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Radiation therapy quality assurance in head and neck radiotherapy – Moving forward

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ABSTRACT

Head and Neck Cancer (HNC) radiation oncologists (ROs) enjoy the immense pleasure of curing patients, working within a large multidisciplinary team to effectively deliver curative intent treatment whilst also aiming to minimise late treatment toxicity.

Secondary analyses of large-scale HNC clinical trials have shown the critical impact of the quality of radiotherapy plans, where protocol non-compliant plans have yielded inferior survival rates approximating 20%. The peer review process in routine day-to-day HNC practice shows that even in major academic centers a significant proportion of RT plans may require changes to the radiotherapy planning volume.

Optimising the therapeutic ratio in HNC has been dramatically facilitated by intensity modulated radiotherapy (IMRT), but that technology has also increased the complexity of HNC radiotherapy treatment and high-volume centers with experienced clinicians may be best placed to deliver this most accurately. International consensus guidelines to standardise or benchmark best practice with respect to the RT-QA process in HNC are needed.

The aim of this paper is to highlight the importance of the RT-QA process in the HNC treatment process and to make some recommendations for its inclusion in both clinical trials and routine clinical practice.

Introduction

Achieving optimal outcomes in head and neck cancer (HNC) treatment is contingent on the delivery of precision medicine across the breadth of diagnostic, therapeutic and supportive care domains involved from diagnosis to cure and ultimately, into survivorship. At the front line, head and neck (HN) clinicians face a myriad of complex decisions, each bringing a unique opportunity to positively (or negatively) impact patient outcomes. High quality head and neck radiotherapy treatment requires the radiation oncologist to be highly proficient across the domains of cancer and radiation biology, medical physics, image interpretation and radiotherapy simulation, treatment and dosimetry review processes [1]. In the process from diagnosis through to completion of radiotherapy treatment, there exists many “links in the chain”, each able to individually influence HNC patient outcomes. The objective of this editorial, however, is to highlight the importance of quality assurance in radiotherapy (RT-QA) in patients undergoing treatment for HNC.

What is RT-QA?

In the broadest and most correct sense, RT-QA conceptually governs all procedures influencing the consistency or accuracy of the radiation prescription, either to the target volumes or the surrounding normal tissues [2]. The quality assurance process of reviewing target volumes, by at least one other radiation oncologist has generally become known as RT-QA in the clinical trials space, while in day-to-day practice it is more widely known as peer review, although the term RT-QA is also used by some. Contouring target volumes is one of the most critical steps in the radiation treatment process, yet a high degree of variability exists between clinicians [3], owing to lack of high level evidence to support clinical target volumes or until recently, internationally agreed on consensus guidelines [4–7]. This inter-observer variability, particularly where tumour coverage may be compromised may have devastating complications for the patient, including poorer loco-regional control and survival [8]. Although several barriers exist to the implementation of an effective RT-QA program, all clinicians strive to reduce preventable human errors, aiming for an optimal radiotherapy

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plan for each patient, resulting in maximal tumour control with minimal treatment-related toxicity.

RT-QA in clinical trials

Secondary analyses of clinical trial data have eloquently demonstrated the impact of poor quality, or non-protocol compliant radiotherapy plans across a range of tumour sites [8–11]. In HNC, the cost to patients is particularly high. This was first quantified in the landmark TROG 02.02 study, the first HNC trial to include a comprehensive RT-QA review process [8,12]. This international study investigated the addition of tirapazamine, a hypoxic cytotoxin to concurrent chemoradiotherapy with high dose cisplatin. Although this study failed to show a therapeutic benefit of tirapazamine, the secondary analysis of the RT-QA data from this study has significantly shaped practice in the HNC arena. Of the 820 patients in this study, 208 (25%) plans were not compliant with the trial radiotherapy protocol, and at a secondary RT-QA analysis, 97 of 206 plans (47%) were predicted to have a significant impact on tumour control probability. Compared to patients treated with plans that were compliant *ab initio*, patients with non-compliant plans suffered significantly lower rates of loco-regional control (54% v 78%) and overall survival (50 v 70%) at two years. The lowest-accruing centers were significantly more likely to submit plans with protocol violations ($<$ 5 patients 29.8%; $\geq$20 patients 5.4%; $p < 0.001$). Wuthrick et al. reported a strikingly similar finding in a retrospective study of RTOG 0129, which evaluated standard versus accelerated fractionation in patients treated with cisplatin chemoradiation [11]. Historical accrual to prior RTOG studies was used to classify centers as either low or high accruing. In a similar finding to the TROG study, higher rates of radiotherapy protocol violations were seen in the low-accruing centers (18% v 6%) and a benefit to patients treated in high-accruing centers was seen with respect to both loco-regional failure (20% v 36%) and overall survival (69% v 51%). While there are some caveats to the assumption that trial accrual rates are a surrogate marker for experience or excellence, the data from both studies clearly demonstrated a relationship between center accrual and radiotherapy protocol compliance.

It should be noted that neither of these studies included patients treated with intensity-modulated radiotherapy (IMRT). Although the introduction of IMRT was a major advance for HNC patients, it is somewhat of a double-edged sword. While the improvements in toxicity are well documented [13–15], it requires the HN radiation oncologist to have a greater appreciation of imaging and tumor drainage pathways. The contouring process became increasingly complex; gone were the large "cover all" fields, now replaced with precisely contoured anatomical structures with highly conformal plans and steep dose gradients. While this allowed for increasing sparing of normal tissue, it introduced the possibility of tumor misses, misses which may be been forgiven with previous techniques. Indeed, new patterns of failure were observed during the initial phase of IMRT implementation, such as an increased risk of base of skull recurrences with the introduction of parotid sparing techniques [16]. In the first RTOG study to assess the feasibility of IMRT in a cooperative group setting, Eisbruch et al. reported that only 5 of 53 evaluable plans had a major violation (PTV coverage $<$ 95%). However, the cost of a violation was significant, and higher loco-regional failure was observed with non-compliant plans (2/4; 50%) than with compliant plans (3/49; $p = 0.04$) [17]. Surprisingly, although experience has increased with IMRT, the benchmarking process for the recent EORTC 1219-DAHANCA 29 study required more than 50% of the 19 recruiting centers to repeat the delineation step of the submission process, with three centers (16%) requested to undertake a third time attempt [18].

Taken together, this data suggests that RT-QA processes remain a vital component in HNC clinical trials. Including RT-QA in large-scale clinical trials, and providing real-time feedback is expensive and time consuming, but radiotherapy, the backbone of most clinical trial HNC protocols, when delivered poorly, is likely to overwhelm the potential impact of any investigative agents. We recently performed a survey of currently registered phase III HNC studies, and concerningly identified that not all studies in the next generation of immunotherapy trials were including RT-QA [19]. Even though robust radiotherapy protocols accompany clinical trials, the previous TROG and RTOG clinical trials demonstrate this on its own does not demand high quality radiotherapy [8,11]. Essentially, running a HNC trial without adequate RT-QA is like driving a car without using a seat belt. It's risky, allowing to chance a large variable, which could affect results in either a positive or negative direction, at great cost to patients and research directions.

The question is what is "adequate" RT-QA in a HNC trial? In the original TROG 02.02 trial, all plans were to be submitted for RT-QA in real time – and 81% complied. This is clearly an expensive exercise, and it may not be the only way to optimise RT quality. Other trials (IAEA DAHANCA trial) have provided RT-QA to a random 10% of cases, but this is not of proven benefit [20]. Not infrequently the details of the RT-QA in any particular trial are not clearly denoted [21,22]. Perhaps a more pragmatic approach is one we took in the TROG 07.04 trial [23]. In this trial each participating centre had to undertake a prospective (pre-accrual) benchmarking exercise. Sites utilised a de-identified sample case from their archives and completed a treatment plan in accordance with radiotherapy guidelines outlined in the protocol. This activity enabled prospective identification of any protocol (mis)interpretations which may result in major deviations.

The RT-QA can, and probably should, be different for prospective phase II trials compared with randomised trials. In the former it doesn't have to be real time, but the quality of the RT delivered needs to be documented to ensure confidence in overall results and accurate interpretation of the study. In a RCT, there needs to be a component of real time RT-QA, and often the utilisation of a benchmark case as described above allows a little more time for the review to be performed (not then delaying a patients start date) and ensures that the investigator is accurately following the trial protocol. The question is what if the most effective intensity of RT-QA thereafter? The data we do have for a gold standard of RT-QA in RCTs is that from TROG 02.02 where the goal was for all cases to be subjected to detailed RT-QA. Subsequent to that study all HNC trials have instigated some form of RT-QA, but the intensity of it has varied widely. It's interesting that the degree of RT-QA is widely perceived as too time consuming and too expensive. This however this would seem a misconception. When one considers the huge impact of RT-QA on HNC patient survival, far in excess of what is achieved from adding systemic therapy, and the cost we readily make for new systemic therapies, then the cost of RT-QA seems very effective.

We need to decide whether HNC RT-QA should focus on random or systematic errors. Even the most experienced HN RO can overlook something because they are tired or distracted, concentrating on one (or seven) aspect(s) and missing one other. To identify that one error would require RT-QA of every case. In our series, the percentage of errors in experienced HN ROs was only in the order of 15% [24]. Reviewing every case in real time to detect 15% errors is perhaps unrealistic. It would seem more efficient to put more energy into detecting systematic errors, those made via misinterpreting either the protocol or the HN anatomy.

We could perform a number of RT-QA options to assess their relative efficiency and efficacy in detecting major protocol violations. These could range from: (1) the standard of the TROG 02.02 study with review of radiology, contouring of volumes and dosimetry for every case; (2) performing review of radiology and contouring of volumes for only 50% of cases; (3) use of benchmarking cases, (this is where ROs are required to complete the contouring and dosimetry on a case as per the trial protocol, that case is then submitted for RT-QA. If there are major violations, they have to resubmit the case. Only when the benchmarking case has no major violations can investigators participate in the study); or (4) the benchmarking case and a percentage (e.g. 25%) of subsequent cases. The only way to ascertain which system is the most efficient compared to the gold standard of the first option would be to RT-QA all cases in the second to forth scenarios to see what number/percentage of major violations were missed. We clearly need further targeted research in this area.

RTQA in routine clinical practice

Implementing a peer-review process in routine clinical practice is feasible [24–30] and generally valued by most participating radiation oncologists [31]. The peer review process affords many benefits, broadly: (1) consistent production of the highest quality radiation plans; (2) a reduction in the stress of delivering curative RT plans that results from a second review by others expert eyes; (3) promoting a culture of quality and safety within departments; and (4) allows sharing of concepts and information between colleagues [32]. However, how do departments implement an RT-QA or peer review process and is it consistent across institutions? Should all plans in a department undergo this rigorous check? Or should the process focus on the cases where the impact is likely to have most significant benefit? A 2011 survey of US academic institutions revealed that > 80% had a formal peer process in place [33]. Voluntary member surveys of the Canadian Association of Radiation Oncologists [31] and the American Society for Radiation Oncology [34] reported that 92% and 83% of members had a peer process in their department, however survey response rate was low (36% and 10% respectively) and respondent bias is likely.

To date, there is no strict international guidelines or consensus on the most appropriate model of RT-QA, either in the HNC setting or otherwise, however several national bodies have made published recommendations on how to conduct the peer review process (Table 1) [35–38]. Although this indicates general agreement internationally that RT-QA in HNC is important, they give no specific implementation guidelines.

It is generally agreed that a RO should not practice HNC without adequate training, i.e. completion of a HNC training fellowship. Similarly, there is agreement that RO departments treating HNC should have an RT-QA programme. The majority of reports on institutional peer review arise from large academic centers (Table 2), but the lower volume and hence less experience in the face of high complexity argues strongly for a RT-QA program in small HN practices. This is supported by the research of Boero and colleagues who reported that patients treated with IMRT enjoyed improved survival when treated by high volume HN providers [37]. While the usual caveats regarding the interpretation of population level databases apply, this study retrospectively reviewed medicare claims in the US, and found that all-cause mortality decreased by 21% for every five HNC patients treated by provider per year. In fact, patients treated by high volume providers had both a decreased risk of both HNC-specific mortality and a decreased risk of aspiration pneumonia. The same effect was not seen in patients treated with conventional radiotherapy. A similar finding was seen in the single institutional study by Amarasena et al., where IMRT was identified as the only predictor of a recommended plan change [25]. Chen et al. reported on 107 recurrent oropharyngeal patients referred for consideration of re-irradiation following prior IMRT treatment [39]. Using a deformable registration platform incorporating the initial treatment plan and the imaging at recurrence, approximately 18% and 41% of failures were deemed to be true and marginal misses respectively.

The question arises as to what is the definition of a small HNC center. In the TROG 02.02 study, all the high accrual centers (with only ~5% RT protocol violations) were treating at least 100 mucosal HNC patients annually (personal correspondence). How can smaller centers enable HNC RT-QA? One obvious method is establishing links between smaller centres and large-volume HN centers. Ballo et al. reported the peer review outcomes from the satellites of a network of centers linked to a major academic centre [39]. Although only a small proportion of patients included in this study were HN (442/2988), the implementation of the peer review process in HN resulted in a significant reduction in the number of recommended changes over a four year period (44.8 to 26.1%). This suggests the process is feasible, with the opportunity to significantly improve the quality of radiotherapy plans in the community. However, not all radiation oncologists may feel comfortable with "off-site" peer review. In a national Canadian survey of radiation oncologists, few (22%) agreed this would be beneficial, while 40% preferred that plans were reviewed by an onsite RO who does not treat that tumour site [31]. In HN radiotherapy treatment, a strong argument could be made against this, given the data suggesting higher quality radiotherapy, improved survival and lower rates of toxicity in patients treated by high volume centres or practitioners [8,11,40]. Timeliness is of paramount importance in this process, and there is general agreeance in the aforementioned guidelines that prospective peer review is preferred, as changes made before treatment, are more likely result in plan changes [36–38,41].

Developing trust and respect between small and large HNC centers takes time and care. Clinicians need to communicate differences in planning parameters respectfully, and concentrate on those that will are likely to have a major impact on tumour control and/or on late treatment toxicities. All clinicians want the best for their patients and so there can, and should be, good "buy in" to RT-QA if it can be imparted in a respectful and constructive manner.

Taken together, the data is compelling to recommend a peer review process in routine clinical practice. Even in high-volume academic HNC institutions, major plan changes are not infrequent following peer review. Incorporating a robust and comprehensive peer review is feasible and the most obvious way of reducing human error in the planning process, ensuring that patients are treated with the highest quality radiotherapy plans. As radiation oncologists aiming for optimal outcomes for our patients, peer review should be standard practice in all centres and there is a strong argument that centers without an adequate RT-QA process should not offer treatments to patients with HNC.

Barriers and challenges to implementing RT-QA

A number of barrier and challenges impede the progress of peer review implementation [37]. These barriers may broadly be categorized into clinician, institutional and disease-specific barriers. Not surprisingly, some clinicians may not embrace or even fear the peer review process. Fears of criticism or litigation may be of concern to some, although others may feel that the peer review process may actually improve plans, leading to reduced risk of putative claims. The ability to successfully implement a RT-QA program relies on a departmental culture of open disclosure, safety and quality. For some, the peer review process may be too cumbersome and time consuming to feel that its worthwhile, and others may not understand the key objectives of the process. Smaller centers may not have sufficient expertise to peer review complex plans. Institutions need also to embrace a culture of peer review, allowing sufficient time and resources to ensure clinicians are able to actively participate in this process. Rapid turnarounds in some settings may be required, for example in the case of urgent repeat planning cases. Incorporating RT-QA into routine clinical practice does come at cost, both in time and resources, but the time is relatively small (generally less than 20 minutes per case as per Amarasena et al. study) and we think given the survival benefits, it needs to be seen as an essential part of the multidisciplinary care that is required to deliver safe and optimal HNC patient outcomes [24].

The future - RT-QA

The overwhelming benefits of RT-QA and peer review would suggest that this has to be incorporated into routine clinical practice. International consensus and guidelines on the most appropriate mode of RT-QA needs to be agreed on. Regulatory authorities should mandate

Table 1
Selected peer review recommendations from national bodies.

Organisation	Date	Recommendations				
		Case selection	Number or percentage of plans for review	Includes review of target volumes	Includes review of treatment plan dosimetry	Suggested Timing of review
UK Royal College of Radiologists [38]	2017	Usually radical cases:- All individualised volumes Any protocol-specified volume that does not conform to the departmental protocol Any protocol-specified volume defined within a new protocol where the volumes is different to that used previously. Palliative treatments where volume definition is as complex as for curative or adjuvant cases	All	Yes	No	Pretreatment
American Society for Radiation Oncology [37]	2013	Not specifically mentioned, but priority given where a meaningful impact on patient-outcome expected	Not specifically mentioned	Yes	Yes	Pretreatment
Canadian Association of Radiation Oncology* [36]	2015	All radiation treatment plans administered with adjuvant or curative intent, and other plans where there is a significant potential for adverse patient outcome if tumour targets and/or normal structures are treated inappropriately	All	Yes	Yes	Pretreament or before 25% of total prescribed dose delivered
Royal Australian and New Zealand College of Radiologists [35]	2013	Random selection	Ideally all, suggest 25 patients/year	Yes	No	As close to point of care episode as possible

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Table 2
Outcomes of the head and neck cancer peer review process from selected studies.

Study	Centre	N	Changes (%)	Major Changes (%)	Minor Changes (%)	Notes
Academic centers						
Amarasena [24]	Peter MacCallum Cancer Centre, Melbourne Australia	548	40.8	14.8	21	Major changes defined as changes to GTV or high dose PTV.
Zairis [29]	Dana-Farber / Brigham and Women's Cancer Center, Boston, USA	182	34.1*	3.3	30.8	Major change defined only by change to GTV; any change to target coverage – 26.4%
Rosenthal [25]	The University of Texas MD Anderson Cancer Center, Houston, USA	134	66	11	55	RT-QA incorporated direct peer review of physical examination; 14% new findings on exam: April to July 2003
Cardenas [28]	The University of Texas MD Anderson Cancer Center, Houston, USA	85	76	35	41	RT-QA incorporated direct peer review of physical examination; 14% new findings on exam: Jan to May 2012
Braunstein [27]	University of California, San Francisco, USA	80	55	34	21	RT-QA Included a neuroradiologist
MacKenzie# [26]	University of Calgary, Alberta, Canada	73	12	0	12	Data includes only post contouring review
Rouette [41]	Province of Ontario, Canada	714	5.9	2.9	1.5	In 1.4% unknown if minor or major change
Community centers						
Mitchell [30]	Joint Radiation Oncology Center, David Grant Medical Center, Travis Air Force Base, California	45	15.6	–	–	Major changes were not reported for the HN group
Ballo [39]	Network of the University of Texas MD Anderson Cancer Center, Houston, USA	442	34.2	–	–	Satellite/Outreach review at associated academic institution

* Contouring changes only.
\# survey of all 14 cancer centers in Ontario, including both academic (6/14) and community centers (8/14); only head and neck data included.

that centers treating HNC, and other complex radiation treatment modalities, demonstrate an adequate RT-QA process. However, the radiation oncology community in general needs to agree on the exact process.

Technology is evolving at a rapid rate, and new technologies may allow for improved and more accurate radiotherapy treatment. The implementation of an automated electronic system to manage the peer review process may reduce the number of missed cases [42]. Machine learning, artificial intelligence, deformable registration, auto-segmenting and radiomics may provide additional refinements to the peer review and contouring process. Adaptive radiotherapy will provide a further opportunity for discussion of peer review. Peer review will form an important component of adaptive treatment, however the additional burden of how best to incorporate this into already stretched head and neck departments will need to be considered before this is implemented.

Conclusion

We are all striving for improving outcomes in HNC patients treated with radiotherapy. The RT-QA or peer review process in patients treated with radiotherapy is an essential component in achieving optimal treatment outcomes in both clinical trials and in routine clinical practice. The evidence suggests that patients treated by high volume centres or providers enjoy improved outcomes. Although national bodies have embraced the peer review process, resources, technology and manpower need to be provided to fully facilitate this process. We urgently need specific targeted research, as mentioned above, to best inform international consensus guidelines that are required for both clinical research and routine clinical practice in order to deliver optimal outcomes for HNC patients.

Conflicts of Interest

None

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