

Deep learning for radiotherapy outcome prediction using dose data

Ane Appelt

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McMedHacks 2022

 @cancerphysicist

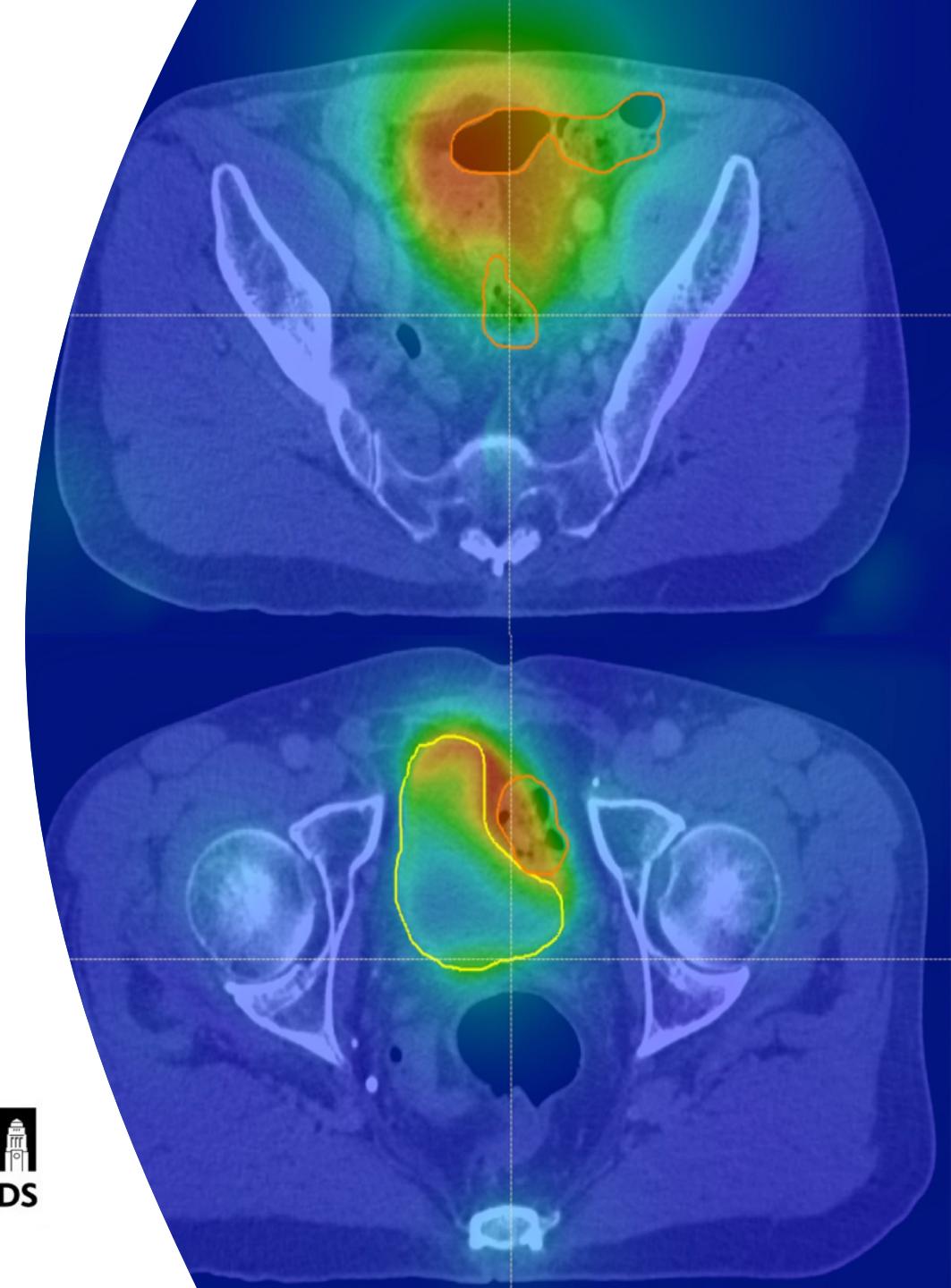


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Together we will beat cancer

UNIVERSITY OF LEEDS



A BIT ABOUT ME

BSc in Physics
University of Southern Denmark



MSc in Elementary Particle Theory
University of Durham, UK



Postgraduate training in Medical Physics
National Danish training scheme, on-the-job training

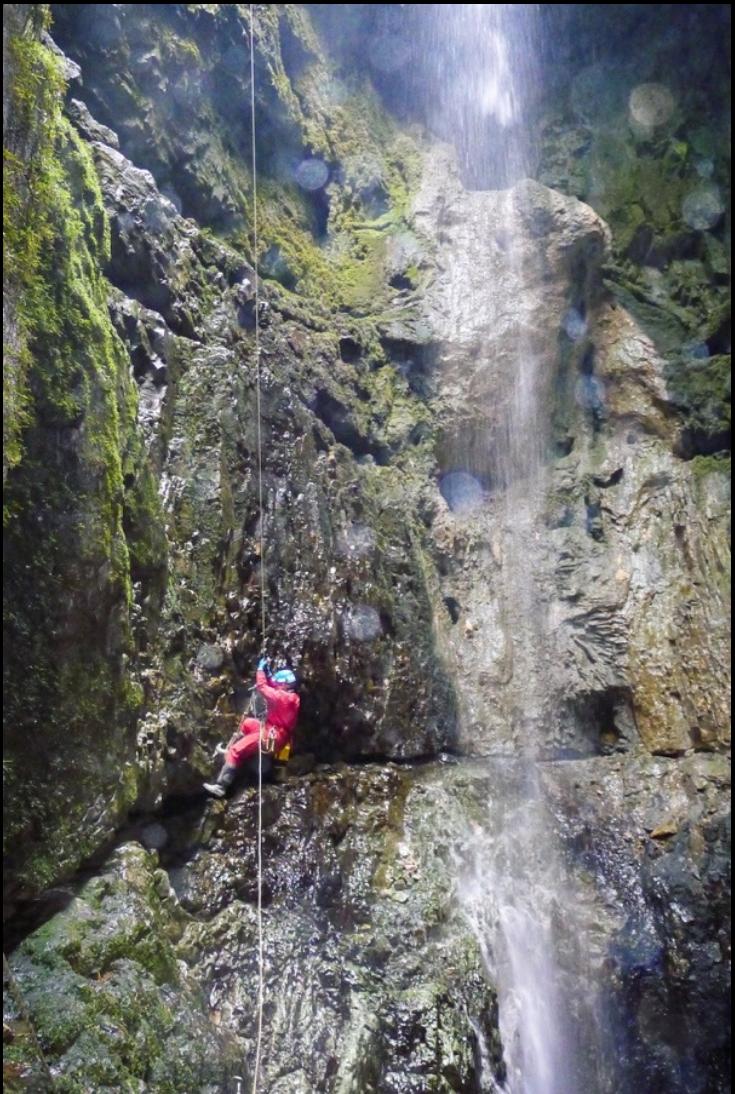


PhD in Clinical Oncology
University of Southern Denmark

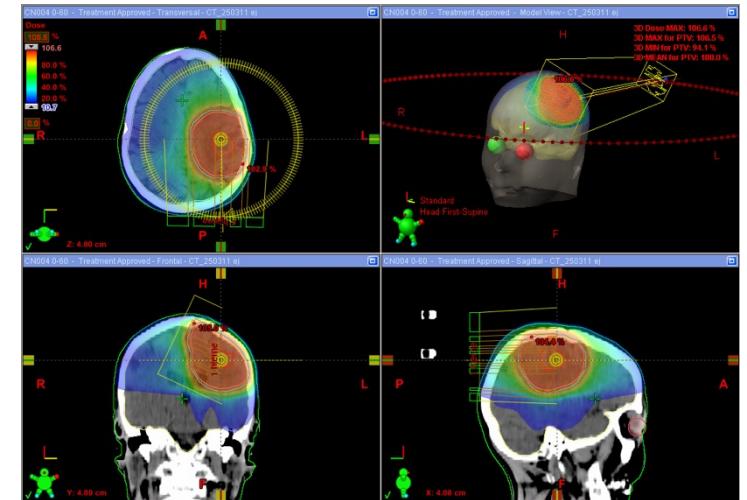
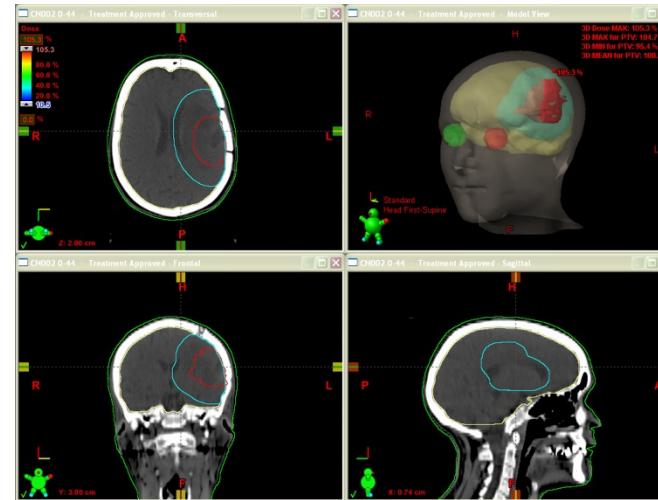


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RADIOTHERAPY



Use of ionising radiation (most commonly high energy x-rays) to treat cancer

(Almost) unique in medicine by having a spatially modifiable treatment intervention

Complex individual patient treatment planning:

- Inverse planning: Large number of degrees of freedom for plan optimisation

3D data on treatment (images, radiation dose distribution) available for each patient

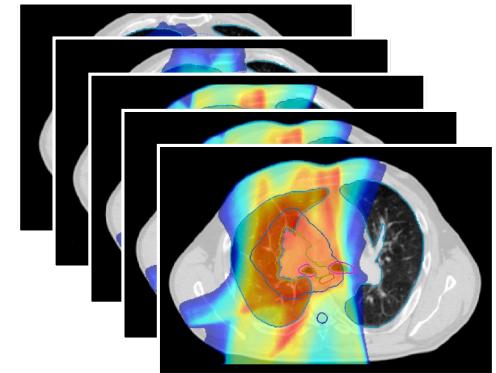
WHY DO WE NEED TO LINK RADIOTHERAPY DOSE TO OUTCOME?

Need models relating treatment details to outcomes, in order to feed back into treatment planning

- Which dose levels should we reduce to prevent toxicity? To which anatomical regions? For patients with which clinical characteristics?

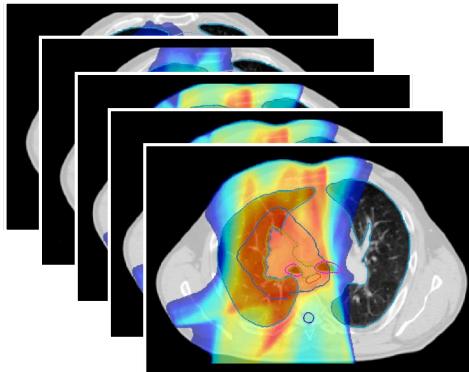
What do we try to achieve with these models?

- Predict patient outcomes (e.g. “who will get treatment toxicity”)
- Understand the relationship between radiation dose distribution and outcome (“which part of the dose distribution matter”)



STANDARD MODELLING METHODOLOGY IN RT

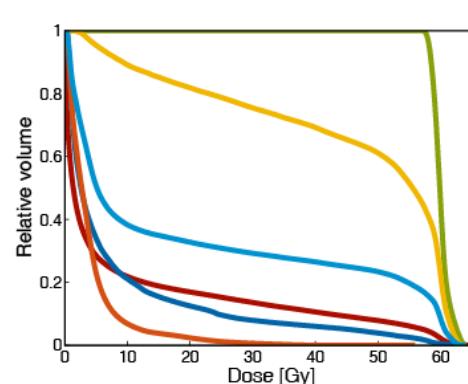
Radiation dose distribution



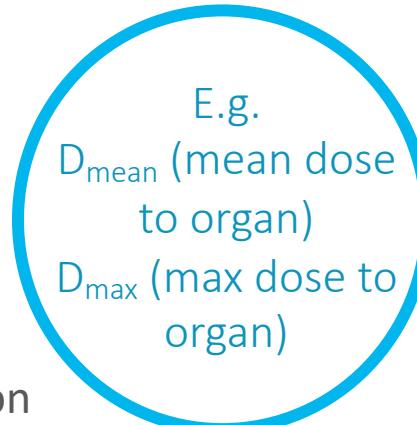
(Probability of) outcome

Use segmentation to reduce dose distribution to dose volume histogram for each organ

- Removes all spatial information
- Assumes equal sensitivity/response of all parts of the organ in question



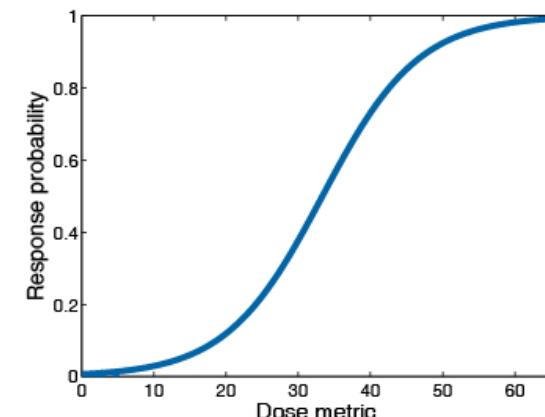
Further reduce dose distribution to a few metrics



Link dose to outcome with generalised linear modelling:

$$y \sim a_0 + a_1 x_1 + a_2 x_2 + \dots + a_n x_n$$

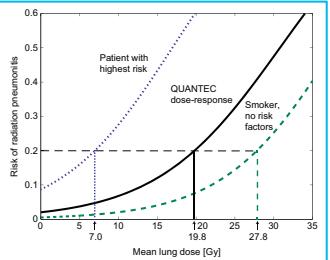
Add in structured data (e.g. patient characteristics, other treatment, etc)



ORIGINAL ARTICLE

Towards individualized dose constraints: Adjusting the QUANTEC radiation pneumonitis model for clinical risk factors

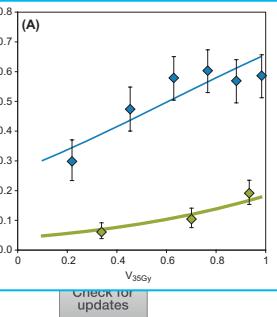
ANE L. APPELT^{1,2}, IVAN R. VOGELIUS³, KATHERINA P. FARR⁴, AZZA A. KHALIL⁴ & SØREN M. BENTZEN⁵



ORIGINAL ARTICLE

Dose-response of acute urinary toxicity of long-course preoperative chemoradiotherapy for rectal cancer

ANE L. APPELT^{1,2}, SØREN M. BENTZEN³, ANDER

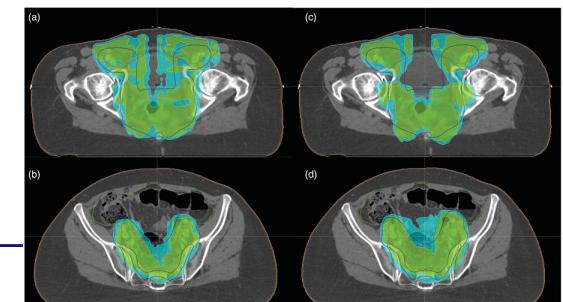


European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:455–466
<https://doi.org/10.1007/s00259-018-4139-4>

ORIGINAL ARTICLE

Discovery of pre-therapy 2-deoxy-2-¹⁸F-fluoro-D-glucose positron emission tomography-based radiomics classifiers of survival outcome in non-small-cell lung cancer patients

Mubarik A. Arshad^{1,2,3} · Andrew Thornton¹ · Haonan Lu¹ · Henry Tam^{2,3} · Kathryn Wallitt^{2,3} · Nicola Rodgers¹ · Andrew Scarsbrook^{4,5} · Garry McDermott⁴ · Gary J. Cook⁶ · David Landau⁶ · Sue Chua⁷ · Richard O'Connor⁸ · Jeanette Dickson⁹ · Danielle A. Power^{2,3} · Tara D. Barwick^{1,2,3} · Andrea Rockall^{1,2,3} · Eric O. Aboagye¹



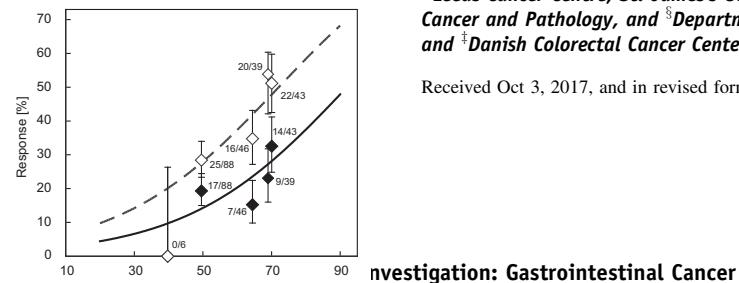
ACTA ONCOLOGICA, 2017
<http://dx.doi.org/10.1080/0284186X.2017.1315174>

ORIGINAL ARTICLE

Feasibility of preference-driven radiotherapy dose treatment planning to support shared decision making in anal cancer

Heidi S. Rønde^a , Leonard Wee^{b,c}, John Pløen^{c,d} and Ane L. Appelt^{c,e}

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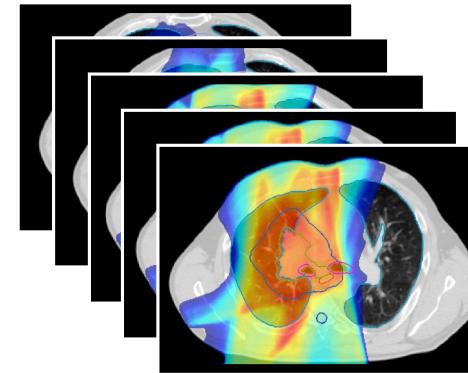
Radiation Dose-Response Model for Locally Advanced Rectal Cancer After Preoperative Chemoradiation Therapy

ANE L. APPELT, MSc, *† JOHN PLØEN, MD, * IVAN R. VOGELIUS, PhD, ‡ SØREN M. BENTZEN, PhD, DSc, § AND ANDERS JAKOBSEN, DMSc*,†

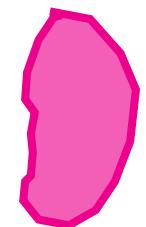
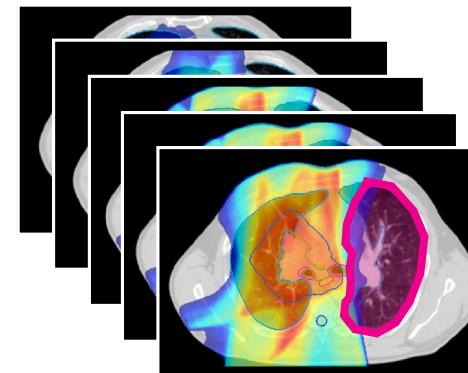
*Department of Oncology, Vejle Hospital, Vejle, Denmark; †University of Southern Denmark, Odense, Denmark; ‡Department of Radiation Oncology, Rigshospitalet, University of Copenhagen, Denmark; §Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

STANDARD MODELLING METHODOLOGY IN RT

Doesn't use the full spatial radiation dose information



CT information is reduced to organ segmentation



E.g.

D_{mean} (mean dose to organ)

D_{max} (max dose to organ)

TRADITIONAL VS MODERN MODELLING CONCEPTS

Dose variable(s)



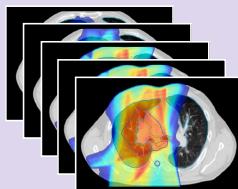
One or a few per patient

Response / outcome measure



One per patient

Traditional radiotherapy modelling

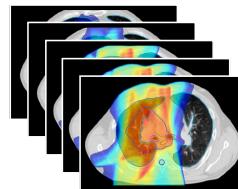


Many per patient
(2D or 3D data)

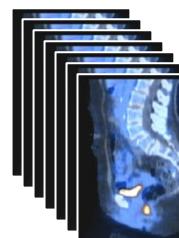


One per patient

Voxel-based analysis (VBA), convolutional neural networks (CNN)



Many per patient
(2D or 3D data)

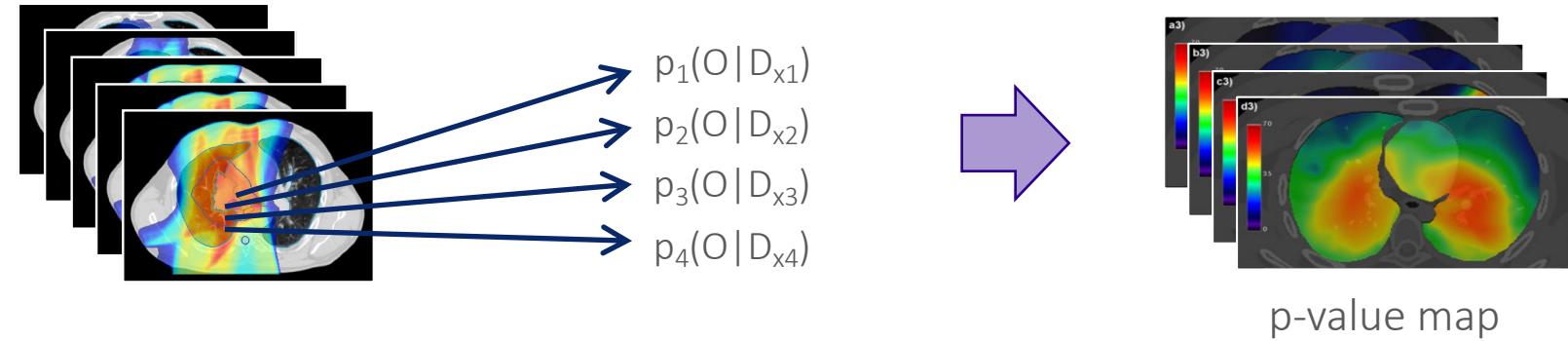


Many per patient
(2D or 3D data)

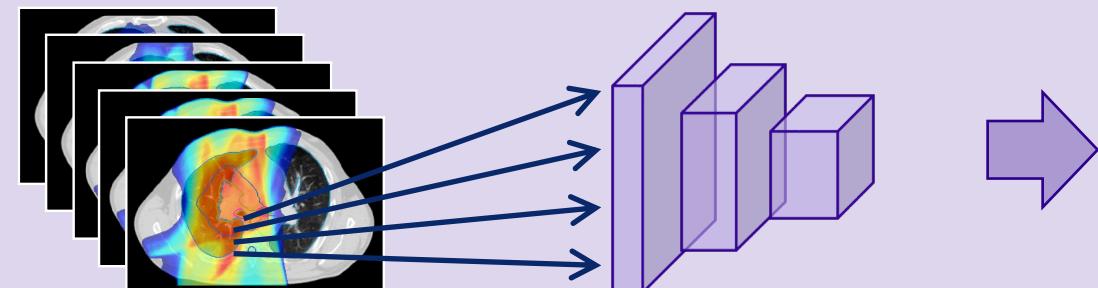
Image-based response models

SUMMARY OF MODELLING CONCEPTS

Voxel-based analysis



Convolutional neural networks



single patient-level
prediction /
classification
 $p(O|D)$

ADVANTAGES OVER TRADITIONAL RADIOTHERAPY MODELLING?

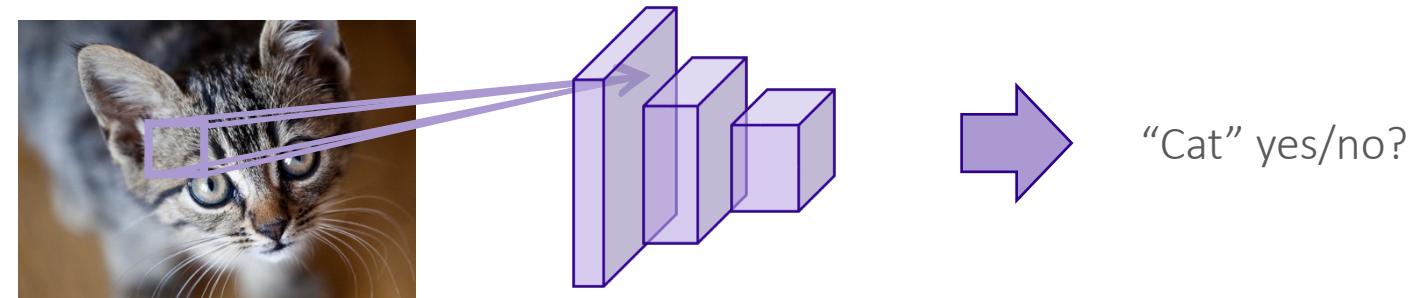
Unique advantage

- Representation of complex dose morphology
- Interaction between imaging features & dose patterns
- Map relationship between local dose and ‘global’ patient response / outcome
- Optimise local dose based on map of regions driving toxicity risk (rather than via dose volume histogram)

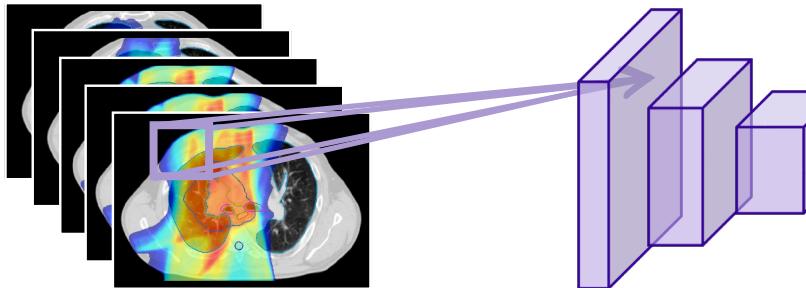
Potential impact

- Better predict who will get toxicity
- New insights into anatomy, pathophysiology and/or regional radiosensitivity variation
- Improve and individualise treatment planning

“JUST ANOTHER CLASSIFICATION PROBLEM”



“JUST ANOTHER CLASSIFICATION PROBLEM”



single patient-level
prediction / classification
 $p(O|D)$

Clinical Oncology 34 (2022) e87–e96

 ELSEVIER

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net



Deep Learning for Radiotherapy Outcome Prediction Using Dose Data – A Review

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- 3D data
- Multi-channel / -modality input
 - Dose, imaging
- Additional structured clinical data
 - Patient characteristics, other treatments, etc
- Need to understand spatial dependencies



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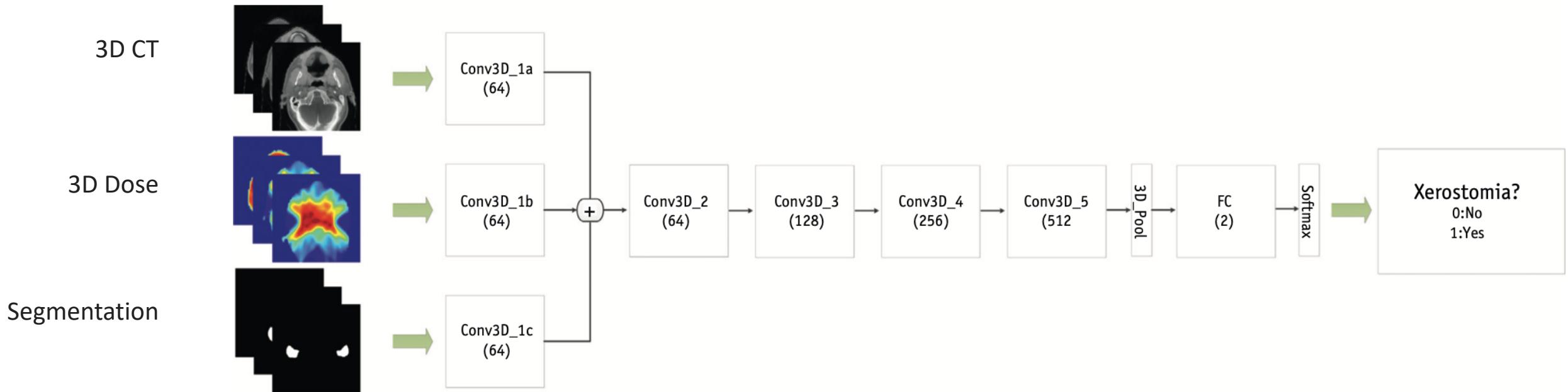
DEEP LEARNING FOR RADIOTHERAPY OUTCOME PREDICTION USING DOSE DATA

Ref	Patient number	Cancer site	Predicted outcome
Zhen 2017	42	Cervical	Rectal toxicity grade ≥ 2
Ibragimov 2018	125	Liver	Late hepatobiliary toxicities grade ≥ 3
Men 2019	784	Head and neck	Late xerostomia grade ≥ 2
Ibragimov 2019	120	Liver	Post-SBRT survival and local cancer progression
Ibragimov 2020	122	Liver	Late hepatobiliary toxicities grade ≥ 3
Welch 2020	160	Oropharyngeal	Locoregional failure at 3 years
Liang 2019	70	NSCLC	Radiation pneumonitis grade ≥ 2
Wang 2020	66	Oropharyngeal	2D axial PET images at mid-treatment (20Gy out of 70Gy)
Yang 2021	52	Post- prostatectomy	Acute patient-reported urinary and bowel symptoms
Liang 2021	217	Thoracic	Radiation pneumonitis grade ≥ 2

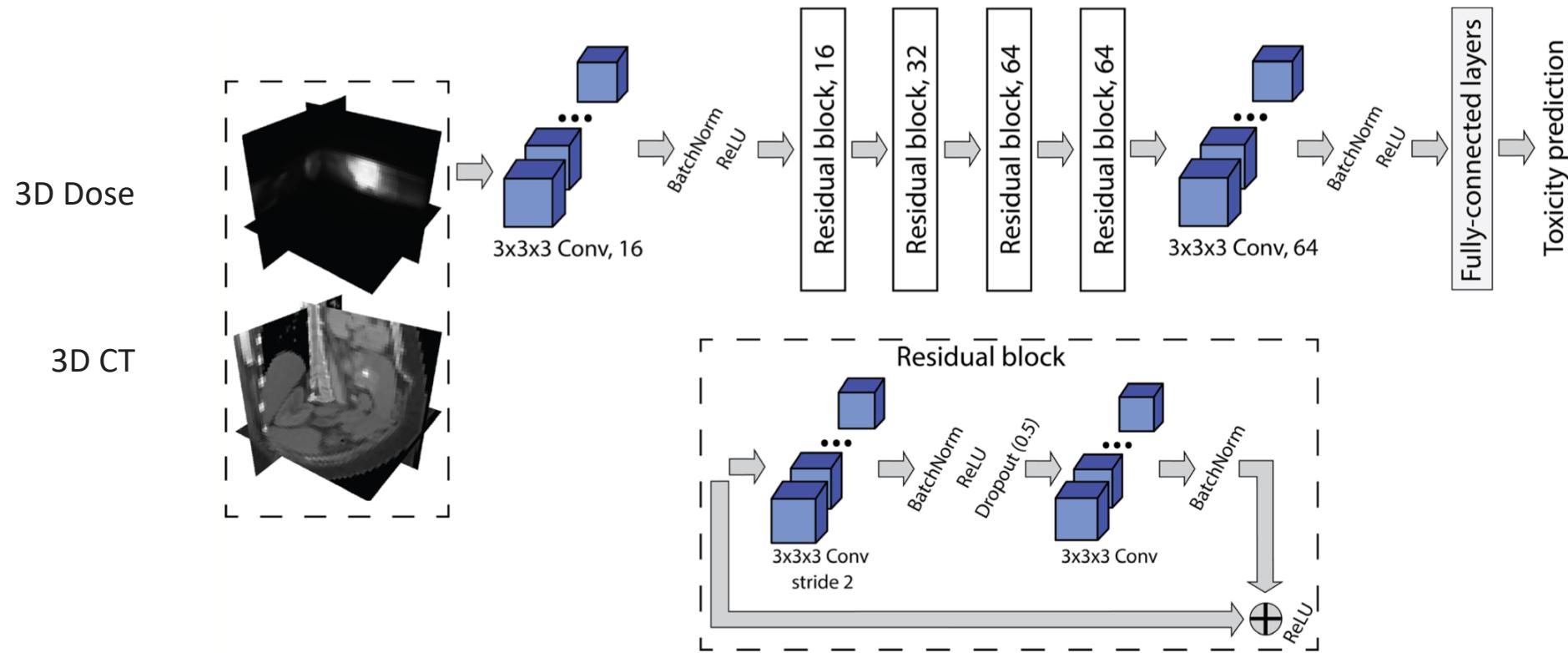
DEEP LEARNING FOR RADIOTHERAPY OUTCOME PREDICTION USING DOSE DATA

Ref	Dose data input	Other input factors	Network architecture
Zhen 2017	2D surface dose flattened from 3D dose	N/A	Pre-trained 2D CNN: 16 convolutional layers => max pooling. 3 FC layers (softmax activation function)
Ibragimov 2018	3D dose distributions	Non-dosimetric features used to train a separate FC network	Pre-trained 3D CNN: 3 convolution layers (w/ dropouts), 2 max-pooling layers, 2 FC layers
Men 2019	3D dose distributions	3D CT, parotid structures	Separate 3D convolution layer for each input => 4 bottleneck 3D layers => pooling => fully connected & softmax loss layers
Ibragimov 2019	3D dose distributions	Non-dosimetric (clinical) features	Multi-path network: Ibragimov 2018 w/ input of 3D dose + 3-layer FC network w/ non-dosimetric features
Ibragimov 2020	3D dose distributions	3D CT	Pre-trained 3D CNN: 10 convolutional layers, (8 mid-layers residual), => FC layer; input concat of 3D dose and 3D CT images
Welch 2020	3D dose distributions	3D CT, contours, clinical features	3-channel 3D CNN w/ dose, CT, structures: 3 convolution layers => BN and maxpooling => 1 softmax FC layer (output of CNN + clinical)
Liang 2019	3D dose distributions	N/A	3D CNN w/ 5 convolutional layers (pre-trained trained for multi-frame video classification) => maxpooling layers + 2 FC layers
Wang 2020	2D dose distributions on axial slices	2D CT, 2D FDG-PET images	3D network: concatenated 2D PET/CT + dose as input; 8 convolutional layers; loss function prioritising GTV/CTV
Yang 2021	3D dose distributions	3D CT scans	2 channels (dose, CT); 3 convolutional layers (pretrained) => maxpooling + FC layer
Liang 2021	3D dose distributions	Ventilation image from 4D-CT; functional dose distribution	Pre-trained 3D CNN w/ 5 layers (Liang 2020) to extract features from each input dataset => feature filtering and selection

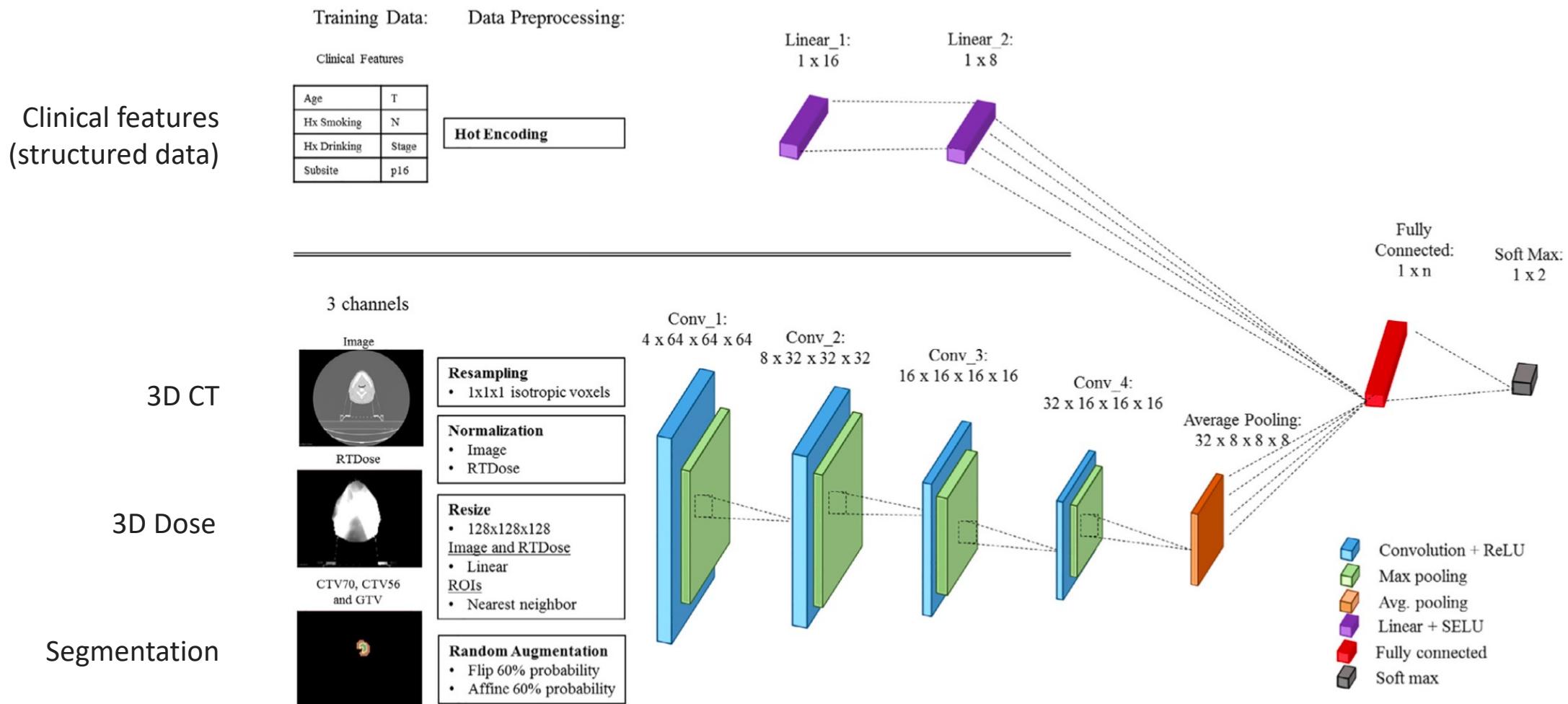
PREDICTING XEROSTOMIA AFTER HEAD & NECK RADIOTHERAPY



PREDICTING HEPATOBILIARY TOXICITY AFTER LIVER SBRT



PREDICTING OF LOCOREGIONAL FAILURE IN HEAD & NECK CANCER



IMPROVED TOXICITY PREDICTION?

Patient number	Cancer site	Ref	Improvement over GLM
42	Cervical	Zhen 2017	
125	Liver	Ibragimov 2018	
784	Head and neck	Men 2019	
120	Liver	Ibragimov 2019	
122	Liver	Ibragimov 2020	-
160	Oropharyngeal	Welch 2020	
70	NSCLC	Liang 2019	
66	Oropharyngeal	Wang 2020	-
52	Post- prostatectomy	Yang 2021	-
217	Thoracic	Liang 2021	

WEAKNESSES

- Separate initial convolutional layers / feature extraction for different spatial data (e.g. dose & CT)
 - Loses the spatial relationship between the data sources
- Pre-trained networks
 - Convolutional layer setup & feature extraction may not be optimal for dose distributions
- Data augmentation
 - Are spatial relationships preserved?
 - Lack of variation
- Lack of external validation!

IMPORTANCE OF REPORTING GUIDELINES

TRIPOD: Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis

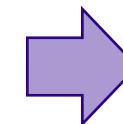
TRIPOD Checklist: Prediction Model Development			
Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	
	5b	Describe eligibility criteria for participants.	
	5c	Give details of treatments received, if relevant.	
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	
	6b	Report any actions to blind assessment of the outcome to be predicted.	
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	
Sample size	8	Explain how the study size was arrived at.	
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	
Risk groups	11	Provide details on how risk groups were created, if done.	
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	
Model development	14a	Specify the number of participants and outcome events in each analysis.	
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	
	15b	Explain how to use the prediction model.	
Model performance	16	Report performance measures (with CIs) for the prediction model.	
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	
Implications	20	Discuss the potential clinical use of the model and implications for future research.	
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	
Funding	22	Give the source of funding and the role of the funders for the present study.	

Common issues in AI / machine learning papers

- Lack of description of clinical problem
- Lack of dataset description
 - In particular outcome description
- Sample size considerations
- Full specification of the model
- External / independent validation

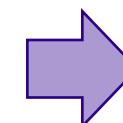
UNDERSTANDING SPATIAL DOSE DEPENDENCE

Which parts of the dose distribution contribute to toxicity risk for the individual patient?

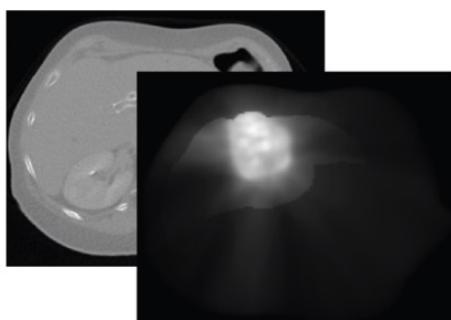


First order effect

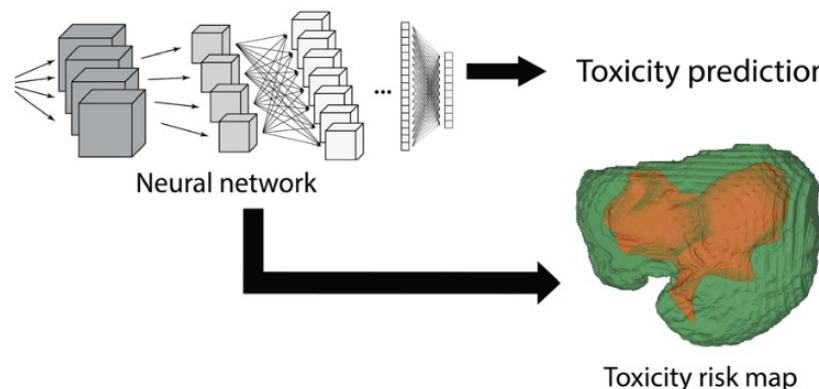
Which parts of the anatomy are more sensitive to changes in dose?



Second order (gradient) effect

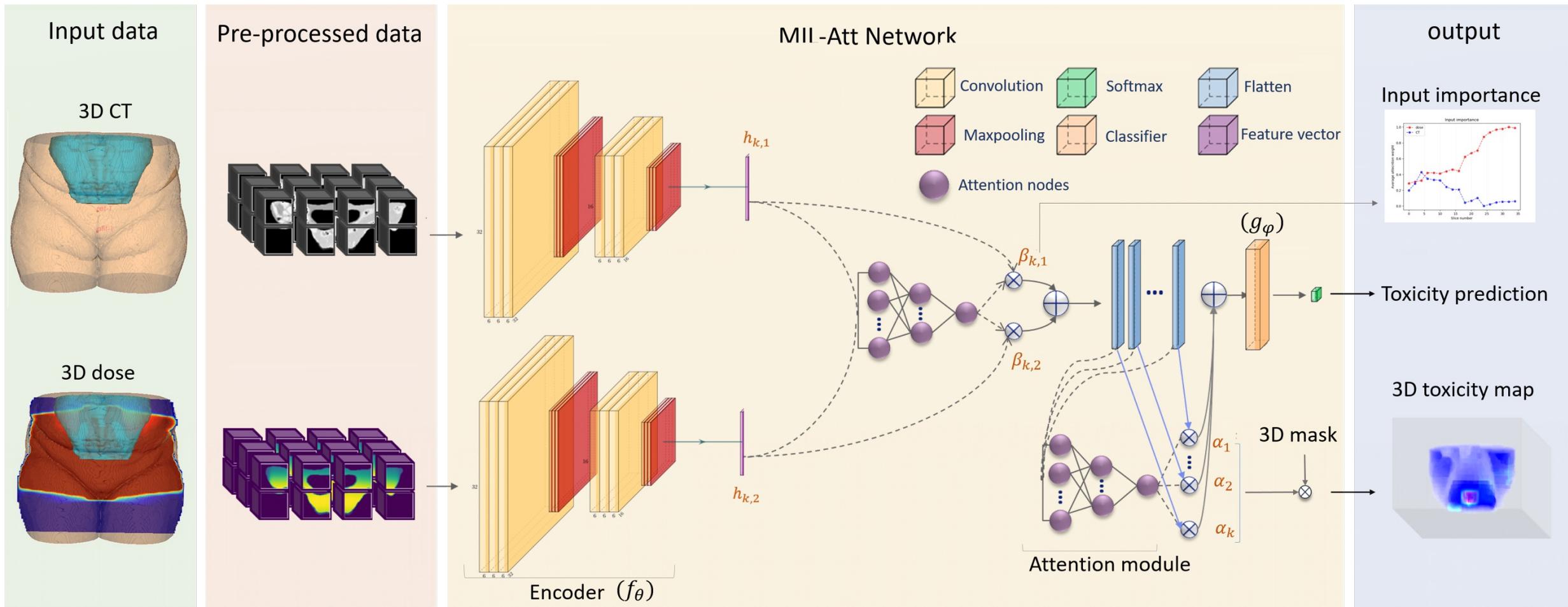


Multimodal input:
1) CT image 2) Dose delivery plan

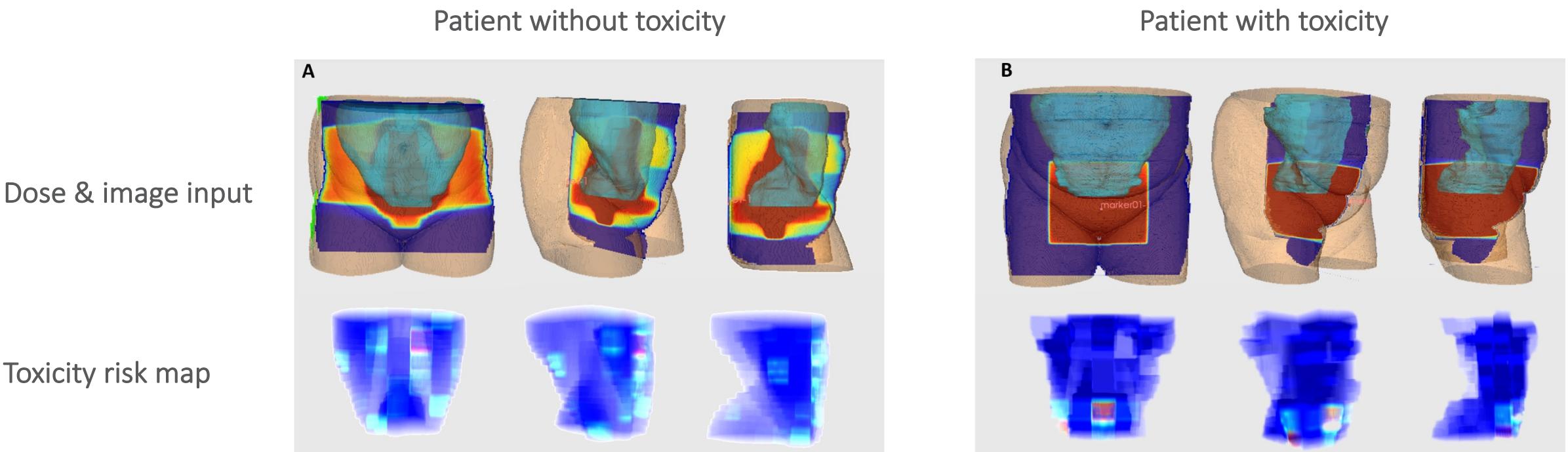


Systematically varied the dose distribution on a per-voxel level, and subtracted the predicted output to provide an estimate of local, patient specific toxicity risk

PREDICTING PATIENT-REPORTED BOWEL TOXICITY AFTER PELVIC RADIOTHERAPY



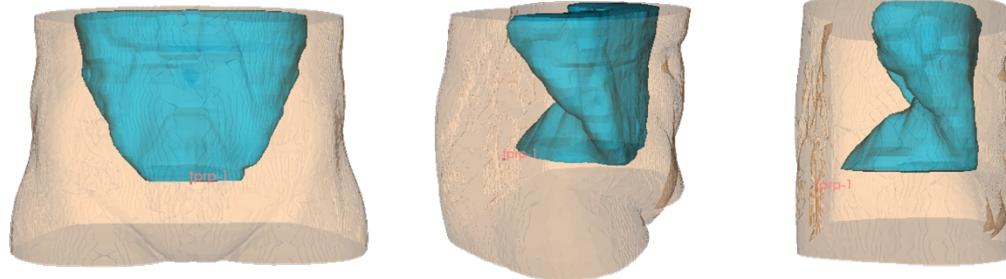
PREDICTING PATIENT-REPORTED BOWEL TOXICITY AFTER PELVIC RADIOTHERAPY



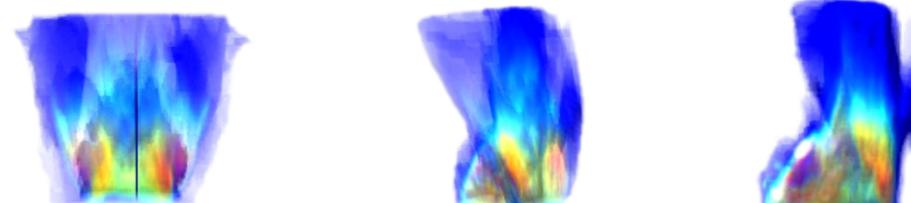
PREDICTING PATIENT-REPORTED BOWEL TOXICITY AFTER PELVIC RADIOTHERAPY

Average patient atlas

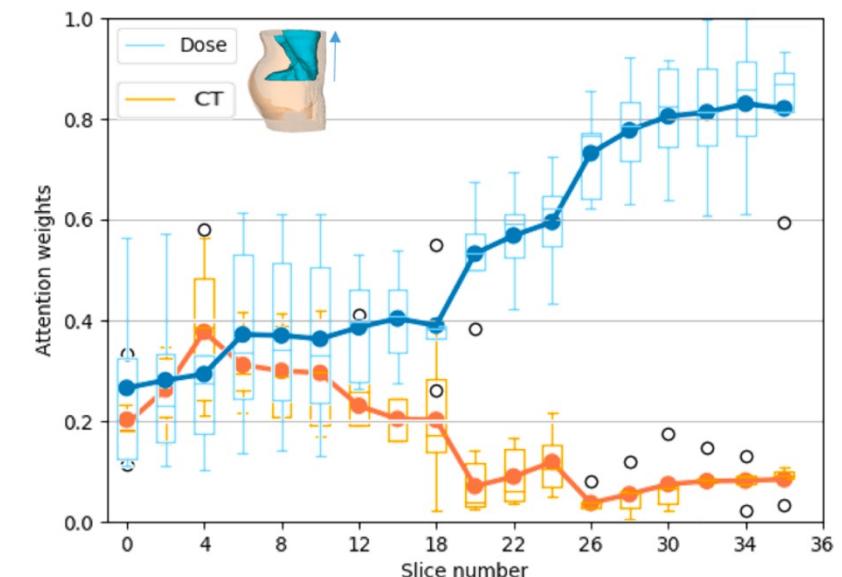
Bowel volume



Dose distribution



Risk map



IMPROVE TREATMENT PLANNING?

Can we use voxel-wise information about toxicity risk directly in dose plan optimisation?

.....

???



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Dr Ali Gooya

Dr Ane Appelt

Dr Alexandra Gilbert

Professor Andrew Scarsbrook

Professor Alejandro Frangi



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THANK YOU!

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Associate Professor, University of Leeds

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 @cancerphysicist



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Together we will beat cancer

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