Clinical Investigation

Optimizing Radiation Therapy Quality Assurance in Clinical Trials: A TROG 08.03 RAVES Substudy

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Summary
Quality assurance (QA) of treatment delivery is essential when conducting clinical trials involving radiation therapy but can be complex and resource intensive. The RAVES TROG 08.03 trial compares adjuvant with early salvage radiation therapy in men with high-risk features after prostate cancer surgery and is recruiting through 32 centers in Australia and New Zealand. The present study aims to explore site and clinician factors associated with major protocol violations to help tailor future quality assurance (QA) protocols.

Purpose: To explore site- and clinician-level factors associated with protocol violations requiring real-time-review (RTR) resubmission in a multicenter clinical trial to help tailor future quality assurance (QA) protocols.

Methods and Materials: RAVES (Radiation Therapy—Adjuvant vs Early Salvage) (Trans-Tasman Radiation Oncology Group 08.03) is a randomized trial comparing adjuvant with early salvage radiation therapy in men with positive surgical margins or pT3 disease after prostatectomy. Quality assurance in RAVES required each clinician and site to submit a credentialing dummy run (DR) and for each patient’s radiation therapy plan to undergo external RTR before treatment. Prospectively defined major violations from trial protocol required remedy and resubmission. Site and clinician factors associated with RTR resubmission were examined using hierarchical modeling.

Results: Data were collected from 171 consecutive patients, treated by 46 clinicians at 32 hospitals. There were 47 RTR resubmissions (27%) due to 65 major violations. The relative rate of resubmission decreased by 29% per year as the study progressed (odds ratio OR, 0.71, P = .02). The majority of resubmissions were due to contouring violations (39 of 65) and dosimetric violations (22 of 65). For each additional patient accrued, significant decreases in RTR resubmission were seen at both clinician level (OR 0.75, P = .02) and site level (OR 0.72, P = .01). The rate of resubmission due to dosimetric violations was only 1.6% after the first 5 patients. Use of IMRT was associated with lower rates of resubmission compared with
Introduction

An important part of modern multicenter radiation therapy clinical trials is treatment plan quality assurance (QA). This ensures that participating institutions are delivering comparable and consistent treatment to the target volumes and normal structures. A QA program defines an acceptable range of deviations from trial protocol, with mechanisms to correct violations that could affect trial outcomes. The importance of good QA is highlighted in the Trans-Tasman Radiation Oncology Group (TROG) 02.02 trial, where the quality of radiation therapy delivered had a greater influence on overall survival than the intervention studied (1). Clinical trial protocol deviations have been shown to reduce efficacy and increase normal tissue complications in numerous other studies (2-4). As such, QA has become a standard part of modern radiation therapy clinical trials.

The use of complex modern radiation therapy techniques has resulted in more rigorous QA programs. Intensive QA results in fewer deviations from protocol; however, limited evidence exists to support the optimal amount and type of trial-specific QA activities (5, 6). The current challenge in clinical trial QA is to reduce the complexity and costs without reducing the efficacy and safety using risk-adaptation strategies.

RAVES (Radiation Therapy—Adjuvant vs Early Salvage)—TROG 08.03 is a multicenter, randomized clinical trial comparing adjuvant with early salvage radiation therapy in men with positive surgical margins or pT3 disease after radical prostatectomy (7). Quality assurance in RAVES requires each clinician and each site to submit a credentialing dummy-run case and for each patient’s radiation therapy plan to undergo external real-time review before commencing treatment. Prospectively defined major violations from trial protocol require remedy and resubmission before starting treatment. Our study aimed to explore site- and clinician-level factors that are associated with protocol violations and real-time-review resubmissions to help tailor future QA protocols.

Methods and Materials

Patient demographics

RAVES is a phase 3, multicenter, controlled trial led by the TROG collaborative group in Australia and New Zealand. Eligible patients had undergone radical prostatectomy for prostate adenocarcinoma and had at least 1 of the following risk factors: positive surgical margins, extra prostatic extension, or seminal vesicle involvement. Patients were randomized 1:1 to either adjuvant radiation therapy commenced within 4 to 6 months of radical prostatectomy or close observation with salvage radiation therapy when prostate-specific antigen rises to ≥0.20 ng/mL.

Radiation therapy protocol

The radiation therapy dose in both study arms was 64 Gy in 32 fractions, 5 fractions per week, to the prostate bed planning target volume. Target volumes were contoured as per the consensus guidelines from the Faculty of Radiation Oncology Genito-Urinary Group (FROGG), with specified dosimetric parameters in the protocol (8). Organs at risk (OARs) included rectum, femur, and bladder, with prospectively specified volumes and dose constraints. An example of contouring in RAVES trial as per the FROGG consensus guidelines is provided in Figure 1. Treatment planning was carried out with 3-dimensional (3D) planning systems, with the ability to use intensity modulated radiation therapy (IMRT) techniques for credentialed sites (7).

QA protocol

A credentialing benchmarking dummy-run case was incorporated into the study design to train radiation oncologists (ROs) and institutions on protocol requirements before recruiting patients. A consensus set of plan review variables and tolerance limits was developed by all the reviewing investigators before start of the trial. Participating ROs were requested to delineate the volumes of interest on a common CT data set before participating in the trial. Participating sites were asked to plan each investigator’s dummy run and the technical data, and dosimetric data were submitted for review before recruiting patients. All dummy-run cases were reviewed by 3 independent reviewers to ensure ongoing consistency in the review process. For sites using IMRT technique, additional QA activities, such as external dosimetric audit (phantom study) and a planning benchmarking dummy-run case verified using the approved in-house IMRT dosimetry QA protocol, were also performed. Sites were only allowed to treat using an IMRT technique after passing IMRT credentialing activities.

Each trial patient receiving radiation therapy underwent real-time review. The target volumes and treatment plans
were reviewed by an independent RO before the start of treatment for each real-time review. Sites and ROs were also given an opportunity to submit their data for advice before submission as a part of the QA protocol. Data were submitted in an anonymized electronic format using the TROG central quality management system and reviewed using SWAN software to enable timely review (9). The technical preparation for the review process took on average between 30 and 60 minutes.

Completed submissions were judged as adequate, minor deviation, or major deviation. Prospectively defined major violations from trial protocol required remedy and resubmission before the patient started treatment. Each submission also generated detailed feedback to the treating site from the QA team.

Data collection

Each submission involved review of up to 82 collected variables with prospectively set limits. Data on simulation, dose, treatment planning, target volume, and OAR were collected for each dummy run and real-time review. Data on patient identification, site, RO, submission date, type of submission (dummy run or real-time review), and radiation therapy technique were collected against each submission. Additional data such as total number of cases, number of cases per year, and days since last submission were calculated for each site and clinician. All major violations were categorized into contouring violations (target volume and OAR), dosimetric violations, or other. All underlying causes of major deviations were recorded.

Analysis

The primary endpoint was the rate of real-time-review resubmission and the factors that influenced this. Predictive factors explored were the incidence of dummy-run resubmission, number of cases, time between initial credentialing and real-time review, time since previous submission, and radiation therapy technique (3D conformal radiation therapy [3D-CRT] or IMRT). Where relevant, these factors were modeled at both the clinician and site levels.

Factors associated with resubmission were examined using hierarchical modeling. Mixed-effects logistic regression (with fixed and random effects) was used to model these variables. Association between number of major violations and treatment technique type (IMRT/3D-CRT) was examined using a Poisson mixed-effects model; within-hospital and clinician effects were treated as random. All statistical analyses were programmed using SAS v9.4 (SAS Institute, Cary, NC).

Results

Cohort characteristics

Between June 2009 and October 2014, data from 171 patients out of 174 consecutively treated patients (98%) were reviewed. A total of 46 ROs from 32 institutions around Australia and New Zealand took part in the trial. All RO and site credentialing dummy-run and real-time-review submissions were available for analysis.

The median total number of patients recruited by each RO was 7 (range, 1-20), with a mean of 2 patients per year, resulting in a submission every 175 days (median). The median number of patients recruited by each site was 9 (range, 1-25), with a mean of 3 patients per year, resulting in a submission after a median of 100 days. The majority of patients were treated with the 3D-CRT technique (69%), and IMRT was used in 31%. The site and clinician level descriptors are shown in Table 1.
Dummy-run results

A total of 3928 variables were reviewed for 57 dummy-run submissions. There were 9 dummy-run resubmissions (16%) due to 32 major protocol violations. Contouring violations accounted for 78% (25 of 32) of major violations, compared with 13% (4 of 32) dosimetric violations and 9% other violations. All major violations were remedied before credentialing with the feedback provided. Ten percent of dummy-run submissions had both contouring and dosimetric violations. There were 70 minor violations split between contouring (50%) and dosimetric (46%) violations. The summary of dummy-run violations is provided in Table 2.

Real-time-review results

A total of 7581 variables were reviewed for 171 consecutive real-time-review submissions. There were 47 real-time-review resubmissions (27% of all cases) due to 65 major violations. All major violations required resubmission and were remedied before patients were treated as part of the trial. A minority of resubmissions (5 of 47) with major violations were deemed appropriate on the basis of clinical circumstances by the reviewing team. There were 11 cases submitted for advice before formal submission. Six of these cases would have resulted in a major violation but were remedied on the basis of feedback, before formal submission. The rate of resubmission decreased by a relative risk of 29% per year as the study progressed (odds ratio [OR] 0.71, 95% confidence interval [CI] 0.54-0.95, P = .02) (Fig. 2). The low number of patients recruited from a small number of trial leading centers explains the low resubmission rate in 2009.

Significant decreases in real-time-review resubmissions were seen at both clinician and site level for each additional patient accrued. For each additional case submitted, the relative risk of resubmission decreased by 25% at the clinician level (OR 0.75, 95% CI 0.59-0.95, P = .02) and by 28% by site (OR 0.72, 95% CI 0.55-0.92, P < .01). The absolute rate of resubmission dropped from 40% for the first patient submitted from each clinician or site to 20% after ≥5 patients (Fig. 3).

The majority of resubmissions were due to contouring (39 of 65) compared with dosimetric violations (22 of 65). The majority of contouring violations (90%) related to target volume (clinical target volume and planning target volume) delineation. The most common dosimetric violation (10 of 22) was failure to meet rectal dose-volume histogram constraints. Dosimetric violations were frequently caused by contouring violations. Only 15 patients (9%) needed resubmission due to dosimetric violations alone. A summary of real-time-review violations (Table 2) and

![Fig. 2](image)

**Fig. 2.** Rate of resubmission (percentage) over time, showing 19% relative risk reduction per year.
description for causes of major violations is provided in Table 3. In addition, there were 114 minor violations distributed between contouring (50%) and dosimetric (50%) violations.

Clinician-specific factors

At the clinician level, dummy-run resubmission was correlated with a 42% increase in relative risk of subsequent real-time-review resubmission, which did not achieve statistical significance (OR 1.42, 95% CI 0.44-4.57). Clinicians requiring dummy-run resubmission had a 39% (18 of 46) resubmission rate during their first real-time review. Higher-accruing clinicians (>5 patients) had a non-statistically significant 37% reduction in resubmission rate compared with low-accruing clinicians (OR 0.63, 95% CI 0.24-1.70). The lowest risk for subsequent resubmission were clinicians that did not need dummy-run or first real-time-review resubmission (17%) compared with the higher-risk group that needed both resubmitted (44%).

At the RO level, days since last submission was not statistically correlated with subsequent real-time-review resubmission. The rate of resubmissions due to contouring violations after 5 patients for a particular RO was 15%. Table 4 describes the association between clinician factors and resubmission rate.

Site-specific factors

High-accruing sites (>5 patients) had a non-statistically significant 53% reduction in resubmission rate compared with low-accruing sites (OR 0.47, 95% CI 0.18-1.21). After the first 5 patients at a particular site, the rate of resubmission due to dosimetric violations alone was only 1.6%.

At a site level, dummy-run resubmission was not correlated with subsequent increase in real-time-review resubmission (OR 0.98, 95% CI 0.27-3.6). Days since last submission was also not correlated with subsequent increase in real-time-review resubmission. Table 4 describes the association between site factors and resubmission rate.

Radiation therapy technique

Use of IMRT was associated with lower rates of resubmission compared with 3D-CRT (OR 0.38, 95% CI 0.15-0.99, P = .05). The use of IMRT was associated with only a 2% incidence of major dosimetric violations, compared with 17% with use of 3D-CRT. The rates of major contouring violations were equal between 3D-CRT (19%) and IMRT (20%) after taking into account of real-time reviews where presubmission advice was provided.

Discussion

Clinical trial radiation therapy QA programs have become more comprehensive and labor-intensive and can be a barrier to trial accrual (6). The current challenge is to optimize the intensity of QA directed by good-quality evidence and to evaluate which components of a QA program deliver the most benefit.

Our study is the first analysis of a prospectively collected real-time-review QA in postoperative prostate cancer radiation therapy. We have observed a resubmission rate of 27%. Despite dummy-run and extensive feedback from QA reviewers during real-time review, our study failed to identify any clinician or site subgroups in whom resubmission rates fall to zero. Our study shows some value in the credentialing dummy-run activity at the clinician level in reducing subsequent major protocol violations.

The rate of resubmission is dependent on the complexity of target volume and OAR volumes and dosimetric...
planning, which are treatment site and trial specific (2). The rate of resubmission in our study is comparable to that previously reported in the adjuvant prostate cancer European Organization for Research and Treatment of Cancer (EORTC 22043-33041) dummy-run study (10). Post—radical prostatectomy radiation therapy represents moderate treatment complexity, as represented by the overall rate of resubmission. The rate of resubmission in our study compares to 20% to 25% in head and neck trials (1, 11), 8% to 10% in lung trials (12, 13), 22% to 70% for central nervous system tumors (14-17), and 5% to 10% in radical prostate cancer trials (18, 19).

The decreasing rate of resubmissions with time indicates the importance of feedback provided during QA in educating the RO and sites, and preventing future protocol violations. This has been seen in most other QA studies and remains an important role for QA (17, 19, 20).

The majority of resubmissions in our study were due to contouring violations, with only 9% of resubmissions due to dosimetric violations alone. This highlights the importance of clinician-specific QA activities. The baseline level of resubmissions due to contouring violations in high-accruing ROs was 15%. This rate of resubmission is likely due to the variability in patient anatomy, ambiguity in delineation, and individual clinical scenarios and thus is unlikely to be reduced further with additional interventions (2, 10). Although some violations need correction for optimal treatment delivery, in other situations some degree of clinician discretion and interaction with the QA team is appropriate. In this situation, the main aim of the real-time review is to manage the former types of violations, but to be able to exercise some flexibility when clinical circumstances require.

Various clinician-specific factors were identified that predicted future real-time-review resubmission. The lowest risk for resubmission was clinicians who did not need dummy-run or first real-time-review resubmission (17%), compared with the higher-risk group that needed both resubmitted (44%). This presents an opportunity to risk-adapt QA by reducing the real-time-review intensity in lower-risk clinicians. Of note, the number of cases per year and time since last submission were not predictors of future need for resubmission.

Most dosimetric violations in our study were caused by contouring violations causing rectal constraints to be exceeded. Most target volume contouring violations were failure to cover the prostate bed volume posteriorly. The level of resubmission due to clinically significant dosimetric violations alone reached a nadir of <2% at high-accruing sites after the first 5 patients accrued. Numerous other studies have also shown an association between number of accrued cases per institution and number of protocol deviations (16, 21, 22). This again reflects the complexity of dosimetric planning required in the post—radical prostatectomy radiation therapy setting. In post—radical prostatectomy radiation therapy, this presents an opportunity to risk-adapt QA activity by reducing the QA intensity involving only contouring real-time review at high-accruing sites.

Our study indicated that advanced radiation therapy technologies such as IMRT were associated with decreased protocol violations. This could be explained by the improved dosimetry achievable with IMRT, the use of IMRT by large-volume centers, and late temporal implementation of technology in the study period. Widespread use of IMRT in Australia and New Zealand occurred during RAVES trial accrual, and our findings indicate that there should not be a barrier to the implementation of advanced radiation therapy technologies in future trials with appropriate QA protocols.

Strengths of this study lie with the prospectively set QA protocol and data collection. All clinicians and sites were required to undergo dummy run, and all patients underwent real-time review before treatment, ensuring completeness of data to help identify factors associated with resubmission. Limitations of the study include the limited number of patients and event rates, resulting in lower statistical confidence for various predictive factors. The results of our study should be interpreted with caution when extrapolating to other tumor sites with differing contouring and planning complexities.

Trans-Tasman Radiation Oncology Group studies now have a risk-adapted approach to QA delivery. This ranges across 3 levels, from minimal for studies where radiation therapy is not part of the research question (eg, the impact of humidification on mucositis risk for head and neck

### Table 4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comparison</th>
<th>Odds ratio</th>
<th>95% Confidence interval (P value)</th>
</tr>
</thead>
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<tr>
<td>Year</td>
<td>Continuous</td>
<td>0.71</td>
<td>0.54-0.95 (.02)</td>
</tr>
<tr>
<td>Treatment technique type</td>
<td>IMRT (vs 3D-CRT)</td>
<td>0.38</td>
<td>0.15-0.99 (.05)</td>
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<td>Dummy-run resubmission, clinician</td>
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<td>0.44-4.57 (.55)</td>
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<tr>
<td>Dummy-run resubmission, site</td>
<td>Yes (vs no)</td>
<td>0.98</td>
<td>0.27-3.6 (.98)</td>
</tr>
<tr>
<td>Days since last submission, clinician</td>
<td>Continuous</td>
<td>1.00</td>
<td>0.99-1.00 (.32)</td>
</tr>
<tr>
<td>Days since last submission, site</td>
<td>Continuous</td>
<td>1.00</td>
<td>0.99-1.00 (.88)</td>
</tr>
<tr>
<td>Cumulative no. of patients, clinician</td>
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<td>0.91</td>
<td>0.82-0.98 (.05)</td>
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<tr>
<td>Cumulative no. of patients, site</td>
<td>Continuous</td>
<td>0.95</td>
<td>0.89-1.02 (.13)</td>
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</table>

Abbreviations as in Table 1.
cancer patients) through to trials of newer techniques such as stereotactic body radiotherapy, where the first 3 to 5 patients from each site have real-time review, and then only once every 3 to 5 cases thereafter (23). On the basis of the results of our study, the current TROG approach of risk stratification and titrating level of real-time review seems to be valid, while maintaining the flexibility to intensify review intensity if protocol violations are consistently observed.

A cost-benefit strategy is likely to be beneficial for future trial QA protocols. The costs incurred by dosimetric analysis and contour reviews have to be reviewed against the evidence-based benefits derived from various QA activities, to help select patients in whom real-time review can be moderated.

Conclusion

The RAVES QA protocol is a useful template for future multi-institute radiation therapy studies. The majority of resubmissions (89%) passed, indicating feasibility to achieve trial protocol requirements while removing clinically significant protocol violations.

Several low- and high-risk factors were identified that may assist with tailoring future clinical trial QA. Because the real-time resubmission rate was largely independent of the credentialing exercise, some form of real-time-review QA is recommended. Greatest benefit from QA was mainly derived early in trial activation and clinician experience.

References