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Original Article

Radiotherapy quality assurance of the prospective randomised EORTC-1219/DAHANCA-29 trial: an individual case review analysis

Najlaa Alyamani [a], André Abrunhosa-Branquinho [b], Coreen Corning [a], Marjan Sharabiani [a], Pierre Castadot [c], Jordi Giralt [d], Joanna Kazmierska [e,f], Warren Grant [g], Melissa Christiaens [h], Milan Tomsej [c], Raquel Bar-Deroma [i], Angelo F. Monti [j], Jean-Jacques Stelmes [k], Enrico Clementel [a], Catherine Fortpied [a], Sandra Collette [a], Coen W. Hurkmans [l,m], Vincent Grégoire [n], Jens Overgaard [o], D.-C. Weber [p,q], Nicolaus Andratschke [r,*]

[a] EORTC Headquarters, Brussels, Belgium
[b] Department of Radiotherapy, Unidade Local de Saúde Santa Maria EPE, Lisbon, Portugal
[c] Radiation Oncology, CHU Charleroi, Charleroi, Belgium
[d] Radiation Oncology, Hospital General Vall D'Hebron, Barcelona, Spain
[e] Radiation Oncology Department II, Greater Poland Cancer Centre, Poznan, Poland
[f] Department of Electroradiology, Poznan University of Medical Sciences, Poznan, Poland
[g] Oncology Centre, Cheltenham General Hospital, Gloucestershire Hospitals NHS Foundation, UK
[h] Department of Radiation-Oncology, University Hospitals Leuven, Belgium
[i] Radiation Oncology, Rambam Health Care Campus, Haifa, Israel
[j] Department of Medical Physics, ASST GOM Niguarda, Milan, Italy
[k] Oncology Institute of Southern Switzerland, Bellinzona, Switzerland
[l] Department of Radiation Oncology, Catharina Hospital, Eindhoven, the Netherlands
[m] Department of Electrical Engineering and Department of Applied Physics and Science Education, Technical University Eindhoven, the Netherlands
[n] Department of Radiation Oncology, Université Catholique de Louvain, St-Luc University Hospital, Brussels, Belgium
[o] Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark
[p] Center for Proton Therapy, Paul Scherrer Institute, ETH Domain, Villigen, Switzerland
[q] Department of Radiation Oncology, Inselspital, Bern University Hospital and University of Bern, Switzerland
[r] Department of Radiation Oncology, University Hospital of Zurich, University of Zurich, Switzerland

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ABSTRACT

Background: The EORTC-1219/DAHANCA-29 trial investigated whether adding nimorazole to accelerated radiotherapy (RT) and chemotherapy improves locoregional control of locally advanced head and neck cancer. As part of the trial's RT quality assurance (RTQA) program, individual case review (ICR) of RT plans was performed to assess protocol compliance and treatment planning quality.

Materials and methods: Nineteen centers submitted RT plans for central review. The trial mandated prospective ICR (p-ICR) for the first five patients per institution, with subsequent plans reviewed retrospectively or as optional p-ICR. Plans were reviewed by radiation oncologists and medical physicists. Plans deemed unacceptable in p-ICR were resubmitted for review, whereas retrospective ICR (r-ICR) cases were reviewed once. Plans were categorized as "Acceptable as per protocol," "Acceptable variation," or "Unacceptable variation.".

Results: RT plans for all 194 randomized patients were reviewed, with 174p-ICRs and 44 r-ICRs. The delineation acceptability rate for p-ICR improved from 69% at the first submission to 93% at final review. p-ICR had an 18% higher acceptance rate (90%) compared to r-ICR (73%). Dose and plan acceptability remained high (97%) at both first and final submission, with minimal differences between p-ICR and r-ICR.

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* Corresponding author.
E-mail address: nicolaus.andratschke@usz.ch (N. Andratschke).

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Conclusion: P-ICR significantly improved CTV delineation quality, ensuring higher protocol compliance and treatment planning accuracy. p-ICRs are recommended for complex treatments, tailored to the performance of individual sites.

Introduction

Head and neck (HN) cancer is the seventh most common cancer worldwide, accounting for 3 % of all cancer incidence [1]. The primary histology is squamous cell carcinoma (SCC), with 60 % of cases presenting as locally advanced disease (stages III and IV) [2]. Radiotherapy (RT) remains the primary treatment modality for these patients, either alone or in combination with chemotherapy [3]. Altered RT fractionation combined with a cisplatin-based chemotherapy regimens has been shown to improve outcomes, as supported by the MARCH *meta*-analysis [4]. However, this *meta*-analysis did not consider critical biological factors such as Human papillomavirus (HPV)/p16 status and the hypoxic tumour microenvironment, which are now recognized as key determinants of prognosis and response in HNSCC [5] .

HPV-negative HNSCCs often harbour more aggressive disease biology, posing a major therapeutic challenge. Hypoxia, on the other hand, is a well-established adverse prognostic factor in HNSCC, promoting radio-resistance and tumour progression. In response, several recent trials have sought to improve outcomes in this population through novel radiosensitizing strategies and individualized treatment approaches [6].

Building on these insights, the EORTC-1219/DAHANCA-29 study was designed as a multicenter, phase III placebo-controlled double-blind randomized trial of accelerated fractionated chemoradiotherapy with or without the hypoxic radiosensitizer Nimorazole in the treatment of HPV/p16 negative HNSCC. Although the trial targeted recruiting over 600 patients, it was prematurely closed after enrolling 194 patients.

Radiotherapy quality assurance (RTQA) plays a central role in ensuring protocol adherence in RT clinical trials. The EORTC has implemented an active RTQA program since 1982 [7], emphasizing the importance of maintaining consistency and enhancing outcomes. Retrospective analyses have demonstrated that appropriately planned and delivered RT treatments lead to better clinical outcomes [8,9]. A review analysis of nine studies also indicated that RTQA non-compliances could impact the primary endpoints by up to 62.5 % [10].

To mitigate these risks, EORTC protocols incorporate pre-treatment benchmark cases, individual case reviews, and centralized review process to ensure adherence. The EORTC-1219/DAHANCA-29 trial included such a program, beginning with a benchmark case procedure published previously [11] and extending to prospective and retrospective individual case reviews (ICRs) This analysis evaluates the results of individual case reviews for delineation and dose planning, aiming to assess protocol compliance and identify strategies to improve RTQA in future trials.

Materials and methods

RT protocol and RTQA requirements.

The EORTC-1219/DAHANCA-29 protocol adhered to ICRU Reports 50, 62, and 83 for defining volumes, prescription points, and dose homogeneity [12–14]. Planning CT scan acquisition, target volume definitions, and organs-at-risk (OARs) delineation were detailed by Christiaens *et al.* [11] and aligned with published guidelines [15–17].

Briefly, CT simulation scans extended from the base of the skull to the lower border of the clavicle, with 2–3 mm slice thickness. Patients were immobilized in the supine position using customized head, neck and shoulder masks. Prescribed doses included 70 Gy in 35 fractions to the therapeutic planning target volume (tPTV) and 54.25 Gy in 35 fractions to the prophylactic planning target volume (pPTV), delivered via intensity-modulated radiotherapy with a simultaneous integrated boost (IMRT-SIB). Protocol-specific dose constraints for the target volumes and OARs are detailed in Supplementary Table-1.

The gross tumour volume (GTV) comprised the primary tumour and positive lymph nodes. Clinical target volumes (CTVs) were categorized into primary and nodal CTVs, further subdivided into therapeutic and prophylactic CTVs. Planning target volumes (PTVs) included a 3–5 mm margin around the CTV. Mandatory OARs included the spinal cord, brain stem, and both parotid glands; if possible, the mandible. For oropharyngeal tumours, the larynx was delineated as an OAR, and for pharyngo-laryngeal tumours, the oral cavity was delineated. Additional avoidance structures to optimize treatment plans, such as to prevent hotspots outside the PTV, could be delineated at the discretion of the treating physician and medical physicist.

Submission of the RT plans.

The trial, initiated in July 2014, aimed to recruit over 600 patients but the trial closed prematurely in February 2018 after recruiting 194 patients from 19 participating institutions. Participating centres submitted anonymized RT plans in DICOM-RT format to the EORTC RTQA platform [18,19], where quality control was performed by the RTQA officer. Plans were reviewed using the VODCA platform (Medical Systems Solutions, Switzerland) by a multidisciplinary team of radiation oncologists (ROs) and medical physicists (MPs).

For each digital RT plan, ROs evaluated target volumes (CTV and PTV) delineations and critical OARs. Once delineations were approved, MPs assessed dose and plan parameters, including energy, slice thickness, dose prescription, target dose distribution, and adherence to OARs constraints. Feedback was provided for unacceptable variations (UVs), allowing sites to revise and resubmit plans to ensure protocol compliance (Supplementary table-3). The RTQA review team included five radiation oncologists and three medical physicists, their evaluations and comments were documented in a webform comprising 35 protocol-specific parameters (Supplementary Table-4).

Central Individual case review (ICR).

The EORTC classifies RTQA into five levels [18].Level I, II, IV, and V were applied in this trial [11,20]. Level IV, individual case review (ICR), involved mandatory submission of treatment data before RT initiation, categorized as follows:

- **Prospective ICR (p-ICR):** For the first five patients recruited at each site, a mandatory p-ICR was required. This involved evaluating target volume delineations and dosimetry (dose and plan) parameters before or within the first five days of RT initiation. Beyond the first five cases, p-ICR became optional but was strongly encouraged for all trial participants to ensure the highest level of protocol compliance.

The review process began with a RO assessing the accuracy and consistency of target and OAR delineations. Upon approval, the treatment plan was forwarded to an MP for evaluation of dosimetric parameters, including dose distribution, adherence to dose constraints, and technical aspects of the RT plan.

If either delineation or dosimetry failed to meet protocol standards, feedback was provided to the treating center, requesting necessary corrections and resubmission of the revised plan. Importantly, dosimetry was not reviewed further if delineations were deemed unacceptable. Whenever feasible, the same reviewer assessed all submissions for a given patient to ensure consistency.

Retrospective ICR (r-ICR): For patients unable to undergo a p-ICR, retrospective reviews were conducted. This included evaluation of delineations and/or dosimetry after five days of RT initiation, ideally

within the first three weeks of treatment to allow for major corrections if needed. The review process closely resembled that of the p-ICR, with the same focus on delineation and dosimetry parameters. However, in r-ICR, resubmissions were not requested and instead, feedback was provided to the treatment center with a request to consider any unacceptable variations for future patients to help to ensure improved compliance for subsequent patients. Dosimetry was also not reviewed for cases where delineations were deemed unacceptable, as in p-ICR. Adapted plans due to tumour shrinkage or weight loss were not included in this analysis.

Parameters for plan assessment.

Treatment plan evaluations adhered to protocol guidelines, with delineation and dosimetric parameters documented in a dedicated electronic Case Report Form (eCRF) Supplementary Table-4. Outcomes were graded [21,22]as Acceptable per protocol (A), Acceptable Variation (AV), or Unacceptable Variation (UV) per the Global Harmonisation Group (GHG) [21,22] criteria (Supplementary Table-2.) Results were communicated to investigators, either approving the plan or suggesting modifications for unacceptable variations. Supplementary Table-3 summarizes the EORTC 1219 RTQA guidelines for ICR submission and evaluation.

Statistical analysis

Descriptive statistics were calculated as proportions for categorical variables. Additionally, data on the number of registered patients, types of variations observed in unacceptable and acceptable variations cases, the number of resubmissions required for unacceptable cases, and the final overall grading were collated. Analyses were conducted using Microsoft® Excel 2016 and SAS® (Statistical Analysis System).

Results

At the time of trial closure, 212 patients were registered. Of these, 194 were randomized into one of the two treatment arms, with 191 initiated protocol treatment. However, three patients did not receive the allocated treatment after randomization (off-protocol) due to reasons such as refusal to use thermoplastic shell, renal dysfunction, or death. Individual case reviews (ICRs) were conducted for all 194 randomized patients (Fig. 1).

The trial protocol mandated p-ICRs for the first five RT plans submitted per site, totaling 68 cases. Optional p-ICRs were encouraged for the remaining 126 cases. Despite these guidelines, p-ICRs were conducted in 82 % (56/68) of mandatory p-ICR group and 72 % (91/126) of optional p-ICR group, resulting in 147 prospective reviews. Retrospective ICRs (r-ICRs) were conducted for 44 plans. For three off-protocol patients, the timing of the review remained unclassified due to unavailable RT start dates (Fig. 1). The median turnaround from p-ICR submission to radiotherapy start was 5 working days (IQR: −1 to 11), with some treatments starting prior to final approval despite guidance to submit ≥ 7 days before start; this reflects a pragmatic balance between

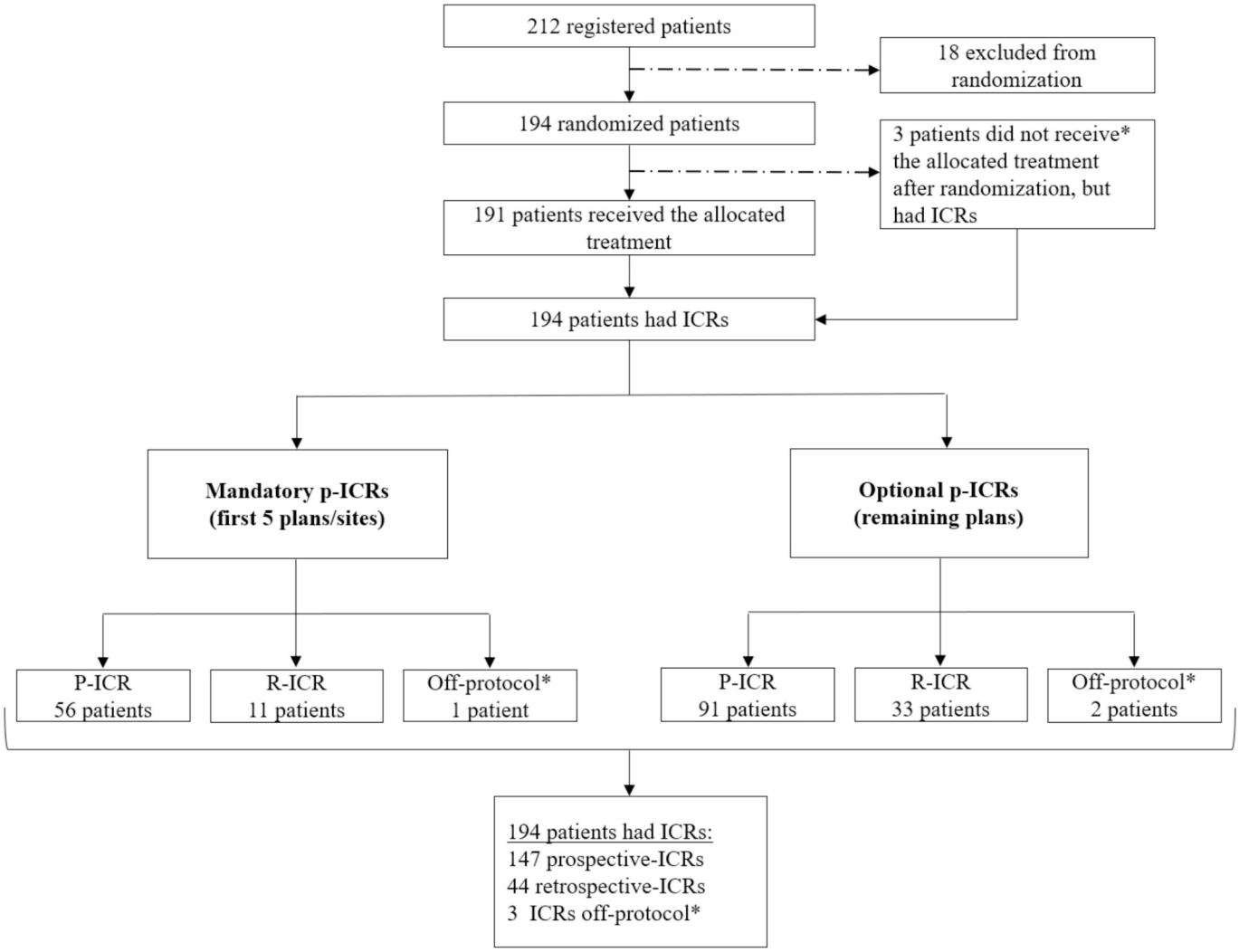

Fig. 1. ICR review timepoint for patients in EORTC-1219.

protocol adherence and timely care.

Among p-ICRs, the delineations of first submission were approved in 69 % (102/147) of cases, evaluated as either per-protocol or acceptable variations. The remaining 31 % (45/147) were deemed unacceptable. Feedback and resubmissions resolved most of these issues, increasing delineation compliance to 93 % (136/147), reflecting a 24 % improvement (Fig. 2**).** In comparison, r-ICRs yielded a 66 % (29/44) acceptance rate for delineation, with 34 % (15/44) remaining unacceptable. Final delineation compliance for p-ICRs exceeded r-ICRs by 27 % (93 % vs 66 % Fig. 3**).**

Prospective dose and plan reviews were conducted for the 136 cases with per protocol or acceptable delineation variations. Of these, 95 % (129/136) were approved, while 4 % (6/136) were deemed unacceptable, and one case (1 %) lacked dose and plan data. After resubmissions, three cases remained unacceptable. For the r-ICRs, 86 % (25/29) of dose and plan reviews were graded as per-protocol or acceptable variation, while four plans were deemed unacceptable. Overall, there was no significant difference in dose and plan compliance between p-ICRs and r-ICRs (Fig. 2**).**

Overall, 26 cases exhibited persistent delineation issues at final review, primarily involving prophylactic nodal CTVs, dose to prophylactic CTV, or dose to therapeutic CTV. Inaccuracies in OAR delineations often involved the brainstem, spinal cord, or spinal cord PRV (Fig. 4**).**

For dose and plan reviews, seven cases remained unacceptable due to deviations from PTV_70 and PTV_54.25 dose constraints **(**Fig. 5**).**

An example of an unacceptable plans is illustrated in (Fig. 6**).**

Discussion

The EORTC-1219 trial demonstrated that prospective individual case reviews (p-ICR) significantly improved the acceptability of delineation plans. Specifically, there was a 24 % improvement in delineation compliance from the first to the final submission, coupled with an 18 % higher compliance rate for p-ICR compared to retrospective individual case reviews (r-ICR). This finding underscores the critical role of p-ICR in optimizing delineation quality. However, the acceptability of dose and plan reviews remained consistently high across both p-ICR and r-ICR, indicating that while p-ICR positively impacted delineation quality, it did not substantially influence the final outcomes of dose and plan reviews. This highlights that dose planning may be more resistant to variation and is less influenced by the timing of the review, which may also be a result of clearly defined protocol constraints and international guidelines.

Radiotherapy quality assurance (RTQA) plays an essential role in clinical trials, particularly for complex treatment like those for head and neck cancers. High compliance with RT protocols has a positive correlation with improved survival outcomes, emphasizing the importance of standardized practices in ensuring effective treatment [8,9]. Despite the established benefits of RTQA, the literature on RTQA process in phase-III clinical trials remains limited [23]. The procedures used in the EORTC-1219 trial aimed to maximize protocol adherence by implementing a benchmark case, conducting mandatory prospective reviews for the first five patients at each site, and to pre-emptively prospectively review as much of the remaining cohort as possible. These efforts led to an improvement in delineation acceptability, with a 24 % increase observed from initial to final review. This finding highlights the effectiveness of p-ICR in identifying and correcting errors in delineation at an early stage.

However, despite the benchmark case for protocol training and clear guidelines for target volume delineation, a considerable number of unacceptable contours were found upon first submission. Many of these could have been detected and thus corrected if comprehensive prospective reviews had been implemented earlier. Furthermore, only 82 % of the mandatory-p-ICR were conducted prospectively, which indicates that there is room for improvement in balancing reviewer workload with the need for timely identification of clinically relevant delineation deviations. This limitation in prospective review implementation may have resulted in delays in detecting some issues, especially at sites where resources for RTQA were limited.

The most common issue identified in unacceptable delineations was

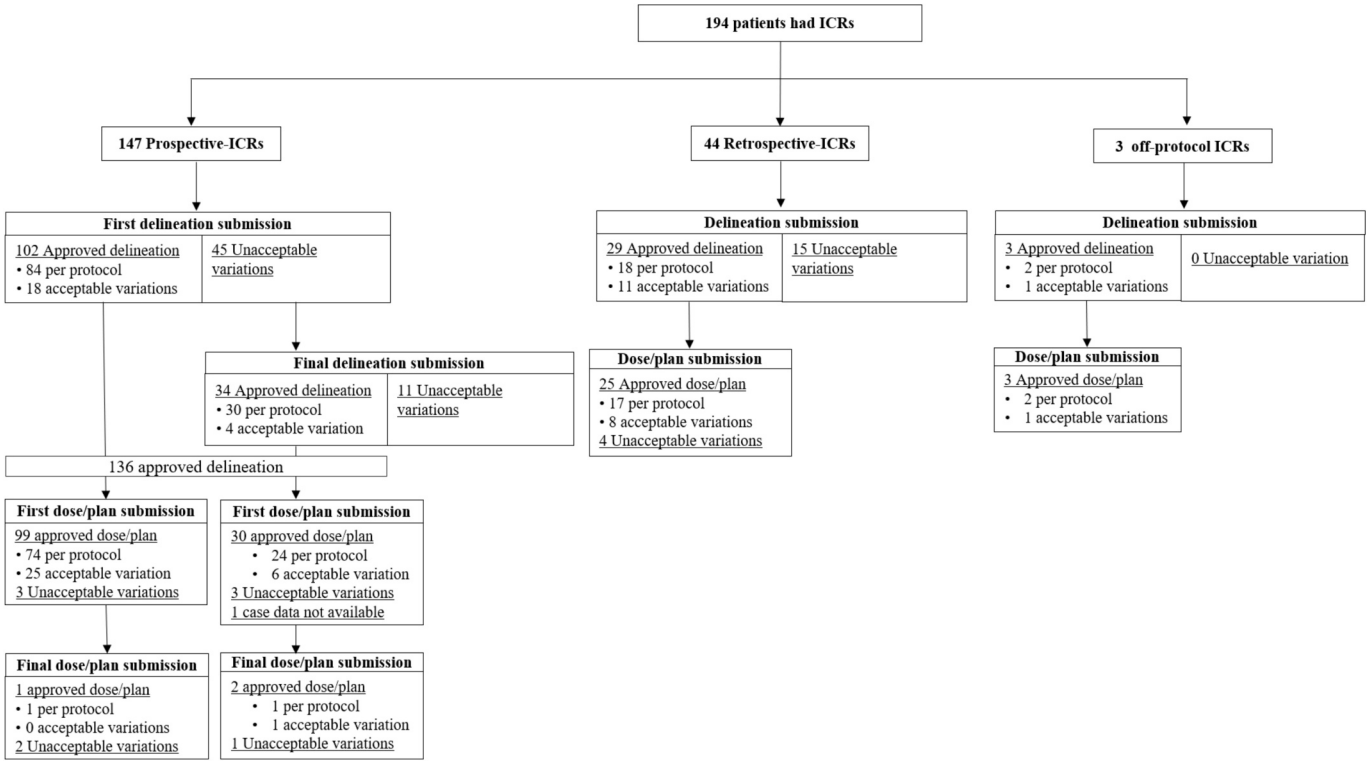

Fig. 2. Prospective vs. Retrospective- ICR outcomes.

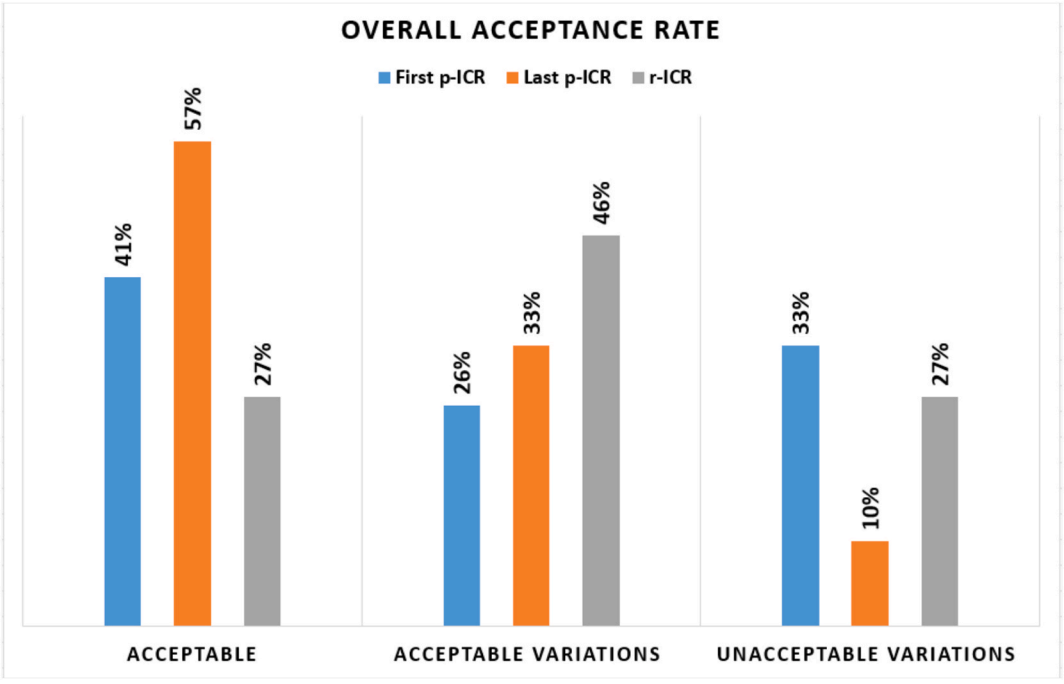

Fig. 3. Overall acceptance rate of p-ICR vs r-ICR.

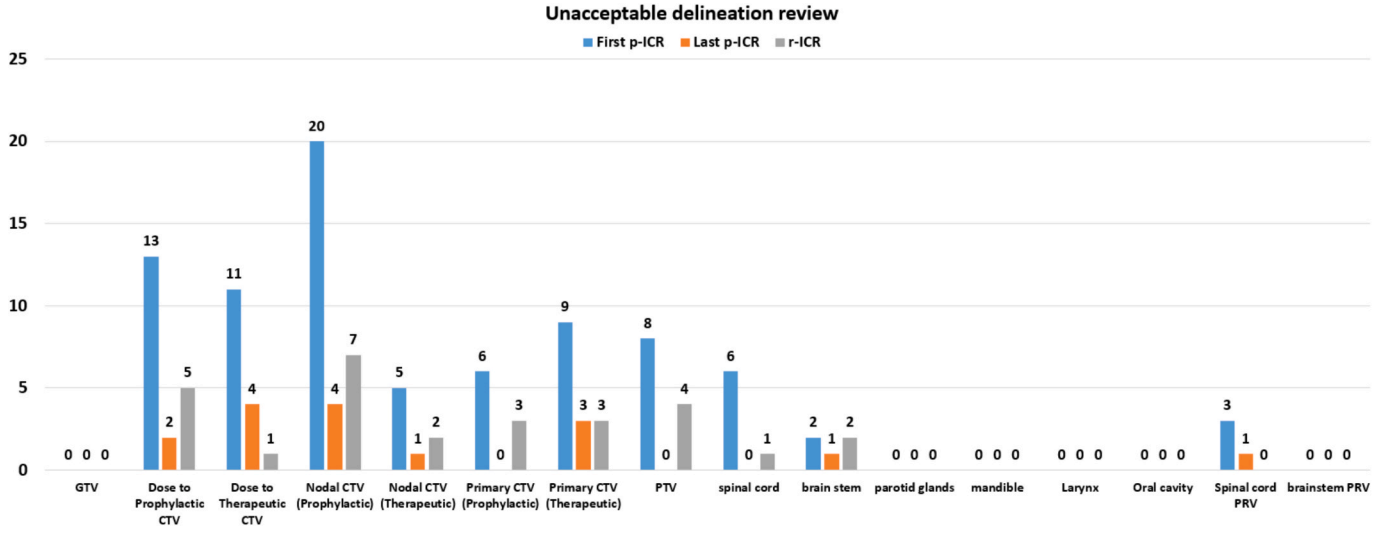

Fig. 4. Causes of unacceptable delineation variations.

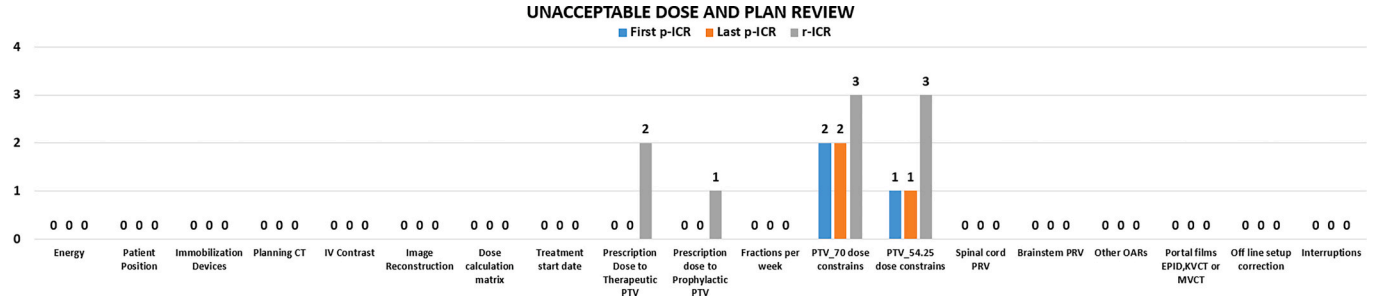

Fig. 5. Causes of unacceptable dose and plan variations.

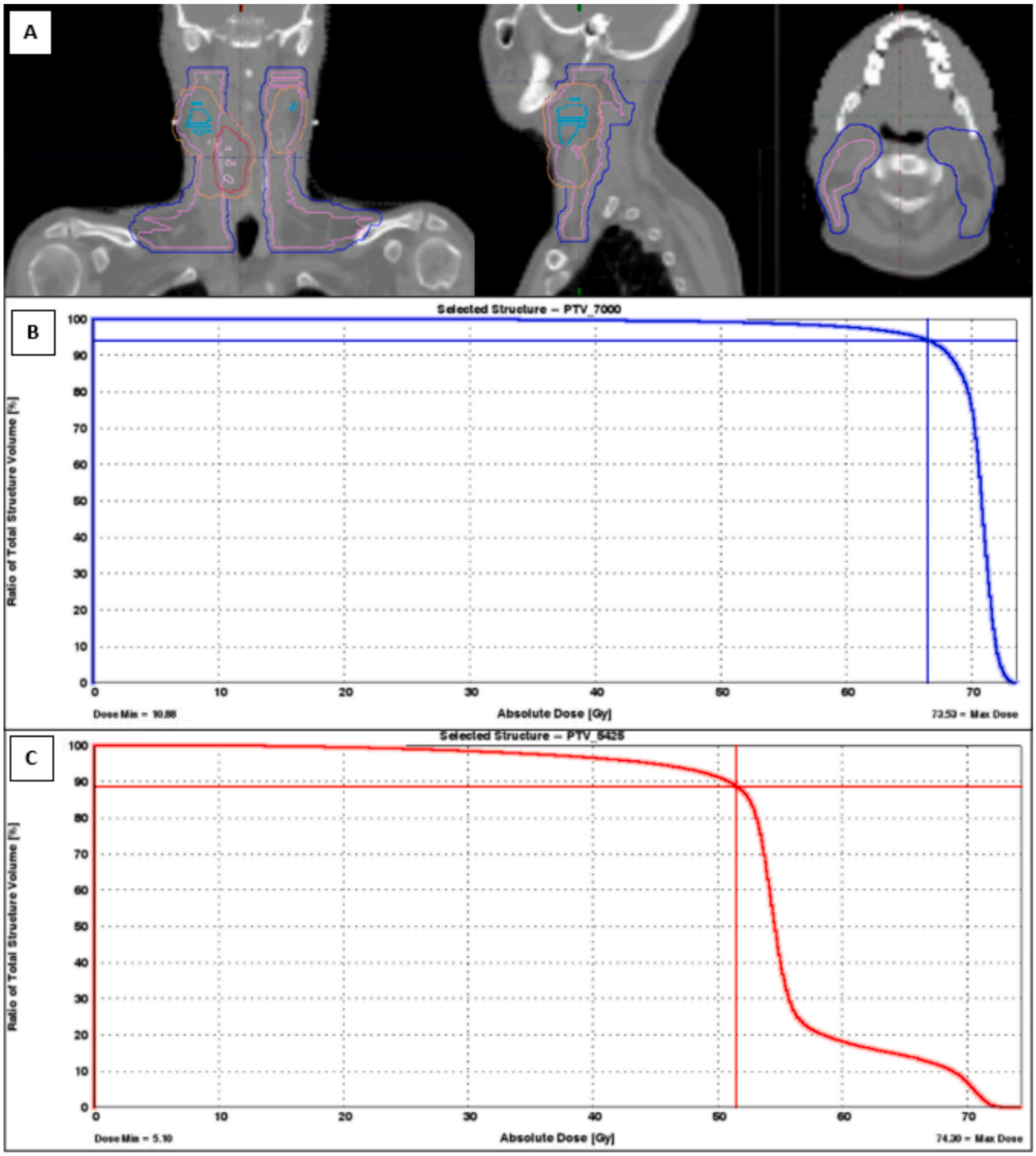

Fig. 6. Example of unacceptable plan.

related to the prophylactic CTV (CTV_5425), particularly in defining the anatomical boundaries of the neck lymph node levels. This finding was somewhat unexpected, as the protocol and referenced international guidelines provide comprehensive details for defining the anatomical boundaries of the neck nodes [24]. Despite these clear instructions, variations persisted, suggesting that further clarification or reinforcement in training may be necessary. Although these variations were protocol violations; the clinical impact of the resulting dose distributions remains unclear.

Although the clinical impact of unacceptable delineation remains uncertain, p-ICR enables proactive correction, which may reduce the risk of unacceptable delineation or dose and plan. However, as most centers adhered to the guideline of initiating planning only after contour approval, only a small subset of cases (~20 patients) had completed plans based on unacceptable initial contours. This limits our ability to quantitively assess dosimetric differences between initial and revised

plans within this trial. Furthermore, central re-planning cannot fully replicate site-level clinical decision-making, which further constrains our evaluation of the true clinical impact. This is an inherent limitation of real-time QA within the context of pragmatic clinical workflows.

Unacceptable dose and plan submissions were relatively low (3 %), and most of these issues were related to non-compliance with dose constraints for PTV_54.25. One potential reason for this could be that some sites did not contour the protocol-allowed cropped PTV, which is designed to reduce skin toxicity in patients without skin involvement. This minor issue highlights the importance of adherence to protocol details.

Interestingly, no significant differences were found between p-ICR and r-ICR regarding dose and plan compliance, this suggests that dose and plan outcomes were more heavily influenced by achievable planning goals, which are shaped by protocol constraints and improved standardization across the trial due to the adoption of international guidelines. The clear, well-established guidelines likely helped reducing inter-planner variability, ensuring a more uniform approach to dose and plan formulation, regardless of the timing of the review.

While p-ICRs have been proven to be a valuable tool in improving RT compliance rate, they are not without challenges as they are time-consuming for involved parties and require careful adherence to complex procedures, which can strain resources at participating centers. To enhance the RTQA process in the future trials, several strategies could be implemented:

1. Structured feedback and Benchmark Comparisons: One approach could involve providing participating institutions with structured feedback, including benchmark comparisons of their performance against other sites. This would foster a learning curve across the centers and help identify areas for improvement early in the trial.
2. Impact Assessment of Delineation Variations: Future studies could also integrate a more quantitative assessment of the impact of delineation variations of the dosimetric outcome. While qualitative evaluations (Per protocol, Acceptable Variations, Unacceptable Variations) have been useful, a deeper exploration into how these variations affect clinical outcomes could provide more actionable insights.
3. AI-Generated Contours for Personalized RTQA: another promising avenue could involve the use of AI to generate contours for treatment planning. By comparing plans based on AI-generated contours to those based on manual delineations, researchers could gain valuable insights into the clinical accuracy of the planning process. Furthermore, this approach could help personalize RTQA for individual trials, potentially optimizing the review process and increasing its efficiency [25].

Conclusions

A p-ICR based RTQA within the EORTC-1219 trial successfully identified a significant portion of noncompliant submissions, particularly related to target and OAR delineation. These issues were promptly corrected, resulting in a high rate of protocol compliance. This demonstrates that prospective RTQA is an essential component of clinical trials, contributing to the accuracy and standardization of treatment planning. However, the implementation of p-ICR could be further optimized, especially at sites with limited resources, to reduce delays in detecting issues early and improve overall compliance across the trial.

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CRediT authorship contribution statement

Najlaa Alyamani: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis. **André Abrunhosa-Branquinho:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation. **Coreen Corning:** Visualization, Supervision, Resources, Formal analysis, Data curation. **Marjan Sharabiani:** Writing – review & editing, Methodology, Formal analysis. **Pierre Castadot:** Writing – review & editing, Software, Data curation. **Jordi Giralt:** Writing – review & editing, Software, Data curation. **Joanna Kazmierska:** Writing – review & editing, Software, Investigation, Data curation. **Warren Grant:** Writing – review & editing, Software, Investigation, Data curation. **Melissa Christiaens:** Writing – review & editing, Software, Investigation, Data curation. **Milan Tomsej:** Writing – review & editing, Software, Data curation. **Raquel Bar-Deroma:** Writing – review & editing, Investigation, Data curation. **Angelo F. Monti:** Writing – review & editing, Investigation, Data curation. **Jean-Jacques Stelmes:** Writing – review & editing, Investigation, Data curation. **Enrico Clementel:** Writing – review & editing, Visualization, Validation, Project administration, Methodology, Data curation, Conceptualization. **Catherine Fortpied:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Sandra Collette:** Writing – review & editing, Resources, Project administration, Investigation, Conceptualization. **Coen W. Hurkmans:** Writing – review & editing, Validation, Software, Data curation, Conceptualization. **Vincent Grégoire:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Jens Overgaard:** Writing – review & editing, Investigation, Data curation, Conceptualization. **D.-C. Weber:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Nicolaus Andratschke:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2025.111141.

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