Multifaceted Radiomics for Treatment Outcome Prediction

Jing Wang, Ph.D.

Associate Professor

Division of Medical Physics and Engineering
Department of Radiation Oncology

UT Southwestern
Medical Center

Outcome Prediction

- **Treatment modality/strategy selection**
- **Treatment (de-)intensification**
  - Increased or reduced dose
  - Additional systemic therapy

Radiation Oncology

UT Southwestern
Medical Center

Predicting distant failure in lung SBRT patients

❑ **Stereotactic Body Radiation Therapy has been established as the standard of care for local control in medically inoperable NSCLC patients:**
  - ➢ High local control rate (>95% in three yeas)
  - ➢ Relatively high distant failure rate (31% in five years, RTOG 0236)

❑ **Stratify patients with high risk of distant failure:**
  - ➢ Additional systemic therapy may reduce the risk and improve overall survival
  - ➢ The toxicity of the systemic therapy could itself contribute to increased mortality

Radiation Oncology

UT Southwestern
Medical Center

Radiomics-based Modeling

❑ Radiomics has shown promising results in constructing imaging-based predictive models:
  ➢ Extraction and analysis of large amount of features from medical images
  ➢ Building a predictive model from extracted imaging features

❑ Most Radiomics methods adopt a single objective (overall accuracy or AUC) to construct the predictive model
  ➢ When data is imbalanced, single objective may not be a good measure
 ➢ Same accuracy: (5+80)/(20+80)=(20+65)/(20+80), but sensitivities are very different: 5/20 vs 20/20

Radiation Oncology	UT Southwestern Medical Center

Why not AUC (area under the receiver operating characteristic curve)?

▪ It summarizes the test performance over regions of the ROC space in which one would rarely operate.

▪ It does not give information about the spatial distribution of model errors.

▪ It weights omission (falsely predicted positive fraction) and commission errors (falsely predicted negative fraction) equally.

(Lobo JM, Jiménez-Valverde A, Real R. AUC: a misleading measure of the performance of predictive distribution models. *Global ecology and Biogeography.* 2008;17(2))
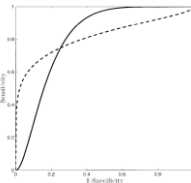
Radiation Oncology	

Multi-objective radiomics

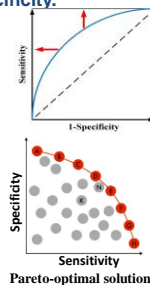❑ **A multi-objective radiomics model that explicitly considers both sensitivity and specificity.**

$$f = \max_{\alpha,\beta}(f_{sen}, f_{spe})$$

where f_{sen}, f_{spe} **are sensitivity and specificity**

$$Pareto_{set} = \{A, B, \cdots, H\}$$

$$Final\ solution = D$$

(Zhou et al, Multi-objective radiomics model for predicting distant failure in lung SBRT, *Phys. Med. Biol*, vol. 62, pp. 4460-4478, 2017)
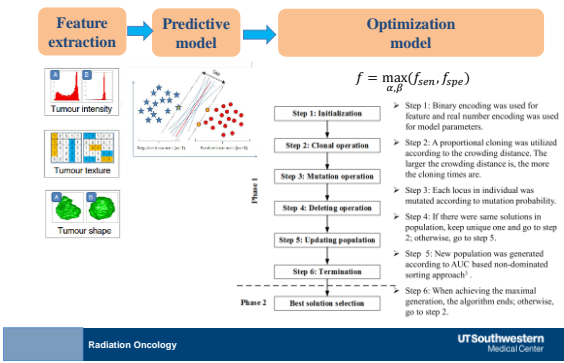

Pareto-optimal solution

Radiation Oncology	UT Southwestern Medical Center

Multi-objective radiomics model

Feature extraction	Predictive model	Optimization model

$$f = \max_{\alpha,\beta}(f_{sen}, f_{spe})$$

Tumour intensity

Tumour texture

Tumour shape

Phase 1

Step 1: Initialization
Step 2: Clonal operation
Step 3: Mutation operation
Step 4: Deleting operation
Step 5: Updating population
Step 6: Termination

Phase 2 Best solution selection

➤ Step 1: Binary encoding was used for feature and real number encoding was used for model parameters.
➤ Step 2: A proportional cloning was utilized according to the crowding distance. The larger the crowding distance is, the more the cloning times are.
➤ Step 3: Each locus in individual was mutated according to mutation probability.
➤ Step 4: If there were same solutions in population, keep unique one and go to step 2; otherwise, go to step 5.
➤ Step 5: New population was generated according to AUC based non-dominated sorting approach[3].
➤ Step 6: When achieving the maximal generation, the algorithm ends; otherwise, go to step 2.

**Radiation Oncology** UT Southwestern Medical Center

---

Distant failure prediction for early stage NSCLC after SBRT

▪ **102 early stage NSCLC patients**

▪ **25 experienced distant failure**

Clinical parameters

Demographic parameters	Tumor characteristics	Treatment parameters	Pretreatment medicine
Age	Primary diagnosis	Number fractions	Antiinflammatories
Ethnicity	Central tumor or not	Dose per fraction	Anitdiabetic
Gender	Tumor size	BED	Metformin
	Histology		Statin
	Location		ACE inhibitor
	Stage		ASA

Abbreviation – BED: biological equivalent dose; ACE inhibitor: Angiotensin-converting-enzyme inhibitor; ASA: Acetylsalicylic acid.

Radiation Oncology UT Southwestern Medical Center


Solutions with PET/CT/clinic as input features
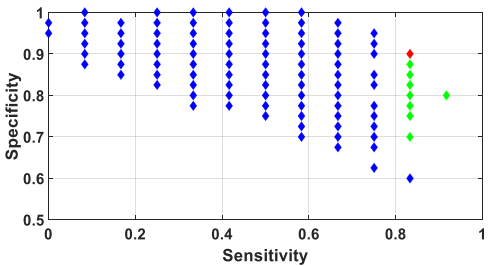
Red label: final selected solution;
Green labels: selected feasible solutions;
Blue labels: unselected solutions

Z. Zhou,…, and J. Wang, PMB, vol. 62, pp. 4460-4478, 2017

Modality	Method	Sensitivity	Specificity	AUC
Clinic	SO-AUC	0.59+0.14	0.88+0.05	0.84+0.01
	TMIA	0.63+0.09	0.82+0.04	0.76+0.05
	IMIA	0.76+0.03	0.88+0.02	0.81+0.04
PET	SO-AUC	0.65+0.15	0.75+0.06	0.78+0.03
	TMIA	0.70+0.04	0.72+0.03	0.69+0.04
	IMIA	0.76+0.08	0.75+0.08	0.75+0.04
CT	SO-AUC	0.68+0.11	0.86+0.04	0.82+0.02
	TMIA	0.79+0.05	0.84+0.03	0.80+0.03
	IMIA	0.81+0.06	0.79+0.05	0.78+0.03
Clinic and PET	SO-AUC	0.54+0.06	0.94+0.02	0.86+0.04
	TMIA	0.75+0.01	0.97+0.02	0.84+0.03
	IMIA	0.77+0.04	0.91+0.04	0.82+0.06
Clinic and CT	SO-AUC	0.54+0.14	0.94+0.02	0.85+0.06
	TMIA	0.58+0.01	0.98+0.02	0.68+0.03
	IMIA	0.77+0.04	0.90+0.03	0.83+0.05
PET and CT	SO-AUC	0.47+0.14	0.96+0.05	0.84+0.02
	TMIA	0.73+0.04	0.86+0.08	0.75+0.07
	IMIA	0.75+0.01	0.81+0.04	0.81+0.04
Clinic, PET and CT	SO-AUC	0.46+0.12	0.97+0.03	0.87+0.02
	TMIA	0.62+0.06	0.98+0.03	0.84+0.04
	IMIA	0.76+0.03	0.94+0.03	0.83+0.04

Multi-objective radiomics model
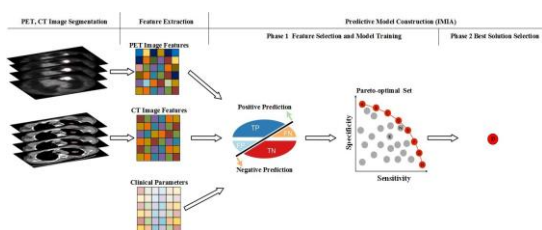
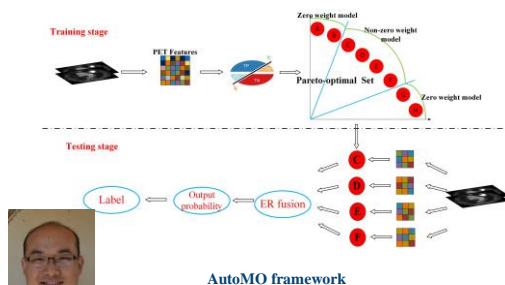**Shortcoming: Manually selecting the optimal model.**

Z. Zhou,…, and J. Wang, PMB, vol. 62, pp. 4460-4478, 2017

Radiation Oncology   UTSouthwestern
                                                     Medical Center
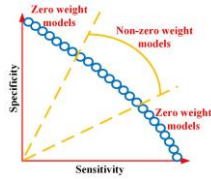
Automated multi-objective model (AutoMO)

AutoMO framework

Radiation Oncology   UTSouthwestern
                                                     Medical Center

AutoMO

➤ **Testing stage:**

Weight:
$$w_j = \begin{cases} \dfrac{f_{sen}^j}{f_{spe}^j} + AUC_j & when\ 0.5 \le \dfrac{f_{sen}^j}{f_{spe}^j} \le 1 \\ \dfrac{f_{spe}^j}{f_{sen}^j} + AUC_j & when\ 0.5 \le \dfrac{f_{spe}^j}{f_{sen}^j} \le 1 \\ 0 & Other\ situation \end{cases}.$$

Radiation Oncology   **UT Southwestern** Medical Center

AutoMO

➤ **Testing stage:**

Final probability output:

$$P_i^* = \frac{\mu \times \left[\prod_{j=1}^J \left(\omega_j P_i^j + 1 - \omega_j \sum_{i=1}^2 P_i^j \right) - \prod_{j=1}^J \left(1 - \omega_j \sum_{i=1}^M P_i^j \right) \right]}{1 - \mu \times \left[\prod_{j=1}^N (1 - \omega_j) \right]}, i = 1,2$$

$$\mu = \left[\sum_{i=1}^2 \prod_{j=1}^J \left(\omega_j P_i^j + 1 - \omega_j \sum_{i=1}^2 P_i^j \right) - (J-1) \prod_{j=1}^J \left(1 - \omega_j \sum_{i=1}^2 P_i^j \right) \right]^{-1}.$$
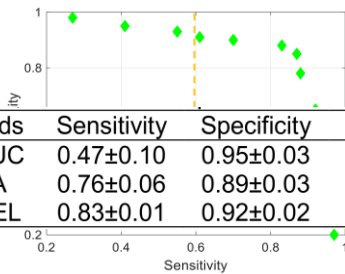
Final Label output:

$$L = \max(P_i^*).$$

Radiation Oncology   **UT Southwestern** Medical Center

Solutions with PET/CT/clinical parameters as input features

Methods	Sensitivity	Specificity	AUC
SO-AUC	0.47±0.10	0.95±0.03	0.84±0.03
TMIA	0.76±0.06	0.89±0.03	0.81±0.04
IMIA-EL	0.83±0.01	0.92±0.02	0.83±0.01

Pareto-optimal solution set

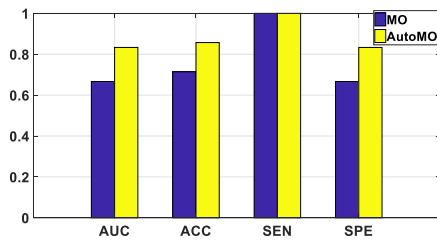**Radiation Oncology**   **UT Southwestern** Medical Center

Distant failure prediction for cervical cancer patients after RT

> *Totally 70 patients treated for cervix cancer with definitive intent between 2009 and 2012 were used.*

> *Patients within stage IB1 to IVA disease treated with EBRT or combined with high dose rate intracavitary brachytherapy and retrievable pre-treatment PET/CT scanning are used.*

> *All the tumors were contoured manually by the radiation oncologists and all the features including intensity, texture and geometry were calculated based on standardized uptake value (SUV).*

Radiation Oncology   **UT Southwestern** Medical Center

Results

> *AUC: area under the curve; ACC: accuracy; SEN: sensitivity; SPE: specificity*

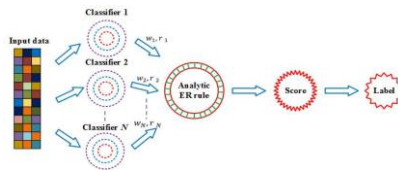**Radiation Oncology**   **UT Southwestern** Medical Center

---

Multifaceted predictive model

- **Multiple Objectives**
  - Single metric such as accuracy or area under a characteristic curve (AUC) can be misleading, especially for imbalanced data
  - We consider both specificity and sensitivity as multi-objective during model training
- **Multiple Measurements**
  - CT, PET, MRI…
  - RNAseq, Cytokine, Proteomics…
- **Multiple Classifiers**
  - Support vector machine, convolutional neural network, logistic regression, Naïve Bayesian,…

Radiation Oncology   **UT Southwestern** Medical Center

Reliable classifier fusion (RCF)

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

Weight and Reliability

- **The relative importance (weight) of each expert is often considered when making the final decision in most situations.**
- **The reliability is different from the relative importance, as the former describes the intrinsic property of expert and latter is the expert's extrinsic feature when comparing with other experts.**
- **When we evaluate the reliability of an expert, a reasonable solution is that we can find several experts who have the similar background with this expert; and the reliability can be evaluated by comparing the decision result with all of other experts.**

Reliability

- **Defined as the similarity between the individual model output probability and other model output probabilities, which satisfies the following conditions:**

$$r_i = \begin{cases} 0 & \text{when } l_i \neq l_j; j = 1, \cdots, N, j \neq i \\ 1 & \text{when } l_i = l_j \wedge p_{l_j} = 1; j = 1, \cdots, N, j \neq i \\ 0 < r_i < 1 & \text{in other situations} \end{cases}$$

- **Dissimilarity of model output probability**

$$D_i = \prod_{j=1, j \neq i}^{N} (1 - p_j), i = 1, \cdots, N,$$

- **Similarity** $\quad S_i = 1 - D_i$

- **Reliability** $\quad r_i(x) = \frac{SL}{N-1} \cdot S_i$

- **Reliable classifier fusion (RCF) outperforms other fusion strategies on UCI public datasets:**

Dataset	Strategy	AUC	Sensitivity	Specificity
Heart	WF	0.85±0.02	0.70±0.02	0.88±0.02
	DSF	0.86±0.01	0.77±0.02	0.87±0.01
	ERF	0.86±0.01	0.76±0.02	0.87±0.01
	RCF	0.88±0.01	0.77±0.02	0.89±0.01
Ionosphere	WF	0.94±0.02	0.78±0.02	0.97±0.01
	DSF	0.92±0.02	0.83±0.02	0.94±0.01
	ERF	0.95±0.01	0.81±0.01	0.96±0.01
	RCF	0.96±0.01	0.82±0.02	0.98±0.01
Mask	WF	0.88±0.02	0.76±0.02	0.84±0.02
	DSF	0.86±0.01	0.88±0.02	0.68±0.02
	ERF	0.91±0.01	0.87±0.02	0.83±0.02
	RCF	0.93±0.01	0.86±0.02	0.86±0.02
Sonar	WF	0.8±0.02	0.71±0.03	0.74±0.03
	DSF	0.78±0.02	0.78±0.03	0.67±0.03
	ERF	0.83±0.02	0.83±0.02	0.69±0.03
	RCF	0.85±0.01	0.84±0.02	0.72±0.02
Spambase	WF	0.94±0.02	0.86±0.03	0.92±0.01
	DSF	0.94±0.01	0.86±0.01	0.91±0.00
	ERF	0.97±0.00	0.93±0.01	0.92±0.01
	RCF	0.98±0.00	0.94±0.01	0.92±0.01

WF: Weighted fusion
DSF: Dempster–Shafer fusion   **ERF:** Evidence Reasoning Fusion   UT Southwestern Medical Center

---

Predicting distant failure for cervical cancer patients after radiation therapy

Multi-classifier V.S. individual classifier

	AUC	Sensitivity	Specificity
Multi-classifier model	**0.83±0.02**	**0.79±0.00**	**0.84±0.03**
Support Vector Machine	0.73±0.04	0.76±0.08	0.68±0.05
Logistic Regression	0.74±0.03	0.74±0.03	0.75±0.03
K-Nearest Neighbors	0.75±0.04	0.78±0.07	0.75±0.04
Discriminant Analysis	0.74±0.02	0.74±0.03	0.74±0.04
Decision Tree	0.76±0.05	0.72±0.04	0.80±0.04
Naïve Bayesian	0.72±0.03	0.76±0.06	0.73±0.04

Z. Zhou,…, J. Wang, ICCR, 2019   UT Southwestern Medical Center

---

Early Prediction of Locoregional Recurrence for H&N after RT

FDG-PET and CT from 100 patients with definitive radiation therapy.

Predictive performance for six individual classifiers and M-radiomics.

classifier	AUC	ACC	SEN	SPE
SVM	0.7308	0.7200	**0.6500**	0.7667
LR	0.7292	0.6700	0.6250	0.7000
DA	0.7129	0.7000	0.6000	0.7667
DT	0.7571	0.7300	**0.6500**	0.7833
KNN	0.7413	0.7100	0.5500	0.8167
NB	0.7173	0.7300	0.6000	0.8167
M-radiomics	**0.7848**	**0.7800**	**0.6500**	**0.8667**

Z. Zhou,…, J. Wang, AAPM, 2018   UT Southwestern Medical Center

Cervical Lymph Node Malignancy Prediction

- ❑ **Lymph node metastasis (LNM): well known prognostic actor for patients with head and neck cancer (HNC)**
  - ❑ negatively influence overall survival
  - ❑ increases the potential of distant metastasis
- ❑ **There is often uncertainty about the malignant potential of lymph nodes (LNs) in head and neck cancer.**
- ❑ **Malignant LN identification strongly depends on physicians' experience.**

Classify involved, suspicious and normal nodes for patients enrolled in the Involved Field Elective Volume De-Intensification Radiation Therapy for Head and Neck Cancer (INFIELD) trial (PI: Sher)
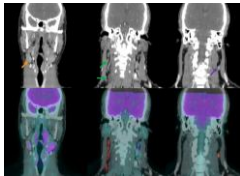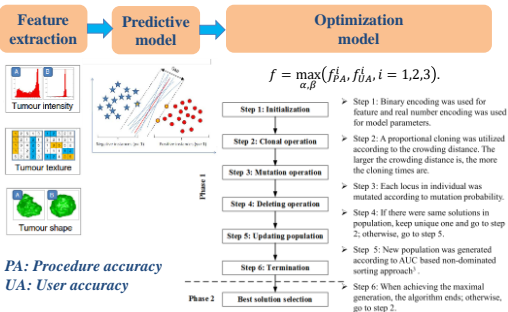

Training data: 85 involved nodes, 50 suspicious nodes, and 30 normal nodes from 42 patients.

Testing data: 22 involved nodes, 27 suspicious nodes, and 17 normal nodes from 18 patients.

Radiation Oncology   UTSouthwestern Medical Center

MO-radiomics

| Feature extraction | Predictive model | Optimization model |

$$f = \max_{\alpha,\beta}(f_{PA}^i, f_{UA}^i, i = 1,2,3).$$

Tumour intensity
Tumour texture
Tumour shape

PA: Procedure accuracy
UA: User accuracy

Step 1: Initialization — ➤ Step 1: Binary encoding was used for feature and real number encoding was used for model parameters.

Step 2: Clonal operation — ➤ Step 2: A proportional cloning was utilized according to the crowding distance. The larger the crowding distance is, the more the cloning times are.

Step 3: Mutation operation — ➤ Step 3: Each locus in individual was mutated according to mutation probability.

Step 4: Deleting operation — ➤ Step 4: If there were same solutions in population, keep unique one and go to step 2; otherwise, go to step 5.

Step 5: Updating population — ➤ Step 5: New population was generated according to AUC based non-dominated sorting approach[1].

Step 6: Termination — ➤ Step 6: When achieving the maximal generation, the algorithm ends; otherwise, go to step 2.

Phase 2 — **Best solution selection**

Radiation Oncology   UTSouthwestern Medical Center
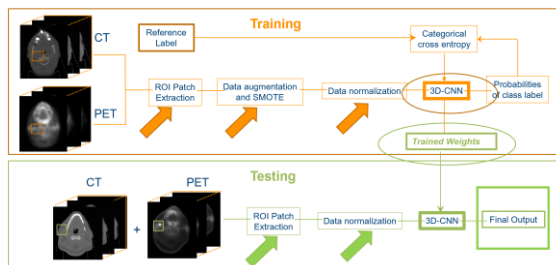
Multi-objective radiomics based prediction

Prediction accuracy measured by confusion matrices on an independent cohort of 18 patients using CT, PET and combination of PET and CT. UA: user accuracy; PA: procedure accuracy

Imaging	Node	Predicted Normal	Predicted Suspicious	Predicted Involved	UA
CT	Normal	13	4	0	0.76
	suspicious	0	23	4	0.85
	involved	1	3	18	0.82
	PA	0.93	0.77	0.82	
PET	Normal	14	3	0	0.82
	suspicious	0	23	4	0.85
	involved	1	5	16	0.73
	PA	0.93	0.74	0.80	
PET & CT	Normal	13	4	0	0.76
	suspicious	0	23	4	0.85
	involved	1	3	18	0.82
	PA	0.93	0.77	0.82	

Feature Set	Accuracy	AUC
CT	0.82	0.88
PET	0.80	0.86
PET & CT	0.81	0.89

Radiation Oncology

CNN-based predictive model

Radiation Oncology   UTSouthwestern Medical Center

CNN-based prediction results

Prediction accuracy measured by confusion matrices on an independent cohort of 18 patients using CT, PET and combination of PET and CT. UA: user accuracy; PA: procedure accuracy

Imaging	Node	Predicted Normal	Predicted Suspicious	Predicted Involved	UA
CT	Normal	15	2	0	0.88
	suspicious	1	20	6	0.74
	involved	1	1	20	0.91
	PA	0.88	0.87	0.77	
PET	Normal	16	1	0	0.94
	suspicious	5	18	4	0.67
	involved	2	2	18	0.82
	PA	0.70	86	0.82	
PET & CT	Normal	16	1	0	0.94
	suspicious	2	23	2	0.85
	involved	1	2	19	0.86
	PA	0.84	0.88	0.90	

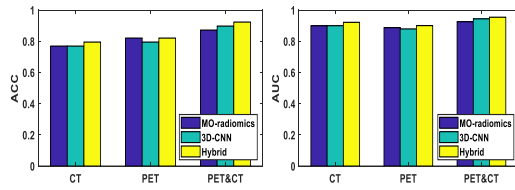| Feature Set	Accuracy	AUC
CT	0.83	0.94
PET	0.79	0.88
PET & CT	0.88	0.95

Radiation Oncology

10

Combination of MO-Radiomics and CNN
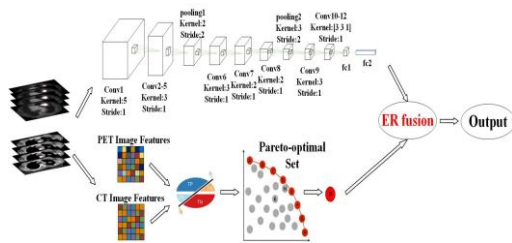
L. Chen,…, J. Wang, PMB, vol. 64, 075011 (13pp), 2019
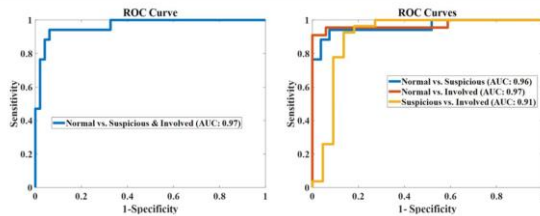
Radiation Oncology UTSouthwestern Medical Center

L. Chen,…, J. Wang, PMB, vol. 64, 075011 (13pp), 2019

Radiation Oncology UTSouthwestern Medical Center
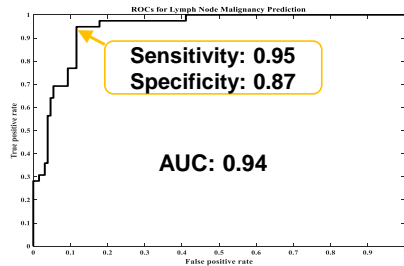

Radiation Oncology UTSouthwestern Medical Center

Results on surgical patients with pathological ground truth

- Training Data: 91 positive/301 benign
- Testing Data: 39 positive/129 benign

Sensitivity: 0.95
Specificity: 0.87

AUC: 0.94

- **https://clinicaltrials.gov/ct2/show/NCT03953976**
- **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).

Radiation Oncology   UTSouthwestern
Medical Center

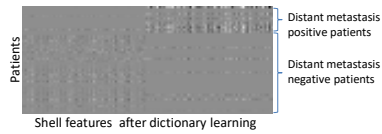
New radiomic feature – Shell feature
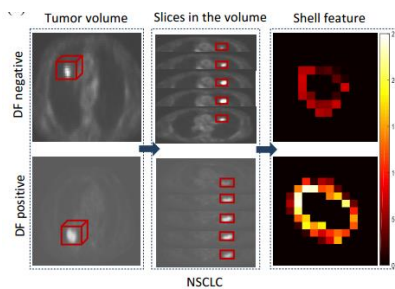
(Hao et al. Phys. Med. Biol., vol. 63, 095007, 2018)

Radiation Oncology   UTSouthwestern
Medical Center

Learned Coefficients of Shell Feature

Distant metastasis positive patients

Distant metastasis negative patients

Patients

Shell features after dictionary learning

(Hao et al. Phys. Med. Biol., vol. 63, 095007, 2018)

Radiation Oncology — UTSouthwestern Medical Center

Predictive performance

- **Metrics: AUC, Sensitivity, Specificity, and Accuracy.**

$$Accuracy = (TP+TN)/(TP+FN+FP+TN)$$

Where TP and TN denote the number of true positives and true negatives; FP and FN indicate the number of false positives and false negatives.

		AUC	Sensitivity	Specificity	Accuracy
SVM	Shell feature	0.80 ± 0.03	0.75 ± 0.04	0.81 ± 0.03	0.79 ± 0.03
	Combined feature	0.71 ± 0.04	0.70 ± 0.01	0.71 ± 0.03	0.70 ± 0.02
DL*	Shell feature	0.82 ± 0.02	0.81 ± 0.02	0.83 ± 0.01	0.81 ± 0.02
	Combined feature	0.73 ± 0.02	0.76 ± 0.03	0.74 ± 0.02	0.74 ± 0.03
DL_SVM**	Shell feature	0.84 ± 0.01	0.81 ± 0.02	0.85 ± 0.02	0.83 ± 0.02
	Combined feature	0.75 ± 0.02	0.75 ± 0.03	0.77 ± 0.03	0.75 ± 0.02

* Gu S, Zhang L, Zuo W, et al. Projective dictionary pair learning for pattern classification, Advances in Neural Information Processing Systems, 793-801 ,2014.

** use sparse coefficients learned by DL as the input of SVM

(Hao et al. Phys. Med. Biol., vol. 63, 095007, 2018)

Radiation Oncology — UTSouthwestern Medical Center

Summary

- **A unified and flexible multifaceted radiomics model is proposed for various applications in radiation therapy:**
  - **Multi-objective: sensitivity, specificity**
  - **Multi-modality: PET, CT, MRI, clinical characteristics, biology**
  - **Multi-classifier: evidential reasoning with reliable fusing for different classifiers such as SVM, CNN, LR, NB…**

Radiation Oncology — UTSouthwestern Medical Center

Acknowledgements

MAIA Lab   **Jing Wang Group**

UT Southwestern
Medical Center