# A Review of the Activities of the ITC in Support of RTOG Advanced Technology Clinical Trials


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## 1 ABSTRACT


**Purpose:** To report lessons learned by the Image-guided Therapy QA Center (ITC) in clinical trials QA software development and digital data QA process in nearly 15 years experience in facilitating QA review for RTOG advanced technology (AT) clinical trials that require digital data submission.

**Materials & Methods:** ITC as part of the Advanced Technology QA Consortium (ATC) developed a modular system for digital data submission, queriable archival storage, and web-based remote QA review (*"ATC Method 1"*), which has been used in support of RTOG AT protocols. This technology has also played a key role in assisting treatment planning system (TPS) manufacturers in verifying that their RTOG Data Exchange and DICOM implementations (CT, RT Structure Set, RT Dose, RT Plan, and RT Image) match ATC's digital data exchange conformance statement. ITC and RTOG have developed credentialing criteria, e.g., on-line Facility Questionnaire and "Dry-Run" test designed to demonstrate participating institution's ability to submit a protocol compliant digital data set prior to placing patients on study. Data are sent to ITC via FTP or media. QA review includes (1) data integrity review by ITC for completeness of protocol required elements, format of data, and possible data corruption; (2) recalculation of Dose Volume Histograms (DVHs) by ITC; (3) review of target volume and organ at risk contours compliance by study chair using web-based *Remote Review Tool (RRT)*; and (4) review of dose prescription and dose heterogeneity compliance by RTOG HQ Dosimetry Group using RRT.

**Results:** To date, 15 TPS (8 vendors) have implemented ATC-compliant RTOG/DICOM export software. ITC has successfully supported 15 RTOG AT protocols (Phase I-III trials). Over 400 institutions have been credentialed to submit digital data and over 4400 digital data sets have been submitted to ITC. Overall, approximately 1/4 of cases submitted on these trials required intervention by ITC to correct data integrity/completeness problems before data could be evaluated by dosimetrists/study chairs. Explicit problems in digital data submission discovered by ITC have been categorized and will be reviewed. Dry Run test experience varies, e.g., for an IMRT protocol only 1/3 of the credentialed institutions passed on first submission. ITC found that submitted DVHs lack consistency due to algorithmic differences among TPSs. For dose distributions with high gradients (e.g., brachy, IMRT), discrepancies in excess of 15% were observed between submitted and ITC-recalculated DVHs for volumes < 50 cc.

**Conclusion:** Experience in managing data for AT clinical trials has demonstrated the need for an active data integrity QA process to assure completeness and integrity of data submitted from participating institutions prior to review for protocol compliance by QA reviewers. Re-calculation of DVHs by ITC is necessary for consistent correlation of dosimetry with outcomes. ITC's web-based RRT is both an effective tool for QA review of AT clinical trials data by study chairs and RTOG Dosimetry Group and an aid to TPS vendors in developing/verifying implementation of digital data export. Future software design should emphasize use of modular architecture with well-defined interfaces to enable integration of commercial-off-the-shelf, open-source and custom software components.



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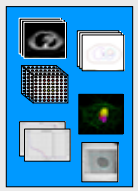
## 2 ITC's HISTORY

- 1992: RTOG recognized the potential for 3-D conformal radiation therapy (3DCRT) and established a 3D QA Center at Washington University in St. Louis to provide 3DCRT quality control for planned multi-institutional 3DCRT clinical trials.
- 1994: NCI funded nine institutions, to form the 3D Oncology Group (3DOG) whose charge was to develop a multi-institutional trial to determine whether 3DCRT could allow safe delivery of escalated doses of radiation in men with prostate cancer.
  - Because of the highly technical/sophisticated nature of this technology, it was critical to create a robust QA process to collect/review image-based planning/verification data for study patients .
  - RTOG was funded by the NCI to manage the 3DOG protocol registration, outcome data management, and statistical analysis.
  - The Image-Guided Therapy Center (ITC), (previously referred to as the RTOG 3DQA Center) was funded to develop the mechanism for data submission, QA review, and assist in establishing the minimal requirements for study participation.
  - Most importantly, the ITC did develop a data exchange specification for the electronic transfer of volumetric treatment planning digital data (referred to as *RTOG Data Exchange Specification*). Using this specification, essentially all of the 3DCRT planning data for each accrual could be transferred in an electronic format for QA review and later outcome analysis.
- 1995: 3DOG protocol participation was expanded and opened (as RTOG 9406) to other RTOG member institutions that could demonstrate that they met the protocol QA requirements, particularly digital data submission to ITC.
- 1998-99: Based on the success of the 3DOG/RTOG 94-06 clinical trial, the NCI recognized the need to expand this form of QA support for all cooperative groups, and in May 1998, issued an RFA (CA-98-006) entitled *Advanced Technology Radiation Therapy Clinical Trials Support* and in 1999 funded the two Advanced Technology Centers (ATCs):
  - a QA consortium headed by the ITC with subcontracts to the Radiological Physics Center (RPC), Quality Assurance Review Center (QARC), and RTOG; and
  - the Resource Center for Emerging Technology (RCET) located at the University of Florida.
- 2002: Two ATC grants consolidated by NCI into a single ATC grant moving RCET into above mentioned QA Consortium headed by ITC.
- 2002-present: ATC is working to eliminate duplication of effort and facilitate sharing of QA resources among cooperative/QA groups and help ensure that appropriate and uniform QA procedures/criteria are developed for AT trials across all cooperative groups.

## 3 Question: What are the special requirements of advanced-technology radiotherapy clinical trials?

### Answer: Digital Data Submission and Remote Review

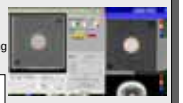
- Protocol Compliant Data Set
  - Patient's Volumetric CT Data Set
  - All protocol-required contours
  - Volumetric 3-D dose distribution (for each fraction group)
  - Beam geometry – orientation and shape
  - DVHs for full dose plan for all protocol volumes/structures
  - Digital films (DRRs or on-line images) optional
- Why not just collect the DVH data?
  - Loss of spatial Information in DVHs
  - Loss of fractionation information in DVHs
  - Variation in dose distributions throughout an organ may lead to different expectations of toxicity for some organs.
  - DVHs may not be adequate for developing dose-response models.
- Allows linkage of volumetric treatment planning data to clinical outcomes data



## 4 ITC'S ROLE IN DEVELOPMENT OF DIGITAL DATA EXCHANGE FOR CLINICAL TRIALS QA

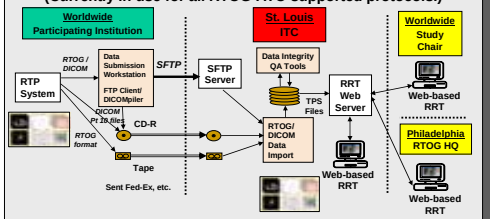
- ITC developed and maintains the *RTOG Data Exchange Specification.*
- Participates in DICOM WG-7 (RT Objects) and the IHE-RO initiative.
- ITC participated in the development of Clinical Trials Identification modules (DICOM WG18).
- Organized 2004 ATC/AAPM/ NEMA DICOM Demonstration
- Hosted series of RTOG/DICOM Implementers' Workshops (1995, 1999, 2001, 2002, 2003, and 2004).
- ITC developed a system of software *("ATC Method 1")* to receive, process, and review volumetric treatment planning data for AT clinical trials. Shown at right ITC web-based Remote Review Tool (RRT).
- ITC assists individual TPS manufacturers in implementing ATC compliant digital data export capabilities.

(See http://atc.wustl.edu)



Screen capture at right showing comparison of RT Structures and isodose curves displayed by RRT (left) and those displayed by vendor's TPS (right).

## 5 ITC's Clinical Trials Remote Review System *(ATC Method 1)* (Currently in use for all RTOG ATC-supported protocols.)

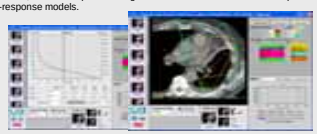



## 6 ITC's Remote Review Tool

ITC data review capabilities include web-based tools, which allow visualization of images, structure sets, dose distributions and dose volume histograms. The treatment planning-verification database maintained by the ITC represents the most comprehensive dataset available for patients treated with advanced technologies and provides researchers the capability to access volumetric dose distributions, which can be evaluated with reference to segmented, volumetric patient image data and be correlated with the protocol outcomes to develop robust dose-response models.

**Remote Review Tool (RRT)**

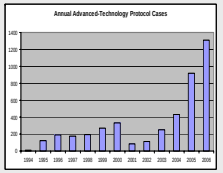
- CT Images (zoom, window/level)
- Structure contours (review, editing)
- Isodose contours
- Interactive DVH display
- Point-dose display

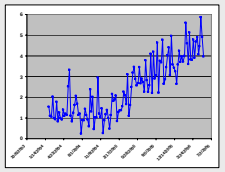


## 7 RESULTS: Digital Data Submitted to ITC

Progress in the development of digital data submission capabilities of commercial treatment planning systems is reflected in the data below. As of Sept. 5, 2006:

- 8 commercial TPS vendors (15 TPSs) have implemented export capability compliant with ITC data import.
- 438 institutions are able to submit data to ITC.
- 4,407 complete digital data sets submitted to ITC over 12 year period
- Yearly accrual statistics are shown in table below. Note that in 2006, YTD accruals exceed all previous 12 month accruals.
- Digital data submitted to ITC (Gbytes/week) continues to grow rapidly.



## 8 Digital Data Integrity QA

The ITC has been accepting, processing and reviewing digital data submissions for support (QA and analysis) of advanced technology protocols for the past 12 years. Over 4400 case data sets have been submitted and processed for review by the ITC. Often data do not come to the ITC in a reviewable form, and the ITC must intervene and investigate issues that need resolution before the data can be processed and reviewed. We refer to this review as *digital data integrity QA*. Very often the receipt of reviewable digital data is an iterative process that requires repeated correspondence with the institution. Over the years several issues have been seen consistently which require intervention by the ITC personnel, and include the following:

1. Misuse of Treatment planning system data export capabilities.
2. Missing protocol required elements or mistakes in protocol understanding.
3. Error in use of digital transfer software
4. New release of treatment planning system with inability to correctly submit ATC compliant data.

Problems in categories 1,2, and 3 are seen on a daily basis. Category 4 occurs much less frequently, but is much more complicated to resolve because it requires software changes by the vendor.

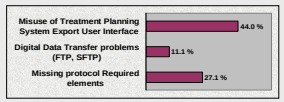
## 9 Digital Data Integrity QA

Table below shows rate of problems requiring intervention by the ITC staff for each RTOG protocol supported by the ITC. 2100 submissions were received for the 0413 protocol, a large phase III study involving partial breast irradiation. Overall for the data collected on 2480 submissions, 660 or 27% required intervention by the ITC staff. Often this intervention included iterative communications with personnel at the institution submitting the data.

| RTOG Protocol | # of submissions | # Cases requiring ITC intervention | % Cases requiring ITC intervention | Interval for which statistics are given |
|---|---|---|---|---|
| 0126 | 183 | 56 | 32 % | 1/2006 – 6/2006 |
| 0413 | 2100 | 570 | 27 % | 2/2005 – 6/2006 |
| 0232 | 37 | 7 | 19 % | 1/2006 – 6/2006 |
| 0522 | 26 | 9 | 35 % | 1/2006 – 6/2006 |
| 0236 | 27 | 3 | 11 % | 1/2006 – 6/2006 |
| 0321 | 73 | 5 | 7 % | 1/2006 – 6/2006 |
| 0117 | 16 | 3 | 19 % | 1/2006 – 6/2006 |
| 0521 | 18 | 7 | 39 | 1/2006 – 6/2006 |
| TOTAL | 2480 | 660 | 27 % | |

## 10 Digital Data Integrity QA

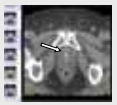
- Chart at right shows the rate of specific errors seen on a daily basis at the ITC. Overall 27% of cases submitted require human intervention by ITC due to errors in submission of the data.




- Two figures below are examples of digital data submitted that required intervention by the ITC before the data could be reviewed by a RTOG study chair.

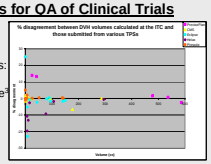
➔Figure on left: example where non square CTs were submitted and numbers of rows & columns were incorrectly specified.

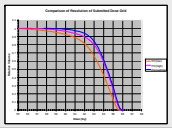
➔Figure on right: example where a CT gantry tilt was used when scanning patient, resulting in a misalignment between CTs & structures (arrow indicate urethra contour and actual location of urethra).



## 11 DVH Analysis: Consequences for QA of Clinical Trials

Graph at right illustrates discrepancies between structure volumes computed by ITC and those submitted digitally from 5 commercial 3DCRT TPSs: Elekta PrecisePlan, CMS FOCUS/XiO, Varian Eclipse, Nucletron Helax TMS, and Philips Pinnacle[3].



- Comparison of submitted vs. calculated DVHs for two different submissions on left graph (a) 5 mm (ITC(low)) dose grid and (b) 2 mm dose grid (ITC(high)).
- Lower resolution DVH demonstrates a major variation according to the protocol, while the submitted DVH shows much better coverage.

## 12 RTOG Protocols Supported by ITC's Clinical Trials Remote Review System *(ATC Method 1)*

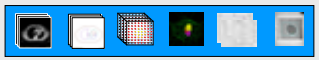
**Completed Protocols**

- **RTOG 9406:** Ph I/II Prostate (3DCRT; 54 institutions credentialed;. 1084 patients registered).
- **RTOG 9311:** Ph I/II Lung (3DCRT; 26 institutions credentialed; 180 patients registered).
- **RTOG 9803:** Ph I/II Brain (3DCRT; 46 institutions credentialed; 210 patients registered).
- **RTOG 0022:** Ph I/II Oropharyngeal (3DCRT/IMRT; 32 institutions credentialed: 69 patients registered).
- **RTOG 0225:** Ph I/II Nasopharyngeal (3DCRT/IMRT; 36 institutions credentialed; 68 patients registered).
- **RTOG 0319:** Ph I/II PBI (3DCRT; 31 institutions credentialed; 58 patients registered)
- **RTOG 0321:** Ph I/II Prostate (HDR; 18 institutions credentialed; 129 patients registered).

**Active Protocols**

- **RTOG 0117:** Ph I/II Lung (3DCRT; 48 institutions credentialed; 48 patients registered).
- **RTOG 0126:** Ph III Prostate (3DCRT/IMRT; 146 institutions credentialed (70 IMRT);1010 patients registered (229 IMRT)).
- **RTOG 0232:** Ph III Prostate (Brachy seeds; 67 institutions credentialed. 228 patients registered)
- **RTOG 0234:** Ph II H&N (IMRT cases only; 51 (IMRT) institutions credentialed. 219 patients registered).
- **RTOG 0236:** Ph II Lung (SBRT; 8 institutions credentialed; 58 patients registered).
- **NSABP B39/RTOG 0413:** Ph III Breast PBI (3DCRT/M/MC; 364 (299CRT/220M/34MC) institutions credentialed. 2080 (785CRT/193M/64MC) patients registered).
- **RTOG 0415:** Ph III Prostate (3DCRT/IMRT; 146 institutions credentialed (70 IMRT); 31 patients registered).
- **RTOG 0418:** Ph II Endometrial/Cervical Ca (IMRT; 70 institutions credentialed; 15 patients registered).
- **RTOG 0421:** Ph III H&N (3DCRT/IMRT; 42 institutions credentialed; 14 patients registered to study).
- **RTOG 0438:** Ph I Liver (SBRT; 1 institution credentialed; 3 patients registered).
- **RTOG 0515:** Ph II Lung (3DCRT/PET; 0 institutions credentialed; 0 patients registered to study)
- **RTOG 0521:** Ph III Prostate (IMRT cases only; 68 institutions credentialed; 54 patients registered ).
- **RTOG 0522:** Ph III H&N (3DCRT/IMRT; 61 institutions credentialed for IMRT; 67 patients registered).

## 13 ITC Treatment Planning-Verification Database and RTOG Clinical Outcome Database Used to Support Secondary Analysis of Clinical Trials Data



- RTOG 9406 data provided – NIH R01 Grant: Dose-Volume Modeling of Late Rectal and Bladder Toxicity (P.I. S. Tucker, Ph.D., M.D. Anderson)
- RTOG 9311 data provided – NIH R01 Grant: Normal Tissue Complication Modeling for Radiotherapy (P.I. J. Deasy Ph.D., Washington Univ.)
- RTOG 9406 data provided – Publication: M. Roach, et al., Penile bulb dose and impotence after 3DCRT for prostate cancer on RTOG 9406: Findings from a prospective, multi-institutional, phase I/II dose-escalation study. IJROBP 60(5): 1351–1356, 2004.

## 14 SUMMARY AND CONCLUSIONS

- ITC and RTOG are part of the Advanced Technology QA Consortium (ATC) that capitalizes on existing infrastructure and strengths of national QA programs.
- ITC has been a leading pioneer in the development of electronic data exchange and software for QA review for radiation therapy clinical trials.
- 8 treatment planning system vendors (15 different planning systems) have released ATC-compliant RTOG/DICOM export software.
- ITC has successfully supported 20 RTOG AT protocols (Phase I-III trials); many more are being planned.
- Over 400 institutions have been credentialed to submit digital data to ITC and over 4,400 full volumetric digital data sets have been submitted to ITC.
- Approximately 1/4 of cases submitted on these trials required intervention by ITC to correct data integrity problems before data could be evaluated by dosimetrists/study chairs.
- Dry Run test experience varies; rapid review for first case and timely review thereafter for early cases appears better suited to achieve quality results.
- Submitted DVHs lack consistency due to algorithmic differences among TPSs; re-calculation of DVHs by ITC is necessary for consistent correlation of dosimetry with outcomes.
- ITC's web-based QA system provides a robust infrastructure for digital data submission, archiving, and web-based QA review of RT objects.
  - has been the enabling technology that has allowed RTOG to uniquely conduct 3DCRT, IMRT, SBRT, HDR, and prostate seeds clinical trials that require volumetric digital data submission.
  - has greatly benefited TPS vendors in developing/verifying implementation of digital data export.
- ITC /RTOG databases are an important resource to facilitate future outcomes research.


## ACKNOWLEDGEMENTS

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