Outcome Prediction for Head and Neck Cancer Adaptive Radiation Therapy Using Pre- and During-Treatment Imaging

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Adaptive Radiation Therapy

- Adaptation to anatomical change
  - Increased therapeutic dose for non-responders, or reduced dose for early responders
- Risk adaptation for treatment (de-)intensification
  - Reduce or eliminate dose to low-risk targets
  - Increased therapeutic dose for non-responders, or reduced dose for early responders
  - Additional systemic therapy for patients at high-risk for distant metastasis

Biomarkers for risk stratification in head and neck cancer

- Human papillomaviruses (HPV) type 16 associated oropharyngeal cancers
  - Markedly improved survival
- Imaging-based markers
  - Pre-treatment PET has prognostic values
    - SUV of the primary tumor was associated with disease-free survival (DFS), OS and local control
  - Often based on a single measurement, e.g., SUVmax or SUVmean

Economopoulou, Panagiota, et al. "Diagnostic tumor markers in head and neck squamous cell carcinoma (HNSCC) in the clinical setting." *Frontiers in oncology* 9 (2019): 827.

AI or Machine Learning

- Analyze/model complex data
  - Integrate information from different sources
    - Imaging (radiological/pathological)
    - Clinical
    - Biology
  - Complex patterns
    - Texture of images

Radiomics-based Modeling

- **Explosion of radiomics studies over last decade**
  - **Imaging-based predictive models**
  - **Extraction and analysis of large amount of features from medical images**
  - **Building predictive models from extracted imaging features, often in combination with other features such as clinical characteristics**

Head and Neck Outcome Prediction

- Toxicity
  - Carbonara et al. Investigation of Radiation-Induced Toxicity in Head and Neck Cancer Patients through Radiomics and Machine Learning: A Systematic Review, J Oncol. 2021
- Treatment failure: distant metastasis, local regional failure
  - Vallieres et al. Radiomics strategies for risk assessment of tumour failure in head-and-neck cancer. Sci Rep. 2017
- Survival
  - Starke, Sebastian, et al. "A hybrid radiomics approach to modeling progression-free survival in head and neck cancers." 3D Head and Neck Tumor Segmentation in PET/CT Challenge. Springer, Cham, 2021.

How to choose a classifier?

- SVM
- Logistic Regression
- Decision Tree
- Discriminant Analysis
- K-Nearest Neighbors
- Naïve Bayesian
- Random forest
- CNN…

Model performance strongly depends on data : different runs on different training, validation, test set splittings may result different preferred classifiers

Multi-Classifier Multi-Objective and Multi-Modality (mCOM)

- **Explicitly considers both sensitivity and specificity, critical for imbalanced dataset.**
- **Instead of choosing a specific classifier, we aim to maximally utilize information extracted by different classifiers.**
- **Lead to more robust prediction results.**

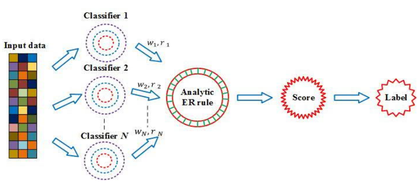
R. Wang, …, and **J. Wang**, Locoregional Recurrence Prediction in Head & Neck Cancer Based on Multi-modality and Multi-view Feature Expansion, *PMB*, 2022

Z. Zhou,…, **J. Wang**, Multifaceted radiomics for distant metastasis prediction in head & neck cancer, *PMB*, 2020

L. Chen, …, **J. Wang**, Combining Many-objective Radiomics and 3-dimensional Convolutional Neural Network through Evidential Reasoning to Predict Lymph Node Metastasis in Head and Neck Cancer, *PMB*, 2019 (Used in two prospective Phase II clinical trials)

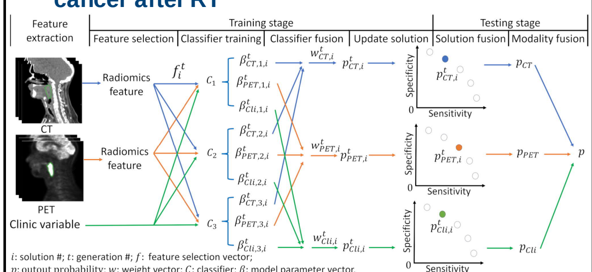
K. Wang, …, **J. Wang,** A multi-objective radiomics model for the prediction of locoregional recurrence in head and neck squamous cell cancers, *Medical Physics*, 2020

Reliable fusion



- Fusing information extracted from individual classifier/source by combining the output scores with both weight and reliability.

mCOM (multi-classifier, objective, modality) for locoregional failure prediction in H&N cancer after RT



(K. Wang, …, J. Wang, A multi-objective radiomics model for the prediction of locoregional recurrence in head and neck squamous cell cancers, Medical Physics, 2020)

- 277 patients from 4 institutions, a public H&N dataset downloaded from TCIA
- 40 experienced locoregional recurrence
- Median follow-up: 43 months
- Median time to locoregional recurrence: 18 months
- Model trained on data from two institutions while tested on other two institutions.

Vallieres M, et al. Radiomics strategies for risk assessment of tumour failure in head-and-neck cancer. Sci Rep, 2017.

Performance of models built with different classifiers and features from different modalities

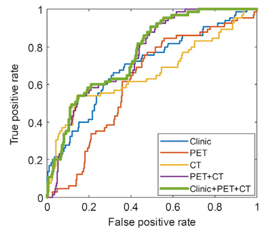
Modality	Classifier	Sensitivity	Specificity	Accuracy	AUC	*P*-value
Clinic	SVM	0.60 ± 0.20	0.67 ± 0.22	0.66 ± 0.16	0.66 ± 0.06	0.51
	LR	0.65 ± 0.07	0.63 ± 0.06	0.63 ± 0.04	0.68 ± 0.02	0.98
	DA	0.62 ± 0.08	0.63 ± 0.05	0.63 ± 0.04	0.67 ± 0.01	0.52
	MC	0.63 ± 0.06	0.65 ± 0.06	0.64 ± 0.06	0.68 ± 0.02	–
CT	SVM	0.52 ± 0.06	0.82 ± 0.08	0.78 ± 0.06	0.66 ± 0.01	0.89
	LR	0.52 ± 0.03	0.84 ± 0.01	0.79 ± 0.01	0.67 ± 0.02	0.59
	DA	0.54 ± 0.00	0.81 ± 0.02	0.77 ± 0.02	0.67 ± 0.01	0.87
	MC	0.54 ± 0.00	0.84 ± 0.02	0.80 ± 0.01	0.69 ± 0.02	–
PET	SVM	0.62 ± 0.09	0.49 ± 0.04	0.51 ± 0.02	0.52 ± 0.01	<0.01
	LR	0.59 ± 0.09	0.50 ± 0.04	0.51 ± 0.03	0.53 ± 0.01	0.02
	DA	0.58 ± 0.14	0.61 ± 0.03	0.61 ± 0.02	0.59 ± 0.03	0.26
	MC	0.62 ± 0.12	0.61 ± 0.03	0.61 ± 0.01	0.62 ± 0.03	–

DA, discriminant analysis, LR, logistic regression; MC, multi-classifier model; SVM, The classifiers comprise support vector machine.

(K. Wang, …, J. Wang, A multi-objective radiomics model for the prediction of locoregional recurrence in head and neck squamous cell cancers, *Med. Phys.* 2020)

Performance of models built with multiple classifiers using features from different modalities

Modality	Classifier	Sensitivity	Specificity	Accuracy	AUC	P-value
Clinic	MC	0.63 ± 0.06	0.65 ± 0.06	0.64 ± 0.06	0.68 ± 0.02	0.02
CT	MC	0.54 ± 0.00	0.84 ± 0.02	0.80 ± 0.01	0.69 ± 0.02	<0.01
PET	MC	0.62 ± 0.12	0.61 ± 0.03	0.61 ± 0.01	0.62 ± 0.03	<0.01
CT + PET	MC	0.54 ± 0.00	0.85 ± 0.01	0.80 ± 0.01	0.76 ± 0.00	0.02
CT + PET+Clinic	MC	0.54 ± 0.00	0.84 ± 0.02	0.80 ± 0.02	0.77 ± 0.00	–



AUC=0.69 in Vallieres M, et al. Radiomics strategies for risk assessment of tumour failure in head-and-neck cancer. Sci Rep, 2017.

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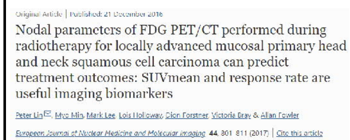
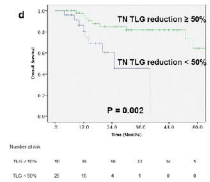
During-treatment Imaging


Nodal parameters of FDG PET/CT performed during radiotherapy for locally advanced mucosal primary head and neck squamous cell carcinoma can predict treatment outcomes: SUVmean and response rate are useful imaging biomarkers

European Journal of Nuclear Medicine and Molecular Imaging 44, 801–811 (2017)



- 75 HNSCC treated by primary RT (± chemotherapy) with curative intent and received FDG PET–CT before (prePET) and during third week of RT (iPET).
- A reduction of more than 50 % in the node total lesion glycolysis (TLG) was the best biomarker for locoregional and regional failure-free survival (FFS), disease-free survival (DFS) and overall survival (OS)

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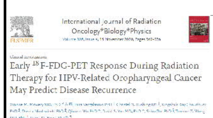
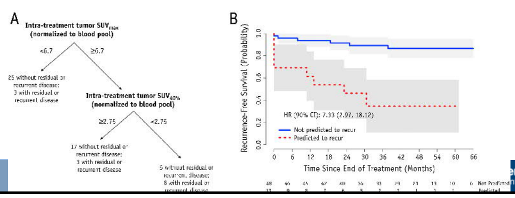

International Journal of Radiation Oncology*Biology*Physics

Early [18]F-FDG-PET Response During Radiation Therapy for HPV-Related Oropharyngeal Cancer May Predict Disease Recurrence

- 62 patients undergoing definitive (chemo)radiation for HPV-related/p16-positive OPC, prospectively enrolled. 18F-fluorodeoxyglucose PET/computed tomography scans performed at simulation and after 2 weeks at a dose of ∼20 Gy.
- Patients with intratreatment SUVmax (normalized to blood pool SUVmean) <6.7 or SUVmax (normalized to blood pool SUVmean) ≥6.7 with intratreatment SUV40% ≥2.75 as less likely to recur.



Intra-treatment FMISO PET

- In 19 patients with human papillomavirus–related oropharyngeal cancers, pre- and intratreatment dynamic fluorine-18-labeled fluoromisonidazole positron emission tomography (PET) was used to assess tumor hypoxia.
- Patients without hypoxia at baseline or intratreatment received 30 Gy; patients with persistent hypoxia received 70 Gy.
- Fifteen of 19 patients were deescalated to 30 Gy. Of these 15 patients, 11 had a pathologic complete response.
- Two-year locoregional control and overall survival were 94.4% (95% confidence interval = 84.4% to 100%) and 94.7% (95% confidence interval = 85.2% to 100%), respectively. No acute grade 3 radiation–related toxicities were observed.

Nadeem Riaz, Eric Sherman, Xin Pei,..., Nancy Lee, Precision Radiotherapy: Reduction in Radiation for Oropharyngeal Cancer in the 30 ROC Trial, JNCI: Journal of the National Cancer Institute, Volume 113, Issue 6, June 2021, Pages 742–751

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Intra-treatment CBCT

- Daily/weekly CBCT is routinely used for patient setup or adaptive therapy
- Change of CBCT-based radiomics (delta-CBCT-radiomics) could reflect the therapy included response
- Adding delta-CBCT-radiomic may improve the performance of models based on baseline imaging/clinical characteristics

- Cohort: 1:2 case-control cohort of patients with HNSCC treated at UTSW with definitive radiotherapy +/- chemotherapy. 90 patients (30 cases) were included with:
  - 89 primary GTVs (23 primaries with LF)
  - 209 nodal GTVs (15 nodes with LF)

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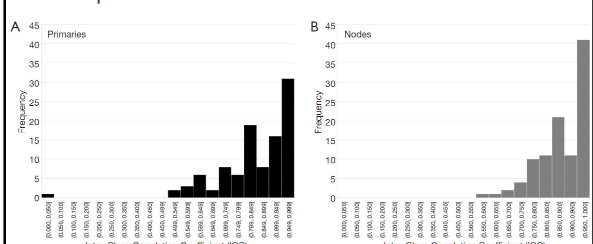
Reproducible CBCT features

- Repeated CBCTs with the same fraction



H Morgan, ..., J. Wang, “Exploratory ensemble interpretable model for predicting local failure in head and neck cancer: the additive benefit of CT and intra-treatment cone-beam computed tomography features”, Quantitative Imaging in Medicine and Surgery, 2021

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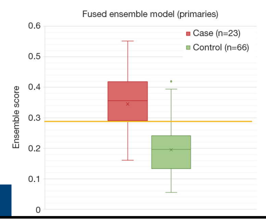
Local failure prediction for primary structures

Model	AUC	95% CI (lower)	95% CI (upper)	P value (*vs.* random chance)†	P value (*vs.* fused ensemble)‡	Max Youden J statistic	Predicted score threshold at max J statistic	Sensitivity (%)	Specificity (%)
Fused ensemble	0.871	0.788	0.954	*0.000*	NA	0.692	0.290	78.3	90.9
Combined feature ensemble	0.853	0.771	0.935	*0.000*	0.494	0.565	0.161	91.3	56.5
Clinical Only ensemble	0.788	0.680	0.895	*0.000*	0.134	0.469	0.252	69.6	77.3
Radiomic ensemble (CT1 + Delta)	0.770	0.655	0.885	*0.000*	*0.017*	0.491	0.237	87.0	49.1
CT1 only ensemble	0.687	0.561	0.813	*0.004*	*0.004*	0.340	0.291	52.2	81.8
Delta only ensemble	0.696	0.571	0.822	*0.002*	*0.013*	0.345	0.208	73.9	60.6

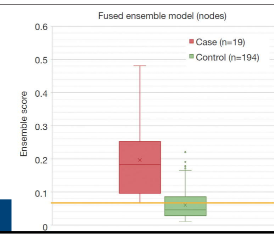
H Morgan et al, Quantitative Imaging in Medicine and Surgery, 2021



Local failure prediction for nodal structures

Model	AUC	95% CI (lower)	95% CI (upper)	P value (*vs.* random chance)†	P value (*vs.* fused ensemble)‡	Max Youden J statistic	Predicted score threshold at max J statistic	Sensitivity (%)	Specificity (%)
Fused ensemble	0.910	0.853	0.967	*0.000*	NA	0.680	0.066	100.0	68.0
Combined feature ensemble	0.893	0.819	0.941	*0.000*	0.212	0.686	0.046	100.0	68.6
Clinical only ensemble	0.865	0.802	0.929	*0.000*	0.080	0.648	0.061	94.7	70.1
Radiomic ensemble (CT1 + Delta)	0.880	0.819	0.941	*0.000*	0.268	0.643	0.060	94.7	69.6
CT1 only ensemble	0.854	0.784	0.924	*0.000*	*0.026*	0.613	0.056	100.0	61.3
Delta only ensemble	0.867	0.803	0.930	*0.000*	0.150	0.613	0.054	100.0	61.3

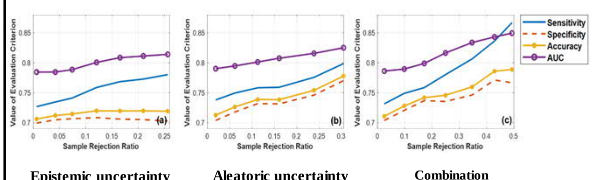
H Morgan et al, Quantitative Imaging in Medicine and Surgery, 2021



Prediction uncertainty?

- Patients are often limited
  - Model may not provide reliable predictions to all the testing samples, especially for those whose characteristics vary significantly from the training dataset distribution
  - Epistemic uncertainty
  - Can be estimated by anomaly scores
- Inherent noise of input data
  - Aleatoric Uncertainty
  - Can be estimated by using test-time augmentation (TTA)

Locoregional recurrence prediction in HNC by learning with rejection option



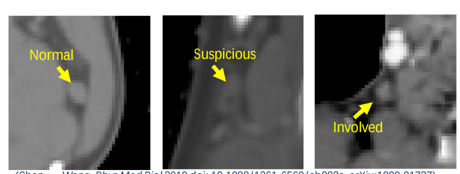
Kai Wang et al, under revision, Medical Physics

Personalized treatment target identification

- Involved nodal radiation therapy for head and neck cancer (HNC) patients
  - Majority of disease sites treated with RT no longer receive elective/prophylactic radiotherapy to clinically-negative areas
  - Despite our ability to tailor the radiotherapy volume and dose to specific areas, IMRT still targets the same lymph node regions as conventional 2D radiotherapy in HNC
  - The toxicity of associated with RT is very high, especially for patients receiving chemoradiation therapy, where acute and late toxicity rates of grade 3 or higher are 80% and 25%-60%, respectively

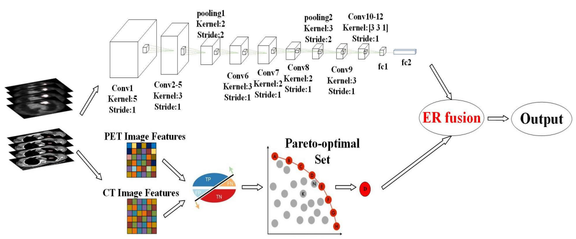
Cervical Lymph Node Malignancy Prediction

- There is often uncertainty about the malignant potential of small and less FDG avid lymph nodes (LNs) in head and neck cancer.
- Malignant LN identification strongly depends on the physicians' experience.
- AI-based clinical decision support tool for physicians to identify malignant LNs more consistently.



(Chen, ..., Wang, *Phys Med Biol* 2019 doi: 10.1088/1361-6560/ab083a, arXiv:1809.01737)

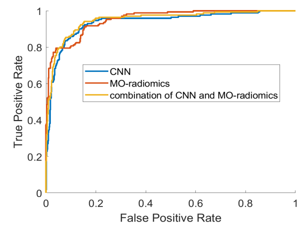
Combination of MO-Radiomics and CNN



(Chen, ..., Wang, *Phys Med Biol* 2019 doi: 10.1088/1361-6560/ab083a, arXiv:1809.01737)

LN malignancy prediction on surgical patients with pathological ground truth

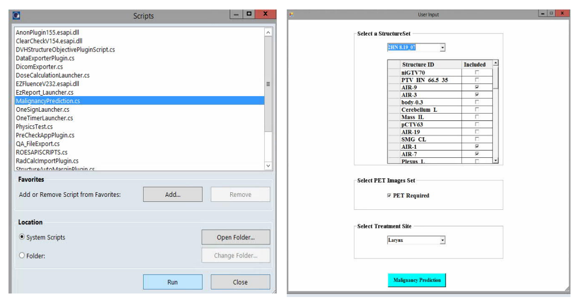
- Training nodes: 116 positive and 438 negative
- Testing nodes: 50 positive and 187 benign



AUC: 0.95 combined model

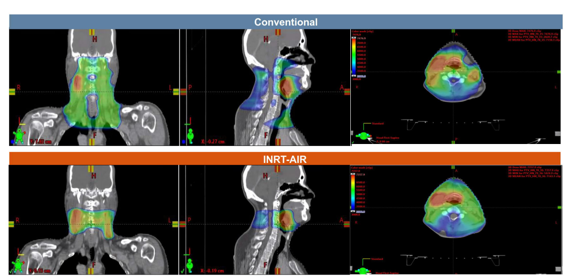
Model deployment for a phase II trial

- INRT- AIR: A Prospective Phase II Study of Involved Nodal Radiation Therapy Using Artificial Intelligence-Based Radiomics for Head and Neck Squamous Cell Carcinoma (PI: David Sher).
- https://clinicaltrials.gov/ct2/show/NCT03953976
- Eliminating elective neck irradiation and strictly treating involved and suspicious lymph nodes

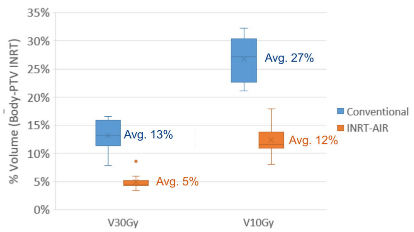


Row	CT Prediction Probability	PET CT Prediction Probability
AIR01	0	0.08
AIR02	0	0.05
AIR03	0.09	0.1
AIR04	0.23	0.51
AIR05	0.27	0.16
AIR06	0	0.01
AIR07	0	0.01
AIR08	0	0.06
AIR09	0.01	0.44
AIR10	0	0.02
AIR11	0	0.01
AIR12	0.06	0.21
AIR13	0.13	0.39
AIR14	0.32	0.82
AIR15	0	0.02
AIR16	0	0.01

Normal tissue dose sparing with INRT-AIR



Comparison of Dose bath of 30 Gy and 10 Gy



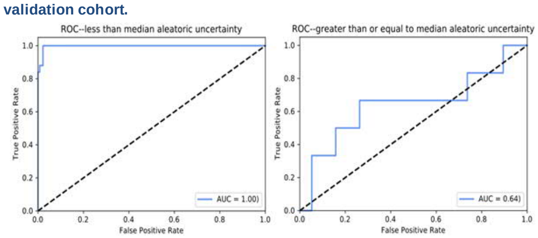
Preliminary results of INRT-AIR trial

- With a median follow-up of surviving patients of 19.6 months, there were no solitary regional recurrences.
- The mean composite MDADI scores at 6 and 12 months were 90.7 and 89.8, respectively and 94.9 and 94.6 at 6 and 12 months with a baseline MDADI score > 75.
- These outcomes are much higher than a cohort of patients treated with standard IMRT with elective neck irradiation from a prospective cohort at Royal Marsden, where mean MDADI composite score 12 months after treatment completion was 72.

- Currently employed in another prospective phase II trial (PI: David Sher)
  - A Prospective Study of Daily Adaptive Radiotherapy to Better Organ-at-Risk Doses in Head and Neck Cancer (DARTBOARD) https://clinicaltrials.gov/ct2/show/NCT04883281

Uncertainty quantification

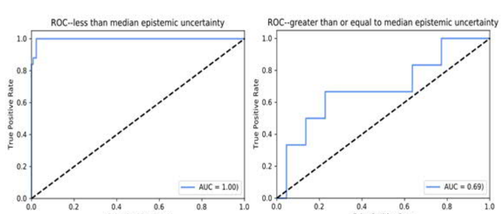
- **Model performance measured on the test data stratified by the median aleatoric uncertainty obtained from the incorrect predictions within the validation cohort.**



(M. Dohopolski, ..., J. Wang, Predicting Lymph Node Metastasis in Patients with Oropharyngeal Cancer by using Convolutional Neural Networks with associated Epistemic and Aleatoric Uncertainty, *PMB, vol. 65, 225002,* 2020)

Uncertainty quantification

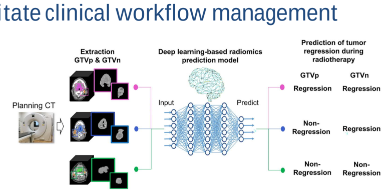
- **Model performance measured on the test data stratified by the median epistemic uncertainty obtained from the incorrect predictions within the validation cohort.**



(M. Dohopolski, ..., J. Wang, Predicting Lymph Node Metastasis in Patients with Oropharyngeal Cancer by using Convolutional Neural Networks with associated Epistemic and Aleatoric Uncertainty, *PMB, vol. 65, 225002,* 2020)

Anatomical change prediction

- Identify which patients can potentially benefit from adaptive RT
- Facilitate clinical workflow management



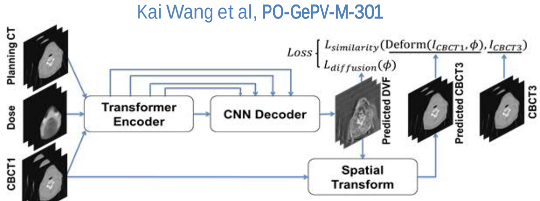
$$\Delta GTVp/treatment\ day = \frac{\text{Initial GTVp volume} - \text{Boost GTVp volume}}{\text{Initial GTVp volume}} / treatment\ day$$

GTVp regression, AUC=0.75
GTVn regression, AUC=0.73

Tanaka, Shohei, et al. "A deep learning-based radiomics approach to predict head and neck tumor regression for adaptive radiotherapy." *Scientific Reports* 12.1 (2022): 1-13.

Predicting Radiotherapy Induced Anatomic Change for Head and Neck Cancer Patients using Vision Transformer

Kai Wang et al, PO-GePV-M-301



$$Loss \begin{cases} L_{similarity}(\mathrm{Deform}(I_{CBCT1}, \phi), I_{CBCT3}) \\ L_{diffusion}(\phi) \end{cases}$$

$$Loss = L_{similarity}\left(\mathrm{Deform}(I_{CBCT1}, \phi), I_{CBCT3}\right) + \lambda L_{diffusion}(\phi)$$

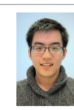
Median (95% confidence)	MSE	SSIM	DC	Volume Difference (cm^3)	ASD (mm)
Planning CT	0.0106 (0.0107, 0.0133)	0.8382 (0.8197, 0.8472)	0.9547 (0.9487, 0.9580)	103.92 (86.32, 159.70)	3.04 (2.94, 3.76)
Week-1 CBCT	0.0079 (0.0079, 0.010)	0.8690 (0.8690, 0.8945)	0.9712 (0.9663, 0.9722)	50.28 (30.24, 74.72)	1.40 (1.40, 1.66)
Predicted week-3 CBCT	0.0068 (0.0067, 0.0088)	0.8976 (0.8748, 0.8998)	0.9723 (0.9665, 0.9717)	0.14 (-14.76, 26.72)	1.28 (1.26, 1.58)

Summary

- Intra-treatment imaging may capture therapeutic induced change
  - Response adaptive therapy
- AI-based imaging analysis could aid in adaptive radiation treatment strategy
  - Risk adaptive treatment management
  - Personalized treatment target

Acknowledgements

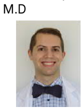
AIRT Lab (PI: Jing Wang/You Zhang)


Kai Wang M.S.


Mike Dohopolski M.D


Liyuan Chen Ph.D.


Zhiguo Zhou Ph.D


Howard Morgan M.D

NIH: R01 EB027898, R01EB020366, R01CA251792
CPRIT: RP110562, RP130109, RP160661
ACS: RSG-13-326-01-CCE