Metodi avanzati per l’analisi 2D/3D di mappe di dose e integrazione in modelli di tossicità: applicazioni cliniche

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Summary
- The «Emami-Burman & Quantec-like organ based» approach to NTCP modelling: Pro’s and Con’s
- Overcoming the «organ-based dogma» of NTCP modelling
- General concepts toward «dose distribution-based» NTCP models
- 3D methods: challenges and limits
- 2D methods in the case of hollow organs/surface layers: a pixel-wise method to assess dose-surface map (DSM) predictors
- Application to urinary toxicity (bladder DSM)

The «Emami-Burman & Quantec-like organ based» approach to NTCP modelling
- ...an intuitive and natural way to describe radiotherapy-induced effects
- Organs as «independent and homogeneous entities» is a robust and practically usable approximation for most end-points
- Supported the translation from «qualitative» to «quantitative» RT ....knowledge condensed into organ constraints/EUDs/NTCPs

Overcoming the «organ-based dogma» of NTCP modelling (?)
- The organ-based DVH approach is clearly a “hard constraint”
- Symptoms cannot be always linked to the irradiation of a single organ without looking what happens in other organs/tissues (the response may depend on the dose to multiple organs)
- Maybe more important, organs are not “homogenous entities” from the point of view of their response to radiation and their functions

Overcoming the «organ-based dogma» of NTCP modelling (?)
- The complexity of sub-structures/tissues within an organ are not considered by DVHs (the dosimetry spatial information is lost).
- Local effects may largely influence (and jeopardize) the apparent “organ-response”
- Overcoming (integrating) the “organ-based dogma” is an important challenge for current research in the field of predictive models of toxicity
- (One of the) “natural” steps to better approximate the complexity of the response of normal tissues to RT
General concepts toward «dose distribution-based» NTCP models

- **“forward”** approach: making hypothesis/assumptions and segmenting organs in pre-defined substructures (for instance: brain segmented in sub-regions according to their functionality)
- Simple extension of the organ-based approach (multiplication of organs/structures)
- Pro’s: testing well assessed functional hypothesis, possibly easy to accomplish
- Con’s: loosing part of the spatial information
- Generalized approach trying to take the whole spatial information into account
- Con’s: challenging, need of large numbers, how translate this information in «constraints»?

- **“backward”** approach: without any additional hypothesis, directly looking to the differences of the dose distributions between patients with vs without toxicity
- Simple extension of the organ-based approach (multiplication of organs/structures)
- Pro’s: «full» search of spatial effects, potentially hypothesis-generating
- Con’s: challenging, need of large numbers, how translate this information in «constraints»?

3D (backward) methods: challenges and limits

- The idea: translating individual dose distributions on “template” patient(s)
- Assessing rules for imaging/dose deformation
- Searching predictors through “voxel-wise” dissimilarity measurement
- Potential for identify regions whose irradiation better discriminate pts with/wout tox
- Robustness of the results mainly depends on the way the deformation is applied and/or on the integrity of the correspondence among patients
- Deform 3D images/dose distribution on a template «mean patient» (prostate registration)
- Looking to local dose differences and assessing significance through t-test
- Method refined with permutation tests replacing t-test (Chen, 2013)

Analogies with «voxel-wise» imaging analyses

- Looking to the distribution of the differences of voxel signals (morphological, functional)......for instance: SPM, Statistical parametric mapping
- Healthy subjects vs ill patients
- Same patient: local changes with time
- ......image-based local changes induced by RT

2D pixel-wise on dose-surface maps (DSM):

- For hollow organs, the surface well represents the organ (i.e.: bladder, rectum, esophagous,...)
- The 3D «voxel-wise» approach may be reduced to a 2D problem
- Implementation of the method and its application to the urinary toxicity case (Bladder)
Generating bladder Dose Surface Maps

Panel 1: Illustration of the process of generating bladder dose surface maps.

Panel 2: Illustration of dose surface distribution and its alignment.

Panel 3: Comparison of dose surface maps with and without toxicity.

Investigating local dose effects in a prospectively followed population (DUE01 study)

- 436 patients with baseline and end-RT IPSS questionnaire available (7 questions, 1 to 5 score, total score between 5 and 35)
- Analysing acute toxicity, excluding patients with bad baseline values: IPSS total >=15, single items (7 questions) >=4
- Patients treated with conventional and moderate hypofractionation (2.35-2.65 Gy/fr, 25-28 fractions), full bladder
- DSMs were aligned at the (I/P) point and caudally cut at the smallest vertical extension present in the sample (25 mm)
- Evidence of local dose effects, mainly for Hypo patients

Robustness of the method

To assess the robustness of the method, DSMs were cut at different vertical extensions, from minimum value of 25 mm until median value of 57 mm.
In progress, future developments...

- Extraction of local dose descriptors and integration in Multi-variable models (a first analysis on 72 pts shows better model’s performances using DSM predictors compared to DVH/DSH)
- Alternative/advanced dissimilarity measurements and automatic feature extraction methods (permutation test approach, Principal Component Analysis, Textural features, distance metrics methods...)
- Application on late urinary toxicity data (DUE01)
- Extension to other organs (rectum, sigmoid, esophagus,....)

Conclusions

- Increasing interest to overcome/integrate the «organ-based dogma» of NTCP modelling
- 3D/2D methods to directly correlate dose distributions of pts with/wout toxicity is challenging
- 2D methods in the case of hollow organs/surface layers are very promising
- A pixel-wise method to assess dose-surface map (DSM) predictors was implemented and applied to a large population of prostate pts included in a prospective study
- Clear evidence of local dose effect (trigone) for acute toxicity with a prevalent threshold effect

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