The Need for Quantitative Imaging in Radiation Oncology Treatment Guidance and Assessment

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ACR IROC NRG Penn Medicine

Disclosure

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PA CURE

Objectives

- A summary of a myriad of imaging markers
- Discussions on the various challenges.
- Examples of quantitative imaging in clinical trials
- IROC As Quantitative Imaging Resource

Quantitative Imaging (QI)

- Definition
  - Extraction of quantifiable radiological biomarkers
- Applications
  - Diagnosis, staging
  - Treatment response assessment
  - Improve prognostication of response to RT
  - “Dose painting”
  - Adaptive treatments based on anatomic or functional responses

PRESS, R. H., SHU, H.-K. G., SHIM, H., MOUNTZ, J. M., KURLAND, B. F., WAHL, R. L., ... BUATTI, J. M. (2018). *THE USE OF QUANTITATIVE IMAGING IN RADIATION ONCOLOGY: A QUANTITATIVE IMAGING NETWORK (QIN) PERSPECTIVE. INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY*BIOLOGY*PHYSICS*. ELSEVIER INC. HTTPS://DOI.ORG/10.1016/J.IJROBP.2018.06.023

TABLE 1. Clinical Indications for Which Imaging can be Performed in a Clinical Trial Setting

Role	Definition	Examples
Diagnosis and staging	To determine whether a lesion is positive or negative for malignancy	F18-FDG PET in lymphoma Nodal staging using F18-FDG PET in head and neck cancers (ACRIN 6685)
Prognostic marker	To determine the expected outcome under standard therapy for the patient's disease stage	Lesion size on anatomic imaging such as CT or MRI “High” versus “Low” SUV on F18-FDG PET in head and neck SCC, NSCLC, and gastroesophageal cancers
Predictive biomarker assay	To differentiate between patients expected to benefit clinically on one treatment relative to another from those not expected to experience such a benefit	I-123 scan predictive for I-131 therapy in thyroid cancer F18-FES PET predictive for hormonal therapy in breast cancer (EAI142)
Pharmacokinetics marker	To confirm that the drug has reached the intended target	F18-FLT PET “flare” in pancreatic cancer (EA2131)
Pharmacodynamic marker	To measure the effects of the drug on the body	Perfusion CT and DCE/DSC MRI in anti-angiogenesis targeted therapy
Early response indicator	To determine the expected ultimate outcome on a particular therapy regimen from changes in a tumor characteristic following a few cycles of treatment	F18-FDG PET response in gastric cancer after neoadjuvant chemotherapy (A021302) During-treatment F18-FDG PET evaluation of external beam radiation in NSCLC (RTOG 1106)
Basis of a Phase II trial end point	A pre- to posttreatment change measurement used to determine whether to proceed to the subsequent Phase III investigation	Complete metabolic response according to F18-FDG PET in cervical cancer
Basis of a Phase III trial end point	A pre- to posttreatment change that serves as a surrogate for a definitive clinical end point	PFS based on anatomic imaging

CT, computed tomography; DCE, dynamic contrast-enhanced; DSC, dynamic susceptibility contrast; FDG, fluorodeoxyglucose; FES, fluoroestradiol; FLT, fluorothymidine; MRI, magnetic resonance imaging; NSCLC, nonsmall cell lung cancer; PET, positron emission tomography; PFS, progression-free survival; SCC, squamous cell carcinoma; SUV, standardized uptake value.

LIN, F. I., HUANG, E. P. AND SHANKAR, L. K. (2017) ‘BEYOND CORRELATIONS, SENSITIVITIES, AND SPECIFICITIES: CASE EXAMPLES OF THE EVALUATION OF ADVANCED IMAGING IN ONCOLOGY CLINICAL TRIALS AND CANCER TREATMENT’, *ACADEMIC RADIOLOGY*. ELSEVIER INC., 24(8), PP. 1027–1035. DOI: 10.1016/J.ACRA.2016.11.024.

Quantitative Imaging Modalities

Anatomic-based imaging

Tomography (CT)

T1- and T2-weighted (MRI)

Functional-based imaging

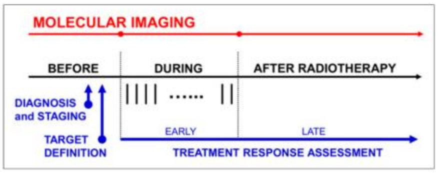
Positron emission tomography (PET)

Single photon emission computed tomography (SPECT)

Perfusion and Diffusion weighted imaging (DSC, DCE, DWI)

Magnetic resonance spectroscopy imaging (MRSI)

Imaging Time Sequence



JERAJ R, BRADSHAW T, SIMON I U. MOLECULAR IMAGING TO PLAN RADIOTHERAPY AND EVALUATE ITS EFFICACY. J NUCL MED [INTERNET]. 2015;56(11):1752–65. AVAILABLE FROM: HTTP://JNM.SNMJOURNALS.ORG/CGI/DOI/10.2967/JNUMED.114.141424

CT

3D CT: Anatomical

4D-CTs: Visualize respiratory motion; Ventilation guided avoidance

Dual-energy CT (DECT): Accurate photon and proton dose calculation

CT (DCE-CT):Target delineation; Assess response to therapies; Predict outcomes after RT

CT-based radiomics: Diagnostic accuracy, prognostic capability, and response prediction

Challenges

CT Radiomics:

Reproducibility of using test-retest analyses

Robustness of image features

PET Tracers

FDA approved:

[18F]-fluorodeoxyglucose ([18F]-FDG)

Na[18F], 18Fluciclovine

[11C]-Choline

[68Ga]-DOTATATE

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FDG PET

Target delineation: HN, lung, lymphoma, pancreatic, anal, rectal

Predictive of RT response

Response assessment

Adaptive RT

Need for standardization to reduce variability

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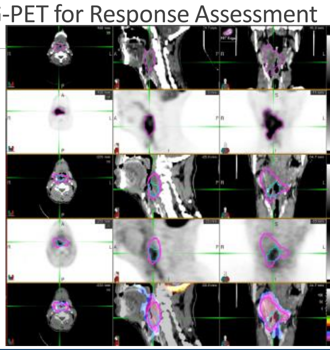
FDG-PET for Response Assessment



PRESS, R. H., SHU, H.-K. G., SHIM, H., MOUNTZ, J. M., KURLAND, B. F., WAHL, R. L., … BUATTI, J. M. (2018). *THE USE OF QUANTITATIVE IMAGING IN RADIATION ONCOLOGY: A QUANTITATIVE IMAGING NETWORK (QIN) PERSPECTIVE*. *INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY*BIOLOGY*PHYSICS*. ELSEVIER INC. HTTPS://DOI.ORG/10.1016/J.IJROBP.2018.06.023

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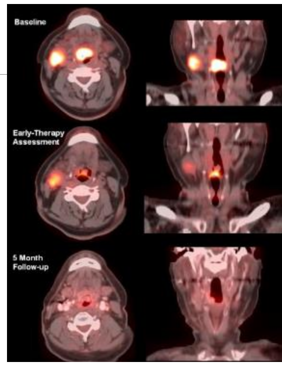
Early Response Predicts Long Term Outcome



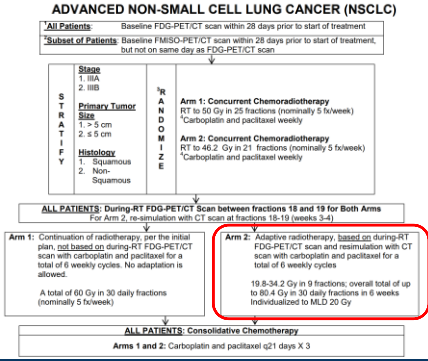
NCCN Recommendations on Use of ^{18}F-FDG PET/CT for Target Definition and Treatment Response Evaluation in Radiotherapy

Cancer type	Target definition	Response evaluation
Cervical	Recommended	Optional
Esophageal	Recommended	Recommended
Head and neck	—	Optional
Hodgkin lymphoma	Optional	Recommended
Non-Hodgkin lymphoma	Optional	Recommended
Non–small cell lung	Recommended	—
Small cell lung	Recommended	—
Pancreatic	Recommended	—

Recommendations are as of 2015. No significant evidence to support use of ^{18}F-FDG PET/CT at this point is indicated with a dash, which does not mean that use of ^{18}F-FDG PET/CT may not be beneficial but merely that evidence at this point is still insufficient.

RTOG 1106/ACRIN 6697

RANDOMIZED PHASE II TRIAL OF INDIVIDUALIZED ADAPTIVE RADIOTHERAPY USING DURING-TREATMENT FDG-PET/CT AND MODERN TECHNOLOGY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)



Question set 3:

Which of the following is the primary objective for RTOG 1106-6697: To determine when an individualized adaptive radiation treatment (RT) plan is applied by the use of an FDG-PET/CT scan acquired during the course of fractionated RT in patients with inoperable or unresectable stage III NSCLC

a) whether tumor dose can be escalated to improve the LRPF rate at 2 years;

b) whether an individualized dose escalation improves overall survival (OS)

c) whether an individualized dose escalation improves progression-free survival (PFS)

d) whether the rate of severe (grade 3+ CTCAE, v. 4) radiation-induced lung toxicity (RILT) differs

Answer: a)

Literature:

Reference: https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1106

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PET with Other Tracers

FLT: Early response, differentiate progression

Hypoxia PET: [18F]- fluoromisonidazole (FMISO)

[18F]-fluoroazomycin arabinoside (FAZA)

[18F]-flortanidazole (HX4)

Cu-ATSM

Adaptive; Dose painting;

Standardization

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Uncertainties for PET/CT QA

Uncertainties and Quality Control Measures for PET/CT in Radiation Therapy Planning

Category	Procedure	Uncertainties	Quality control
Scanning protocol	Patient preparation	Metabolism levels (^{18}F-FDG)	Limit physical activity
		Blood glucose levels (^{18}F-FDG)	Measure fasting blood glucose with exclusion criteria
		Bowel size/positioning	Use fasting protocol
	Radiotracer injection	Residual activity in syringe	Measure/correct for residual activity
		Decay correction errors	Synchronize scanner clock
Acquisition	Patient positioning	Spatial offset between PET and treatment-planning CT	Ensure consistent patient positioning using identical positioning devices
		Quantitative uncertainties from attenuating objects	Avoid placing objects outside image field of view
	Scanning	Patient motion	Implement motion management strategies
		Attenuation correction uncertainties from iodine contrast material	Acquire separate low-dose CT scan or apply corrections
		Equipment failure or electronic drift	Calibrate detector and equipment frequently
		Increased SUV because of longer uptake period	Apply strict protocol for uptake period
Reconstruction	Reconstruction	Selection of optimal image reconstruction method/parameters	Benchmark algorithms using phantoms (task-specific)
		Randoms, scatter, attenuation, detector sensitivity, and partial-volume effect	Apply appropriate calibrations and corrections
Analysis	Segmentation	Differentiation of normal tissue and tumor uptake	Know radiotracer's normal biodistribution
		Segmentation uncertainties	Develop segmentation protocol; benchmark algorithms with phantoms
		Limited spatial resolution and sensitivity	Include margins
	Quantification	Quantitative accuracy	Calibrate PET scanner to dose calibrator
		Selection of relevant quantitative measures	Compare semiquantitative metrics with kinetic analysis-derived parameters; consult literature
		Quantitative differences between scanners/institutions	Quantitatively harmonize scanners
Treatment planning	Target definition	Registration errors	Benchmark algorithms using physical or digital phantoms; crop images
		Motion	Use same motion management method as was used during imaging

JERAJ R, BRADSHAW T, SIMONČIČ U. MOLECULAR IMAGING TO PLAN RADIOTHERAPY AND EVALUATE ITS EFFICACY. J NUCL MED [INTERNET]. 2015;56(11):1752–65. AVAILABLE FROM: HTTP://JNM.SNMJOURNALS.ORG/CGI/DOI/10.2967/JNUMED.114.141424

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Variability in Imaging and Sample Size

Frequencies of Specific Issues During Scanner Qualification*

Issue	No. of scanners during: T0 period (65 scanners)	T2 period (44 scanners)†
Uniformity problem	7	0
SUV outside specifications	14	3
Phantom filling issue	4	3
Reconstruction problem	6	5
Improper acquisition	3	0
Incomplete submission	11	2
Problem with forms	5	1
Total	50	14

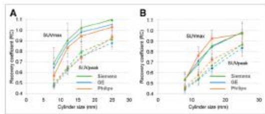


FIGURE 4. Recovery coefficients (defined as ratio of measured SUV to true SUV) as function of cylinder diameters for static brain (A) and body (B) acquisitions.

Differences in Scanner Qualifications for 3 Time Periods

Parameter	T0 No.	T0 Percentage	T1 No.	T1 Percentage	T2 No.	T2 Percentage
No. of scanners passing first time	25	38	34	87	35	67
No. of scanners passing eventually	39	60	5	13	13	25
Total no. of scanners passing	64	98	39	100	48	92
Total no. of scanners	65		39		52	

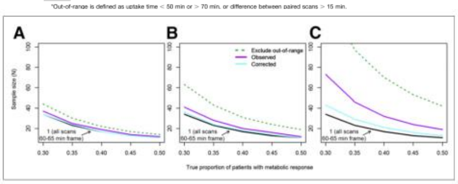
SCHEUERMANN JS, REDDIN JS, OPANOWSKI A, KINAHAN PE, SIEGEL BA, SHANKAR LK, ET AL. QUALIFICATION OF NATIONAL CANCER INSTITUTE–DESIGNATED CANCER CENTERS FOR QUANTITATIVE PET/CT IMAGING IN CLINICAL TRIALS. J NUCL MED [INTERNET]. 2017;58(7):1065–71. AVAILABLE FROM: HTTP://JNM.SNMJOURNALS.ORG/LOOKUP/DOI/10.2967/JNUMED.116.186759

Effects of Injection-to- Acquisition Time Variability on Required Sample Size

Sensitivity and Specificity Derived from Simulated Time–Activity Curves and Uptake Times

Sampling and correction scenario	Excluded	Sensitivity	Specificity
Scenario 1 (all scans 60–65 min)	—	96% (94%–97%)	99% (98%–100%)
Scenario 2	—	92% (90%–93%)	99% (98%–100%)
2 exclude out-of-range*	20%	94% (92%–95%)	100% (99%–100%)
2 corrected†	—	95% (93%–96%)	99% (99%–100%)
Scenario 3	—	89% (86%–90%)	96% (95%–97%)
3 exclude out-of-range*	44%	93% (91%–95%)	99% (98%–100%)
3 corrected†	—	93% (92%–95%)	99% (98%–100%)
Scenario 4	—	73% (70%–76%)	91% (89%–92%)
4 exclude out-of-range*	64%	82% (78%–86%)	98% (95%–99%)
4 corrected†	—	87% (85%–89%)	98% (97%–99%)

*Out-of-range is defined as uptake time < 50 min or > 70 min, or difference between paired scans > 15 min.



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MR

T1- and T2-weighted

Perfusion, DWI

Diffusion tensor imaging (DTI)

Spectroscopy

Tumor delineation

Prediction of RT response

Planning adaptation

Assessment of treatment response

Perfusion MR

Dynamic contrast enhanced (DCE) MRI

1) Ktrans; 2) Kep 3) Vp and Ve

Dynamic susceptibility contrast (DSC) MRI

Cerebral blood volume (CBV);cerebral blood flow (CBF);

Mean transit time (MTT)

Differentiate tumor progression

Predict for survival outcomes e.g. ACRIN 6677/RTOG 0625; ECOG-ACRIN (NCT03115333)

DCE-MRI Ktrans values for targeting radio-resistance

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DWI MR

Early response in Clinical Trials:

Esophageal cancer (NCT03151642); HNC (NCT02497573, NCT00581906); Prostate cancer (NCT02319239); Rectal cancer (NCT02233374); Pediatric sarcoma (NCT02415816), and Cervical cancer (NCT01992861)

3 T allows for higher b value

QA and standardization of ADC for segmentation and radiomics

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MRS/MRSI

Diagnosis: Tumor grade

Response assessment: Differentiate tumor progression and radiation necrosis.

Target delineation and dose escalation

Example: Prostate: tumor id for brachy therapy guidance

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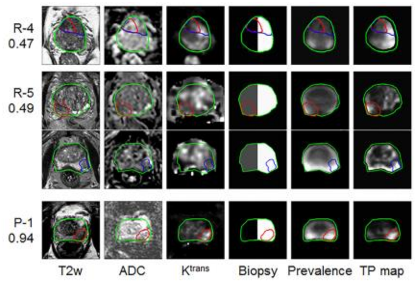
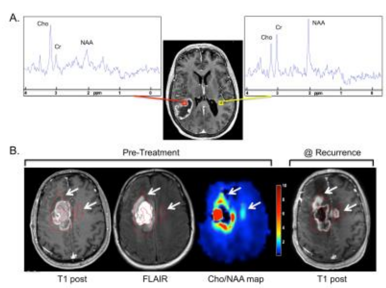
Multi-parametric MR for Tumor Definition



VAN SCHIE, M. A., DINH, C. V., HOUDT, P. J. VAN, POS, F. J., HEIJMINK, S. W. T. J. P., KERKMEIJER, L. G. W., … VAN DER HEIDE, U. A. (2018). CONTOURING OF PROSTATE TUMORS ON MULTIPARAMETRIC MRI: EVALUATION OF CLINICAL DELINEATIONS IN A MULTICENTER RADIOTHERAPY TRIAL. *RADIOTHERAPY AND ONCOLOGY*. HTTPS://DOI.ORG/10.1016/J.RADONC.2018.04.015

EPSI for Tumor Delineation



PRESS, R. H., SHU, H.-K. G., SHIM, H., MOUNTZ, J. M., KURLAND, B. F., WAHL, R. L., … BUATTI, J. M. (2018). *THE USE OF QUANTITATIVE IMAGING IN RADIATION ONCOLOGY: A QUANTITATIVE IMAGING NETWORK (QIN) PERSPECTIVE. INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY*BIOLOGY*PHYSICS*. ELSEVIER INC. HTTPS://DOI.ORG/10.1016/J.IJROBP.2018.06.023 26

MR for Outcome Prediction

Table 3: Basic MR functional imaging types that have shown promise in predicting outcomes for various tumor types.

Type of measurement	Functional imaging method	Known as	What is measured
Perfusion	Dynamic contrast enhanced	DCE, permeability	Gadolinium-induced shortening of T1
	Dynamic susceptibility contrast	DSC	Gadolinium-induced shortening of T2*
	Arterial spin labeling	ASL	Intrinsic contrast enhancement generated from magnetization of arterial blood
Diffusion	Diffusion weighting imaging	DWI	Gradient-induced sensitization of molecular diffusion
Metabolic function	Spectroscopy	MRSI	Chemical composition based on resonant frequency
Oxygenation	Bold-level oxygen dependent	BOLD, fMRI	T2* differences in oxy- and deoxyhemoglobin

GISELE C. PEREIRA, MELANIE TRAUGHBER, AND RAYMOND F. MUZIC, JR., "THE ROLE OF IMAGING IN RADIATION THERAPY PLANNING: PAST, PRESENT, AND FUTURE," BIOMED RESEARCH INTERNATIONAL, VOL. 2014, ARTICLE ID 231090, 9 PAGES, 2014. HTTPS://DOI.ORG/10.1155/2014/231090. 27

MRI Radiomics

Discern benign from malignant lesions

Identify radiation necrosis after RT

Generate automatic tumor segmentation algorithms

Improve prognostic capabilities

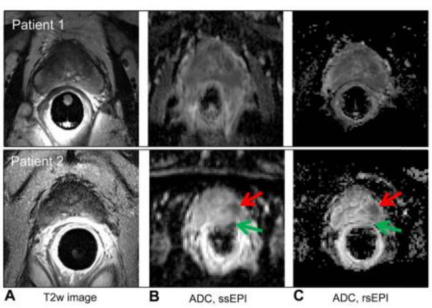
Deep learning to correlate with genomic phenotypes

Challenge:

Validate robustness radiomic features

Imaging processing platforms that facilitate the discovery and validation of radiomic biomarkers

DWI MR Blurring and Distortion



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Question set 1:

Extracting quantitative transport parameters from DCE-MRI acquisitions is challenging. The selection of different perfusion analysis softwares corresponded to within-subject coefficient variation for $K_{trans,}$ in the range,

a) 28.3% - 48.8%

b) 48.3% - 68.8%

c) 68.3% - 88.8%

d) 38.3% - 58.8%

Answer: b)

Literature:

Jaffray DA, Chung C, Coolens C, Foltz W, Keller H, Menard C, et al. Quantitative Imaging in Radiation Oncology: An Emerging Science and Clinical Service. Semin Radiat Oncol [Internet]. 2015 Oct 1 [cited 2018 Apr 10];25(4):292–304. Available from: https://www.sciencedirect.com/science/article/pii/S1053429615000557

Imaging Variability & Outcome

Table II. Quantitative quality control definitions for diffusion MRI and fDM analysis.

Parameter	Score = 1 (Unusable)	Score = 2 (Unusable)	Score = 3 (Usable)	Score = 4 (Good)	Score = 5 (Great)
Distortion/artifacts	Severe, affecting tumor	Moderate, affecting tumor	Moderate, not affecting tumor	Mild, not affecting tumor	No distortion or artifacts
ADC values (NAWM)	Negative values	Non-physiological range (0-0.4 $\mu m^2/ms$)	Lower or higher than normal, but within physiological range (e.g. 0.4-0.6 $\mu m^2/ms$; 0.8-1.0 $\mu m^2/ms$)		Within normal range (0.6-0.8 $\mu m^2/ms$)
ADC values (CSF)	Negative values	Non-physiological range (0-1.5 $\mu m^2/ms$; 4.0+ $\mu m^2/ms$)	Lower or higher than normal, but within physiological range		Within normal range for CSF
Registration of ADC maps with Baseline ADC maps	Severe misalignment, tumor not aligned	Moderately misaligned, tumor not aligned	Moderately misaligned, but tumor is aligned	Slightly misaligned, but tumor is largely aligned	Perfectly aligned

123 available, 84 (68%) >=3, 58 (47%) = 5

ELLINGSON BM, KIM E, WOODWORTH DC, MARQUES H, BOXERMAN JL, SAFRIEL Y, ET AL. DIFFUSION MRI QUALITY CONTROL AND FUNCTIONAL DIFFUSION MAP RESULTS IN ACRIN 6677/RTOG 0625: A MULTICENTER, RANDOMIZED, PHASE II TRIAL OF BEVACIZUMAB AND CHEMOTHERAPY IN RECURRENT GLIOBLASTOMA. INT J ONCOL [INTERNET]. 2015 MAY [CITED 2017 DEC 12];46(5):1883–92. AVAILABLE FROM: HTTP://WWW.NCBI.NLM.NIH.GOV/PUBMED/25672376

Overall Survival by QC Score

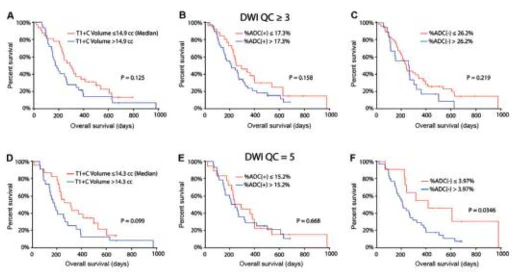
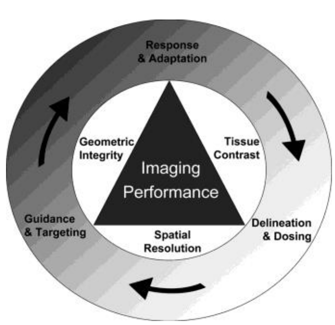


Diagram depicting the importance of optimizing imaging performance based on the fundamental objectives of radiotherapy (outer circle).



Laura A. Dawson, and Cynthia Ménard The Oncologist 2010;15:338-349

The Oncologist

Question set 2:

Major impediments to broad adoption of molecular imaging include:

a) Lack of clinical evidence, immature technology, tracer scarcity, and inadequate recommendation.

b) Lack of clinical evidence, immature technology, lack of reimbursement models, and inadequate recommendation.

c) Lack of clinical evidence, inadequate training, lack of reimbursement models, and inadequate recommendation.

d) Lack of clinical evidence, lack of analysis tools, tracer scarcity, and inadequate recommendation.

Answer: c)

Literature:

Jeraj R, Bradshaw T, Simon i U. Molecular Imaging to Plan Radiotherapy and Evaluate Its Efficacy. J Nucl Med [Internet]. 2015;56(11):1752–65. Available from: http://jnm.snmjournals.org/cgi/doi/10.2967/jnumed.114.141424

Home > Research > Research Areas > Clinical Trials > NCI's National Clinical Trials Network

NCI National Clinical Trials Network Structure

The NCTN structure includes five U.S. Network groups and the Canadian Collaborating Clinical Trials Network. Membership in the individual NCTN groups is based on criteria that are specific to each group. Sites can belong to more than one group, and membership in at least one group allows a site to participate in the trials led by any NCTN group for which their investigators are qualified. Consequently, researchers from the LAPS, NCORP, other academic centers, community practices, and international members associated with the Network groups may all enroll patients onto NCTN trials. Clinical trials led by NCTN groups may receive support from the IROC Group, ITSAs, and tissue banks, according to the scientific needs of the trials.

NCI National Clinical Trials Network Structure

ENLARGE

IROC Mission

Provide integrated radiation oncology and diagnostic imaging quality control programs in support of the NCI's NCTN Network thereby assuring high quality data for clinical trials designed to improve the clinical outcomes for cancer patients worldwide

IROC As a QI Resource

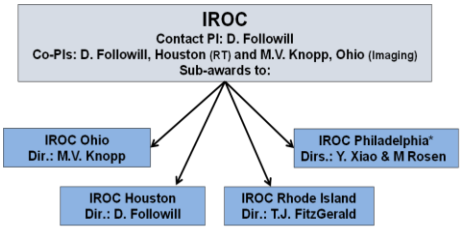
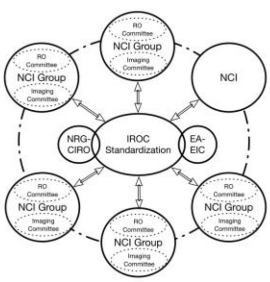


Figure 1: IROC QA Centers, PIs and funding relationship with ACR. * ATC primarily supports IROC Philadelphia.

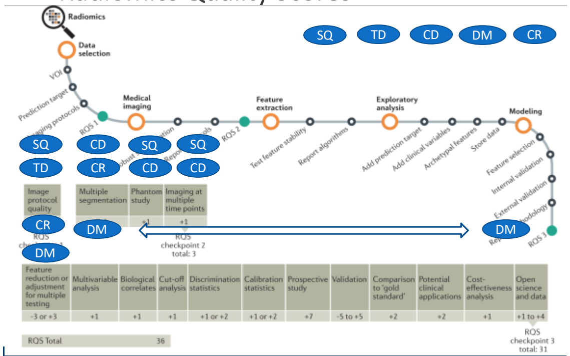
IROC, CIRO, EIC and NCTN groups



IROC's Five Core Services

1. Site Qualification (SQ) SQ
   (FQs, ongoing QA, proton approval, resources)
2. Trial Design Support/Assistance (TD) TD
   (protocol review, templates, help desk, key contact QA centers)
3. Credentialing (CD) CD
   (tiered system to minimize institution effort)
4. Data Management (DM) DM
   (pre-review, use of TRIAD, post-review for analysis)
5. Case Review (CR) CR
   (Pre-, On-, Post-Treatment, facilitate review logistics for clinical reviews)

Radiomics Quality Scores



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Summary

- ❑ QI essential for radiation therapy and have been incorporated in clinical trials
- ❑ Many challenges face appropriate usage of QI
- ❑ IROC as an resource for QI

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Thank you

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