduction of kV cone-beam CT by Jaffrey et al.[8] Similarly devices such as megavoltage CBCT tomotherapeutic imaging and in-room CT approaches (CT-on-rails)[9] became available. These commercialized technical advances allowed the monitoring of not only isocentric error, but also multipoint/multi-ROI displacement as well as morphometric alteration in soft tissues. Altogether, this allowed more accurate treatment delivery through image-guided radiotherapy (IGRT). IGRT has provided insight in the magnitude of anatomical changes that occur during treatment. This was initially demonstrated by Barker et al, showing in-room-CT-derived quantitative assessment of tumor and parotid alteration via daily imaging.[9] They demonstrated a nearly 70% reduction in GTV volume with a median mass displacement of >3 mm at the end of radiation treatment in patients with head and neck cancers, as well as significant alterations in parotid volumes during static therapy. They thereby provided a good example of Yan's updated definition of ART, "to customize each patients' treatment plan to patient-specific variation by evaluating and characterizing the systematic and random variations through image feedback and including them in adaptive planning."[10]

The extent of the customization as proposed Yan,[10] has changed over time. In early ART the main purpose was often to confirm set-up accuracy, perform serial plan dose delivery consistency with pretherapy planning (ie, verification), or to maintain treatment as planned at onset (ie, without CTV modification). In other words: to keep both target and OAR dose equal to that of the original treatment plan, by accounting for anatomical changes in the adaptive plan.[11,12] In this regimen, additional OAR sparing compared to the original plan was a de facto bonus, rather than an intended goal of adaptation.

Modern ART

Current practice, however, more often specifies OAR sparing as the leading purpose or most important benefit of ART.[13,14] Unfortunately, the existing clinical data on the effect of ART is sparse, as is clearly shown by review of the limited prospective data available (Table 1, adapted from Castelli et al).[15]

The unintended benefit of sparing OARs during ART may be the underlying cause for the gap in literature, as ART clinical implementation has preceded clinical trials, despite a frankly limited trove of direct Level I evidence. Regardless of the limited evidence, a recent survey by Krishnatry et al of 32 institutions at the Tata Memorial Hospital Radiotherapy Practicum,[16] showed that 92% of respondents listed head and neck as a site of adaptive therapy implementation. Despite the benefits, though, ART is not without implementation costs. Krishnatry et al noted in their survey: "84% of the respondents were willing to increase the use of ART in practice and believed (strongly) that ART improves clinical outcomes (70%), productivity (66%), and the therapeutic ratio (88%). The most important hindrances were the lack of equipment (48%), training (36%), and tools/management support (26%)."

This illustrates that, depending on frequency, timing and ad- hoc or planned nature of ART, it is consistently regarded asa resource-heavy and time-consuming intervention. The technical and procedural efforts required have prevented full-scale implementation (at present, to our knowledge, no site uses adaptive planning for *all* head and neck definitive cases). In head and neck cancer, the barriers for full-scale implementation are often a function of the need for human-defined (or at least, approved) regions of interest via target volume segmentation. The "equipment," "tools," and "education" needs of Krishnatry et al likely refer to this as-yet-unmet need. To date, several automated/semiautomated segmentation approaches have been investigated leveraging CT and MRI for OAR[17-19] and PET for gross tumor volume (GTV).[20] For example, using the combination of a deep learning neural network and a shape representation model, Tong et al recently published a competitive algorithm that can delineate 9 OARs on a new scan under 10 s.[21] Similarly, Cardenas et al[22,23] have shown that rapid CTV generation can be performed with machine learning approaches, obviating an often time-consuming step in target delineation. Although these results are promising, general consensus remains that automatic segmentation has yet to completely replace physician contouring, as manual checks and sometimes adjustments remain necessary[24]; Voet et al,[25] for example, showed that a commercial-software-autosegmented CTV protocol delivered clinically meaningful undercoverage,

Table 1 Clinical Benefits of ART in Patients With Head and Neck Cancer

Author (year)	Nb Patients		Tumor site	Total dose (Gy)	Replanning Strategies		Follow-Up (months)	Clinical Endpoint		
	ART	No ART			Nb	Timing		Loco-regional Control and Survival	Acute Toxicity	Late Toxicity
Schwartz et al[11,*]	22	0	OPC	66-70	1 or 2	16th and 22th fr	31	2-year LRC = 95%	G III mucosal = 100% G II xerostomia = 55% G III xerostomia = 5%	Full preservation or functional recovery of speech and eating at 20 months
Kataria et al[69]	36	0	LAHNC	70	1	54 Gy		2-year DFS = 72% 2-year OS = 75%	G II-III mucosal = 100%	G II xerostomia= 8% G II mucosal = 11% No G III
Yang et al[70,*]	86	43	NPC	70-76	1 or 2	15th and/or 25th fr	29	2-year LRC 97.2% (ART) 82.2% (no-ART) $P = 0.04$ 2-year OS 89.8% (ART) 82.2% (No-ART) $P = 0.47$		Improvements in quality of life with ART
Chen et al[71]	51	266	LAHNC	60b 70μ	1	40 Gy (10-58Gy)	30	2-year LRC 88% (ART) 79% (No-ART) $P = 0.01$ 2-year OS 73% (ART) 79% (No-ART) $P = 0.55$	G III: 39% (ART) 30% (No-ART) $P = 0.45$	G III: 14% (ART) 19% (No-ART) $P = 0.71$
Zhao et al[72]	33	66	NPC	70	1	15th ($\pm$5) fr	38	3-year LRFS 72.7% (ART) 68.1% (No-ART) $P = 0.3$		No difference except less xerostomia and mucosal with ART for N2 and N3 patients

Abbreviations: ART, adaptive radiotherapy; b, Adjuvant RT; Fr, fraction; DFS, disease-free survival; LAHNC, locally advanced head and neck cancer; LRC, loco-regional control; LRFS, loco-regional free survival; Nb, number; Nb pts, number of patients; NPC, nasopharyngeal carcinoma; OPC, oropharynx cancer; OS, overall survival; μ, definitive RT

* prospective studies (non-randomized).

which was not reflected decisively in similarity metric assessment, despite potential clinical risk if implemented without oversight. Despite this need for continued physician involvement, automated/semiautomated OAR segmentation tools have been shown to improve segmentation time, with performance metrics approaching human performance in selected cases in randomized blinded human performance trial.[18] These time savings, ideally, pave the way for more facile clinical implementation of head and neck adaptive trials and protocols.

Contrasting the limited amount of clinical trials for ART in head and neck cancer, there is a large amount of in silico trials, aiming to assess the optimal time and frequency of adaptive replanning, as well as a robust way of patient selection for this tool (Table 2, excerpted from a systematic review by Castelli et al).[15] However, subsequent clinical implementation of this data remains both rarely attempted and underreported. And although the in silico results convincingly show benefit for OAR when ART is utilized to spare them, currently no international guidelines exist on how or when to apply ART for head and neck cancer.

Terms of ART: Toward a Critical Nomenclature of ART Intent

A “term of art” indicates “a word or phrase that has a precise, specialized meaning within a particular field or profession.”[26] Sadly, in many cases the lack of clear terminology and specification has served to obfuscate the application of ART, and certainly hampered clinical reproducibility. Chief among vagaries is the lack of a definitive nomenclature for plan intent. That is to say, if adaptive therapy can encompass dose escalation, OAR de-escalation, static plan verification, and shrinking volumes simultaneously, does ART have any intrinsic meaning at all?

The proliferation and increased use of the term “adaptive therapy” thus means that a plethora of approaches can fall under the nominal umbrella of ART. To overcome this, we have sought to define a formalism for defining the relative planning intent of a given ART trial (Table 3), with the aim of specifying and categorizing future efforts in prospective ART approaches.

For example, despite the lack of international consensus or guidelines on various aspects of ART, there is a currently an on-going multicenter phase 2 clinical trial in which ART is an implemented treatment arm. The ARTFORCE study is an ongoing randomized clinical trial for head and neck cancer patients who are treated with concomitant cisplatin and standard or adaptive high-dose radiotherapy.[27,28] The high-dose radiotherapy consists of a redistribution of dose to the primary tumor, in which the 50% of the GTV with the highest uptake on F-18-fluorodeoxyglucose-positron emission tomography scan is defined and subsequently boosted in such a way that 2% is boosted to 84 Gy, while the mean dose remains 70 Gy for the GTV. The adaptive part consists of a CT-scan in week 2 of treatment, with a new treatment plan per week 3 of treatment. This new plan has the same constraints for tumor and OAR dose as the original and only allows for limited target volume adaptations and associated additional sparing of OAR, nor additional dose to the tumor. It is isotoxic, isotreatment ART, or ART_{ex_aequo}. Unique about this trial is that it is indirect proof of the feasibility of multicenter and standardized ART. Unfortunately because the ART is done in the experimental arm, a comparison of toxicity or outcome discriminating only for ART will not be possible based on the results.

The future will require additional definitions of ART, as using images solely to ensure stable dose comapred to simulation and thus "keep treating what you planned to treat", (i.e. serial plan verification) such as in ART_{ex_aequo} will belong to the past. In fact, ART in head and neck cancer has already changed from ART_{ex_aequo} to a regimen that seeks extra OAR sparing: ART_{OAR}. Alternatively, dose escalation to the primary tumor and/or adjusting the CTV based on images made during treatment can be performed. For this, we propose the following terms: ART_{amplio} to indicate ART with the purpose of dose escalation to the CTV; ART_{reduco} to indicate ART in which the CTV is cropped to the new anatomy, and ART_{totale}, in which both dose escalation to the CTV and reduction of CTV to the new anatomy are goals (Table 3). ART_{reduco} is currently being clinically investigated using MR-guided adaptation in a prospective cohort, as will the safety and toxicity reduction of this regimen.[29]

ART Techniques

The same ambiguity remains, not only to the intent of an ART protocol, but to the mechanics or technique of its implementation. Figure 1 illustrates a selection of possible typologies of ART implementation for head and neck cancer, with increasing temporal replannning resolution.

In Figure 1A, a “fixed-interval” approach is implemented, wherein the $CT_{simulation}$ image and dose data are registered to a single (often midtherapy) time point. In many cases, the initial plan is recalculated or superimposed on the midtherapy anatomy, and, if dose constraints are not met, a single adaptation is performed. This approach is computationally and workflow efficient, and may have particular utility in scenarios such as proton therapy, where contour and anatomic deviations may be mitigated by midtherapy verification adaptation.[30]

Figure 1B denotes an approach designated as “triggered” adaptation. In these scenarios, typically weekly imaging is acquired, and iteratively reviewed throughout therapy for plan deviation based on qualitative or quantitative triggers. Threshold “triggers” for replanning can encompass cachexia/weight loss, surface contour or mask fit changes, OAR/CTV volume alteration, increased daily or systematic set-up deviations, as detailed in a review paper by Brouwer et al.[14] Furthermore, this approach can be combined with the “fixed-interval” approach shown in Figure 1A, when both planned midtherapy and ad hoc “triggered” adaptation are performed (eg, Schwartz et al, wherein a single fixed interval adaptation

Table 2 Dosimetric Benefits of ART in Patients With Head and Neck Cancer (From Castelli et al)

Author (year)	Nb Patients	Replanning Strategies		Dosimetric Analysis			Dosimetric Benefit		
		Nb	Timing	Time Point to Cumulate the Dose	Method to Cumulate The Dose	Total Dose for the Comparison (Gy)	Parotid Gland (Dmean)	Spinal Cord (Dmax)	Target Volume (PTV)
Capelle (2012)[73]	20	1	3rd week	2	Average DVH	66	−0.6 Gy *	−0.6 Gy *	+0.5 Gy (D1%)*
Castelli (2015)[74]	15	6	Weekly	7	DIR	70	−3.8 Gy*	–	–
Dewan (2016)[75]	30	1	40 Gy	2	DVH	30	IL −6 Gy* CL −2.2 Gy	−66 Gy*	More uniform coverage Decrease V110% by 2*
Duma (2012)[76]	11	1	16th (9th-21st) fr	1	DVH	2	No variation	−0.14 Gy	–
Jensen (2012)[4]	15	2 to 4	– IL-3.8%	3 to 5	DIR	70	CL: − 11.5%†	–	Improvement of coverage by 8%
Olteanu (2014)[77]	10	2	8th and 18th fr	3	DIR	70	−6%†,*	–	Higher minimum and lower maximum doses
Schwartz (2013)[11]	22	1 or 2	16th and 22nd fr	2 or 3	DIR	70	−0.7Gy*	–	Increase coverage and dose homogeneity
Zhao (2011)[72]	33	1	15th (±) fr	2	DVH	37.5 Gy (20-50 Gy)	Decrease mean dose*	–	–

Abbreviations: CL, contralateral; D1, dose received by 1% of the volume; DIR, deformable image registration; Dmax, maximum dose; Dmean, mean dose; DVH, dose volume histogram; fr., fraction; IL, ipsilateral; Nb, number; Nb pts, number of patients; PTV, planning target volume; V110%, Percentage of target volume receiving 110% of the dose prescribed (hot spot); -, not assessed.

* *P* value < 0.05.

† Median dose.

Table 3 ART Terminology

Name	Technique	Tumor Dose	OAR Dose	Example Study/Trial
ART_{ex_aequo}	Serial plan verification to ensure pre-therapy plan parameters are stable	=	=	Van Kranen et al[78]
ART_{OAR}	Reduced OAR dose; pre-therapy CTV is conserved	=	↓	Schwartz et al[11,31]
ART_{amplio}	Increased dose to tumor; isotoxic (or lower) OAR dose	↑	=	ADMIRE (Al Mamgani et al[79])
ART_{reduco}	"Shrinking CTV" for on-treatment responders	=	↓	MR-ADAPTOR (Bahig et al[29])
ART_{totale}	Increase dose to subvolume of initial CTV	↑	↓	UZ Gent DBPN trials[77,80-84]

Abbreviations: CTV, clinical target volume; DBPN, dose painting by numbers; OAR, organ at risk.

was planned, with up to 2 additional "as needed" triggered adaptations utilized.[11,31]

However, both fixed-interval and triggered ART approaches fail to incorporate any intervening image/dose data, and often eschew dose accumulation. Any dose accumulation performed in these regimens would be interpolations depending on image granularity. Alternatively, both "serial" and "cascade" ART approaches allow dose accumulation during in the ART procedure. For serial ART, this is done off-line and upon request. In cascade ART, the dose up to and including the most recent image/fraction/day is automatically accumulated, and these data are available at the time of ART, which we will now elaborate further.

Figure 1C, which has been alternately referred to as "serial," "one-to-many," or "sequential" adaptation involves high-frequency (>=weekly) volumetric imaging and registration to the initial plan. However, though each $Image_{Fraction}$ to $Image_{planning}$ assessment is repeated, the cumulative deformation vector fields (DVFs) are not concatenated, meaning that aggregate dose accumulation is not occurring throughout the course of therapy, unless requested. Consequently, interval OAR/GTV deformations during therapy are unincorporated, and dose is "forward projected" with increasingly large temporal and geometric differential(s) from the planning scan. This approach is currently the default implementation for both a ViewRay and an Elekta MR-Linac system. The 0.35 T ViewRay system for MR-guided RT systems is detailed by Raghavan et al,[32] in a study where registration of the $MRI_{Fraction}$ to the initial $MRI_{planning}$ was performed prior to manual segmentation. The 1.5 T Elekta MR-LinAc configuration (Elekta Unity system)[33] allows rigid and nonrigid registration of $MRI_{planning}$ to daily fractions, and either a "adapt-to-point" (virtual isocentric alignment) or "adapt-to-shape" (volume-based replanning).

Ideally, in a computational resource unbounded space, the scenario in Figure 1D is preferred, dubbed "iterative" or "cascade" ART. In this approach, daily deformation in geometry and set-up error are incorporated subsequent to all fractions, meaning interval change in volume is minimized and preserving a DVF "chain" by which OAR/CTV voxel reduction/morphometric alteration can be tracked with increased precision. Dose accumulation in concert with therapy is a natural result, allowing "delivered cumulative dose" to be readily assessed. While such an approach is theoretically possible on several vendor systems, active implementation of such a data-rich approach has yet to be done, and thus represents a demonstrable "postmodern ART" application in need of vendor/manufacturer support.

Perspective in ART

In addition to specification of the terms of ART and techniques of ART, a fundamental need exists for definition of the relative reference anatomy for reporting ART. That is to say, if anatomy is dynamically changing, is a plan judged by its conformance to the original "simulation plan", or are constraints judged on the accumulated dose after any given number of fractions? The importance of reference frame specification is illustrated in Figure 2A, which shows a series of weekly cascade registrations performed on an in silico case (red arrows) via interval deformable image registration/dose accumulation (denoted by visual representation of DVFs). In this scenario, the parotid glands, which lost almost 25% of their total volume, have the cumulative ROI at simulation mapped iteratively via "DVF" chain to parotid ROI voxels at end therapy. In contrast, the reverse procedure, termed "dose back projection" (green arrows), expands the end-therapy parotid ROI iteratively "back through time" to map the post-therapy volume to the simulation reference anatomy/dose grid. These distinct approaches can lead to disparate dose display, as in Figure 2B (DVF/dose accumulation) and C (deformation back-projection) which shows not only the effect of DVF/dose accumulation, but the capacity for parotid dose reduction if, at each registration step, weekly dose adaptation had been performed. Notably, the difference in frame of reference upon estimated parotid dose is in the same order of magnitude or greater than the alteration consequent to weekly adaptation.

A different perspective is illustrated by the pink arrows, indicating a methodology in which all subsequent images are mapped to the simulation scan. Each perspective has its own advantages and disadvantages. The most apparent disadvantage of cascade DVFs being (both for forward and back-projection) that it is subject to continuous error propagation. However, in the scenario where all images are

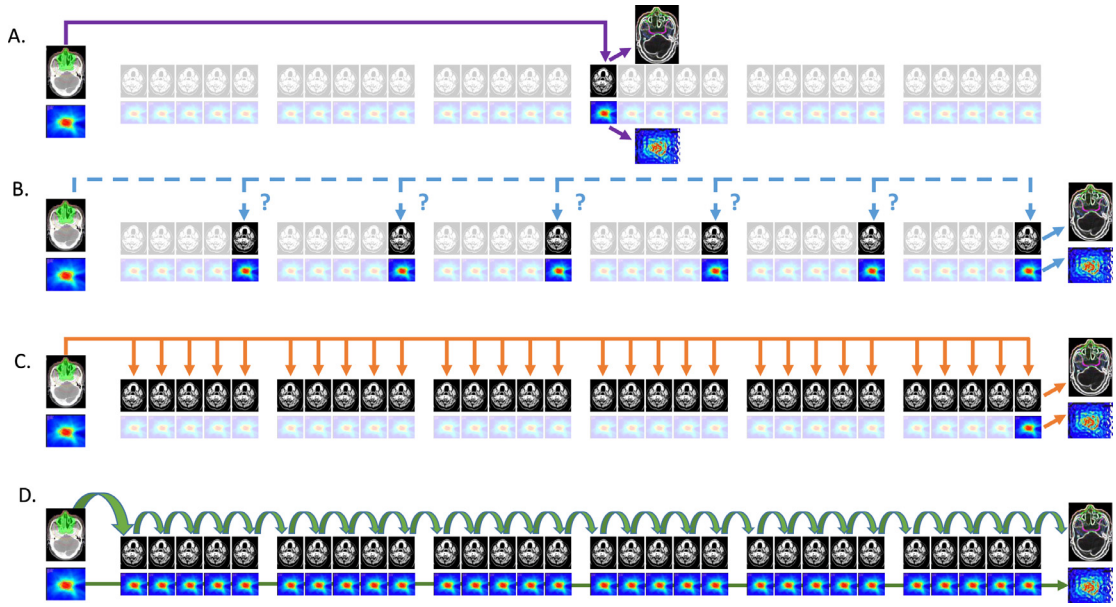

Figure 1 Possible typologies of ART implementation. A: fixed interval approach; B: 'triggered' ART; C: serial ART; D: cascade ART. ART, adaptive radiation therapy.

mapped to a single reference, the deviation from that reference increases over time, leading to increased uncertainty within the DVF.

This "perspective problem" is especially pronounced when significant target or OAR volume shrinkage is observed. Indeed, substantial volume loss over the course of treatment can result in serious inaccuracies in dose accumulation, especially in head and neck cancer patients, because they may have observed significant volumetric changes with regard to tumor or tissue. These volumetric alterations, may inadvertently lead to intrinsic failures dose estimation of deformable registration algorithms, as eloquently explained by Zhong and Chetty,[34] whose exemplary illustration is recapitulated for parotid volume reduction in

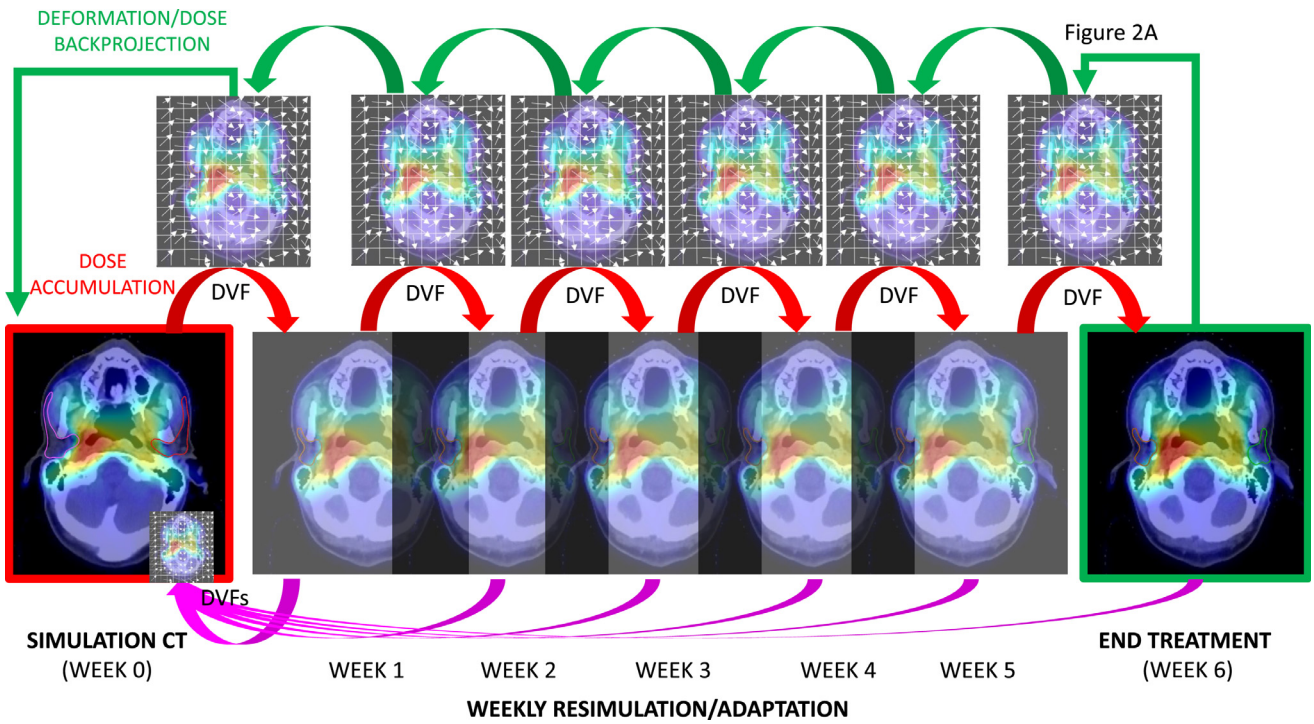

Figure 2 The importance of the reference frame in ART A: forward calculation with dose accumulation, and back-projection; B: Dose-volume histogram (DVF/dose accumulation); C: dose-volume histogram (deformation back-projection).

Figure 3. In this example, a theoretical parotid gland from the initial time point (T_1), receiving a uniform dose (D) of 2 Gy, experiences a 50% reduction in volume (Vi) shrinking to half its original size, such that the original volume (V_1) is double the end volume (V_2) at a second time point (T_2), with a corresponding loss of mass (M^i; ie, $M_1 = 2 * M_2$. If a deformable registration algorithm, φ_1, maps all voxels in V_1-V_2, to measure the *dose-to-date*, the resultant dose accumulation (termed by Zhong and Chetty[34] as "deformable dose accumulation," but here called simply dose accumulation) results in an underestimation of energy delivered (E). Similarly, dose back-projection (eg, "dose mapping"),[34] the projection of dose from V_2 to V_1 via deformation φ_2 results in underestimation of dose delivered when energy conservation is considered. A similar observation is seen in DIR algorithms that maintain "mass conservation" whereby additional structures (such as a mouth stent or flap reconstruction) are overfitted by intensity matching- or similarity-driven DIR approaches.[35] Biomechanical models, which include prior knowledge of relational data in addition to intensity data can mitigate this effect.[34,36,37] However, as the original authors note, caution must be used when large proportional volumetric changes are encountered in either tumor or tissue, and careful algorithm selection for particular applications and quality assurance thereof is thus *de rigueur*.

Cataloguing ART

In order to assess, nay appreciate ART, one must be able, in an analogical fashion, to determine not only the intent of the artist, but also the technique used, and allow for ART to be readily archived, catalogued, and reproduced. In an effort to assist the interested reader, process-level considerations for potential standardization are detailed as queries (and easily converted to a checklist format) in Table 4. These disparate considerations point to unmet needs specific to ART. While several reports have defined recommendations for clinical trial implementation,[38] dose prescription and reporting,[39,40] uncertainty margination,[41-43] region of interest (ROI) and dose volume histogram (DVH) nomenclature,[44] commissioning of IGRT systems,[45,46] implementation and reporting of image registration techniques,[47] modeling,[48] and reporting guidelines,[49] as yet no single standardized reporting structure exists to allow the massive amounts and permutations of image, margination, dose, clinical, and relational data generated by even a small adaptive head and neck clinical trial to be reportable in an efficient manner, let alone consistent with FAIR Guiding Principles for scientific data management[50] (*vide infra*, Table 5), and the use of radiation oncology specific ontology systems at clinical scale remains exciting, but nascent.[44,51-53] Nonetheless, we believe that use of a series of self-directed queries and careful consideration of the multiple factors involved can assist even established programs with managing ART implementation, and can provide a reference for those developing protocols.

The field of radiotherapy has become increasingly more complex. ART is an illustration of this, with increasing number and complexity of disparate information sources which must be aggregated to extract meaningful data. For instance, the volume, temporal, and spatial correlation of multiple elements (patient data, accumulated dose, images, DVH, DVF, positional shifts, and toxicity/outcome) must be carefully collated, organized, curated, recorded, and reported.[54-59]

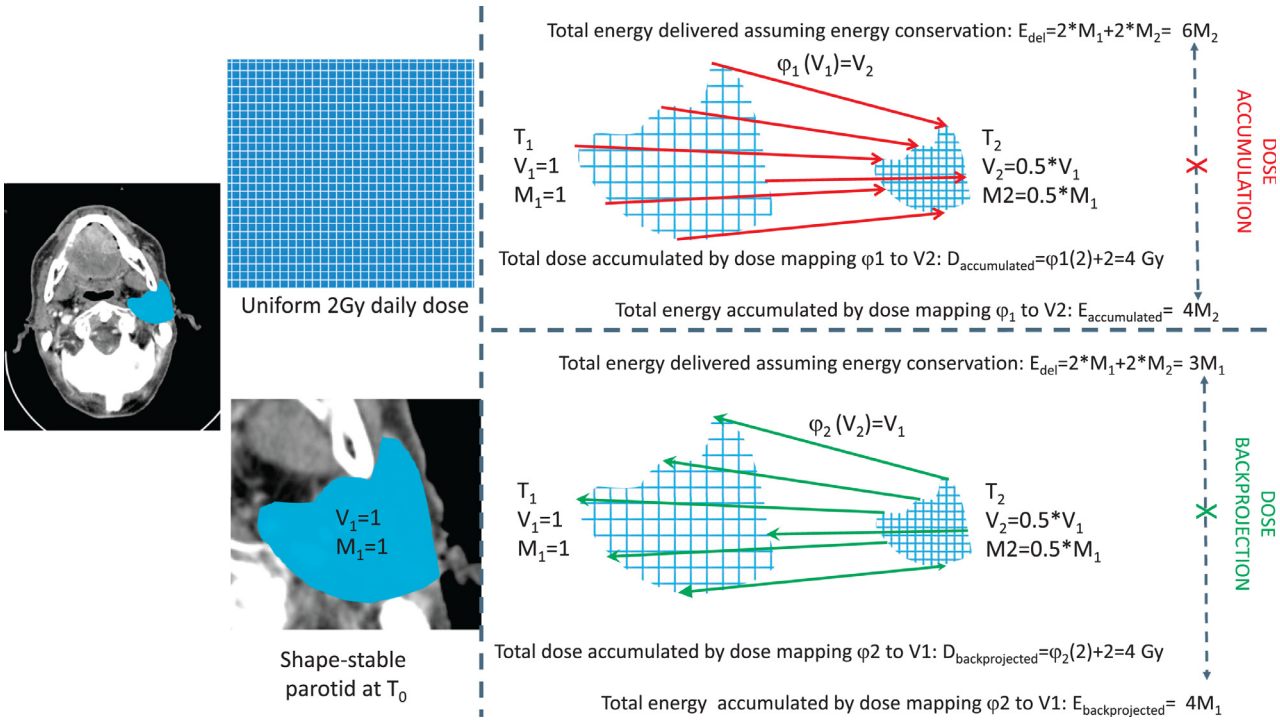

Figure 3 Volume loss and dose accumulation. V, volume; M, mass; φ, deformable registration algorithm; E_{DEL}, energy delivered; T_0, start of treatment. After Zhong and Chetty.[34]

Table 4 Practical Process-Level Considerations and Queries in Design and Reporting of Adaptive Clinical Trials and Observational Adaptive Regimens

Process	Clinical Consideration	Query Formulation	Subqueries/Examples	Suggested Guidance Document(s)
Adaptive regimen prescription/ intent documentation	*A priori* definition of clinical plan intent	-What is the physician-defined clinical intent of the adaptive regimen?	What conceptual approach underlies the adaptive trial/regimen (viz Table 1)? -Define, if possible the expected magnitude of clinical benefit in terms of locoregional control or toxicity reduction. Examples: - "Reduce by 15% Grade 3 acute symptoms due to inadvertent elective risk PTV overdosage in the presence of >10% weight loss." - "Improve local control probability by 15% via an isotoxic dose escalation of residual PET-derived high-risk regions on mid-therapy imaging."	38,39,40,47,85
	A priori definition of dosimetric aims of adaptive regimen.	What is the intended dosimetric intent of the adaptive regimen?	Examples: - "Shrinkage of CTV/PTV as tumor regression occurs through weekly offline adaptation, while ensuring >95% coverage of weekly PTVadapted". - "Ensure parotid V15 overdosage of less than 5% deviation from pre-therapy prescription via weight loss and deformation is prevented by mid-treatment verification." - "Replan patient if systematic set-up error exceeds a pre-specified tolerance of >3mm."	
Pre-therapy imaging/ simulation	Annotation of worklow for initial planning image acquisition, as well as subsidiary images utilized for therapy planning.	What immobilization strategy/devices were implemented at simulation?	Was this method standardized for all patients in regimen/trial?	85,86
		Was additional imaging (PET/MR/CT) used for pre-therapy treatment planning?	If so, have all images utilized been archived and registered with the simulation DICOM dataset?	47
Target delineation/OAR initial segmentation	Specification, in a reproducible manner, of segmentation process for initial planning.	Were TVs/OARs segmented manually? Were any TVs/OARs segmented by automated/ semi-automated processes?	If so, using what quality assurance procedures[87], guidelines[88-90] and nomenclature [44] in the TPS? -If so, using what software/version/approach? -Are automated/semi-automated ROIs annotated to differentiate manual vs automated[19,22,23,93-97] vs. assisted [18,25] segmentation?	88-92,44
Initial dose prescription/ evaluation	Reporting utilized parameters of interest for planning, as well as the reference model for potential dose modification.	What were pre-therapy dose-constraints implemented for TVs/OARS? If constraints were based on a biological model, which one(s)?	If using a reference constraint(s) (e.g. QUANTEC[98-104] or other extant models,[3,74,100,105-112] note prior reference/model.	48,103,113
Serial on-treatment imaging	Explicit exposition of implemented processes for image acquisition and image-guided translational/ set-up error modification.	Is reimaging performed online (e.g. CBCT, CT-on-rails, MRI-LinAc), or offline (inter-fraction CT resimulation)?	-What is the frequency of on-treatment re-imaging? -Are all on-treatment images archived?	47 45 46

(continued on next page)

Table 4 (Continued)

Process	Clinical Consideration	Query Formulation	Subqueries/Examples	Suggested Guidance Document(s)
		Are additional offline image-data implemented (e.g. contrast CT, PET, diagnostic MRI), and if so, how utilized?	Is the method of offline-images (e.g. PET-guided dose-painting[80,82-84,114-118]) clearly defined?	
			Are all utilized offline-images archived with co-registration to closest interval online volumetric images?	
		Are serial on-treatment translational corrections applied using IGRT in the presence/absence of simultaneous image-registration?	-If so, are translational shifts performed relative to ROI(s), isocenter, or fiducial(s)?	
			-Are all image-based shifts recorded and archived with matched IGRT image dataset?	
Replanning/ Plan adaptation	Overt description of the methodologic approach to planned/delivered dose calculation, as well as associated ROI/segmentation and related dose-constraint monitoring.	Is the replanning strategy online (i.e. while patient is on treatment device) or offline (occurring between treatment fractions)?	-What is the frequency/interval of adaptive replanning[119-121]?	47
			-What software/version/algorithm is utilized for replanning/adaptation?	
		What if any, are the replanning criteria/action level specified (e.g. % underdosage of target, overdose of an OAR)?	-Are replanning criteria fixed interval, reactive (e.g. once a dose constraint has been exceeded/unmet) or proactive (triggered by a projected dose or dose trajectory model)?	
			-If so, specify action level.	
		Are non-dosimetric surrogate criteria (e.g. systematic set-up error, morphometric alteration, ROI superimposition on daily IGRT) used as a trigger for replanning?	If so, specify action level.	
		Are ROIs for adaptation (re) segmented manually, semi-automated, or fully DIR-propagated?	-Are all propagated and manually generated ROIs archived with daily images after IGRT/replanning review?	
			-Is faculty/staff approval required for relevant ROIs, and if so, are these annotated and timestamped?	
		Is serial manual review of criteria/action level performed (i.e. does a human "check the DVH") or is automated triggering performed?	-Are all generated/reviewed DVHs (or analogous metrics[122]) archived?	44
			-If faculty/staff approval is performed, are relevant DVHs annotated and timestamped?	
Uncertainty margination	Estimation of the relative daily uncertainty accounted for by margin expansion, and disclosure of site-specific rationale/measurements used to calculate/justify utilized margins.	-Are isotropic margins implemented? If so, provide an IGRT-system specific population estimator.	Are deformable phantoms[36,123-128], digital phantoms[129-131], or other QA methods employed to generate trial/regimen-specific margins, or are standard institutional margins employed?	38,47,132
		-For anisotropic approaches, describe the margin calculation approach.		
		Are margins population-derived, or patient specific?		
		How do margination strategies account (if at all) for registration uncertainty?		

(continued on next page)

Table 4 (Continued)

Process	Clinical Consideration	Query Formulation	Subqueries/Examples	Suggested Guidance Document(s)
Image Registration/Dose accumulation assessment	Coherent and understandable explication of serial image/dose relational processes, allowing clear representation of how serially derived image and dose data are analyzed and assessed during treatment, as well as the manner by which the completed therapy course image and dose alterations are summarized.	By what method is image-registration performed: rigid, or deformable?	-If deformable, using what approach (e.g. biomechanical atlas-based, B-spline, DEMONS) and via what software/version?Describe performance metrics for software selection, if available.[35,36] -To what reference data are images used for evaluation/replanning coregistered (e.g. planning simulation, previous daily on-line imaging, or offline imaging)? -Are all DVFs archived? -Are DVFs annotated so that it is readily determined whether they were actually utilized for treatment, or as a function of *post hoc* plan summation?	[47,133]
		By what approach is dose-summation performed (e.g. iterative dose-accumulation, or superimposition of delivered dose)?	-What software/version/algorithm is used for initial and replanning dose calculation[37]? -Describe utilized dose delivery quality assurance methods (e.g. pre-therapy phantom dosimetry[36,123-128], EPID-dosimetry[134]) and frequency relative to imaging/plan adaptation. -Is accumulated dose iteratively recorded, archived and summarized? Are final accumulated dose and backprojected dose archived/summarized[34]?	
Data description/ dissemination	Collation of all relevant and informative data elements of the adaptive trial/regimen into a coherent and FAIR-compliant format for reporting of clinical, technical, and dosimetric observations/outcomes and data sharing.	Have relevant clinical outcome data been recorded using an established ontology/nomenclature[51-53]?	Example: If locoregional control is an endpoint, are failure events mapped to delivered/accumulated dose and acquired pre-therapy imaging[135-139] using an accepted methodology/nomenclature[140,141]? Are the data described, not just in free text format, but using a recognized informatics ontology[51-53]?	[49]
		Has relevant patient- and cohort-specific plan intent/ TPS/IGRT/adaptive replanning/archival system data been collated into a single repository that meet FAIR criteria [50,142]?	If so, are all data compatible with DICOM-RT linked (e.g. via DVF) to a common reference geometry and FAIR-compliant (i.e. machine searchable) image, ROI, and DVH nomenclature? When possible, are clinical data embedded within the DICOM-standard[143,144]?	[44,47,50,52,53,142]
		After trial/protocol completion and/or publication, can archived trial/adaptive protocol data be shared, either directly, or via distributed learning systems, to allow learning from extant data [67,68,121,145]?		

Table 5 The FAIR Guiding Principles (From Wilkinson et al)

Guiding Principle/ Attribute	Definition	Adaptive Trial Example
Findable	F1. (meta)data are assigned a globally unique and persistent identifier F2. data are described with rich metadata (defined by R1 below) F3. metadata clearly and explicitly include the identifier of the data it describes F4. (meta)data are registered or indexed in a searchable resource	After completion and publication of an adaptive trial, data are anonymized and deposited in a public repository (e.g. TCIA),[67,68] and labeled with a permanent digital object identifier (DOI).[146] The DOI/repository and a data summary are then submitted as a data descriptor to a relevant journal (such as *Medical Physics* or *Nature Scientific Data*) and PubMed-indexed for easy searchability.
Accessible	A1. (meta)data are retrievable by their identifier using a standardized communications protocol A1.1 the protocol is open, free, and universally implementable A1.2 the protocol allows for an authentication and authorization procedure, where necessary A2. metadata are accessible, even when the data are no longer available	Other investigators, having located the data from PubMed or journal sites, can readily download the dataset from TCIA using the NBIA Data Retriever app[147] to query the permanent repository and download the anonymized image and dose data.
Interoperable	I1. (meta)data use a formal, accessible, shared, and broadly applicable language for knowledge representation. I2. (meta)data use vocabularies that follow FAIR principles I3. (meta)data include qualified references to other (meta)data	Data from the adaptive trial, including all images, dose, and adaptive plans are stored using the DICOM-RT standard.[148,149] Additional clinical data and is either embedded within the DICOM header, referenced with relevant files/systems,[143,144] associated with semantic data (e.g. Resource Description Framework via the Radiation Oncology Ontology[51,53,60] framework) to allow the data to be used across multiple vendor and vendor neutral software(s) or for distributed learning.
Reusable	R1. meta(data) are richly described with a plurality of accurate and relevant attributes R1.1. (meta)data are released with a clear and accessible data usage license R1.2. (meta)data are associated with detailed provenance R1.3. (meta)data meet domain-relevant community standard	Using the aforementioned data, the adaptive protocol is reconstructed *in silico*, and used by several other sites to benchmark their internal adaptive processes and develop new segmentation and automated replanning approaches; the original data are cited in subsequent publications,[150] and are widely used as a benchmarking/performance estimator for a new adaptive trial workflow development.

ART thus represents the index case of an unmet need for "Big Data" information support, both for ensuring patient safety and for correlating image-dose-response data in a clinical utilizable manner.[60] However, if the present situation persists, it will remain almost impossible to effectively reconstruct an institutions' specific adaptive protocol in the absence of identical vendor-supplied treatment planning, registration, archiving, electronic medical record, toxicity and patient-reported outcomes collection, and outcome monitoring, barring significant resource allocation.[61]

Consequently, we must as a specialty, commit to making ART FAIR. While an art fair is the public display of many artists, ARTists in head and neck cancer should commit to public display of data, whenever possible, using the recently presented "FAIR Guiding Principles for scientific data management and stewardship."[50] The FAIR framework (Table 5), if executed, would, in the authors' estimation, do more to accelerate adaptive trials than any other technical or computational advance, as it would allow sites to evaluate their systems using established datasets, query alternative practices, and perform in silico studies with shared normative "controls." FAIR software and QA processes could allow "beta testing" on public adaptive head and neck datasets. To our knowledge, a limited number of FAIR-compliant head and neck radiotherapy datasets exist,[62-66] primarily on the Cancer Imaging Archive,[67,68] and to our knowledge none are adaptive cases, nor complete in terms of full reporting of dose/toxicity/response data. Thus, we call on our fellow ARTists to commit to FAIR-ness, data sharing and transparency in developing the tools and processes necessary to enable wide-scale, safe, easy, and effective ART through becoming an invigorated, enthused, and sharing ART collective.

Conclusion

In summary, this seminar has aimed to illustrate challenges and opportunities, in addition to a high-level survey of ART in head and neck cancer. Unfortunately, head and neck ART

is, at present, not standardized nor widely utilized. We sought to provide possible guidelines for standardization in the various aspects of ART, that is, specification of the intent with which ART is performed; the terms of ART used, or a disambiguation of the nomenclature; technical aspects considered at the implementation of ART; and, importantly, rigorous and standardized means of reporting. While some of these aspects are the responsibility of clinicians and physicists performing ART, continued creative and collaborative efforts with vendors will be necessary to make futuristic ART possible and of benefit to our shared head and neck patients.

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