Treatment (de)escalation
- The physicist perspective

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How do we optimise our use of radiotherapy?

Indication
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Indication

Cohort

Schedule & dose  Target
How do we optimise our use of radiotherapy?

Indication

Cohort

Schedule & dose  Target

Per patient
How do we optimise our use of radiotherapy?

- **Indication**
- **Cohort**
  - Schedule & dose
  - Target
- **Per patient**
- **Per voxel**
RT for NSCLC as exemplar

Central role played by (chemo)radiotherapy

Locoregional control & toxicity challenges

No further benefit of dose escalation?
RT for NSCLC as exemplar

Central role played by (chemo)radiotherapy

Locoregional control & toxicity challenges

No further benefit of dose escalation?

Worse survival associated with:
- Tumour location
- Oesophagitis/dysphagia
- Planning target volume
- Heart dose

Optimising the therapeutic window?

Increased dose: Increased survival from disease control AND mortality from toxicity

Meta-regression of 6957 NSCLC patients in 68 studies, taking into account
- Stage
- Chemotherapy
- Alpha/beta & repopulation
- Stage

Nix et al. Radiother Oncol 2019 (in press)
Using Genomically Adjusted Radiation Dose (GARD) to personalise treatment prescriptions

Gene expression-based radiosensitivity index (RSI) - a surrogate for intrinsic cellular radiosensitivity

Optimal dose for tumour control in 1,747 patients with NSCLC

Optimal RT dose for each patient that maximizes tumour control and limits toxicity:
Ideal personalized therapeutic ratio

Further personalisation - TCP & NTCP adjusted for clinical risk factors

Individualized dose-response for radiation pneumonitis (iQUANTEC)

Smoker, no risk factors

Patient with highest risk:
- Pulmonary co-morbidities
- Tumour in the middle/lower
- No history of smoking or current smoking habit
- >63 years old
- Sequential chemotherapy
What does a good treatment plan look like?
Why do we try to deliver a homogeneous dose?

‘Tradition’

Optimisation of tumour control

Brahme (1984):
- TCP will be at maximum for zero standard deviation of dose in tumour
- Optimise minimum dose to the tumour

Webb & Nahum (1993)
- “if the clonogenic cell density is constant throughout the tumour then a uniform dose distribution produces the highest TCP for a fixed energy deposition”
RT as adjuvant therapy

Large elective fields

Large treatment delivery margins
Large volume of normal tissue in target

- Large elective fields
- Large treatment delivery margins
- RT as adjuvant therapy
Large volume of normal tissue in target

Homogeneous dose limited by normal tissue tolerance
Inhomogeneous dose distributions driven by 3D information about target volume

Surrogate measure of clonogenic cell density & number

Per-voxel dose prescription

Inhomogeneous dose distribution

Per-voxel dose optimisation

"Dose-painting by numbers"

Søren Bentzen, 2005

Bentzen. Lancet Oncol 2005; 6: 112-17
Measures to guide dose deposition

Aim: inhomogeneous dose deposition driven by per-voxel dose-dependence of local control

"prescription function that is the mathematical link between a specific value [of an imaging variable] and the optimum clinical dose to be prescribed to the corresponding voxel”

• Measure
Measures to guide dose deposition

Aim: inhomogeneous dose deposition driven by per-voxel dose-dependence of local control

“prescription function that is the mathematical link between a specific value [of an imaging variable] and the optimum clinical dose to be prescribed to the corresponding voxel”

- Measure
  - “Same risk across entire target”
  - “Higher risk in macroscopic tumour”
  - “Less risk in edge of target”

- Assume
Measures to guide dose deposition

Aim: inhomogeneous dose deposition driven by per-voxel dose-dependence of local control

"prescription function that is the mathematical link between a specific value [of an imaging variable] and the optimum clinical dose to be prescribed to the corresponding voxel"

- Measure
- Imply
- Assume
Voxel-specific failure risk to guide dose redistribution

Failure-probability driven dose painting (Ivan Vogelius)

H&N SCC failures more likely to happen in high PET uptake volumes

Per-voxel dose-dependent failure risk

Phase I trial of 18F-Fludeoxyglucose based radiation dose painting with concomitant cisplatin in head and neck cancer
**Heterogeneous FDG PET-guided Dose Escalation in NSCLC**
- a phase III trial by the Danish Oncological Lung Cancer Group (DOLG)

Inhomogeneous failure risk
- Primary vs nodal targets
- FDG-PET avid volumes

7 centres recruiting
200 / 350 patients enrolled

Median dose escalation in first 30 trial patients:
- PET GTV-T: 93.9 Gy
- PET GTV-N: 73.0 Gy

Standard homogeneous dose
- PET GTV-T ≤ 95 Gy / 33 #
- PET GTV-N ≤ 74 Gy / 33 #
- PTV ≥ 66 Gy / 33 #

Heterogeneous, FDG-guided dose escalation
- PET GTV-T ≤ 95 Gy / 33 #
- PET GTV-N ≤ 74 Gy / 33 #
- PTV ≥ 66 Gy / 33 #

Randomisation
- Standard dose possible
- Equivalent normal tissue (lung) dose

Møller et al. Radiother Oncol 2017;124:311-317
NCT02354274: Novel Approach to Radiotherapy in Locally Advanced Lung Cancer
- Heterogeneous FDG-guided Dose Escalation With Concomitant Navelbine
Treatment individualisation

- Dose (de)escalation
- Treatment individualisation
- Personalised medicine in RT

Per-voxel optimisation of normal tissue dose

Patient & clinician preferences
Heterogeneous Dose De-escalation in NSCLC  
- a phase II trial by the Danish Oncological Lung Cancer Group (DOLG)

Patients who:
• Are not fit for CRT with 66 Gy in 33 fractions
• Standard dose plan to 66 Gy not acceptable wrt dose to normal tissue
• (Attempt) 66 Gy / 24# to primary tumour
• (At least) 50 Gy / 24# to involved lymph nodes

NCT03742687: HERAN - Heterogeneously Hypofractionated Radiotherapy for Locally Advanced NSCLC
Treatment individualisation

Dose (de)escalation

Treatment individualisation

Personalised medicine in RT

Per-voxel optimisation of normal tissue dose

Patient & clinician preferences

Technical challenges
Counter-arguments

• “We don’t know what the target is”
Variation in tumour outlining for early rectal cancer

APHRODITE radiotherapy workshop, unpublished data
Counter-arguments

• “We don’t know what the target is”

• Actually delivered plan may not differ significantly from standard homogeneous plan

• Hard to QA and report

• Lack of clinical data to demonstrate benefit
What does it mean to put patients first?

Plan optimisation to be driven not just by DVHs ...

Develop the technology to plan and deliver

Physicists - step up!