QART in clinical trials: An EORTC update

Coen Hurkmans

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Manager: Christos Melidis
Coordinator: Julia Rengier

Medical Advisors:

CNS	Brigitta Baumert (Maastricht, NL) Sara Erridge (Edinburgh, UK)
Head and Neck	Hans Langendijk (Groningen, NL) Sandra Nuyts (Leuven, B)
Breast	Philip Poortmans (Tilburg, NL) Wilfried Budach (Dusseldorf, D)
Lung	Ursula Nestle (Freiburg, D) Xavier Geets (Brussels, B)
Gastro-Intestinal	Philip Maingon (Dijon, F) Oscar Matzinger (Lausanne, CH)
Genito-Urinary	Christopher Scrase (Ipswich, UK) Fons van den Bergh (Groningen, NL)
Others:	Nomination of ad hoc person as required
Physicist advisors:	Raquel Bar-Deroma (Haifa, IL) Coen Hurkmans (Eindhoven, NL) Angelo Monti (Como, I) Milan Tomsej (Charleroi, B) Hayley James (Ipswich, UK)
RT Technologists:	Frederic Duclos (Lausanne, CH) Marjolein van Os (Rotterdam, NL)
Observers:	Christos Melidis (Brussels, B) Liisa Pylkkanen (Clinical Research Physician, EORTC HQ)
Coordinator	Julia Rengier (ROG Administrator)

content

- Subsites: definition and QA rules
- Standard trial protocol chapters
- Digital platform
- Future challenges
- Virtual phantom

(sub)sites: an oncology perspective

Increasing complexity of multidisciplinary clinical studies:

➔ extends to integrated disciplines:

- imaging
- laboratory expertise
- pathology

➔ constantly evolving and more regulated environment

➔ ensure international and multidisciplinary efficiency

SPECIALISATION ➔ division of tasks over several sites!

Subsites: What are the issues?

Who is responsible/contact person?

➔ for the trial management/administrative work?

➔ for legal liability?

➔ for patient information and contacts?

➔ for retrieving info from all departments (at/in several sites)

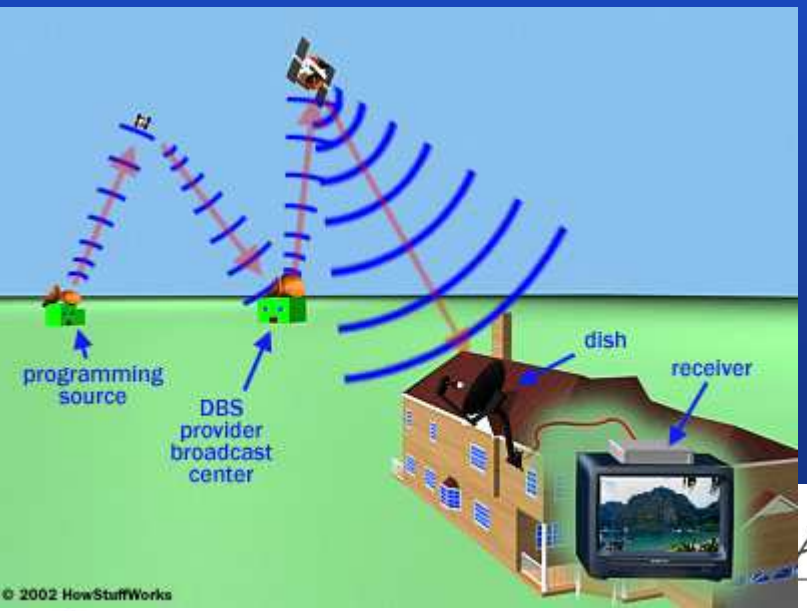
Working procedures of the collaborating departments?

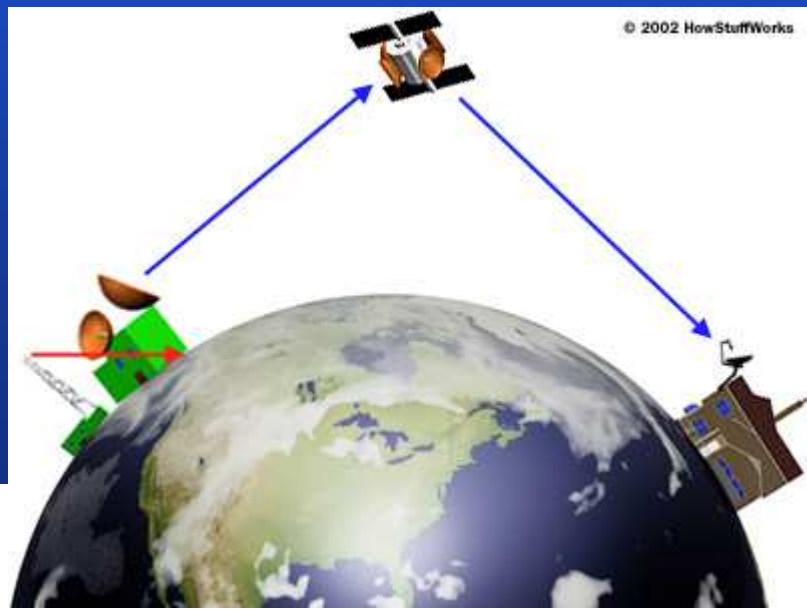
Working procedures between the collaborating departments?

Differences between countries?

How to count accrual?

Members structure and network





f cancer therapy

Definitions:

EORTC:

Sub-site: when part of the activities related to study (e.g. RT) is carried out at a different location than the main PI's institution
- research sub-site: in which protocol treatment activity is performed (e.g. RT or protocol specific TR investigations)
- if only routine tasks (follow-up pts, subsequent non protocol surgery, RT, Chemo, regular CT, regular blood samples, ...) ➔ not considered as performing clinical research activities

Note: main site is not allowed to dispatch study labeled drug to any sub-site.

Definitions:

EORTC:

Merged institutions = 1 site: if sites are part of the same entity, but have different physical addresses (e.g. one hospital with two different campuses) or several hospitals are under the same umbrella and

have common Board of Directors and common Ethics Committee

So: only one FQ, ERDA, DR, DDIQA, ICR, CDC procedure

European Journal of Cancer (2012) 48, 1049–1054

Available at www.sciencedirect.com

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Position Paper

Development of clinical trial protocols involving advanced radiation therapy techniques: The European Organisation for Research and Treatment of Cancer Radiation Oncology Group approach

A. Fairchild [a], R. Bar-Deroma [b], L. Collette [a], K. Haustermans [c], C. Hurkmans [d], D. Lacombe [a], P. Maingon [e], P. Poortmans [f], M. Tomsej [g], D.C. Weber [h], V. Gregoire [i,*]

Table 1
Summary of required protocol components.

Title	• Include information on the trial design
Summary table	• Provide a concise outline of key points such as main inclusion criteria, treatment arms and target acc
Background and rationale	• Describe the evidence base for the rationale, importance and choice of treatment arms including dose fractionation schedules • Include the hypothesis on which the main statistical considerations are based
Trial objectives	• State the main clinical question(s) to be addressed by the trial • Define briefly the main primary and secondary end-points
Patient selection	• List eligibility and ineligibility criteria
Trial design	• State the type of trial and whether it is randomised • Include an easily understandable study schema or flow diagram with an overview of treatment schedules, mary objective and total sample size
Pre-treatment evaluation	• Explain the schedule of investigations needed to evaluate eligibility (including histologic confirmation), p nostic factors and baseline values of parameters to be used as end-points • Include any other pre-treatment assessments such as specialist consultations
Surgery (if any)	• Outline any invasive staging and therapeutic procedures, peri-operative care and surgical quality assur
Radiation therapy	• Describe minimum requirements for facilities and equipment, along with instructions pertaining to all pl of RT preparation and delivery • Expected toxicities, their management, dose and schedule modifications and withdrawal criteria shou described
QA for radiation therapy	• Define the level(s) of QA to be implemented, specifying timing of each (prior to site activation versus d patient accrual)
Systemic therapy	• Outline types of agents, dose, route, schedule, and treatment duration • Expected toxicities, their management, dose and schedule modifications and withdrawal criteria shou described • Logistics to be considered include supply, packaging, dispensing, storage, reconciliation and QA
Central review procedures	• Explain objectives and procedures for central (pathology, imaging, other) review
Follow-up	• Summarise methods used for assessing study end-points (clinical evaluation, lab tests, imaging, other) their timing
End-points and response criteria	• Clearly define primary and secondary end-points, how they will be measured as well as length of requ follow-up • State the data required to determine the types of response and confirm progression • Give guidelines for treatment at relapse, if any
Registration and randomisation	• Explain procedures for assignment of patient identification number, registration, randomisation, alloca ratio, blinding/unblinding and stratification
Administrative procedures	• Methods of data collection and other administrative requirements of investigators must be described • Data control procedures and foreseen on-site quality control should be mentioned
Adverse event and pregnancy reporting	• For toxicity, specify definitions, grading, assessment tools and reporting procedures • Explain regulations regarding pregnancy reporting
Ethical considerations	• Refer to laws, regulations, and guidelines which will govern conduct of the study, and include a patient sent form and patient information sheet
Statistical methods	• Discuss end-point calculation and stratification factors • Provide a sample size estimate, its underlying assumptions and expected accrual rate • Describe the statistical methods and populations to be used in the analysis • Protocol early stopping rules and interim analyses should be explained, along with the roles of the Inde dent Data Monitoring Committee and Data Safety Monitoring Board
Quality of life (if any)	• Specify objectives, assessment tools, schedule and statistical considerations
Translational research	• Explain objectives; material to be obtained; schedule; instructions for handling, transfer and storage of ples and statistical considerations
Additional administrative sections	• Administrative responsibilities • Trial sponsorship and funding • Trial insurance • Publication policy • Administrative signatures • References
Appendices	• Staging system • Performance status • Imaging acquisition protocols • Guidelines for target volume selection and delineation • Method of response evaluation • Acute and late toxicity grading scale • Form submission schedule • Patient consent form • Quality of life instruments

International Journal of
Radiation Oncology
biology • physics

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Critical Review

Redesigning Radiotherapy Quality Assurance: Opportunities to Develop an Efficient, Evidence-Based System to Support Clinical Trials—Report of the National Cancer Institute Work Group on Radiotherapy Quality Assurance

Justin E. Bekelman, M.D.,* James A. Deye, Ph.D.,† Bhadrasain Vikram, M.D.,† Soren M. Bentzen, Ph.D.,‡ Deborah Bruner, Ph.D.,* Walter J. Curran Jr, M.D.,§ James Dignam, Ph.D.,¶ Jason A. Efstathiou, M.D., D.Phil.,‖ T.J. FitzGerald, M.D.,# Coen Hurkmans, Ph.D.,** Geoffrey S. Ibbott, Ph.D.,†† J. Jack Lee, Ph.D.,†† Thomas E. Merchant, M.D.,‡‡ Jeff Michalski, M.D.,§§ Jatinder R. Palta, Ph.D.,¶¶ Richard Simon, D.Sc.,‖‖ Randal K. Ten Haken, Ph.D.,## Robert Timmerman, M.D.,*** Sean Tunis, M.D.,††† C. Norman Coleman, M.D.,† and James Purdy, Ph.D.‡‡‡

EORTC *The future of cancer therapy*

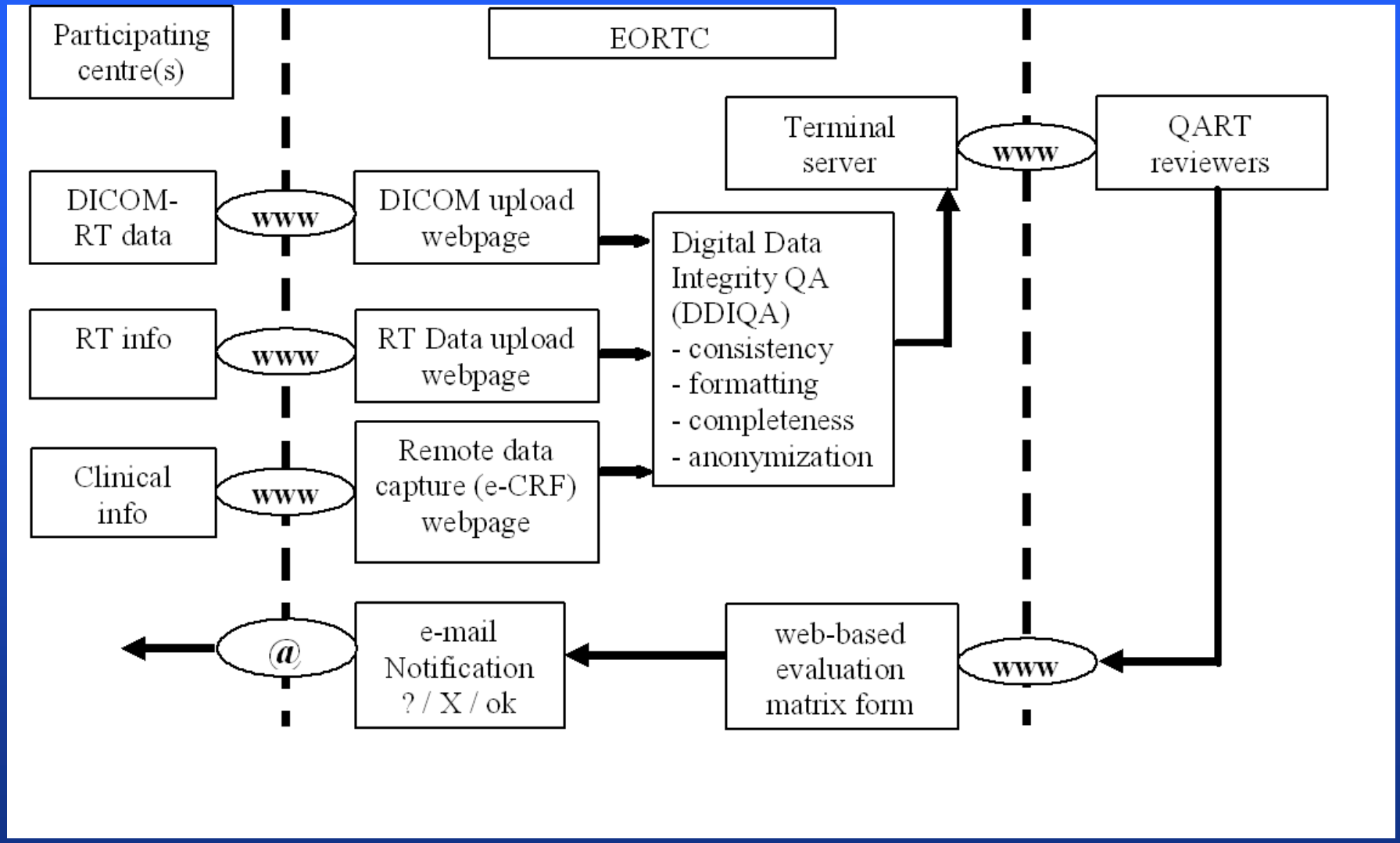
catharina ziekenhuis

Table 3 Recommendations for clinical trial quality assurance

1. Develop a tiered (and more efficient) system for clinical trial QA and tailor intensity of QA to clinical trial objectives; tiers include general credentialing, trial-specific credentialing, and individual case review
2. Establish case QA repository
3. Develop evidence base for clinical trial QA and introduce innovative prospective trial designs to evaluate QA as part of RT clinical trials
4. Explore feasibility of consolidating clinical trial QA in the United States and harmonizing QA and credentialing requirements across cooperative groups

Abbreviations: QA = quality assurance; RT = radiotherapy.

Digital platform



Radiotherapy and Oncology 100 (2011) 150–156

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Review

Quality assurance for prospective EORTC radiation oncology trials: The challenges of advanced technology in a multicenter international setting

Damien C. Weber[a], Philip M.P. Poortmans[b], Coen W. Hurkmans[c], Edwin Aird[d], Akos Gulyban[e], Alysa Fairchild[e,*]

available at www.sciencedirect.com

ScienceDirect

EORTC Radiation Oncology Group: 50 years of continuous accomplishments

Vincent Grégoire[a], Harry Bartelink[b], Jacques Bernier[c], Michel Bolla[d], Jean-François Bosset[e], Laurence Colette[f], Karin Haustermans[g], Jean-Claude Horiot[c], Coen W. Hurkmans[h], René Mirimanoff[i], Philip Poortmans[j], Damien C. Weber[k], Philippe Maingon[l]

IMRT credentialing by phantom irradiation

A joint RPC and EORTC ROG Experience

Coen Hurkmans

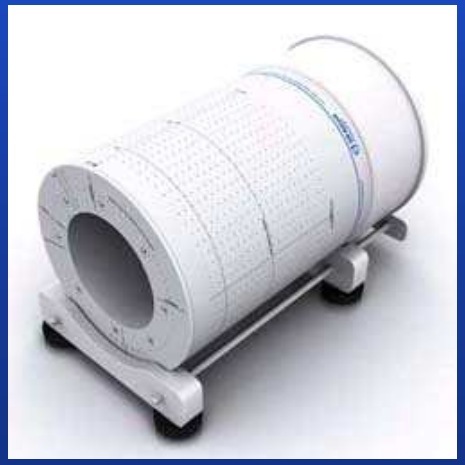
A. Molineu A, D. Followill D, R. Moeckli, V. Vallet, C. Melidis, D. Weber D.

Project goal

1. To credential EORTC centers for the use of IMRT in a phase III Head and Neck trial.

2. To compare credentialing through the use of the RPC H&N phantom and through the institutions own phantom.

Institutions own “virtual” phantom



Advantages:

- Less time consuming
- Less costly
- Less prone to user errors

Disadvantage:

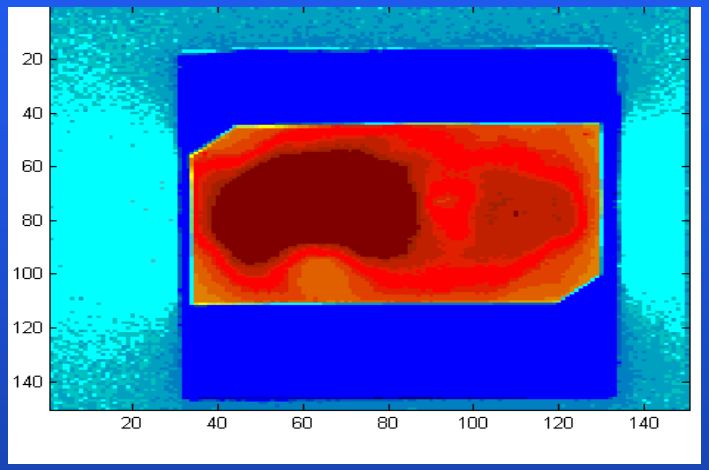
- No experience yet
- Phantom dependent results

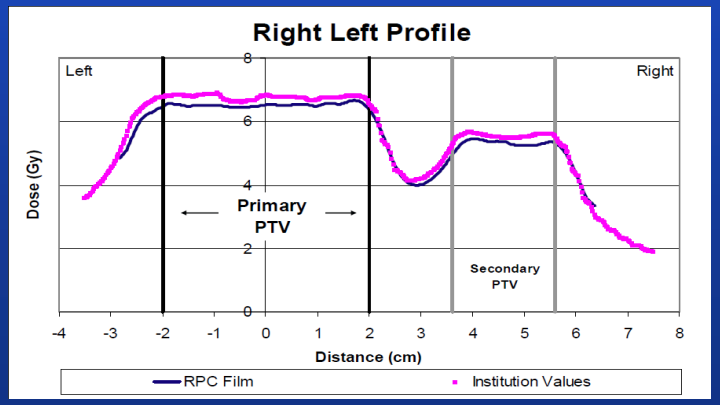
Data overview

- 25 EORTC centers received RPC phantom
- 9 centers provided virtual phantom data

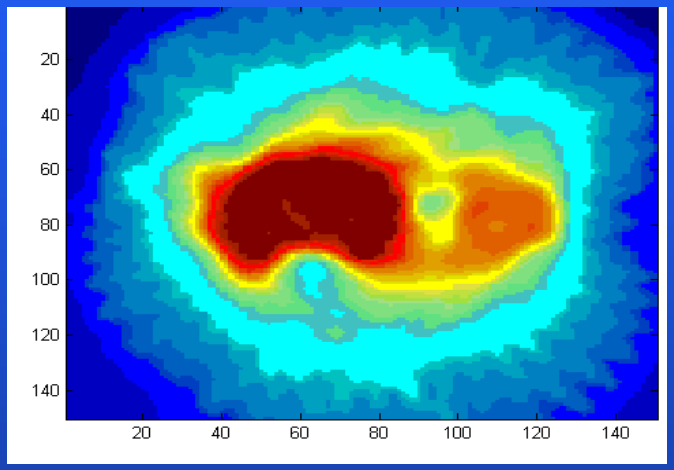
RPC H&N phantom data analysis

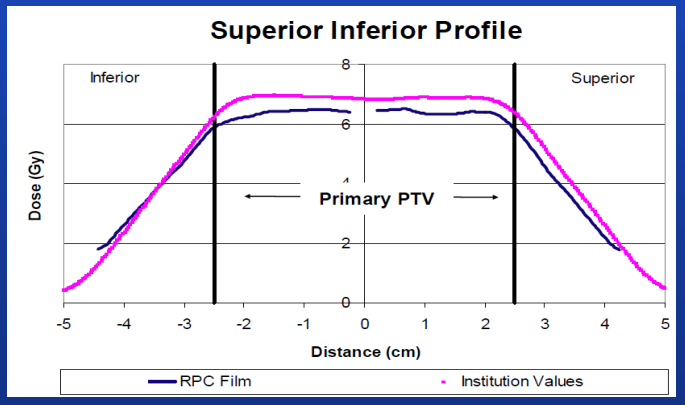
RPC computed Filmarray





Planned dose

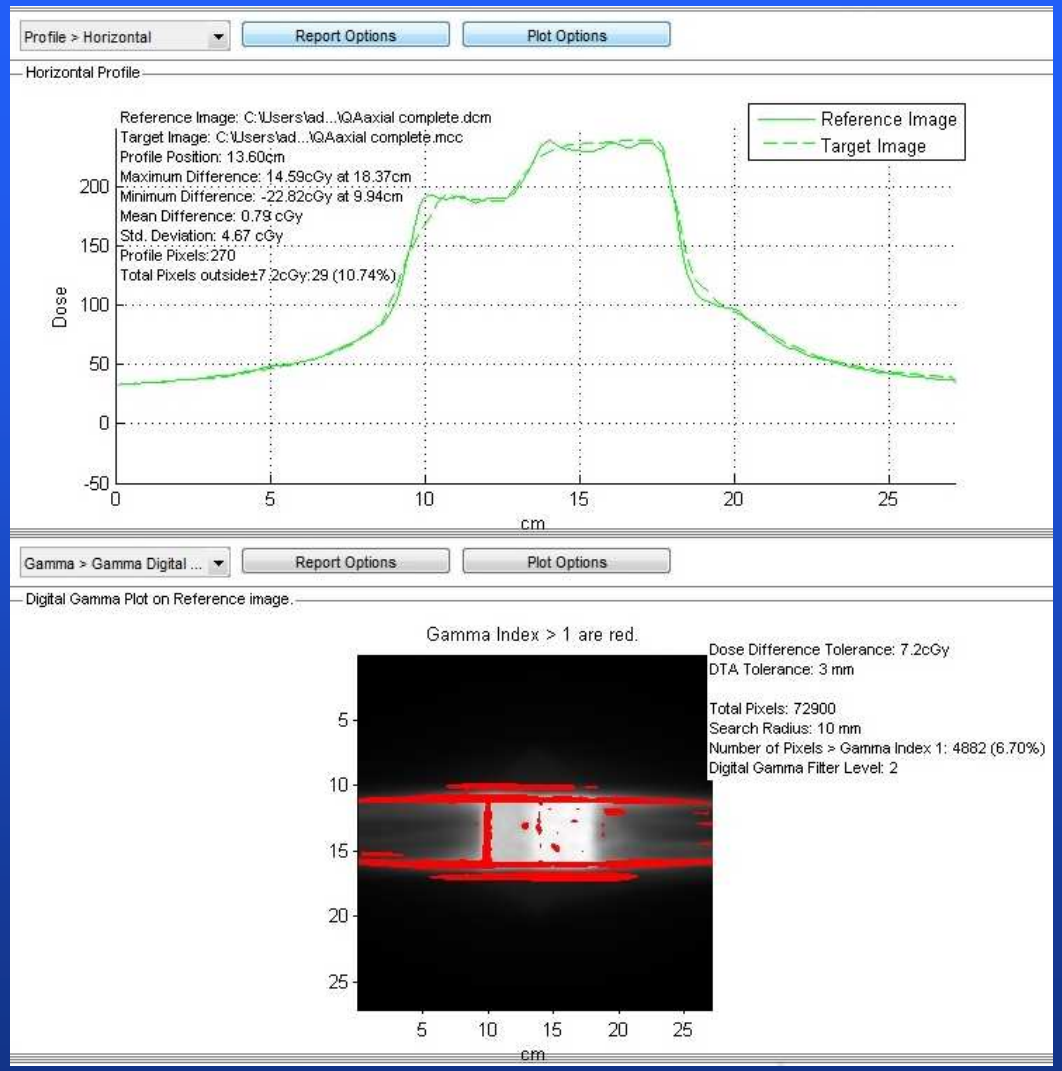




1D Gamma analysis (along axial or sagittal line)

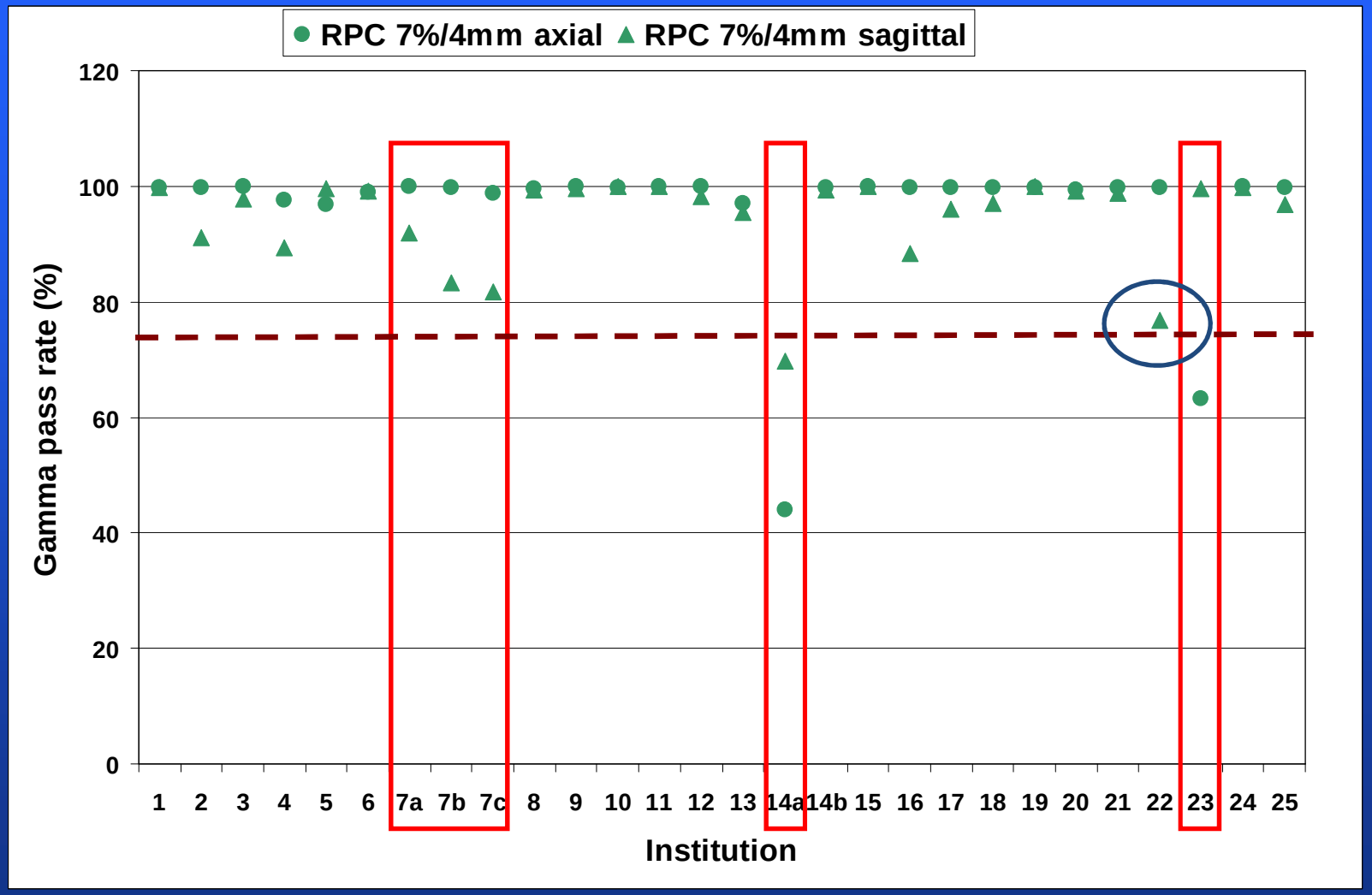
Absolute dose based on TLD

Virtual phantom data analysis



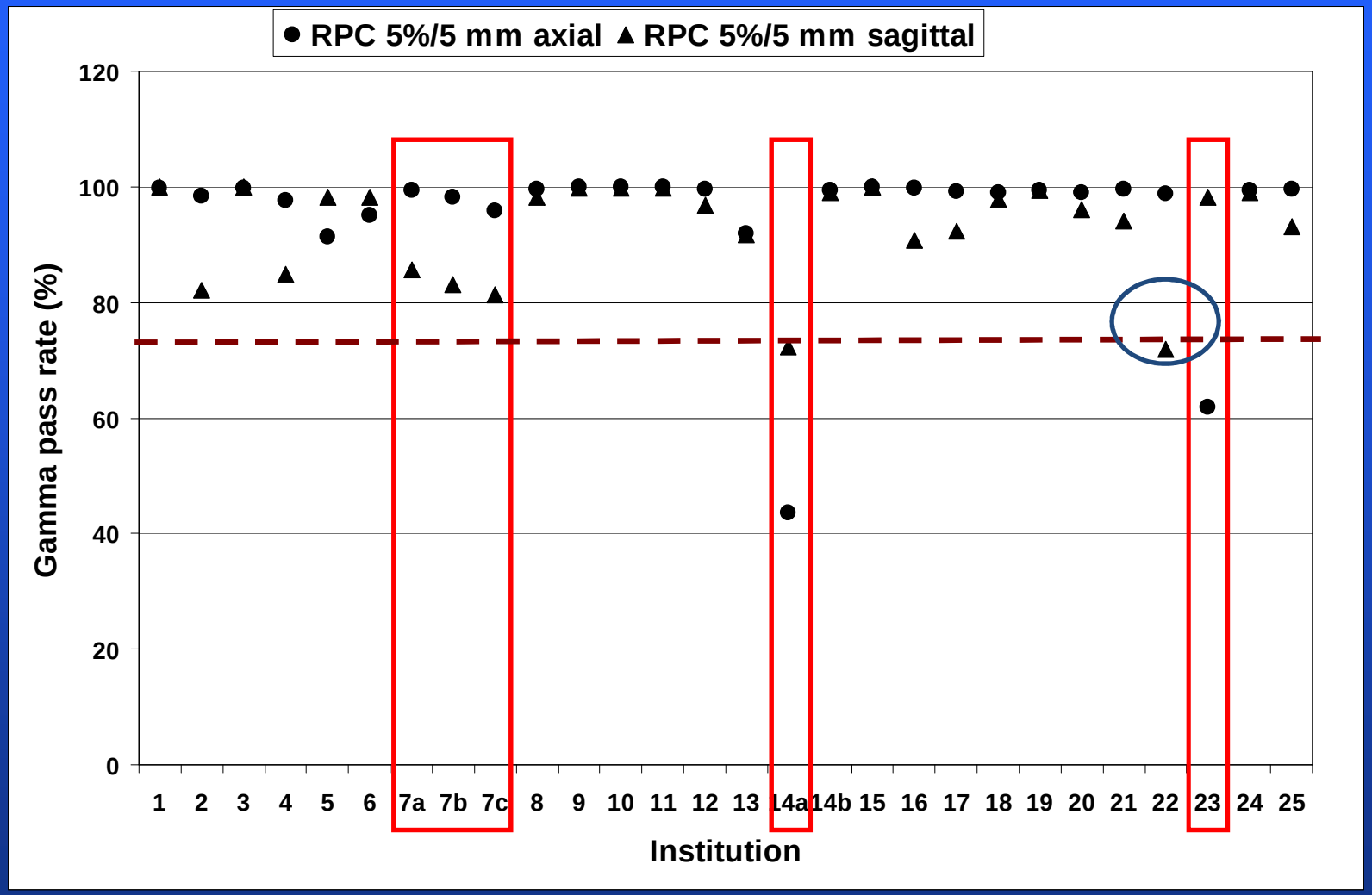
- Based on DICOM RT-Plan, RT-Dose and measurement files
- Performed with RIT
- 2D Gamma analysis

RPC phantom results



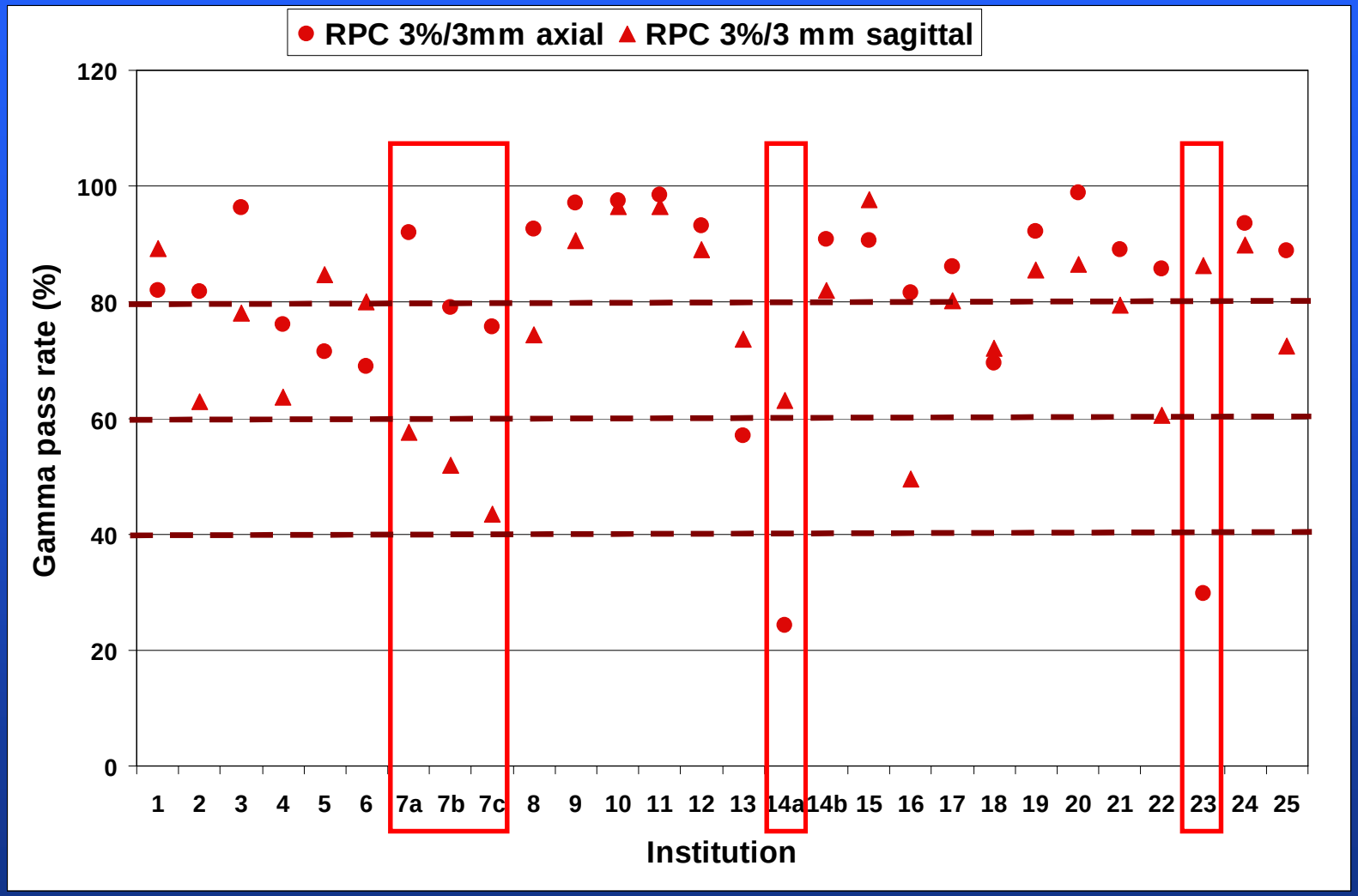
- reproducible
- 14a failure: Table height 1 cm off
- 23 failure: Left-right 1 cm off
- 22 pass if 75% pass rate used

Gamma criterion 5%/5mm



- reproducible
- 14a failure: Table height 1 cm off
- 23 failure: Left-right 1 cm off
- 22 failure

Gamma criterion 3%/3mm



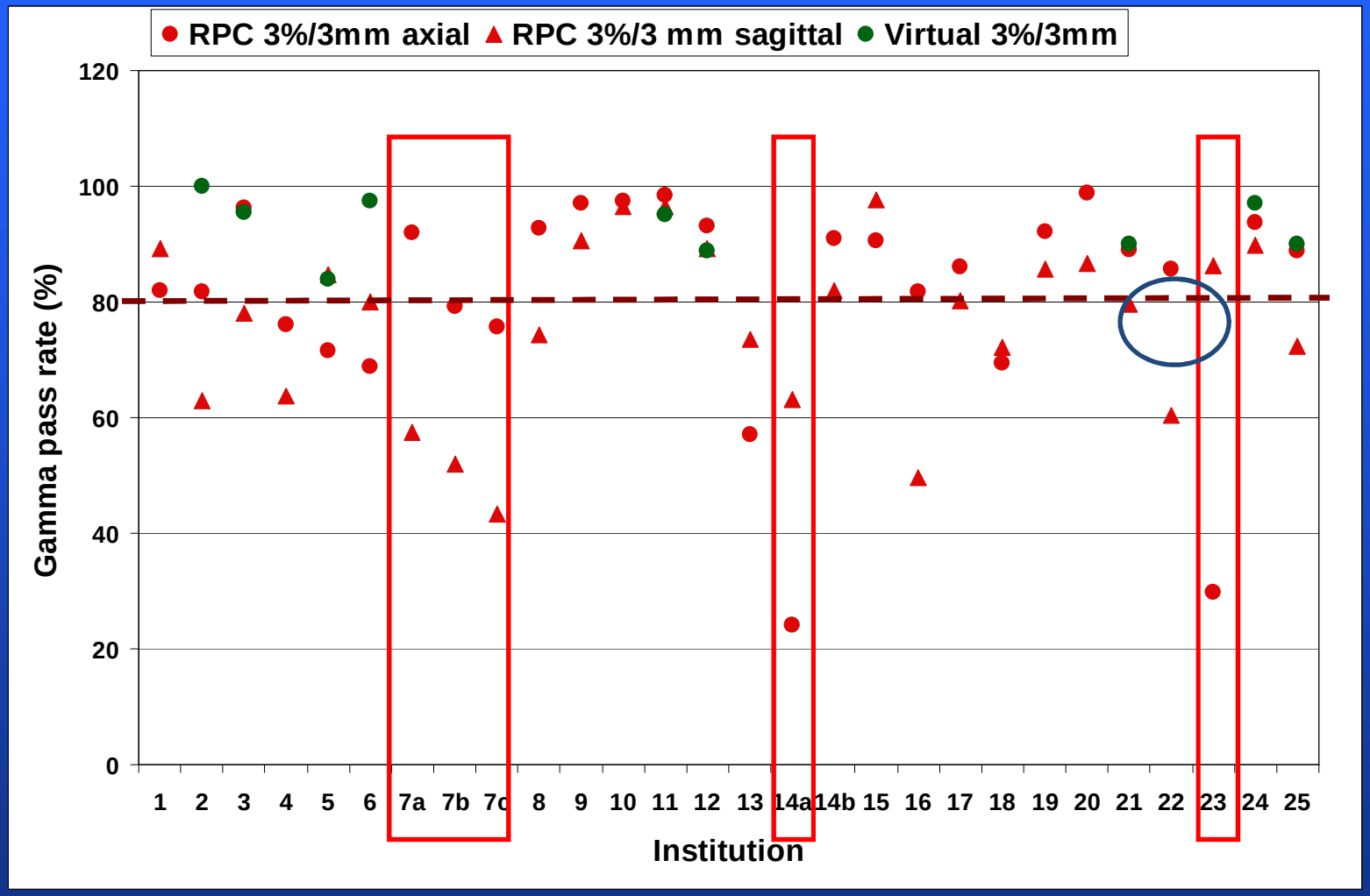
- reproducible?

80%: 16 / 25 fail

60%: 5 / 25 fail

40%: 2 / 25 fail

Virtual phantom results



- only 9 centers
- all pass 3%/3mm

Conclusions

- 24 out of 25 EORTC centres have been credentialed
- 7%/4mm detects outliers
- 3%/3mm criterion would result in few centres credentialed by RPC H&N phantom
- Virtual Phantom pass rates for 3%/3 mm much higher