Image Guided Radiotherapy

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Image Guided RadioTherapy (IGRT):
a comprehensive view (7Ds)
What is medical imaging?

- Techniques and processes used to create images of the human body for clinical purposes
- Radiography, Fluroscopy, CT, Ultrasound, MRI, PET CT, Endoscopy, Cartoons...
- How is medical imaging used in Radiotherapy?
Imaging-Cycle

- Delineation
  - GTV, CTV, PTV, OAR
- Determination of Biology
- Detection & Diagnosis Cancer
- Determination of Treatment
- Diagnosis of outcome
- Determination of treatment response
- Dose distribution Design (PTV)
- Dose delivery

modified from Greco & Ling Acta Oncol 2008
(D1) Detection, Diagnosis, Determination of treatment

- improvements in (cancer-specific) survival -

• Screening programs (Mammography, endoscopy, tests)

• Diagnosis at earlier stage → more effective treatment options (cervix, breast, colorectal, prostate, stomach, oesophagus...)

• More appropriate stage (risk) assessment (CT/MRI) → more appropriate treatment strategy allocation

• More appropriate spread assessment (e.g. PET CT)

Decision: local (where), regional, systemic approach (e.g. lung)
Common screening programmes

Breast Cancer
- Mammmography

Prostate Cancer
- Tests (blood, ...)
- Prostate Specific Antigen (PSA)

Colorectal Cancer
- Colonoscopy

Cervix Cancer
- Cytology
Lung Tumor
CT, PET CT
Tumor/Target volume and dose volume concepts in Radiation Oncology

- The International Commission on Radiation Units and Measurements (ICRU (since 1927)) has as its principal objective the development of internationally acceptable recommendations:
  - Quantities and units of radiation and radioactivity
  - Procedures suitable for the measurement and application of these quantities in clinical radiation oncology and radiobiology

ICRU defines a common language for clinical practice and for medical and scientific communication in Radiation Oncology
Gross Tumor Volume (GTV)

- the gross palpable or visible / demonstrable extent and location of malignant growth.
- based on information from a combination of diagnostic modalities
  - clinical examination, endoscopy (light imaging)
  - X-Ray, CT, MRI, ultrasound, PET CT, etc.,
  - Histology after biopsy

TIME AND IMAGING MODALITY ARE IMPORTANT!!!
Cartoon drawings for comprehensive view clinical and (different) imaging findings
Gross Tumor Volume (GTV)

- Comparison among various modalities for the definition of the primary head-and-neck tumor GTV.
- Upper panel: GTV imaged prior to any treatment
  - contrast-enhanced CT: GTV-T: volume of 25.8 ml.
  - fat-saturated T2-weighted MRI: GTV-T: volume of 28.5 ml.
  - FDG-PET: GTV-T: volume of 22.2 ml.

GTV during treatment

Lower panel: GTV imaged after an absorbed dose of 20 Gy.
- GTV-T (CT, 20 Gy): volume of 16.3 ml.
- GTV-T (FDG-PET, 20 Gy): volume of 12.5 ml.
Findings at time of diagnosis

Findings at time of brachytherapy

Fig. 5.1: GTV_{init} and GTV_{res} in cervix cancer

**Dimensions (cm):**
Width: 7  
Thickness: >5  
Height: >5  
Vaginal inv.: 0.5 (right fornix)

**Dimensions (cm):**
Width: 3.5  
Thickness: 2  
Height: 2  
Vaginal inv.: 0
MRI: Initial tumour extension (3D RT) pattern of response (4D RT) for adaptive MRI based planning

Dimopoulos et al. StrahlOnkol 2008
The challenge of change in tumour volume and tumour configuration during treatment

Various patterns
GTV response

Corresponding various patterns of adaptive CTVs
(D2) Delineation of GTV, CTV, PTV + organs at risk

• from planar imaging („2D“)
  – skin cancer (basalcelllelepitheliom)
  – X-ray Sim, individual blocks
  – Hodgkin´s Disease (2D-4D)
  – Boost Head and neck (clinical)(2D-4D)

• to volumetric imaging („3D“)
  – CT (MRI, US) based
  – GTV, CTV, PTV
  – ICRU 50&62 73&78&83&89 definitions
Volume definition (ICRU language)

• The process of determining the volume for the treatment of a malignant disease consists of several distinct steps.

• Different volumes may be defined, e.g. due to:
  – varying (assumed) concentrations of malignancies
  – probable changes in the spatial relationship between volume and beam during therapy
  – movement of patient
  – possible inaccuracies in the treatment setup.

• ICRU Reports define and describe several volumes:
  GTVs, targets and normal structures
  to aid in the treatment planning process
  to provide a basis for treatment comparisons
ICRU Report 50

• 1993 - 3D-CRT

  \[ \text{GTV} \quad \text{visible tumor} \]

  \[ \text{CTV} = \text{GTV} + \text{microscopic spread (lymph node, perivascular, perineural)} \]

  \[ \text{PTV} = \text{CTV} + \text{geometric uncertainties (organ motion, tumor & patient movement, inaccuracies of beam & patient setup)} \]

• Appearance of new imaging modalities (MR, PET), technological progress (virtual simulation, MLC, IMRT), more information about target/organ movement lead to
  – Report 62 (Supplement to Report 50)
Clinical Target Volume (CTV)

- the tissue volume that contains a demonstrable GTV and/or sub-clinical microscopic malignant disease, which has to be eliminated.
- often includes an area directly surrounding the GTV that may contain microscopic disease and other areas considered to be at risk and require treatment.
- is an anatomical-clinical volume:

  CTV-T (Tumor),
  CTV-N (involved lymph Node)
  CTV-M (Metastasis)
ICRU Report 62

- Gross tumor volume: GTV
- Clinical target volume: CTV
- Organ at risk: OAR
- Planning target volume: PTV
- Internal target volume: ITV
- Treated volume or TV
  - Volume enclosed by specific isodose (D98%)
- Planning organ-at-risk volume:
- Remaining volume at risk: RVR
  - Remaining volume at risk
  - (Patient – (CTV + OARs))
Volume definition

Target Volume definition

Interobserver variability in delineation...


R. P. Petersen et al.
I. J. Radiation Oncology ● Biology ● Physics Volume 69, Number 1, 2007

Rasch et al. Radiation Oncology 2010, 5:21

R.J.H.M. Steenbakkers et al. / Radiotherapy and Oncology 77 (2005) 182-190
4D – Intrafraction motion (lung)

- 4D CT
  - feasibility of 4D CT
  - 4D also at treatment machine (4D CBCT)

Sonke et al (Red 2008)
Intrafraction motion reducing safety-margins by use of IGRT (CTV-PTV/IORV) from 5 to 2-3 mm from 10 to 7 mm.

"dancing PROSTATE"
"Amsterdam prostate waltz"

"Vienna prostate waltz"
4D – Interfraction change (cervix)

- MRI: Initial tumour extension (3D RT)
- pattern of spread and response (4D RT)
- for adaptive MRI based radiotherapy (BT)

Changing GTV and CTV
Changing overall topography

Dimopoulos et al. IJROBP 2006
ICRU volume concepts (from 62 to 83 and 89)

- ICRU concepts have been traditionally based on morphology/anatomy
- Margins account for temporal effects
- Concepts are in transition with subvolumes for GTV defined based on functional imaging, and/or GTV response.

Target concepts imply structure boundaries!
change in tumour volume and tumour configuration during treatment

Various patterns of GTV response

Corresponding various patterns of adaptive CTVs

ICRU/GEC ESTRO Report 89
Fig 5.3
Limitations of CT

- CT in many anatomical sites: large inter- & intra-observer variability
- MRI provides improved soft tissue contrast with better visibility and a large amount of sequences

Some remarks on MRI

- image distortion evaluation (MRI)
- image co-registration necessary (?)
- MRI+Linac
Volume definition

- Selection and delineation of the CTV and the OAR is a medical decision,
  - results from a clinical judgment involving many factors, e.g. pathology and imaging findings, imaging.
- Delineation of the GTV and the CTV should be independent of the irradiation techniques, and influenced only by oncological considerations.
(D3) Determine biological attributes
„bio-imaging“ - multimodal imaging

- Tumor hypoxia (H&N, Cervix…)
- Angiogenesis – microvessel density and perfusion (MRI)
- ……Varia……Lactate etc…..

Ling et al. 2000

Baumann et al. 2008
**Supplementary Figure S1:** Example of mp-MRI and PET findings for one patient: T2w (a), DCE T1w (b), ADC map (c), $K_{\text{trans}}$ map (d) and MRS (Cho+Ci)/Cr ratio map (e). The lesion is visible in the peripheral zone at the right posterior part of the gland. For comparison $[^{11}\text{C}]$Acetate PET-CT (f), planning CT (g) and planning CT fused with T2w MR image (h) are shown as well. [1]
Determine „biological“ attributes from response...

...with repetitive morphologic imaging
(D4) Dose distribution design

- 2D radiotherapy
- 3D conformal radiotherapy
- Adaptive Radiotherapy („shrinking field technique“)
- IMRT
- VMAT/Tomotherapy
- Dose Boosting/Painting (non uniform)

Fletcher 1980

- Image guided Brachytherapy

start of treatment – 3 weeks after start
Barker et al 2006
• These volumes may be constructed on TPS automatically with an appropriate margin.

introduced to ensure that dose delivered to CTV & OAR match the prescription & constraints.
Margins

- Most important for clinical radiotherapy.
- Depend on
  - CTV/OAR motion \(\rightarrow\) internal margins (ICRU 62)
  - patient set-up and beam alignment \(\rightarrow\) external margins
- Margins may be non-uniform but should be three dimensional.
- Joint assessment of radiation oncologist and medical physicist
- A reasonable way of thinking would be:
  “Choose margins so that the target is in the treated field at least 95% of the time.”
Margins in RO and Image Guidance

Geometric uncertainties are commonly accounted for by margins
Internal Target Volume (ITV)

(complex R&D issues)

- ICRU Report 78: “In practice, it might not be necessary to explicitly delineate the ITV, but the IM (as well as the SM) must be taken into account when delineating the PTV.”

- ICRU Report 83: “The ITV is considered an optional tool in helping to delineate the PTV.”
Planning Target Volume (PTV)

- In contrast to the CTV a geometrical concept.
- It is defined to select appropriate beam arrangements, taking into consideration the net effect of all possible geometrical variations, in order to ensure that the prescribed dose is actually absorbed in the CTV.
- The PTV includes the internal target margin and an additional margin for set-up uncertainties, machine tolerances and intra-treatment variations.
How to define PTV?

- Analyze ALL uncertainties and use appropriate margin recipe
- Systematic errors (Treatment preparation): setup error, organ motion during planning CT, delineation errors, equipment calibration errors
- Random errors (Treatment execution): inter- & intra-fraction variation
Margins in photon and proton RT
(complex R&D issues)

• **Report 83** provides margin recipes for PTV and PRV in photon therapy (ref. van Herk, Ten Haken and McKenzie)

• **Report 78** “PTV requires different margins lateral, distal and proximal to the CTV. “

• “Daily practice” in PT: Beams can be designed directly for the CTV, taking into account the need for internal and external margins within the aperture design, without reference to a PTV beams.
  – Nevertheless, PTVs must be defined since they are required for reporting purposes.

*The delineation of the PTV is a required part of the treatment prescription*
Dose Boosting and Painting

- coined by CC Ling et al (Red 2000)
- challenges dogma of homogeneity in target
- functional imaging for volumetric map of radiobiological factors
- lack of clinical trials “endpoints”
MR imaging before treatment (T2)
(a) Central lobe, (b) peripheral zone, (c) tumor, (d) prostate.
Definition of target volumes and dose prescription

CTV Low Risk  CTV Intermediate Risk  CTV High Risk
Dose Painting: where?

Fig. 2. Segmentation of target volumes. (a) Computed tomography-based gross tumor volume (GTV_CT) outlined by radiation oncologist. (b) Positron emission tomography-based gross tumor volume (GTV_PET) outlined by same radiation oncologist. QVM = qualitative visual method. (c) Positron emission tomography-based volume, outlined using gross tumor volume 40% maximal uptake method (single maximum) (GTV_PET_40%_max). (d) Positron emission tomography-based volume, outlined using gross tumor volume 15% maximal uptake method (single maximum) (GTV_PET_15%_max).
(D5) Dose delivery assurance („IGRT“)

- near real-time imaging during treatment delivery

- Ideally:
  - 3D volumetric study of soft tissue structures
  - efficient acquisition and comparison
  - process for clinically meaningful intervention

- commercial systems
only partly achieve these needs
(Short) History of IGRT

1951: The very beginning … intended +/- 1cm

Since 1969: X-ray localisation film

Since 90s: Electronic Portal Imaging Device

„State of the Art“ in IGRT: CBCT
achieved +/- 1mm

A (short) history of image-guided radiotherapy
Dirk Verellen*, Mark De Ridder, Guy Storme
UZ Brussel, Oncologisch Centrum, Radiotherapie, Belgium
Radiotherapy and Oncology 86 (2008) 4–13
Where do we need what (R&D)?

- Where there is little movement, e.g. brain, (H&N)
  - bony landmarks
  - 2D MV, kV imaging with „well-thought-out“ correction protocol probably sufficient

- Where targets move relative to bony anatomy
  - 2D imaging with radio-opaque markers
  - no info on normal tissue or tumor conformation

- Where targets move relative to OAR:
  3D imaging for comparison (e.g. SRT lung, liver)
  - online imaging \(\rightarrow\) systematic and random errors corrected
„dancing PROSTATE“
„Amsterdam prostate waltz“

Reducing safety-margins by use of IGRT (CTV-PTV/IORV)
from 5 to 2-3 mm
from 10 to 7 mm

„Vienna prostate waltz“

Linac A
Image guided Radiotherapy
Today’s Technology for Image Guidance

- Beam quality
  - MV (3 – 6 MV)
  - kV (80 – 130 kV)

- Beam collimation
  - CBCT
  - FBCT

- Dimensions
  - 2D
  - 3D

- Rail-track-, ceiling/floor-, gantry-mounted

Current IGRT technology on/in the linac is X-ray based
Maximal conformity at maximal costs?

Radio-Oncology

Upcoming tools and "toys" for advanced treatment
- Cyberknife
- Proton IMPT
- Carbon ions
- IMAT / VMAT
- Tomotherapy
- IGRT + IGART
- Stereotactic RT
- IMRT
- MLC
- 3D
- 2D

Upcoming tools and "toys" for morphologic + biological imaging

Out

come

Courtesy Dietmar Georg, Vienna
Image Guided Radiotherapy (IGRT)

- Reduction of setup and internal margins
- Reduction of side effects
- Enables dose escalation
- Room or rail-track mounted system
- Gantry or couch mounted system

![Image Guided Radiotherapy Diagram]
Image Guidance in proton therapy

- Example MedAustron: Imaging Ring (MedPhoton)
(D6) Deciphering treatment response
(CR, PR, SD, PD/ time pattern)

Standard:
- Morphological changes;
  clinical exam., light imaging (endoscopy),
  US/CT/MR

Upcoming:
- Comparison pre-at and post treatment
  functional imaging (FDG)-PET CT, fMRI

Present Developments
- Measurement of RT induced metabolic changes (cellular proliferation - FLT, Apoptosis, …)
- ADC (apparent diffusion coefficient) DWI, K trans, (DCE) etc.
At diagnosis: 5 cm wide, 5 cm thick, 7 cm high: 88 cm$^3$

At first BT: 2 cm x 3 cm x 3 cm, 9 cm$^3$, good remission, sufficient for intracavitary BT

6 months after treatment: Continuous Complete Remission

3/2005: CCR: local control
(D7) Diagnosis of outcome (after treatment)

Image assessment after certain time intervals

- Tumour remission (complete)
- Lung fibrosis (transient)

after

Definitive

Stereotactic RT

in T1 lung cancer
Stage IIIB, 6 cm, insufficient response (9/2000)
no adapatation of application technique
Intracavitary BT alone

after EBRT, first BT
second BT
third BT

at diagnosis

Optimisation based on intracavitary BT alone
HR CTV
D90: 67 Gy

Parametrial/pelvic wall recurrence 8/2001
4D analysis of tumour spread, target coverage and recurrence

Insufficient Tumour remission (cervix cancer stage IIIB):
no adaptation of application technique
correlation to DVH parameters

At Brachytherapy
9 mths later: Recurrence

Dimopoulos et al. 2010

Diagnosis

At Brachytherapy
Brachytherapy (standard)
9 mths later: Recurrence

Prescribed dose
85 Gy

Dimopoulos et al. GEC-ESTRO 2005
Example of one patient with rectal ulceration in distal rectum at the anterior rectal wall. The location of this ulceration corresponded to the small area of 0.1cc of rectum receiving a dose of 108 Gy EQD2.

\[
\begin{align*}
D_{2cc} &= 81 \text{ Gy EQD2} \\
D_{1cc} &= 90 \text{ Gy EQD2} \\
D_{0.1cc} &= 108 \text{ Gy EQD2}
\end{align*}
\]

high dose area corresponding to 0.1cc

Imaging-Cycle

Detection & Diagnosis Cancer
Determination of Treatment

Delineation
GTV, CTV, PTV, OAR

Determination of Biology

Dose distribution Design (PTV)

Dose delivery

Diagnosis of outcome

Determination of treatment response

modified from Greco & Ling Acta Oncol 2008
IGRT: a comprehensive view (7D): activities within this overall frame

- Detection/Diagnosis cancer, Determinat. treatment
- Delineation of target (CTV/PTV), Organs at Risk
- Determining biological attributes
- Dose distribution design (PTV)
- Dose delivery assurance
- Determining treatment response
- Diagnosis of outcome (recurrence/morbidity)

Major clinical relevance

modified from Greco&Ling 2008
Mulitmodal Imaging

Research
Work in progress
Multiparametric imaging

• Combining image-derived parameters to increase diagnostic accuracy
  ➔ improved sensitivity and specificity due to complementary information
  ➔ reduced patients burden: cost- and time-effectives
  ➔ suitable for diagnosis and treatment planning

• Multiparametric?
  ➔ anatomy
  ➔ Vascularization
  ➔ Perfusion/permeability
  ➔ cellularity/proliferation
  ➔ chemical composition
Cervix cancer (CCa) characterization with mpMRI and $[^{18}\text{F}]\text{MISO}$ and $[^{18}\text{F}]\text{FDG}$

- **Dataset**: 11 CCa patients scanned with mpMRI, $[^{18}\text{F}]\text{MISO}$ and PET $[^{18}\text{F}]\text{FDG}$ in two separate scanners
  
  ➔ demonstrated feasibility of multiparametric $[^{18}\text{F}]\text{MISO}$/FDG PET-MRI
  
  ➔ assessed for tumor volume, enhancement kinetics, diffusivity, and $[^{18}\text{F}]\text{FDG}$/ $[^{18}\text{F}]\text{MISO}$-avidity
  
  ➔ descriptive statistics and voxel-by-voxel analysis of MRI and PET parameters were performed

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*Pinker K. et al 2016*
Early CCa treatment response with mpMRI and $^{18}$F]MISO

- Dataset: 6 CCa patients undergoing chemoradiotherapy, scanned with mpMRI and $^{18}$F]MISO PET in two separate scanners in 4 time-points
  - demonstrated feasibility of multiparametric $^{18}$F]MISO PET-MRI EBRT response assessment
  - high patient drop-out rate – study moved to PET/MR
  - spatio-temporal variation of hypoxia in between scanning timepoints
  - no voxel-wise correlation between hypoxia and mpMRI parameters
  - complementarity of PET and MRI derived parameters needs further investigations

Georg P. et al – manuscript in preparation
Early CCa treatment response with hybrid PET/MR using $[^{18}\text{F}]\text{MISO}$

- Recruitment ongoing: 2 patients underwent full protocol, 2 patients in progress, mpMRI and $[^{18}\text{F}]\text{MISO}$ PET scans performed on a hybrid PET/MR scanner in 4 timepoints
  - ethics committee amendment approved, new SOP and imaging sequences for the PET/MR, technical developments to adjust the scanner for RO needs
  - demonstrated feasibility of multiparametric $[^{18}\text{F}]\text{MISO}$ PET/MR for EBRT response assessment (patient position as at treatment)
  - decreased patient drop-out rate (1 patient resign due to chemotherapy side effects)
Implementation of new PET tracers (pilot study)

- **Early cancer treatment response** using $^{68}$Gd-Pentixafor (hybrid MR-PET)
  - based on 85 studies and over 11000 patients data:
    - “CXCR4 over-expression is associated with poor prognosis in cancer”
  - can be used as discriminator of necessity for more aggressive treatment
  - potential use in radiotherapy response assessment

- **Cooperation with Division of Nuclear Medicine** - ethics committee application in revision for patients with cancer:
  - lung
  - pancreas
  - head and neck

*Courtesy A. Haug*
PCa characterization with CT perfusion (pilot study)

- To implement CT perfusion imaging protocol in diagnosis and treatment assessment of PCa
  - ongoing recruitment for the pre-RT baseline CT perfusion
  - optimization of the CT perfusion protocols on two diagnostic CT scanners
  - preparation for the feasibility study on EBRT assessment with CT perfusion

Courtesy P. Apfaltrer and F. Baar
Imaging data analyses

- **Based on descriptive statistics**
  - performed in predefined regions of interest (ROIs)
  - geometrical parameters (volume, distance etc.)
  - grey level or biologically modeled quantitative parameters statistics (mean, max, min etc.)

- **Based on voxel by voxel analyses**
  - spatial correlation as additional degree of freedom
  - requires good spatial agreement between investigated modalities (fusion or hybrid imaging)
  - provides information on ROI’s heterogeneity
Imaging data analyses – textural features

- Based on image histogram (1st order statistics)
- Based on gray-level co-occurrence matrices (2nd order statistics)

- Median
- Minimum
- Maximum
- Skewness
- ...
Association between pathology and texture features of mpMRI of the prostate