Radiomics Prediction Models of Oropharyngeal SCC Recurrence: Improving Performance with Metastatic Lymph Node Features

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Disclosure of Conflict of Interest

- I do not have a relationship with a for-profit and/or a non-for-profit organization to disclose

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Outline

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- Background and Relevance
- Study Design and Data
- Image Segmentation and Features
- Machine Learning Classification
- Results
- Conclusion

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Purpose

- To compare the performance of prediction models of treatment response based on texture analysis of the primary tumour and metastatic lymph nodes in patients with squamous cell carcinoma of the oropharynx
- *Specifically, can combining the primary tumour + metastatic lymph node features improve the accuracy of predictions?*

Background and Relevance

- Radiomics uses advanced image processing to detect patterns/features in medical images
- Correlations between these features and clinical variables are modelled using advanced statistical analysis and machine learning
- These models may offer more precise, personalized prognostication of survival and treatment response in oncology patients

Background and Relevance

- Previous radiomics studies in H&N have focussed on the primary tumours rather than lymph nodes
- Example endpoints have been tumour grade, benign vs. malignant tissue, HPV or p53 status, survival, and treatment response:
  - Aerts *et al*. were one of the earliest and largest ventures, identifying a set of radiomic features linked to overall survival in independent sets of lung and H&N cancer patients
  - Parmar *et al*. identified radiomic feature selection approaches that showed good accuracy and consistency for prediction of 3-year overall survival in H&N cancers
- By contrast, only a few recent studies have focussed on metastatic H&N lymph nodes:
  - Scalco *et al*. analyzed one cervical lymph node from pre-treatment CT and MR images for predicting treatment response in a 30-patient dataset

Selected H&N Ca Radiomics Studies

Authors	Date	Modality	Size	Cancer Sites	Treatment	Endpoint
Vallieres et al.	Oct 2013	FDG-PET	67			HPV, LRF, mets
Zhang et al	Dec 2013	CT	72	Oral Cavity, Larynx, HPx	iCT, CRT	OS
Cheng et al.	Sep 2013	PET	70	ORP	CRT	PFS, DFS (2y)
Aerts et al.	Jun 2014	CT	474 TRN 545 VAL	Lung, ORPx, Larynx (mixed)	RT, CRT	MS
Cheng et al.	Mar 2015	PET	88	ORP	CRT	PFS, DFS
Buch et al.	Jul 2015	CT	40	ORP		HPV status
Parmar et al.	Jun 2015	CT	578 TRN 320 VAL	Lung (TRN), ORPx, Larynx (VAL)	RT, CRT	OS, T stage HPV status
Leijenaar et al	Aug 2015	CT	464 TRN 542 VAL	Lung (TRN), ORP, Larynx (VAL)	RT, CRT	MS (2000d)
Parmar et al.	Dec 2015	CT	101 TRN 95 VAL	ORP, Larynx	RT, CRT	OS (3y)
Dang et al.	Jan 2015	MRI	16	ORP, HPx		P53 status
Hatt et al.	Jan 2015	FDG-PET	555	H&N and others		OS
Scalco et al.	Sep 2016	CT, MR	30	LNs, ORP, NSPx, HPx, Larynx	CRT	CR, LRF (2y)
Fujita et al.	Jan 2016	CT	46	ORP, HPx, Larynx		HPV status
Fruehwald-Pallamar et al.	Feb 2016	MRI	100			Benign vs. malignant
Park et al.	Feb 2016	MRI	27	ORP		Tumour type
Riesterer et al.	2016	CT	215	ORP, HypoPx, FoM, Glottis	CRT	LC
Altazi et al.	Oct 2016	PET/CT	50	ORP	RT	LRF, DM
Vallieres et al.	Mar 2017	CT/PET	300	SCC H&N (GTV primary + node)	CRT	LRF, DM, PFS, OS
Head et al.	Mar 2018	CT	465	ORP	CRT	LRF
Ranjbar et al.	Mar 2018	CT	107	ORP		HPV Status

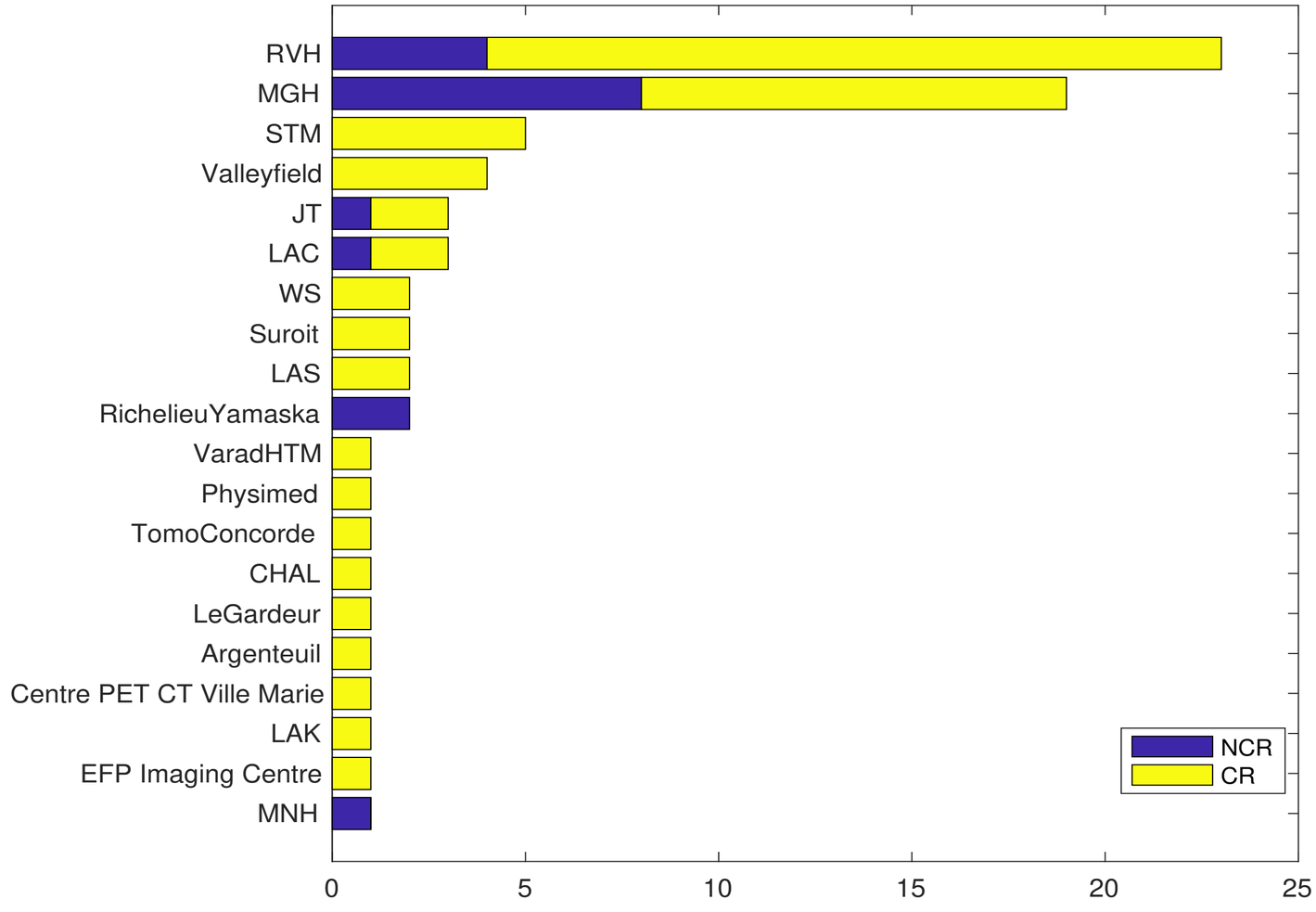
Study Design

- **Endpoint**
  - Complete Response (CR):
    - Disappearance of the primary tumour; pathological lymph nodes must be of normal size
  - Non-Complete Response (NCR):
    - Persistence or recurrence the primary tumour or a lymph node
    - A new lesion identified on a follow up study (locoregional or distant metastasis)
    - Cancer-related death
- **Patients**
  - Retrospectively recruited from McGill University Health Centre electronic records (2006–2016)
  - Squamous cell carcinoma primary tumour of the *oropharynx*
  - Regional lymph node metastasis (Clinical Stage III or IV)
  - Treatment with chemoradiotherapy, bioradiotherapy, or radiotherapy only
  - Minimum 24 months (+/- 90 days) of follow up
  - Pre-treatment contrast-enhanced CT scan of the neck no more than 90 days before treatment
  - Clearly documented treatment response at 24 months
  - No resection of primary tumour or radical lymph node dissection prior to end of treatment
  - No distant metastasis or metachronus cancer
  - No recurrent or previously treated SCC of the head and neck
  - No history of cancer in remission for less than 3 years
  - No death or recurrence before completing treatment

Which Lymph Node?

- *One* "most pathological" lymph node in the primary drainage pathway of the primary tumour was selected.
- Metastases *assumed* for pathologic-appearing nodes.
- Imaging criteria:
  - Levels II, III > 15 mm or retropharyngeal > 8 mm max axial
  - Cluster > 2 level II borderline nodes > 9-10 mm max axial
  - Focal internal inhomogeneity
  - Rounded shape rather than elongated
  - Thickened enhanced rim with infiltration of the adjacent fat of soft tissue structures.

CT Images



Distribution of CT scans by location. Scans were performed at the MUHC and several outside institutions: 1–3 mm slice thickness, 512x512 matrix, and peak voltage 120–140 kVP.

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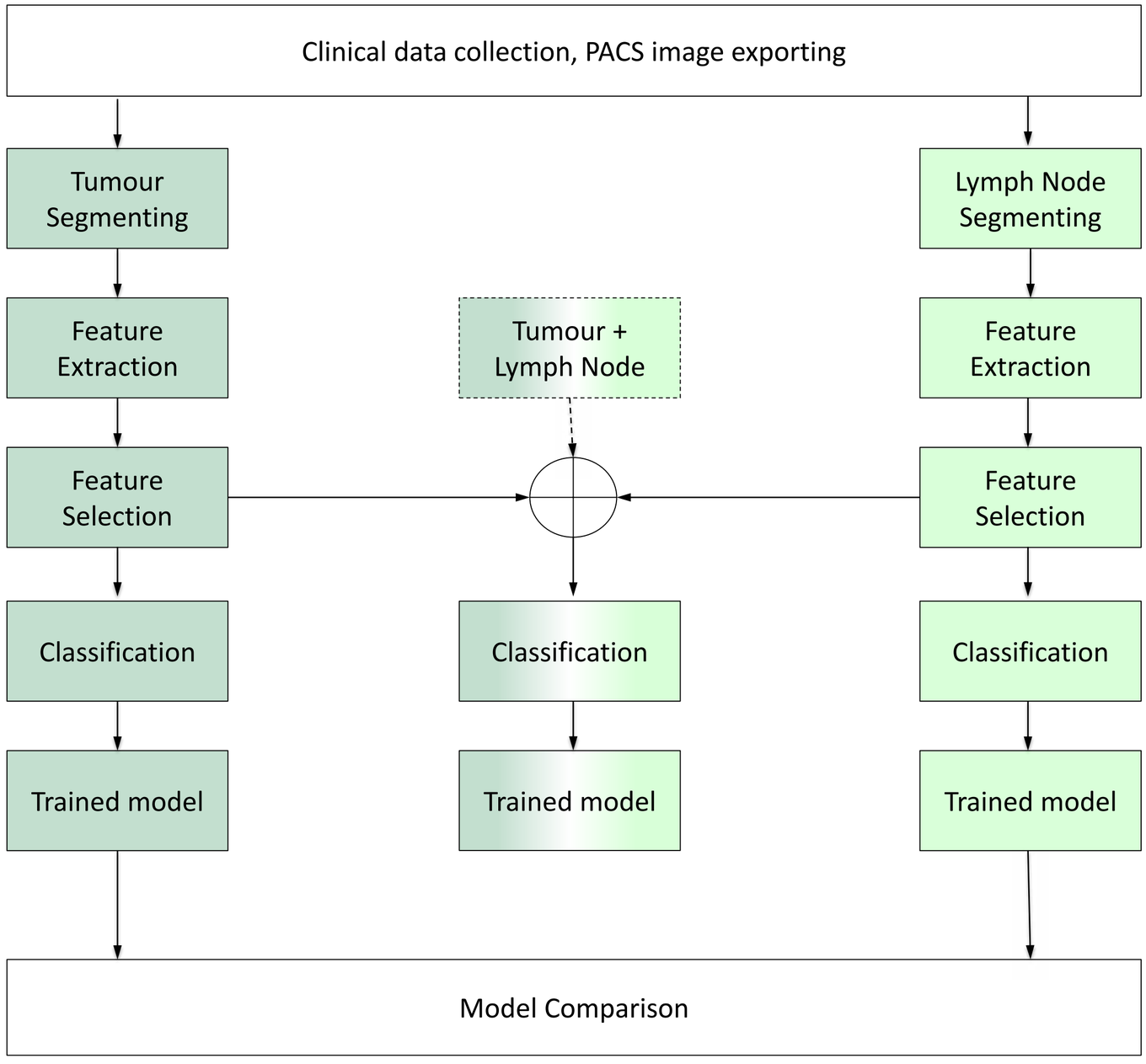
Selected Patient Data

Total Patients Evaluated	**175**
Age at Diagnosis (years)	60
Included	84
Excluded	91
Surgery	33
No pretreatment CT	20
Metastasis or other Cancer at diagnosis	14
Incomplete records	9
Follow up < 24m	13
Other	2
Response Characteristics	
Complete Response (CR)	63
Non Complete Response (NCR)	21
Locoregional Recurrence (LR)	11
Distant Metastasis	10
Died of disease (DOD) (<24m)	6
Alive with disease (ALD)	15

Selected Patient Data

Treatment Characteristics	
Chemoradiotherapy	58
Radiotherapy	3
Bioradiotherapy (Cetuximab)	10
Cancer Characteristics	
Mean primary tumour size (cm)	2.8
Mean target lymph node size (cm)	2.6
Tx (occult primary)	6
T1	11
T2	38
T3	11
T4	18
N0	5
N1	13
N2	64
N3	2
p16 +ve	51
p16 -ve	6
p16 not documented	27

Radiomics Workflow



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Radiomics Workflow

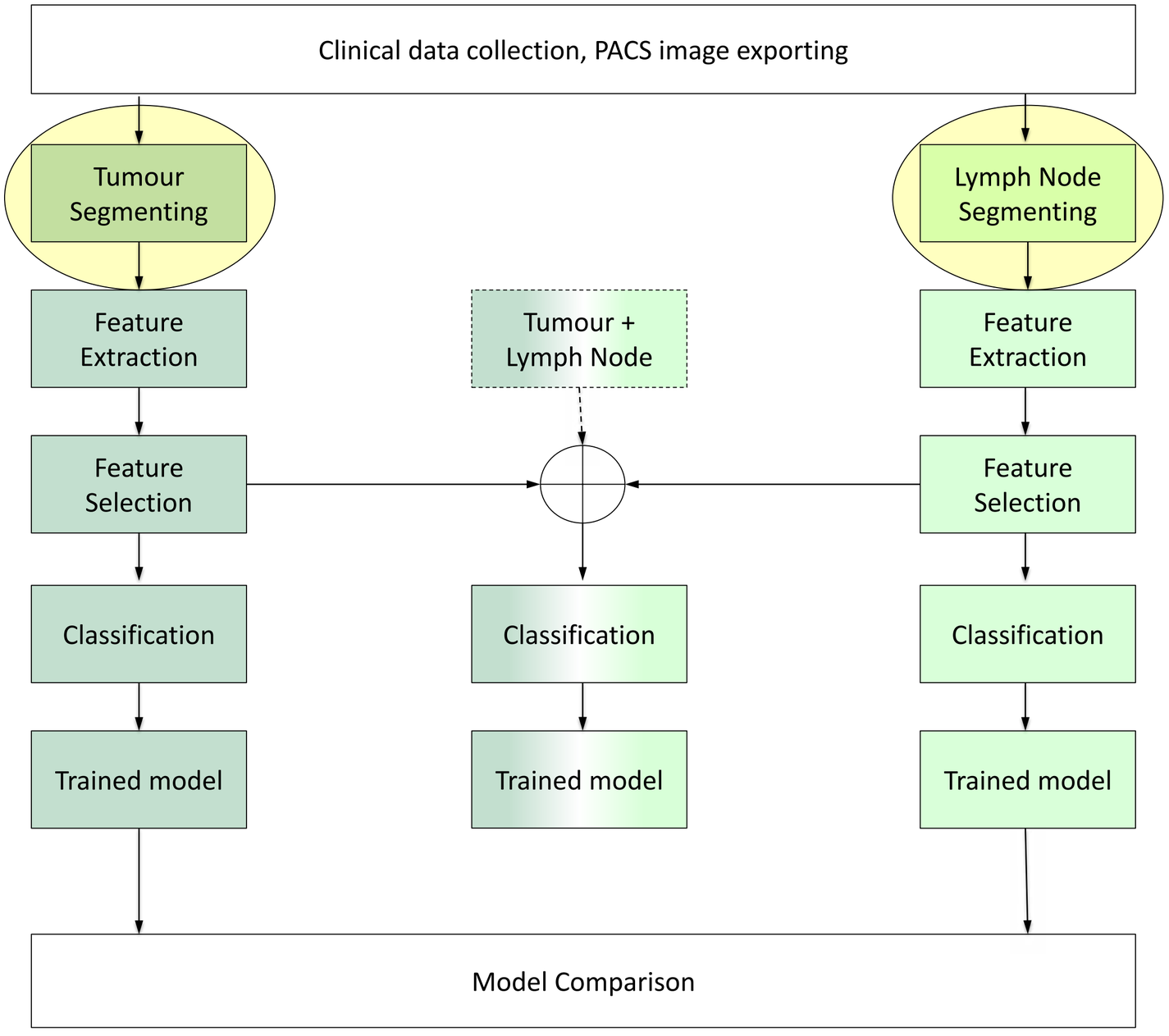

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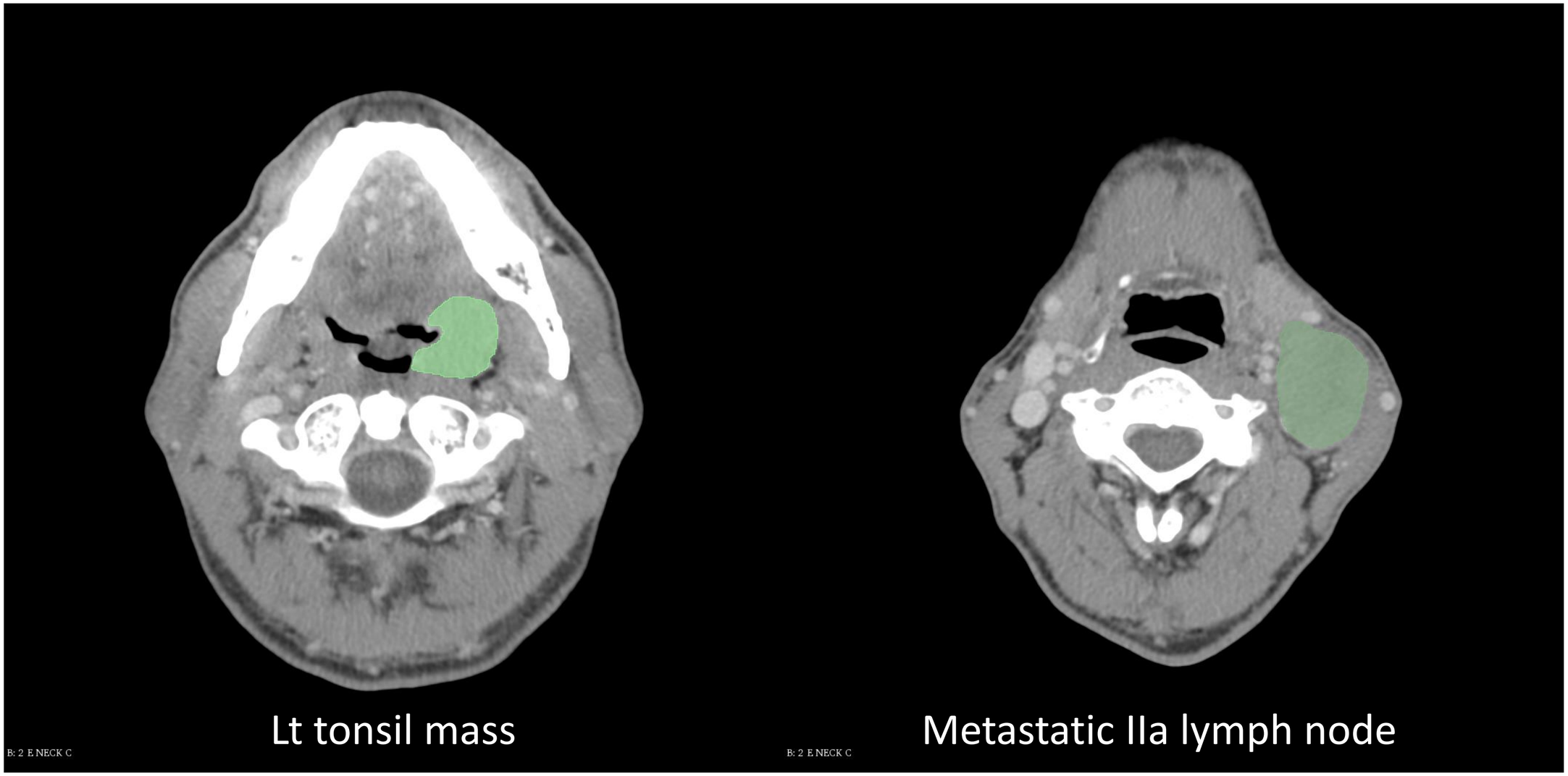
Image Segmentation

- Manual 2D segmentation was performed using 3Dslicer over two passes
- Findings from MRI, PET and clinical notes guided the segmentations
- Slice with gross demonstrable tumour area of primary and lymph node constituted the ROIs
- Avoided slices with volume averaging or where tumour was obscured by metal artefact
- Prominent internal vessels were excluded from the ROIs
- Images/masks Stored as NRRD (Nearly Raw Raster Data)

Example Segmentations



Lt tonsil mass

Metastatic IIa lymph node

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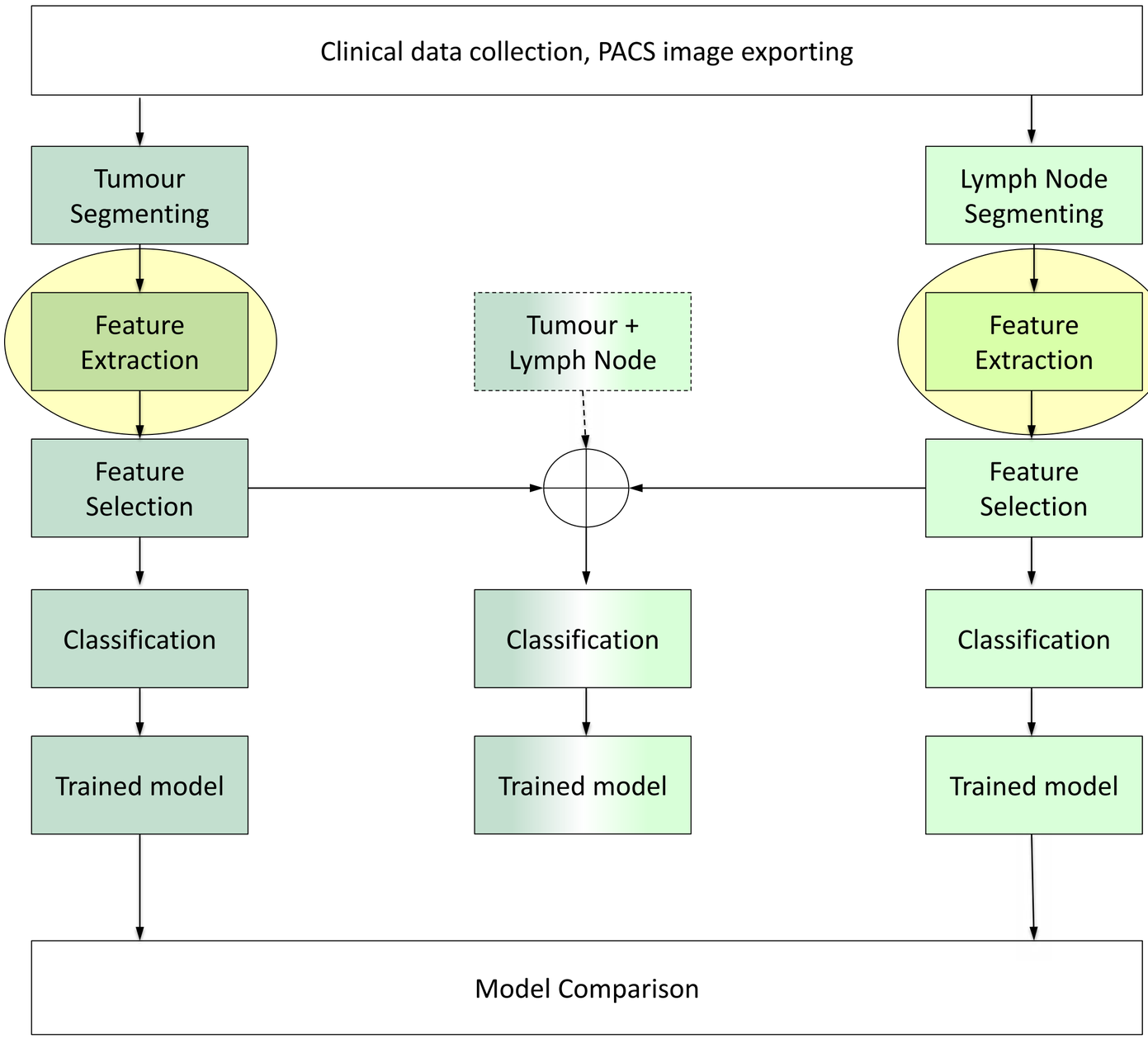
Radiomics Workflow



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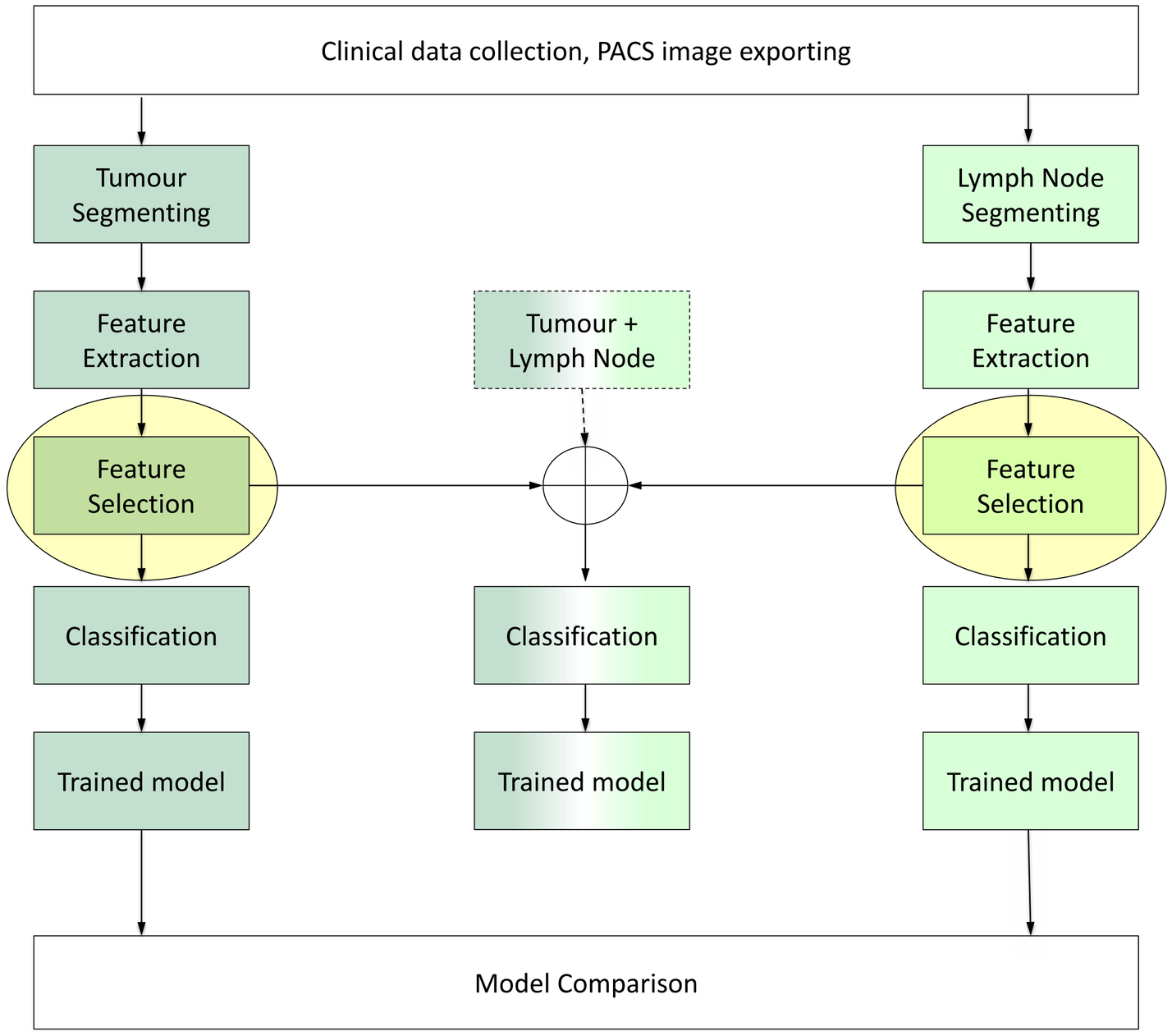
Feature Extraction

- Features computed with *pyradiomics,* a state-of-the-art, open-source software package from Harvard/Maastricht University
- A total of 787 first, second and third order features were computed in both native image domain and 8-band Wavelet decomposition
- First-order statistics describe the distribution of voxel intensities, e.g., mean, energy, entropy, kurtosis, skewness
- Second-order statistics describe the three-dimensional size and shape, e.g., compactness, surface volume, maximum diameter etc.
  - These 27 features were discarded since the analysis was in 2D
- Third-order statistics describe spatial distribution of voxel intensities, e.g., GLCM, GLSZM, GLRLM, GLDM

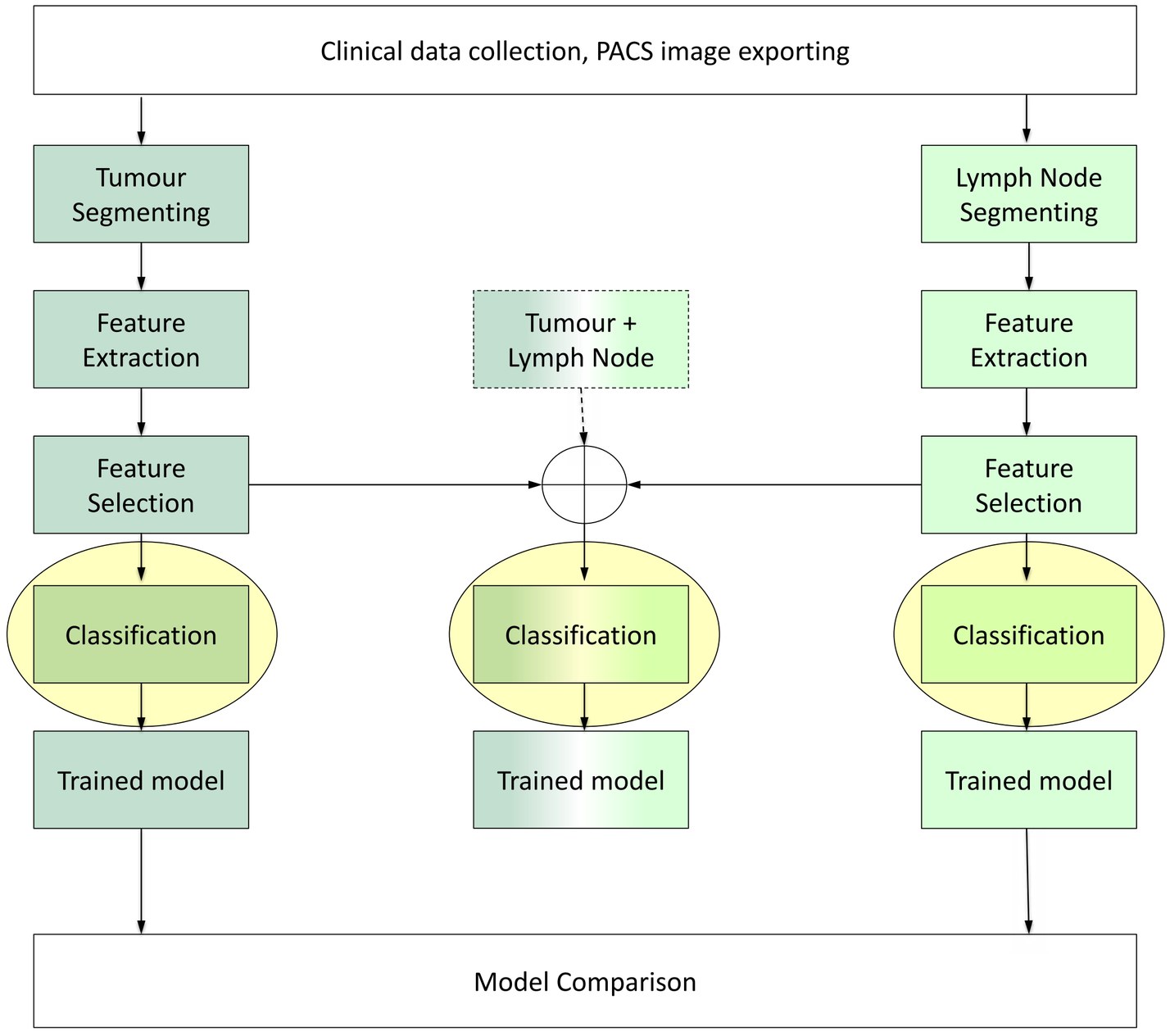
Radiomics Workflow



Feature Selection

- 760 features imported into Matlab for feature selection and machine learning classification
- Spearman's rank correlation computed between each feature vector, *F*, and the outcome vector *Y*
- 10 tumour features and 10 lymph node features with highest rank correlation were selected as feature subsets
- A combined tumour + lymph node subset was formed by selecting 10 features with highest rank correlation from these two subsets

Radiomics Workflow



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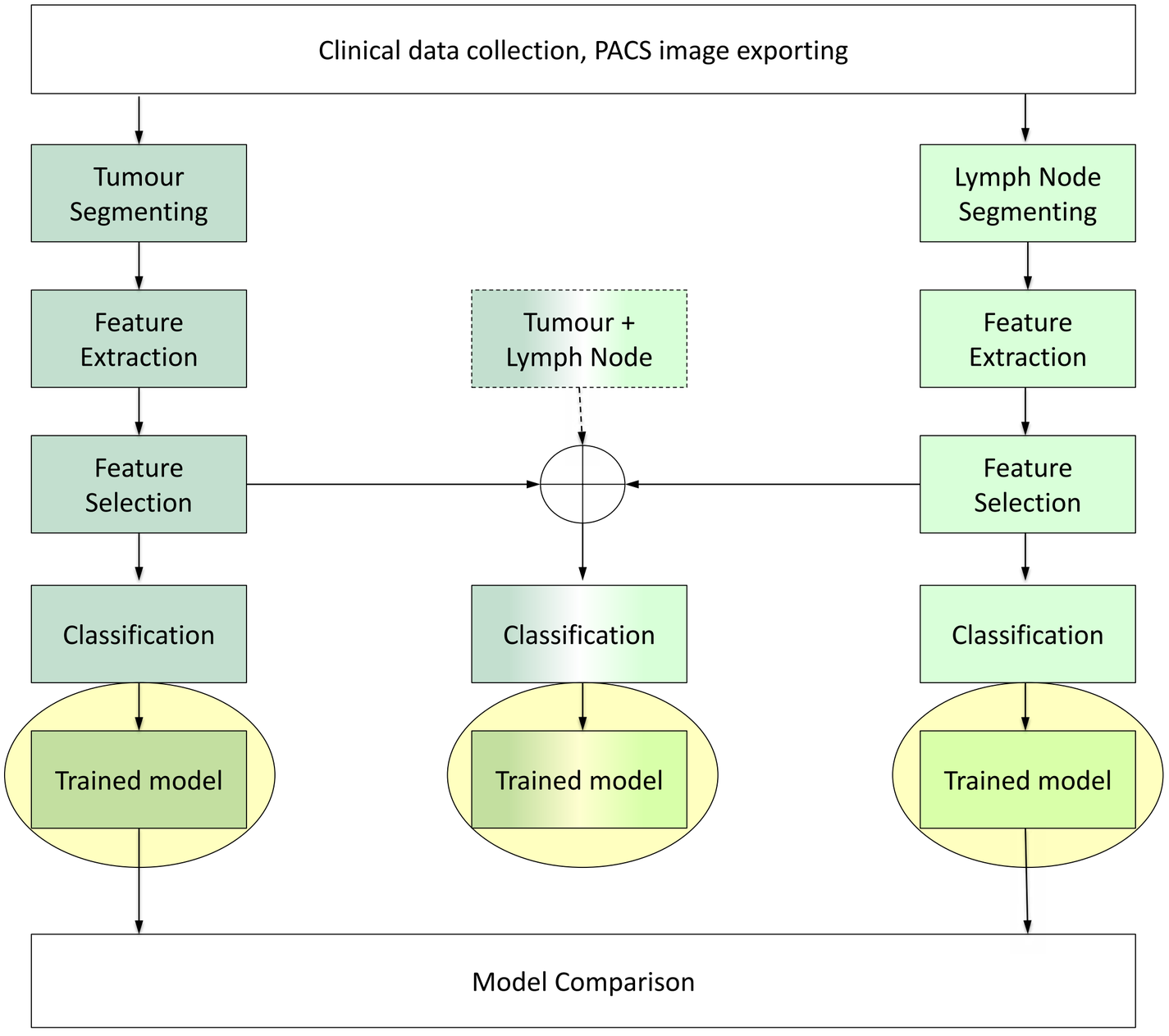
Machine Learning

- A custom software framework was developed in Matlab using 10 different machine learning classifiers and the 10 selected features
- 100 prediction models were trained on each group by varying the number of features from 1 to 10 for all 10 classifiers
- Undersampling was used on each pass to correct imbalance, yielding new distributions of 2/3 complete responders to 1/3 non complete responders
- 5-fold cross validation was used for model validation rather than holdout due to limited sample size
- The area-under-the-curve (AUC) was calculated as the averaged average of the undersampled and cross validation subsets

Radiomics Workflow



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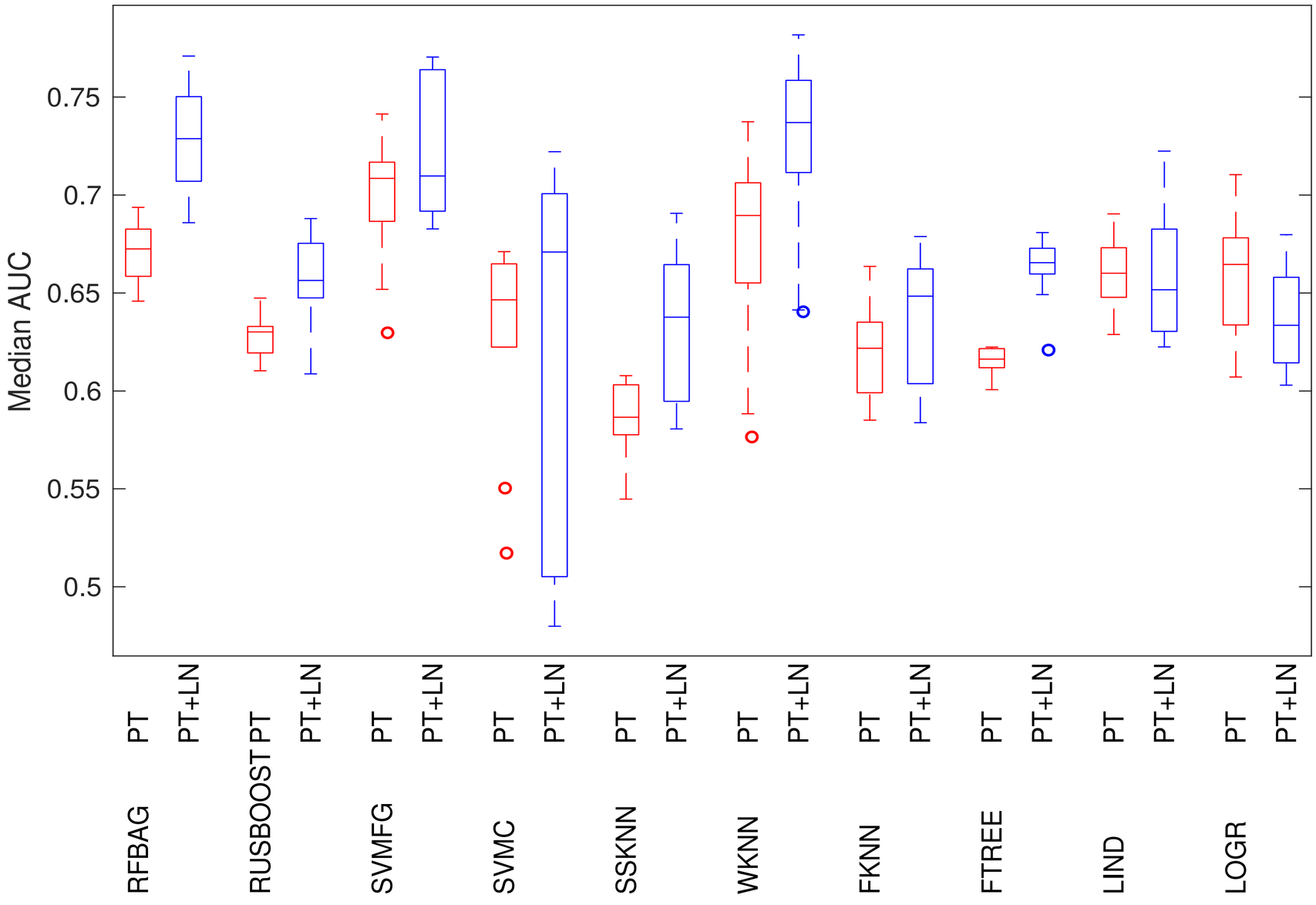
Results

- The Wilcoxon rank sum test, using Bonferroni correction, showed a statistically significant increase in AUC for the combined primary tumour + lymph node models vs. the primary tumour only models (p=4.78x10^{e-4})
- Specifically, 4-of-10 models, RFBAG, RUSBOOST, SSKNN, and FTREE, had higher AUCs
- There was no significant difference in AUC between the primary tumour and lymph node models (p=0.49)

AUC T-only vs. T+LN models



Four classifiers (RFBAG, RUSBOOST, SSKNN, and FTREE) had a statistically significant increase in AUC when the combined primary tumour + lymph node radiomics signature was used.

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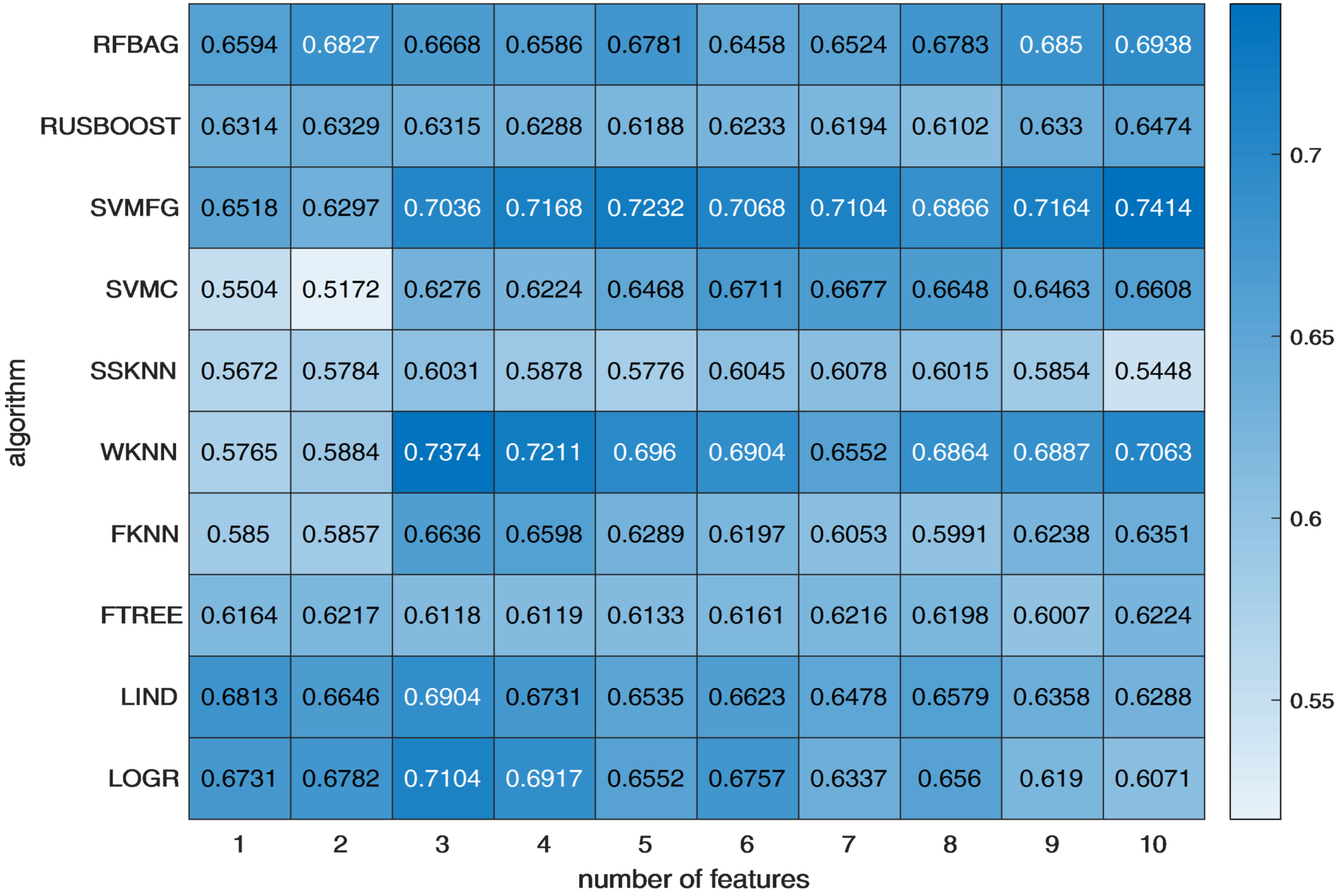
AUC Tumour Model



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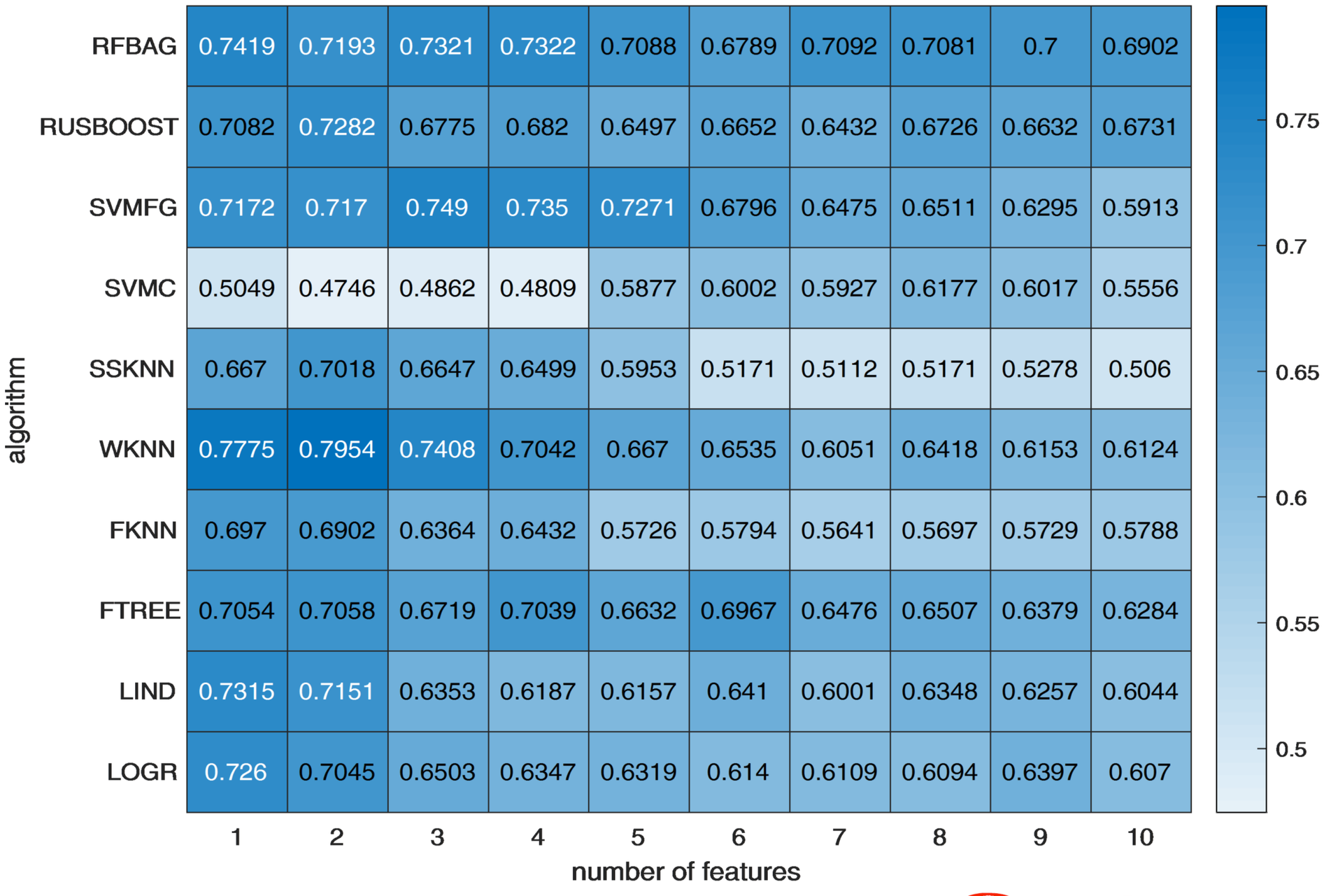
AUC Node Model



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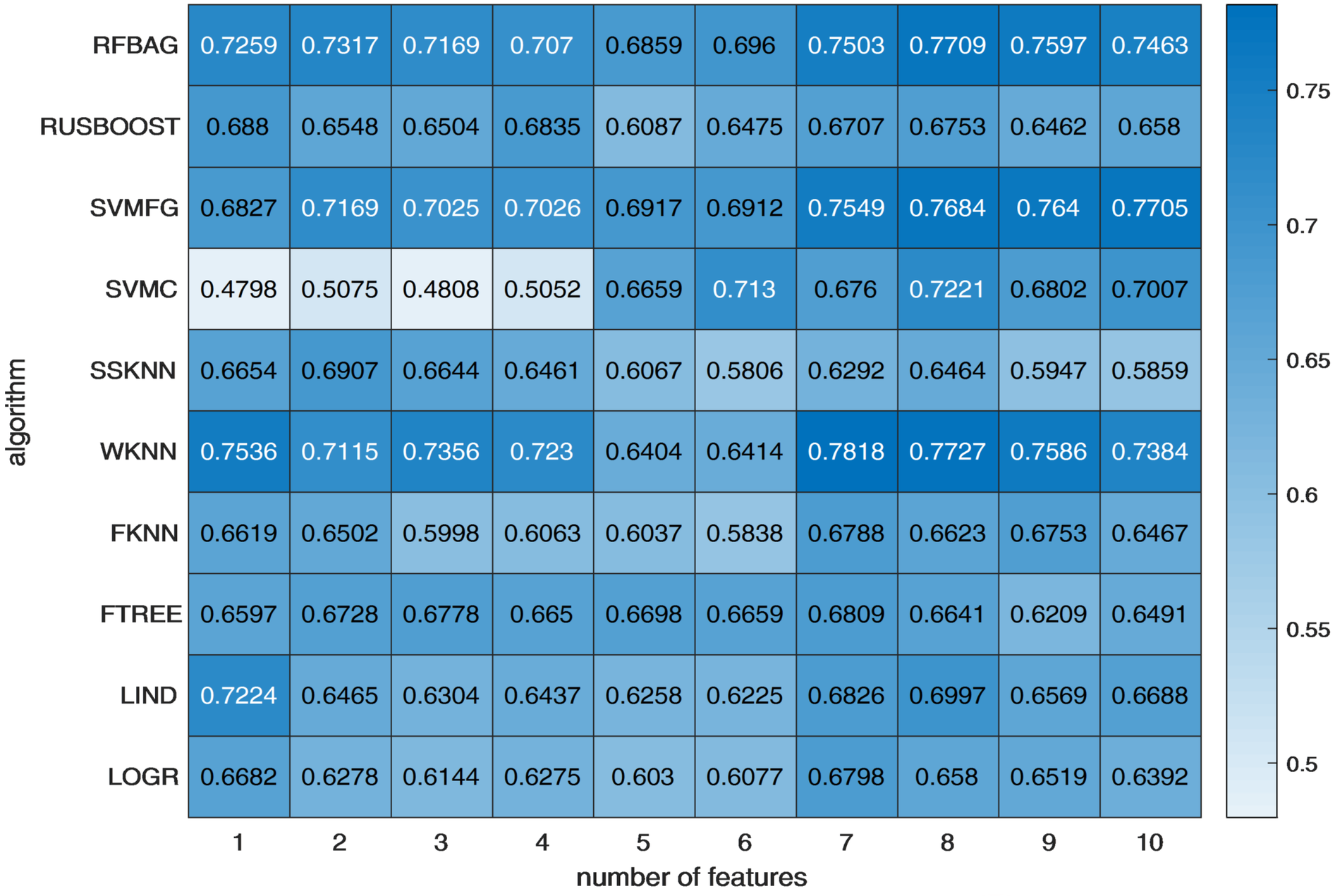
AUC Tumour + Node Model



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Conclusion

Regarding radiomics prediction models in OPSCC:

- Preliminary results suggest that combining primary tumour *and* metastatic lymph features yields a statistically significant higher average AUC compared to using primary tumour features only.

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Conclusion

Regarding radiomics prediction models in OPSCC:

- Future work may consider including metastatic lymph node features in the gross tumour volume to improve predictor performance.

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Thank you

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