Prospective review of radiotherapy trials through implementation of standardised multi-centre workflow and IT infrastructure

Sarah Gwynne[1,2], Gareth Jones[2,3], Rhydian Maggs[2,3], David Eaton[4,5], Elizabeth Miles[5], John Staffurth[2,6],Lisette Nixon[2,7], Ruby Ray[6], Geraint Lewis[2,3], Tom Crosby[3*], Emiliano Spezi[2,8*]

[*] Joint last authors

1. South West Wales Cancer Centre, Swansea, UK

2. NISCHR Cardiff RTTQA Centre, Cardiff, UK

3. Velindre Cancer Centre, Cardiff, UK

4. Radiotherapy Physics, Mount Vernon Hospital, Northwood, UK

5. NCRI RTTQA Team, Mount Vernon Hospital, Northwood, UK

6. Institute of Cancer and Genetics, School of Medicine, Cardiff University, Cardiff, UK

7. Wales Cancer Trials Unit, Cardiff University, Cardiff, UK

8. School of Engineering, Cardiff University, Cardiff, UK

This work has been presented in part as a poster presentation at the 56th ASTRO Annual Meeting 2014, San Francisco, USA and as an oral presentation at UKRO 2015, Coventry, UK

Acknowledgements

The authors would like to acknowledge the clinical reviewers for the NeoSCOPE QA programme, Somnath Mukherjee (SM), Maria Hawkins (MH) and Ganesh Radhakrishna (GR).

ARISTOTLE and NeoSCOPE trials were funded by Cancer Research UK project grants CRUK/08/032 and C44694/A14614 respectively.

Prospective review of radiotherapy trials through implementation of standardised multi-centre workflow and IT infrastructure

Abstract

Objectives

We sought to develop a process that would allow us to perform prospective review of outlining in trials using expert reviewers based in multiple centres.

Methods

We implemented a specific IT infrastructure and workflow that could serve all organisations involved in the RTQA process

Results

Data was processed and packaged in the Computational Environment for Radiotherapy Research binary format and securely transmitted to the expert reviewer at the designated remote organisation. It was opened and reviewed using the distributed CERR-compiled application and standardised report sent to the respective centre. Centres were expected to correct any unacceptable deviations and resubmit outlining for approval, prior to commencing treatment. 75% of reviews were completed and fed back to centres within 3 working days. There were no delays in treatment start date.

Conclusion

Our distributed RTQA review approach provides a method of prospective outlining review at multiple centres, without compromising quality, delaying start of treatment or need for significant additional resources. Future progress in the area of prospective individual case review will need to be supported by additional resources for clinician time to undertake the reviews.

Advances in knowledge

Trial groups around the world have formulated different approaches to address the need for prospective review of radiotherapy data with clinical trials, in line with available resources. We report a UK solution that has allowed the workload for outlining review to be distributed across a wider group of volunteer reviewers, without the need for any additional infrastructure costs and has already been adopted within the UK radiotherapy trials community.

Introduction

It is now well established that radiotherapy (RT) trial outcomes are related to protocol compliance and quality of the delivered RT[1-7]. The detrimental effects of non-compliance to

protocol can be minimised by a robust RT Quality Assurance (RTQA) Programme[3,8]. UK RT trials are encouraged to undertake some form of pre-accrual assessment of outlining[7] and planning, which can take the form of a benchmark case, or a dummy run[9]. While this approach is associated with improved protocol compliance[3]; to ensure the ongoing quality of the RT delivery within the trial, depending on the complexity of the RT, it should be complemented by some form of on-trial assessment (individual case review, ICR) [10].

The UK National Radiotherapy Trials Quality Assurance (RTTQA) group operates from four sites, ours being one of the host sites. Much of the ICR for trials supported by this group has been retrospective, in keeping with many other international trials. This does not allow protocol deviations to be identified and corrected prior to an individual patient commencing treatment. ARISTOTLE [1], a phase III trial for locally advanced rectal cancer, was the first trial in our RTTQA centre to undertake prospective ICR (prior to start of treatment), but was reliant on a single clinician working in the centre to perform all the reviews. The NeoSCOPE[11] trial was re-introducing neoadjuvant chemoradiotherapy prior to oesophagectomy into the UK and there were concerns about increasing post-operative morbidity and mortality with this approach. In order to ensure that non protocol-compliant RT was not the cause for any excess toxicity, prospective ICR review of all cases up to the first toxicity assessment (after 20 patients had completed treatment) was undertaken. This necessitated a more sustainable approach to prospective ICR, allowing multiple reviewers not necessarily based at one of the RTTQA centres to participate in the process, without compromising on quality. Here we report on how we achieved this.

Methods

For the purpose of ICR we implemented a specific IT infrastructure and workflow that could serve all organisations involved in the RTQA process. The main requirements that we identified for the former are outlined in Table 1. The CERR (Computational Environment for Radiotherapy Research) met all of these requirements. It was custom built and validated for the purpose of analysing and sharing RT data for research purposes[12] and our RTTQA group had previous experience of its use .[13] A compiled version (a stand alone version without the need for license or specific IT infrastructure) was provided by the Database and IT Solutions subgroup of the UK RTTQA group[2]. It can be downloaded at a remote site within minutes and a user guide is also made available.

Results

The workflow process

[1] http://www.ctc.ucl.ac.uk/TrialDetails.aspx?TrialID=48

[2] http://www.rttrialsqa.org.uk/rttqa/

In step 1 all centres were asked to submit the outlining data (all target volumes including organs at risk) in DICOM format along with the relevant diagnostic information (CT, EUS and PET reports). The former was done with the centre-specific Treatment Planning System (TPS). Data was anonymised at the treating centre, as per trial regulations and exported in DICOM format, and securely transmitted to the RTTQA Centre.. All transferred data was stored locally on a dedicated RTTQA drive.

Centres were encouraged to submit outlining as soon as it was available, and given the option to either wait for feedback, or proceed with the planning on the understanding that the outlines may need to be modified. In step 2, anonymised DICOM data were received by our RTTQA Centre and were checked for integrity and validated by the trial QA contact. This consisted of ensuring all data was complete and anonymised and could be processed in CERR, along with a visual check of the outlines and correlation with the plan assessment form. Data were then processed and packaged in the CERR[12] binary format and securely transmitted to the expert reviewer at the designated remote organisation. In step 3 the expert reviewer received the binary package, which was opened and reviewed using the distributed CERR-compiled application. The review was then carried out, a standardised report prepared and submitted to our RTTQA Centre and sent to the respective centre. Dialogue between the reviewer and the centre was undertaken if an unacceptable deviation or a data query was identified. A detailed review of the planning was also undertaken but is beyond the scope of this paper.

Use of the workflow in NeoSCOPE

The ICRs for outlining in this trial were undertaken by 5 upper GI clinical oncologists (SG, TC, SM, MH, GR, all NeoSCOPE Trial Management Group members) on a rota basis, only one of whom was based at the RTTQA centre. Reviews for patients outlined using 3D or 4DCT (both allowed in the trial) were assigned according to the expertise of the reviewers. In order to minimise inter-reviewer variation, all of the reviewers had been part of the RT protocol development group and had undertaken the pre-accrual assessment process in their respective centres. A standardised proforma for review and feedback was used, which detailed pre–agreed acceptable and unacceptable deviations for outlining.

Prospective ICR was undertaken for the first 20 patients recruited to the trial as described above, regardless of recruiting centre and previous performance. However, as recruitment from the 15 participating centres was not at the same rate, prospective ICR was also extended to the first recruited case from each centre, repeating the process if there were any unacceptable deviations, until there was a satisfactory submission. Centres were expected to correct any unacceptable deviations and resubmit outlining for approval, prior to commencing treatment. The intention was to feed back to centres within 3 working days and this was achieved in 75% of reviews with a median of 2 days. There were no delays in treatment start date. Subsequent cases were subject to ‘timely retrospective review’, with

review within 2 weeks (10/25#) of the start of RT. This approach was intended to minimise the burden of the initial rigorous QA requirements on departments which were performing well, but still allow identification of a significant error in sufficient time for correction to be made to at least half the number of remaining fractions. This target was achieved in 93% of reviews, with 40% before the start of treatment. 39 (47%) real-time and 44 (53%) timely-retrospective reviews were undertaken. 9 cases required resubmission, 6(67%) were real time and 3(33%) timely retrospective. The compiled version of CERR has now been made available to the other RTTQA centres for trials involving a range of anatomical sites.

Discussion

Historically, most RTQA of gastrointestinal RT trials has been retrospective[2]. Given recent evidence for the relationship between protocol deviations and poor outcome, we no longer believe it is acceptable to simply collect the data on deviations retrospectively, since there is no opportunity to correct prior to, or during the course of the treatment, or to provide feedback to the clinician involved. However, the move to prospective ICR is both labour and resource intensive[14,15]. If prospective ICR is to be performed in a timely manner and avoid delays in the patient's treatment, feedback to centres is needed within 3 working days. The RTTQA group has limited funding to provide the expertise for outlining review and the four centres are not expected to offer high level clinical expertise in outlining, which is viewed to be the responsibility of the Chief Investigator or nominated radiotherapy lead. In reality the workload and timescales are too onerous for a single clinician in most cases and there has been an urgent need to develop a robust process to involve multiple reviewers, who would often be based outside of the four RTTQA centres

The first trial to use prospective ICR in our RTTQA centre was ARISTOTLE. In this trial a single clinician reviewed all the outlines and provided feedback to centres within 48 hours. While feasible for this particular trial as one of the lead members of the Trial Management Group was based at the RTTQA centre, this is not a model that can be applied to all trials and a move towards a multi-clinician approach is recommended. We have been able to implement a distributed review process through the use of a secure, fast and reliable IT infrastructure and a distributed application specifically designed to review RT data. The application used in this work is platform independent, enabling the review to be conducted under the same conditions as if the review was conducted in the RTTQA centre.

Recently Skripcak *et al.*[16] reported on challenges and possible solutions for the strategic development of international research data exchange framework in radiation therapy and oncology and identified three major classes of data pooling models: Centralised, Decentralised and Hybrid. Our approach used a decentralised model in which data are collected, validated and processed at the designated RTTQA centre by expert trial QA staff. These data are then securely transmitted to the review sites, as appropriate, in anonymised form. In this model the applications needed to technically access the data and review the

clinical case are distributed and installed at the review centre and managed by the local IT department, following local rules and security protocols. Furthermore our approach minimises possible interoperability issues between the different clinical IT solutions implemented in institutions participating to the trial. The procedure that we implemented ensures completeness and quality of the data submitted for review to individual centres because the information is processed, validated and standardised in a single file format that is checked for integrity before leaving the RTTQA centre. This also facilitates and speeds up the real time review process.

Different approaches have been adopted to address the issue of prospective ICR [14,15,17-19]. The EORTC have reported the development of a digital central review facility, where centres upload data through a secure website and then the reviewers, who may not be based at the central RTQA centre, are able to remotely access the data through a terminal server[20]. The International Society of Paediatric Oncology (Europe) high risk neuroblastoma group have developed a web-based platform which allows remote uploading of radiology and RT-related data and images from the participating centres, allowing remote review by clinicians in a timely fashion, without the need to meet in one place at one time[19]. In the USA, the leading QA centres serving the current National Cancer Institute clinical trial programme have been brought together to form a single organisation administered by the American College of Radiology Clinical Research Centre in Philadelphia. This new organisation, will be known as the Imaging and Radiation Oncology Core Group[18]. Real-time reviews are conducted by a faculty from the University of Massachusetts. Study chairs wishing to perform retrospective reviews have a secure Virtual Private Network (VPN) connection to the database and can access the information (T Fitzgerald, personal communication). SWAN[17] was developed in Australia with the aim of facilitating objective analysis, quality assurance and review of digital treatment planning data from TROG multi-centre RT trials. It is utilised for central review, pre-accrual benchmark cases and credentialing. It has unique properties in that it can perform automatic reviews and reporting which allows specific fields in a data export to be examined for adherence to protocol criteria. While not removing the need for manual review, it can reduce the time needed for review by identifying errors in data submission prior to being sent to a clinician for review.

The trend is for trials to become more complex and more costly[14]. Continued progress requires dedicated resources. Plan reviews and dosimetry audits have been supported by funding of dedicated physicist time, but across Europe most of the outlining reviews are undertaken by clinicians (e.g. chief investigators or other member of the trial management group) on a voluntary basis,, or by clinical fellows supported by grants from various sources[14]. The RTOG have shown that in four of their trials, including the most recent trial of IMRT for anal cancer, the major deviations were inaccurate target volume delineation[3] and additional resources are needed to ensure we can continue to provide high quality review of outlining for future trials.

Conclusion

Our distributed RTQA review approach provides a method of prospective outlining review at multiple centres, without compromising quality, delaying start of treatment or need for significant additional resources. Future progress in the area of prospective ICR will need to be supported by additional resources for clinician time to undertake the reviews.

References

1. Peters LJ, O'Sullivan B, Giralt J, et al: Critical Impact of Radiotherapy Protocol Compliance and Quality in the Treatment of Advanced Head and Neck Cancer: Results From TROG 02.02. Journal of Clinical Oncology 28:2996-3001, 2010

2. Weber DC, Tomsej M, Melidis C, et al: QA makes a clinical trial stronger: Evidence-based medicine in radiation therapy. Radiotherapy and Oncology 105:4-8, 2012

3. Willett CG, Moughan J, O'Meara E, et al: Compliance with therapeutic guidelines in Radiation Therapy Oncology Group prospective gastrointestinal clinical trials. Radiotherapy and Oncology 105:9-13, 2012

4. Abrams RA, Winter KA, Regine WF, et al: Failure to Adhere to Protocol Specified Radiation Therapy Guidelines was Associated with Decreased Survival in RTOG 9704—A Phase III Trial of Adjuvant Chemotherapy and Chemoradiotherapy for Patients with Resected Adenocarcinoma of the Pancreas. International Journal of Radiation Oncology Biology Physics doi:10.1016/j.ijrobp.2010.11.039 2011

5. Crane CH, Winter K, Regine W, et al: Phase 2 study of Bevacizumab with Concurrent Capecitabine and radiation followed by maintenance gemcitabine and bevacizumab for locally advanced pancreatic cancer: Radiation Oncology Group 0411. Journal of Clinical Oncology 27, 2009

6. Roques TW: Patient Selection and Radiotherapy Volume Definition d Can We Improve the Weakest Links in the Treatment Chain? Clinical Oncology 26:353-355, 2014

7. Ohri N, Shen X, Dicker AP, et al: Radiotherapy Protocol Deviations and Clinical Outcomes: A Meta-analysis of Cooperative Group Clinical Trials. Journal of National Cancer Institute 105:387-393, 2013

8. Evans CM, Burnet NG, Hall E, et al: The Radiotherapy Clinical Trial Research Landscape in the UK Between

2004 and 2013: A Cross-sectional Analysis. Clinical Oncology 27:491-494, 2015

9. Melidis C, Bosch WR, Izewska J, et al: Global Harmonization of Quality Assurance Naming Conventions in Radiation Therapy Clinical Trials. Internation Journal of Radiation Oncology Biology Physics 90:1242-1249, 2014

10. Gwynne S, Spezi E, Sebag-Montefiore D, et al: Improving radiotherapy quality assurance in clinical trials: assessment of target volume delineation of the pre-accrual benchmark case British Journal of Radiology 86:20120398 2013

11. Mukherjee S, Hurt C, Gwynne S, et al: NEOSCOPE: a randomised Phase II study of induction chemotherapy followed by either oxaliplatin/capecitabine or paclitaxel/carboplatin

based chemoradiation as pre-operative regimen for resectable oesophageal adenocarcinoma. BMC Cancer 15:48, 2015

12. Deasy JO, Blanco AI, Clark VH: CERR:a computational environment for radiotherapy research. Medical Physics 30:979-985

2003

13. Gwynne S, Spezi E, Wills L, et al: Inter-observer Variation in Outlining of Pre-trial Test Case in the SCOPE1 Trial: A United Kingdom Definitive Chemoradiotherapy Trial for Esophageal Cancer. International Journal of Radiation Oncology Biology Physics 84:1037-1042, 2012

14. Weber DC, Poortmans PMP, Hurkmans CW, et al: Quality assurance for prospective EORTC radiation oncology trials:The challenges of advanced technology in a multicenter international setting

Radiotherapy and Oncology 100:150-156, 2011

15. Bekelman J, E, Deye J A, Vikram B, et al: Redesigning radiotherapy quality assurance: Opportunities to develop an efficient, evidence-system to support clinical trials. Internation Journal of Radiation Oncology Biology Physics 83:782-790, 2012

16. Skripcak T, Belka C, Bosch W, et al: Creating a data exchange strategy for radiotherapy research: towards federated databases and anonymised public datasets. Radiotherapy and Oncology 113:303-9, 2014

17. Ebert MA, Haworth A, Kearvell R, et al: Detailed review and analysis of complex radiotherapy clinical trial planning data:Evaluation and initial experience with the SWAN software system. Radiotherapy and Oncology 86:200-210, 2008

18. Fitzgerald T J: A new model for imaging and radiation therapy quality assurance in the national clinical trials network of the National Cancer Institute. internation Journal of Radiation Oncology Biology Physics 88:272-273, 2014

19. Gaze M N, T B, Dieckmann K, et al: Devlopment of an electronic database for quality assurance of radiotherapy in the International Society of Paediatric Oncology (Europe) high risk neuroblastoma study. Radiotherapy and Oncology 97:593-595, 2010

20. A Fairchild, Collette L, Hurkmans C, et al: Do results of the EORTC dummy run predict quality of radiotherapy delivered within multicentre clinical trials? European Journal of Cancer 48:3232-3239, 2012

Table 1 – Summary of main requirements for the UK RTTQA workflow and software to be used for real time review of multi-centre radiotherapy trials.

Workflow	Comply with good clinical practice and data protection regulations
	Decentralised or hybrid data pooling model
	Accessible and secure data transfer
	Network speed and reliability
	Validation of completeness and quality of data
	Standardisation of data format and consistent quality review moving from a single to a multiple site basis
	Simplified process that meets prospective ICR requirements
Software	Distributable to both RTTQA and non-RTTQA centres
	Operating system independent
	Standalone with no additional equipment required
	Read in digital data exported from multiple TPS and PACS (DICOM, DICOM-RT, RTOG formats)
	Easy to use with functionalities and tools similar to those found in TPS
	Centrally developed and maintained
	Locally managed (IT remote organisation)

TPS – treatment planning system, ICR – individual case review, PACS – picture archiving and information system, RT – radiotherapy