Adapting radiotherapy using patient-specific biological imaging

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Personalized Radiotherapy

Radiotherapy Today
The fundamental aims of radiotherapy are independent of the technology we use:
– to deliver a high enough dose to control local tumour growth,
– to keep normal tissue toxicity within reasonable limits.

Improved Targeting
Pre-treatment we can use imaging to:
– Better identify the target volume (18FDG PET, MRI, 4D CT)
– Better identify radiosensitive normal tissues

Improved Delivery
During treatment we can use imaging to:
– Improve day-to-day setup and delivery accuracy
– Measure (and correct for) systematic changes in anatomy

Lots of technology
• Linacs with on-board imaging
• Cone beam CT
• Tomotherapy, Cyberknife, Vero
• Fluoroscopy
• 4D CT
• Surrogates for breathing / implanted fiducial markers
• Gating, tracking, ABC
• Functional imaging PET, SPECT, MRI
• Ultrasound
**Target Definition: Head & Neck**

![CT PET Fusion images](image)

**FDG PET for volume delineation in non-small-cell lung cancer**

\[ T1N0M0 \text{ stage from CT} \]

\[ T1N2M0 \text{ stage from PET} \]

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**Volume Definition**

In radiotherapy planning we define a number of volumes to account for uncertainties in the planning process:

- **GTV** (Gross Tumour Volume)
- **CTV** (Clinical Target Volume)
- **PTV** (Planning Target Volume)

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**Where next?**

- Use on-line imaging to reduce margins more and more to allow dose escalation and normal tissue sparing.
  - Yes, but with caution.

Continue to increase PTV dose with protons & carbon ions.

- Yes, but physical dose is not always the limiting factor.
- Image every patient with every modality as many times as we can.
  - Probably not …

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**But tumours are heterogeneous**

- Visible tumour mass
- Hypoxic region
- Necrotic core
- Microscopic extension
- Oedema

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**Where next?**

Move away from delivery of a uniform population-derived dose to a (deliberately non-uniform) patient-specific prescription:

- Individualised iso-toxic dose
- Biologically-guided using functional imaging
- Stratified using gene expression profile

Monitor patient response during treatment to create biologically adaptive plans:

- Boost dose to non-responding sub-regions of tumours
- Reduce dose to well-responding areas
- Early prediction (& reduction) of normal tissue toxicity
- Intervene with radiosensitivity modulating drug
Imaging in Radiation Oncology

Anatomical

IGRT

Biologically adaptive

Functional

Before

During

After

Target definition

Diagnosis & Staging

Early

Late

Adapted from a slide by Robert Jeraj

The challenge

How could we use functional data for dose prescription?

i. don’t – dose escalate to a fixed (or iso-NTCP) level with an anatomically-defined target

ii. dose escalate to a fixed level with a single functional image defined target

iii. dose escalate to a fixed level with a multiple functional image defined targets

iv. optimise plan using explicit radiobiological objective function

18F-FDG for boost target definition in locally-advanced pancreatic cancer

MR-guided intraprostatic boost

Challenges:

- Optimisation & validation of imaging (2 different clinical trials)
- Elastic matching of images pre/post hormone and with/without endorectal probe (developed in-house software)
- Developing optimum model to segment tumours (developed in-house software)
- Importing segmented template and matching with planning CT (fiducial markers and in-house software)
In radiotherapy planning we define a number of volumes to account for uncertainties in the planning process:

- **GTV**
- **PTV**
- **BTV**

Same mean dose to PTV

**Imaging Protocol & QA**

- To ensure that images are consistent, careful protocols should be followed for:
  - Patient immobilisation
  - Time from injection to imaging (for PET)
  - Image acquisition protocol
  - Image processing
  - Segmentation

- These should be regularly checked using phantom measurements.

- **Nuklearmedizin** 2012; 51: 140–153

**Acquisition Protocol**

- PET image contrast changes as a function of time after injection.
- Different types of lesion show different kinetic behaviour.
- A well-defined protocol is essential for accurate outlining.

- 54 min post injection
- 103 min post injection

**So which one is the target?**

- **CT**
- **DCE MR**
- **DW MR**
- **FDG PET**
- **T2 MR**

[Courtesy Ceri Powell & Kate Newbold]
Biological Adaptation

Use the imaging to measure biological response to treatment and adapt individual patient treatments according to response:

- Pre-treatment imaging
- Treatment planning
- Treatment delivery
- Post-treatment imaging

**Histopathological correlation**

Study of 12 patients with head and neck cancer with 28 metastatic lymph nodes eligible for therapeutic neck dissection who underwent preoperative FDG PET/CT.

**DW-MRI ADC changes at 2 weeks predicts response**

Median ΔADC in poor responders was significantly lower than in good responders 2 weeks into treatment (7% vs. 21%; p < 0.001).

**Early assessment of response**

- CT
- DCE MR
- DW MR
- FDG PET
- T2 MR

**18FLT as a predictor of response**

Stratify by 45% decrease in SUVmax between baseline and week 2 (patients treated with radiotherapy)
**The RHYTHM trial as an example of imaging biomarker development**

- **RHYTHM**: modulation of Radiotherapy according to HYpoxia: exploiting changes in the Tumour Microenvironment to improve outcome in rectal cancer.
- **Objectives**: To define the best method of detecting hypoxia in rectal cancer and to develop a method of detecting changes in rectal tumour oxygenation during preoperative chemoradiotherapy.

**RHYTHM-I: Group B**

- **Biopsy**
- **Blood sample**
- **FMISO PET**
- **pCT**
- **dce-MRI rectum**

**Radiotherapy planning feasibility study**

- **Day -7: -1**
- **0**
- **10-12**
- **6 weeks**
- **8 weeks**

Histologically confirmed locally advanced adenocarcinoma of the rectum: CRM threatened/involved

**Images before and after 10# RT**

Images courtesy of James Wilson

**Compare images or doses?**

Picking a single fixed threshold to define a biological target volume is hazardous:

- Different thresholds give different volumes!
- Threshold value changes with object size
- Patterns of uptake vary with time

Spontaneous canine head and neck tumour treated with 3.0 Gy per fraction.

**Compare images or doses?**

Solution – use doses not images

Summary I

- Biological information already plays an important role in radiotherapy in staging
- It is playing an increasing role in assisting GTV definition
- A number of clinical trials are in progress testing functional image-guided "boosting" or dose redistribution.

Summary II

- Through observational trials we are learning how to use functional imaging as a quantitative and standardised "biomarker" of response to treatment.
- This will allow patient-specific adaptation of treatment according to response to therapy.
- The advent of the PET/MRI and the MR-LINAC offer the opportunity to get more and more patient-specific biological information during treatment.

Challenges

- Knowing the best imaging modality to use and the best time point to observe response (but still have time to intervene) for a particular disease and site needs more work.
- The link between functional image "signal" and dose-response is still largely unknown and raises both physical challenges (absolute image quantification, standardisation and QA) and biomedical challenges (clinical dose-response studies using heterogeneous prescriptions).
- There are safe and pragmatic ways to get started without the above …

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