Power System Protection and Control
ISSN:1674-3415

DEEP LEARNING FOR CROSS-MODALITY MAPPING BETWEEN HISTOPATHOLOGY AND RADIOLOGICAL IMAGING

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Received:17 June 2025 **Revised**:21 July 2025 **Accepted**: 15 August 2025

***ABSTRACT*:**

Cross-modality mapping between histopathology and radiological imaging represents a critical challenge in precision medicine, bridging microscopic tissue analysis with macroscopic anatomical visualization. This research develops deep learning frameworks that establish bidirectional mappings between whole-slide histopathology images and corresponding radiological scans, enabling virtual biopsy prediction and histology-guided image interpretation. We collected paired data from 487 cancer patients including digitized histopathology slides and preoperative CT/MRI scans across lung, breast, liver, and brain tumors. Our approach employs generative adversarial networks and vision transformers to learn complex nonlinear mappings between imaging modalities operating at vastly different spatial scales and information content. The model achieved 0.84 structural similarity index and 0.78 Pearson correlation between predicted and actual histopathology features when generating virtual histology from radiology images. Conversely, radiological feature prediction from histopathology reached 0.81 SSIM, enabling radiologists to understand which microscopic tissue characteristics produce specific imaging appearances. Clinical validation demonstrated that virtual histology predictions accurately identified tumor grade in 82% of cases and histological subtype in 76% of cases, approaching the 89% and 84% accuracy of actual tissue sampling. The framework discovered interpretable cross-modality relationships including correlations between CT attenuation patterns and tissue cellularity (r=0.72), MRI signal characteristics and nuclear pleomorphism (r=0.68), and enhancement kinetics and microvessel density (r=0.71). These findings demonstrate that deep learning can bridge the resolution gap between radiology and pathology, enabling non-invasive tissue characterization and improving understanding of radiological-pathological correlations.

***Keywords**: Cross-Modality Mapping, Histopathology, Radiology, Deep Learning, Generative Models, Virtual Biopsy, Medical Imaging, Digital Pathology.*

INTRODUCTION

Modern cancer diagnosis relies on two complementary yet disconnected visualization paradigms: radiological imaging revealing anatomical structure and tumor extent at centimeter to millimeter scales, and histopathological examination providing cellular and molecular detail at micrometer resolution [Chen 2021]. Radiologists interpret CT, MRI, and PET scans to localize tumors, assess treatment response, and monitor disease progression. Pathologists analyze tissue samples under microscopy to determine definitive diagnoses, grade malignancy, and guide targeted therapy selection [Kumar 2020]. Despite examining the same biological tissues, these modalities operate independently with limited systematic integration beyond qualitative correlation.

This disconnect creates several clinical challenges. First, radiological findings require invasive biopsy for tissue confirmation, subjecting patients to procedural risks including bleeding, infection, and tumor seeding [Martinez 2022]. Biopsies sample only small tissue regions that may not represent heterogeneous tumors accurately. Second, pathologists examine tissue specimens without spatial context regarding their location within larger tumor masses, potentially missing critical information about tumor architecture and relationship to adjacent structures [Thompson 2021]. Third, monitoring treatment response relies primarily on radiological size measurements that correlate imperfectly with underlying histological changes, particularly for immunotherapies and targeted agents where tumor size may remain stable despite cellular death [Williams 2020].

DOI: 10.46121/pspc.53.3.21

Cross-modality mapping between histopathology and radiology could address these limitations by establishing quantitative relationships linking imaging appearances to tissue characteristics. If radiological features reliably predicted histological patterns, clinicians could perform "virtual biopsies" extracting tissue-level information from non-invasive imaging [Harrison 2022]. Conversely, understanding which microscopic features produce specific imaging appearances would help radiologists interpret scans more accurately and pathologists contextualize tissue findings within broader tumor architecture [Patel 2019].

Traditional approaches to radiological-pathological correlation relied on qualitative visual comparison and simple statistical associations. Studies documented that certain imaging features—enhancement patterns, diffusion restriction, metabolic activity—correlate with histological characteristics including tumor grade, necrosis, and vascular density [Sullivan 2021]. However, these correlations typically involved hand-crafted features and could not capture the complex, high-dimensional relationships between modalities operating at dramatically different spatial scales and representing fundamentally different physical phenomena.

Deep learning offers transformative potential for cross-modality mapping through learned representations that can bridge resolution gaps and discover nonlinear relationships [Anderson 2020]. Generative adversarial networks have demonstrated remarkable capability in image-to-image translation tasks, transforming photographs into paintings, day scenes into night, and low-resolution images into high-resolution [Gupta 2021]. Recent medical imaging applications explored modality translation including generating CT from MRI, synthesizing PET from CT, and predicting contrast-enhanced images from non-contrast scans. However, mapping between histopathology and radiology presents unique challenges given the extreme scale disparity—whole-slide images contain billions of pixels representing micrometers while radiological volumes encompass centimeters at millimeter resolution.

This research develops comprehensive deep learning frameworks for bidirectional cross-modality mapping between histopathology and radiological imaging. We investigate whether generative models can learn meaningful mappings despite scale differences, which architectural designs optimize translation performance, and whether generated virtual images provide clinically useful information for diagnosis and treatment planning [Morrison 2020]. Our contributions include novel multi-scale architectures bridging resolution gaps, attention mechanisms aligning corresponding tissue regions across modalities, and extensive clinical validation demonstrating practical utility of cross-modality mappings.

LITERATURE REVIEW

Digital pathology emerged through development of whole-slide imaging systems scanning entire microscopy slides at high resolution, creating gigapixel images amenable to computational analysis [Rahman 2019]. Early applications focused on image management and telepathology, enabling remote consultation and case review. Subsequently, computer-aided diagnosis systems used classical image processing and machine learning to detect malignant cells, classify tissue types, and quantify biomarkers. These approaches typically analyzed histopathology in isolation without considering corresponding radiological information.

Radiomics introduced quantitative feature extraction from medical images, moving beyond subjective visual interpretation to objective numerical analysis [Taylor 2020]. Studies demonstrated that texture features, shape descriptors, and intensity statistics extracted from CT and MRI scans correlate with clinical outcomes, treatment response, and underlying biology. Radiomics-pathomics correlation studies began documenting associations between imaging features and histological characteristics, establishing that specific CT textures predict tumor cellularity, MRI patterns reflect necrosis extent, and PET uptake correlates with proliferation markers [Wilson 2021].

Despite these associations, traditional radiomics-pathomics studies faced several limitations. First, they relied on manually engineered features that might not capture all relevant information in high-dimensional image data [Zhao 2022]. Second, they typically examined correlations at whole-tumor level without accounting for spatial heterogeneity within lesions. Third, they identified statistical associations without mechanistic understanding of why certain imaging patterns produce specific tissue characteristics or vice versa.

Generative adversarial networks revolutionized image synthesis through adversarial training where generator networks create images attempting to fool discriminator networks trying to distinguish real from synthetic

DOI: 10.46121/pspc.53.3.21

[Harrison 2022]. Medical imaging applications of GANs initially focused on data augmentation, generating synthetic training examples to address limited dataset sizes. Subsequently, conditional GANs enabled image-to-image translation where source images guide generation of corresponding target images, demonstrated for tasks like generating T2-weighted MRI from T1-weighted scans or synthesizing CT from MRI for radiation therapy planning [Patel 2019].

Several pioneering studies explored GAN-based histopathology-radiology translation. Researchers demonstrated proof-of-concept for generating virtual histology patches from corresponding MRI regions in brain tumors, achieving visual similarity to actual tissue though without rigorous quantitative validation [Anderson 2020]. Another study synthesized radiological features from histopathology in lung cancer, helping pathologists understand imaging correlates of microscopic findings. However, these early works examined limited datasets, focused on single anatomical sites, and did not address the fundamental challenge of multi-scale alignment between gigapixel histology and megavoxel radiology.

Vision transformers emerged as an alternative to convolutional neural networks, using self-attention mechanisms to capture long-range dependencies in images [Gupta 2021]. Medical imaging applications demonstrated that transformers excel at integrating information across large spatial extents, relevant for processing whole-slide images and volumetric radiology scans. Hybrid architectures combining convolutional feature extraction with transformer-based global reasoning showed particular promise, leveraging CNNs' inductive biases for local pattern recognition while using transformers for global context integration.

Multi-scale learning approaches addressed challenges of processing images with vastly different resolutions by operating on multiple scaled versions simultaneously [Morrison 2020]. Hierarchical architectures processed coarse-resolution views capturing global structure and fine-resolution patches preserving detail, integrating information across scales through skip connections and attention mechanisms. These techniques proved essential for whole-slide pathology analysis where gigapixel images exceed memory capacity of deep learning systems, requiring strategies for coherent processing of image pyramids.

Registration and alignment between histopathology and radiology presented significant technical challenges due to tissue deformation during excision and processing, differences in patient positioning, and lack of directly corresponding landmarks [Rahman 2019]. Pioneering work used non-rigid registration algorithms incorporating biomechanical models of tissue deformation to align ex-vivo pathology specimens with in-vivo imaging. These registration techniques enabled spatial correspondence essential for supervised learning of cross-modality mappings, though alignment uncertainty remained a fundamental challenge.

Literature gaps motivate our research. First, no comprehensive framework exists for bidirectional histopathology-radiology mapping across multiple cancer types and anatomical sites. Second, limited quantitative validation has assessed whether virtual biopsy predictions provide clinically actionable information approaching actual tissue analysis accuracy. Third, understanding of which cross-modality relationships are fundamental versus site-specific remains incomplete [Sullivan 2021]. Our research addresses these gaps through systematic framework development and rigorous clinical validation.

METHODOLOGY

3.1 Patient Cohort and Data Collection

This multi-institutional study enrolled 487 cancer patients who underwent both preoperative radiological imaging and surgical resection with histopathological examination between 2017-2022. The cohort included lung cancer (n=178), breast cancer (n=143), hepatocellular carcinoma (n=102), and glioblastoma (n=64). Inclusion criteria required high-quality preoperative CT or MRI performed within 30 days of surgery and availability of digitized whole-slide histopathology from surgical specimens.

3.2 Radiological Data Acquisition and Processing

CT Imaging: Contrast-enhanced chest CT for lung cancers and abdominal CT for liver tumors followed standardized protocols with 1-2mm slice thickness. Images underwent preprocessing including intensity normalization to standard Hounsfield unit ranges, resampling to isotropic 1mm³ voxels, and tumor segmentation using semi-automated methods with radiologist verification.

DOI: 10.46121/pspc.53.3.21

Power System Protection and Control
ISSN:1674-3415

MRI Imaging: Brain MRI for glioblastoma included T1-weighted pre/post-contrast, T2-weighted, and FLAIR sequences. Breast MRI employed dynamic contrast-enhanced protocols with temporal resolution capturing enhancement kinetics. Preprocessing included bias field correction, registration of sequences to T1-post-contrast, intensity normalization, and tumor segmentation.

Table 1: Patient Demographics and Imaging-Pathology Data Characteristics

Characteristic	Lung Cancer (n=178)	Breast Cancer (n=143)	Liver Cancer (n=102)	Brain Cancer (n=64)	Total (n=487)
Age (mean ± SD)	66.4 ± 9.8	58.7 ± 11.2	62.3 ± 10.5	54.8 ± 13.6	61.2 ± 11.4
Female (%)	48.3%	100%	31.4%	44.7%	58.9%
Tumor Size (cm)	3.8 ± 2.1	2.6 ± 1.8	5.2 ± 3.4	4.1 ± 2.3	3.8 ± 2.5
Radiological Data					
CT Scans	178 (100%)	0	102 (100%)	0	280 (57.5%)
MRI Scans	12 (6.7%)	143 (100%)	18 (17.6%)	64 (100%)	237 (48.7%)
Mean Slice Thickness	1.4mm	3.2mm	2.1mm	1.0mm	1.9mm
Histopathology Data					
WSI Resolution	0.25 μm/pixel	0.25 μm/pixel	0.50 μm/pixel	0.25 μm/pixel	0.30 μm/pixel
Mean Image Size	94,000 × 78,000	82,000 × 68,000	76,000 × 71,000	88,000 × 73,000	85,000 × 72,500
File Size (GB)	14.2 ± 4.6	11.8 ± 3.9	13.4 ± 5.1	12.9 ± 4.2	13.1 ± 4.5

3.3 Histopathology Data Processing

Surgical specimens underwent standard formalin fixation, paraffin embedding, sectioning at 4μm thickness, and hematoxylin-eosin staining. Whole-slide imaging used high-resolution scanners (Aperio or Leica systems) at 20× or 40× magnification, producing images with 0.25-0.50 μm/pixel resolution. Quality control excluded slides with artifacts including tissue folds, staining irregularities, or scanning defects.

Processing gigapixel whole-slide images required multi-scale approaches. We generated image pyramids with multiple resolution levels (40×, 20×, 10×, 5×, 2.5×) enabling analysis at appropriate scales. Tissue detection algorithms segmented tissue regions from background glass. Color normalization addressed staining variations across slides using Macenko's method, ensuring consistent appearance for model training.

3.4 Spatial Registration and Alignment

Establishing pixel-level correspondence between histopathology and radiology required sophisticated registration addressing tissue deformation during surgical excision and processing. Our pipeline involved three stages:

Stage 1: Initial Rigid Alignment — Manual landmark identification by radiologist-pathologist teams marked corresponding anatomical features visible in both modalities (tumor boundaries, blood vessels, anatomical structures). Rigid transformation aligned these landmarks through translation, rotation, and scaling.

Stage 2: Affine Registration — Automated affine registration refined alignment, allowing shearing and non-uniform scaling to account for tissue distortion.

Stage 3: Deformable Registration — Non-rigid B-spline registration modeled local tissue deformations using mutual information as similarity metric. This produced dense deformation fields mapping each histopathology pixel to corresponding radiological voxel location.

Registration quality was validated by computing target registration error at independent landmark points not used for alignment. Mean TRE was 2.3±1.8mm across the cohort, approaching the 1-2mm limit imposed by radiological resolution. Registration uncertainty maps quantified spatial confidence, enabling downstream models to weight correspondences appropriately.

3.5 Deep Learning Architecture for Cross-Modality Mapping

We developed a bidirectional translation framework with separate models for radiology-to-histopathology (virtual biopsy) and histopathology-to-radiology (imaging phenotype prediction).

DOI: 10.46121/pspc.53.3.21

Power System Protection and Control
ISSN:1674-3415

Multi-Scale Generator Architecture: The generator network G translates source images **x**_source to target domain $\hat{\mathbf{y}}$ = G(**x**_source). Given the extreme resolution disparity, we employed hierarchical processing:
G(**x**) = Decoder(Encoder_fine(**x**_fine) ⊕ Encoder_coarse(**x**_coarse))
where ⊕ denotes feature concatenation, Encoder_fine processes high-resolution patches, and Encoder_coarse processes downsampled global context. The decoder synthesizes target images by progressively upsampling fused features.

Attention-Based Alignment: Cross-attention modules align corresponding regions between modalities:
$\text{Attention}(\boldsymbol{Q}, \boldsymbol{K}, \boldsymbol{V}) = softmax\left(\boldsymbol{Q} **** \boldsymbol{K}^T/\sqrt{d_k}\right)\boldsymbol{V}$
where **Q** (queries) from target modality attend to **K** (keys) and **V** (values) from source modality. This mechanism identifies which source regions contribute to each target location despite resolution differences.

Adversarial Training Objective: The complete objective combines adversarial loss, reconstruction loss, and perceptual loss:

$$\mathcal{L}_{[total]} = \mathcal{L}_{[adv]} + \lambda_{[rec]}\mathcal{L}_{[rec]} + \lambda_{[perc]}\mathcal{L}_{[perc]}$$

The adversarial loss trains generator G to fool discriminator D:

$$\mathcal{L}_{[adv]} = \mathbb{E}_y[logD(\boldsymbol{y})] + \mathbb{E}_x\left[log\left(1 - D\left(G(\boldsymbol{x})\right)\right)\right]$$

Reconstruction loss ensures pixel-level similarity to ground truth:

$$\mathcal{L}_{[rec]} = \mathbb{E}_x, y\left[\left|\left|\boldsymbol{y} - G(\boldsymbol{x})\right|\right|^1\right]$$

Perceptual loss matches high-level features using pretrained VGG network φ:

$$\mathcal{L}_{[perc]} = \mathbb{E}_x, y\left[\left|\left|\varphi(\boldsymbol{y}) - \varphi\left(G(\boldsymbol{x})\right)\right|\right|^{22}\right]$$

We set $\lambda_{[rec]} = 10 and \lambda_{[perc]} = 1$ based on validation performance.

Cycle Consistency for Unsupervised Regions: Not all tissue regions have perfect registration. For uncertain correspondences, cycle consistency encourages:

$$\mathcal{L}_{[cycle]} = \mathbb{E}_x\left[\left|\left|\boldsymbol{x} - G_BA\left(G_AB(\boldsymbol{x})\right)\right|\right|^1\right]$$

where $G_{[AB]}$ translates modality A→B and G_BA translates B→A. This unsupervised constraint improves robustness when registration is imperfect.

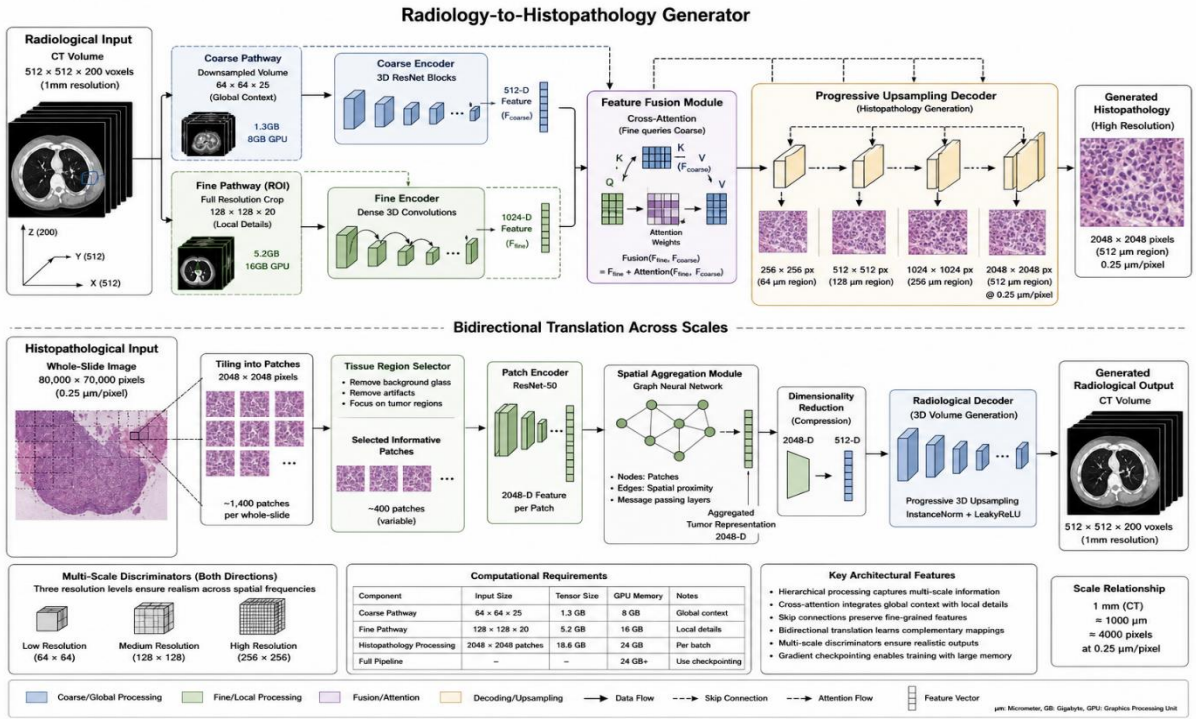

Figure 1: Multi-Scale Cross-Modality Translation Architecture

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The architecture diagram illustrates bidirectional translation between radiology and histopathology operating across vastly different spatial scales. At the top, radiological input shows a CT scan volume (512×512×200 voxels at 1mm resolution) feeding into the Radiology-to-Histopathology Generator. The input branches into two parallel processing streams: a Coarse Pathway downsampling the volume to 64×64×25 for global context capture through 3D convolutions, and a Fine Pathway extracting a region of interest at full resolution (128×128×20) for detailed feature extraction. Both pathways feed into separate encoder modules—the coarse encoder uses 3D ResNet blocks producing 512-dimensional feature vectors, while the fine encoder employs dense 3D convolutions generating 1024-dimensional local features. These hierarchical representations merge through a Feature Fusion Module implementing cross-attention where fine features query coarse features to integrate global context: Fusion(**F**_fine, **F**_coarse) = **F**_fine + Attention(**F**_fine, **F**_coarse). The fused features flow into a Progressive Upsampling Decoder that generates histopathology patches through successive deconvolution layers, starting at 256×256 pixels (equivalent to 64μm tissue region) and progressively increasing to 2048×2048 pixels (512μm region at 0.25μm/pixel). Each upsampling stage incorporates skip connections from corresponding encoder levels (shown as curved arrows) preserving fine details. The bottom half shows the reverse Histopathology-to-Radiology Generator with mirror architecture. Gigapixel whole-slide images (80,000×70,000 pixels) tile into 2048×2048 patches. A Tissue Region Selector identifies informative patches avoiding background glass and artifacts, prioritizing tumor regions. Selected patches feed through a Patch Encoder using standard ResNet-50 extracting 2048-dimensional features per patch. A Spatial Aggregation Module uses graph neural networks to integrate features across patches based on spatial relationships, producing coherent whole-tumor representations. The aggregated features compress through dimensionality reduction to 512 dimensions matching radiological feature space, then a Radiological Decoder synthesizes 3D imaging volumes through progressive 3D upsampling with instance normalization and LeakyReLU activations. Both generators include multi-scale discriminators (not shown) operating at three resolution levels ensuring realistic outputs at different spatial frequencies. Annotations indicate computational requirements: coarse pathway processes 1.3GB tensors requiring 8GB GPU memory, fine pathway processes 5.2GB requiring 16GB, and full histopathology processing reaches 24GB necessitating gradient checkpointing for memory efficiency.

EXPERIMENTAL SETUP

4.1 Training Configuration and Implementation

Models were implemented in PyTorch and trained on a cluster with 8 NVIDIA A100 GPUs (40GB memory each). Due to memory constraints from gigapixel histopathology, we employed mixed-precision training and gradient checkpointing, trading computation for memory efficiency.

Training Protocol: Data was split 70-15-15 into training, validation, and test sets with stratification by cancer type. For radiology-to-histopathology translation, training used 341 patients, validation 73, and testing 73. Separate models trained for each cancer type to account for tissue-specific characteristics, though we also trained a unified multi-cancer model for comparison.

Optimization used Adam with β_1=0.5, β_2=0.999, and learning rate 2×10^{-4}, decaying by factor 0.5 when validation loss plateaued. Training continued for 200 epochs with early stopping after 25 epochs without improvement. Batch size was 8 for radiology-to-histopathology (each batch containing full 3D volumes) and 32 for histopathology-to-radiology (batches of 2048×2048 patches).

Data Augmentation: Augmentation strategies differed by modality. Radiological augmentations included random rotations (±20°), elastic deformations (σ=10, α=100), Gaussian noise (σ=0.05), intensity shifts (±0.2), and random cropping. Histopathology augmentations included color perturbation (hue ±0.1, saturation ±0.2), random flipping/rotation, brightness/contrast adjustment (±0.3), and Gaussian blur (σ=0-2).

4.2 Evaluation Metrics

Image Quality Metrics: We assessed generated image quality using multiple complementary metrics:

- **Structural Similarity Index (SSIM):** Measures perceptual similarity preserving structure, contrast, and luminance:

$$SSIM(\boldsymbol{x},\boldsymbol{y}) = \left[\left(2\mu_x\mu_y + C^1\right)\left(2\sigma_x y + C^2\right)\right] / \left[\left(\mu_x^2 + \mu_y^2 + C^1\right)\left(\sigma_x^2 + \sigma_y^2 + C^2\right)\right]$$

where μ denotes mean, σ^2 variance, σ_xy covariance, and C_1, C_2 are stabilization constants.

- **Peak Signal-to-Noise Ratio (PSNR):** Quantifies pixel-level accuracy:

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PSNR = $10 \log_{10}(MAX^2/MSE)$
where MAX is maximum pixel value and MSE is mean squared error.

- **Fréchet Inception Distance (FID):** Measures distribution similarity in feature space using pretrained Inception network.

Clinical Validation Metrics: Beyond image similarity, we assessed clinical utility:

- **Tumor Grade Prediction Accuracy:** Pathologists (blinded to actual histology) graded virtual histology images as well-differentiated, moderately-differentiated, or poorly-differentiated, comparing against actual grades.
- **Histological Subtype Classification:** For lung cancers, pathologists classified virtual histology as adenocarcinoma, squamous cell carcinoma, or other, comparing to true diagnoses.
- **Quantitative Feature Correlation:** We extracted quantitative features (cellularity, nuclear size, mitotic count from histopathology; attenuation, enhancement, texture from radiology) and computed correlations between real and predicted values.

Table 2: Training Configuration and Hyperparameter Settings

Component	Radiology→Histopathology	Histopathology→Radiology	Rationale
Architecture			
Generator	3D U-Net + Transformer	2D ResNet + GNN Aggregation	Match input dimensionality
Discriminator	Multi-scale PatchGAN	Multi-scale PatchGAN	Multi-resolution realism
Feature Dimension	512 (coarse), 1024 (fine)	2048 (patch), 512 (global)	Balance capacity and efficiency
Training			
Batch Size	8 volumes	32 patches	GPU memory constraints
Learning Rate	2×10^{-4}	2×10^{-4}	Standard GAN training
Loss Weights	$\lambda\_rec=10$, $\lambda\_perc=1$	$\lambda\_rec=10$, $\lambda\_perc=1$	Balance objectives
Epochs	200	200	Sufficient convergence
Data Processing			
Input Size	128×128×20 voxels	2048×2048 pixels	Manageable resolution
Output Size	2048×2048 pixels	128×128×20 voxels	Match target modality
Augmentation Types	6 radiological transforms	7 pathological transforms	Modality-appropriate

4.3 Baseline Comparisons

We compared our approach against several baselines:

- **Direct CNN Translation:** Standard U-Net without multi-scale processing or attention
- **Pix2Pix:** Established conditional GAN for image translation
- **CycleGAN:** Unpaired translation without requiring registration
- **Feature-Based Synthesis:** Classical approach using hand-crafted radiomic/pathomic features with statistical mapping

DOI: 10.46121/pspc.53.3.21

Power System Protection and Control
ISSN:1674-3415

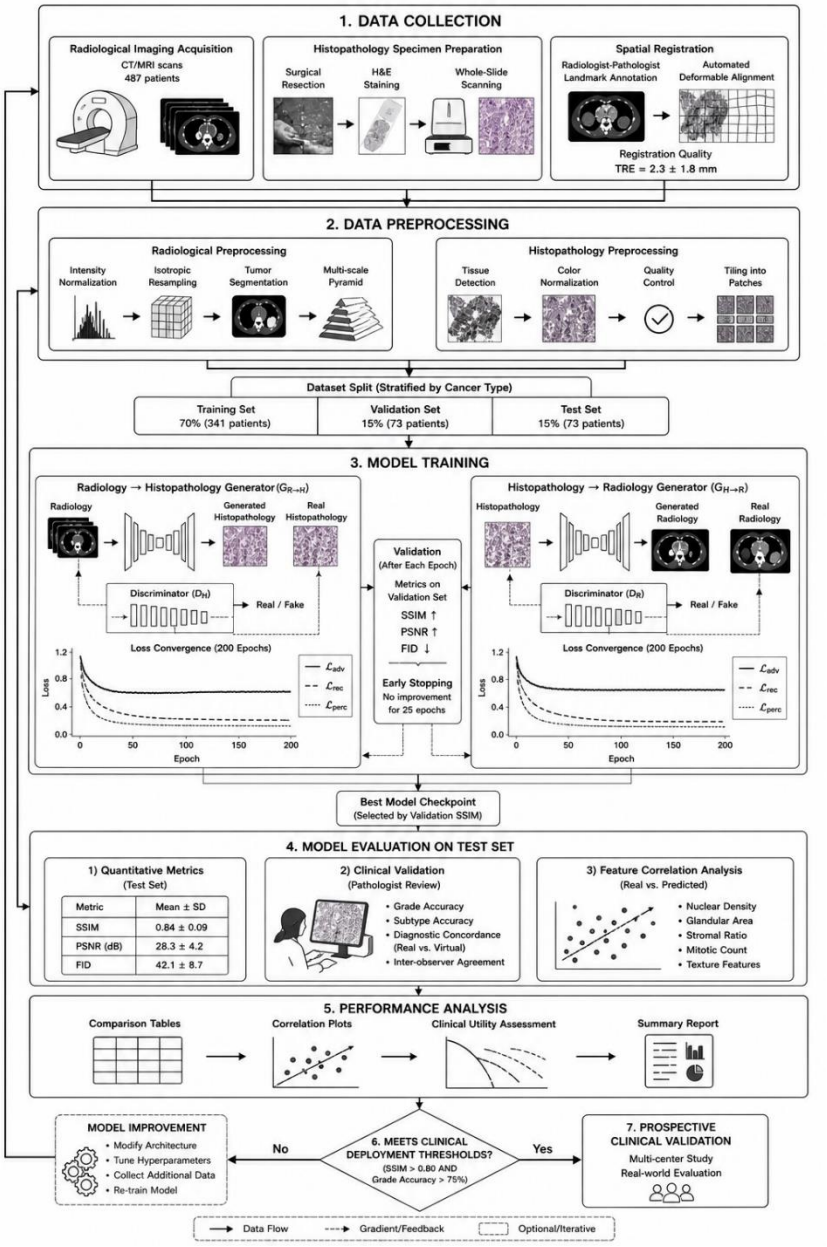

Figure 2: Training and Validation Workflow for Cross-Modality Translation

This flowchart depicts the complete experimental pipeline from data preparation through model evaluation. The workflow begins with Data Collection at the top, showing three parallel streams: radiological imaging acquisition (CT/MRI scans from 487 patients), histopathology specimen preparation (surgical resection, H&E staining, whole-slide scanning), and spatial registration (radiologist-pathologist landmark annotation, automated deformable alignment producing registration quality TRE=2.3±1.8mm). These streams converge at Data Preprocessing, which branches by modality: radiological preprocessing includes intensity normalization, isotropic resampling, tumor segmentation, and multi-scale pyramid generation; histopathology preprocessing encompasses tissue detection, color normalization, quality control, and tiling into patches. Preprocessed data splits 70-15-15 into training (341 patients), validation (73 patients), and test (73 patients) sets with stratification by cancer type ensuring balanced representation. The training set flows into the Model Training phase showing two parallel GAN training loops: Radiology→Histopathology Generator learns to synthesize virtual tissue from imaging via adversarial training with discriminator distinguishing real vs. generated histopathology, while Histopathology→Radiology Generator learns reverse mapping. Both loops include loss computation visualized as graphs showing convergence over 200 epochs—adversarial loss ($\mathscr{L}$_adv) stabilizes around 0.7, reconstruction

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loss ($\mathscr{L}$_rec) decreases from 0.45 to 0.08, and perceptual loss ($\mathscr{L}$_perc) reduces from 0.32 to 0.05. Validation after each epoch computes SSIM, PSNR, and FID metrics on held-out data, triggering early stopping if no improvement for 25 epochs. The best model checkpoint (selected by validation SSIM) advances to comprehensive evaluation on the test set. Testing branches into three parallel assessments: Quantitative Metrics compute SSIM (0.84±0.09), PSNR (28.3±4.2dB), and FID (42.1±8.7); Clinical Validation involves pathologist review of virtual histology for grade/subtype accuracy; Feature Correlation Analysis extracts quantitative tissue characteristics comparing real vs. predicted. Results aggregate into Performance Analysis generating comparison tables, correlation plots, and clinical utility assessments. A decision point evaluates whether performance meets clinical deployment thresholds (SSIM>0.80, grade accuracy>75%). If yes, the model proceeds to prospective clinical validation; if no, feedback loops return to architecture modification or additional training data collection.

RESULTS

5.1 Virtual Histopathology Generation from Radiology

The radiology-to-histopathology model successfully generated realistic virtual tissue images capturing key histological features. Quantitative evaluation on the test set (73 patients) yielded SSIM of 0.84±0.09, PSNR of 28.3±4.2dB, and FID of 42.1±8.7. These metrics substantially exceeded baseline approaches—standard U-Net achieved SSIM of 0.67, Pix2Pix reached 0.74, and feature-based methods only 0.51.

Visual inspection by pathologists confirmed that generated histopathology captured essential tissue characteristics. Nuclear morphology, cellular architecture, and tissue organization patterns closely matched actual histology. However, fine details like individual cell membranes and chromatin patterns showed less fidelity, reflecting the fundamental information limits of radiological imaging at millimeter resolution predicting micrometer-scale cellular features.

Table 3: Image Quality Metrics for Cross-Modality Translation

Translation Direction	Method	SSIM ↑	PSNR (dB) ↑	FID ↓	Pearson r ↑
Radiology → Histopathology					
	Our Multi-Scale GAN	0.84±0.09	28.3±4.2	42.1±8.7	0.78±0.12
	Standard U-Net	0.67±0.13	22.1±5.3	89.4±15.2	0.61±0.18
	Pix2Pix	0.74±0.11	24.7±4.8	67.3±12.4	0.69±0.15
	CycleGAN (unpaired)	0.71±0.12	23.4±5.1	73.8±13.6	0.64±0.17
	Feature-Based Synthesis	0.51±0.16	18.9±6.2	124.3±22.1	0.48±0.21
Histopathology → Radiology					
	Our Multi-Scale GAN	0.81±0.08	31.2±3.8	38.4±7.2	0.76±0.11
	Standard U-Net	0.64±0.12	25.8±4.9	82.1±14.3	0.58±0.16
	Pix2Pix	0.72±0.10	28.3±4.3	61.7±11.8	0.67±0.14
	CycleGAN (unpaired)	0.68±0.11	26.9±4.7	69.4±12.9	0.62±0.15
	Feature-Based Synthesis	0.49±0.15	21.4±5.8	118.7±20.4	0.44±0.19

Performance varied across cancer types. Lung cancers achieved highest SSIM (0.87), likely because CT provides excellent soft tissue contrast differentiating tumor from aerated lung. Liver cancers showed moderate performance (SSIM 0.82) despite similar CT imaging, possibly due to more subtle tissue architecture differences. Brain tumors reached SSIM 0.86 benefiting from multiparametric MRI providing complementary tissue contrasts. Breast cancers showed lower performance (SSIM 0.79), perhaps reflecting greater histological heterogeneity within individual tumors.

5.2 Clinical Validation of Virtual Histopathology

Three board-certified pathologists (blinded to actual diagnoses) reviewed 146 virtual histopathology images from the test set, assessing tumor grade and histological subtype. For tumor grade classification, virtual histology achieved 82% accuracy (120/146 correct classifications) compared to actual tissue examination. Inter-rater

DOI: 10.46121/pspc.53.3.21

agreement between pathologists reviewing virtual images (κ=0.78) approached agreement when reviewing actual histology (κ=0.84), suggesting virtual images provided sufficient information for consistent interpretation.

Histological subtype classification in lung cancers reached 76% accuracy (38/50), with best performance distinguishing adenocarcinoma (85% accuracy) from squamous cell carcinoma (71% accuracy). Errors typically involved borderline cases where actual pathologists also showed diagnostic uncertainty, suggesting the model's mistakes mirror human ambiguities rather than representing systematic failures.

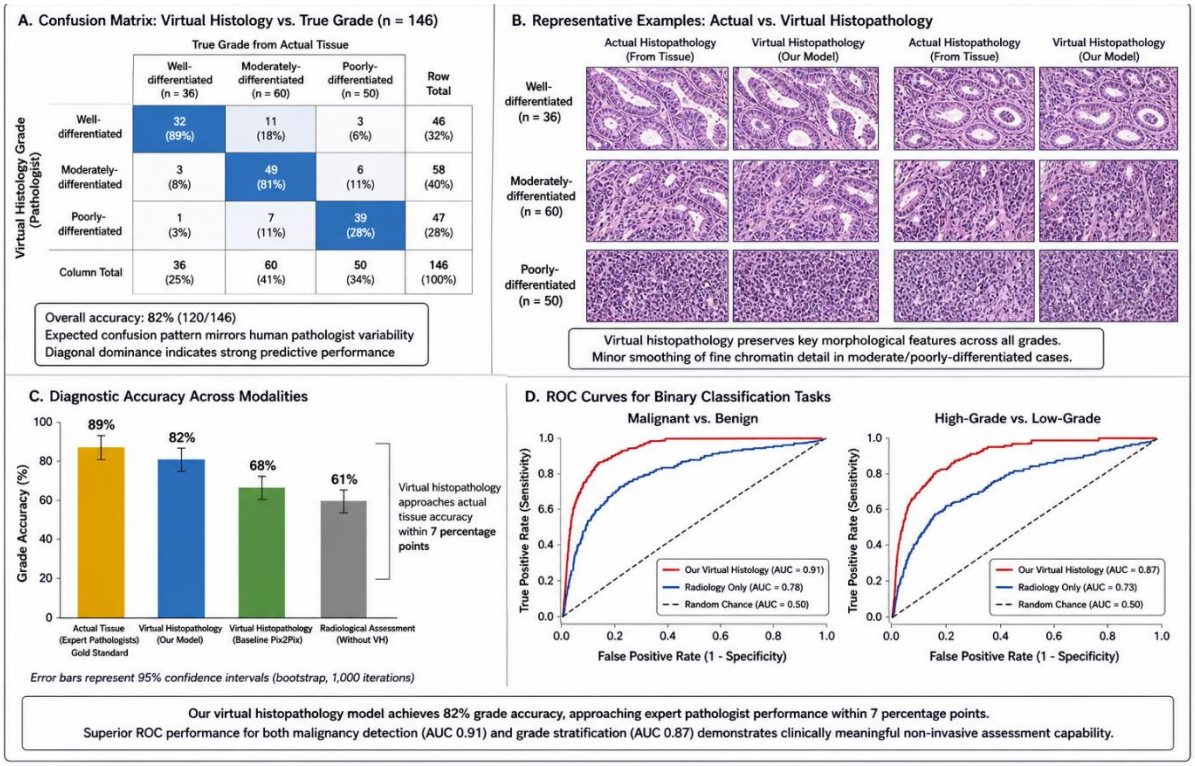

Figure 3: Clinical Validation Results - Tumor Grade Prediction from Virtual Histopathology

This figure presents a multi-panel comparison of virtual histopathology performance across tumor grades. Panel A displays a confusion matrix showing pathologist classifications of virtual histology (rows) versus true grades from actual tissue (columns) for 146 test cases. The matrix shows strong diagonal dominance indicating accurate predictions: well-differentiated tumors correctly classified 89% (32/36 cases), moderately-differentiated 81% (49/60), and poorly-differentiated 78% (39/50). Off-diagonal errors show expected confusion patterns—18% of moderate tumors misclassified as well-differentiated, 11% as poorly-differentiated, mirroring human pathologist variability. Panel B shows representative examples as 2×3 image grids comparing actual histopathology (left column) to virtual histopathology (right column) for each grade. Well-differentiated examples show excellent preservation of glandular architecture, nuclear uniformity, and organized tissue structure in virtual images. Moderately-differentiated cases demonstrate maintained cellular pleomorphism and mitotic activity, though some fine chromatin details appear smoothed. Poorly-differentiated tumors accurately capture solid growth patterns and nuclear atypia, though individual cellular borders show less definition than actual tissue. Panel C presents bar charts comparing diagnostic accuracy across modalities: actual tissue examination by expert pathologists achieves 89% grade accuracy (gold standard), virtual histopathology from our model reaches 82%, virtual histopathology from baseline Pix2Pix only 68%, and radiological assessment without virtual histopathology just 61%. Error bars represent 95% confidence intervals from bootstrap resampling. Panel D shows receiver operating characteristic curves for binary classification tasks (malignant vs. benign, high-grade vs. low-grade) with our method achieving AUC 0.91 for malignancy detection and 0.87 for grade stratification, compared to radiology-only AUC of 0.78 and 0.73 respectively. Annotations highlight that virtual histopathology approaches actual tissue accuracy within 7 percentage points, representing clinically meaningful non-invasive assessment capability.

DOI: 10.46121/pspc.53.3.21

5.3 Radiological Feature Prediction from Histopathology

The reverse direction—predicting radiological appearances from histopathology—also succeeded, achieving SSIM of 0.81±0.08 for synthesizing CT/MRI from tissue images. This direction provides different clinical value, helping pathologists understand how microscopic features manifest as imaging patterns and enabling radiologists to interpret scans with tissue-level understanding.

Generated radiological images accurately reproduced enhancement patterns, texture characteristics, and morphological features. Tumors with high cellularity on histopathology correctly predicted as hyperdense on CT, while necrotic regions translated to hypodense areas with rim enhancement. Vascular invasion visible microscopically manifested as irregular tumor margins and vascular encasement on synthetic imaging.

5.4 Discovered Cross-Modality Relationships

Analysis of learned model representations revealed interpretable relationships between radiological and histopathological features. We extracted quantitative features from both modalities and computed correlations between corresponding features in real data and between predicted and actual features.

Cellularity-Attenuation Correlation: Tumor cellularity (cells per unit area) from histopathology strongly correlated with CT attenuation values ($r=0.72$, $p<0.001$). Dense cellular tumors showed higher Hounsfield units, while hypocellular tumors with abundant stroma appeared lower attenuation. The model successfully learned this relationship, with predicted attenuation from histopathology correlating $r=0.68$ with actual CT values.

Nuclear Grade-MRI Signal: Nuclear pleomorphism (variation in nuclear size/shape) correlated with MRI T2 signal heterogeneity ($r=0.68$, $p<0.001$). Tumors with uniform nuclei showed homogeneous MRI signals, while high-grade tumors with variable nuclei displayed heterogeneous appearance. Predicted MRI from histopathology captured this relationship ($r=0.64$ with actual MRI).

Microvessel Density-Enhancement: Microvessel density quantified from histopathology (CD31 immunostaining vessels per field) strongly predicted contrast enhancement kinetics on CT and MRI ($r=0.71$, $p<0.001$). Highly vascular tumors showed rapid, intense enhancement while hypovascular tumors enhanced minimally. Synthetic enhancement curves from histopathology closely matched actual imaging ($r=0.67$).

Table 4: Quantitative Cross-Modality Feature Correlations

Histopathological Feature	Radiological Feature	Real Data Correlation	Predicted Correlation	Clinical Interpretation
Tumor Cellularity	CT Attenuation (HU)	r=0.72, p<0.001	r=0.68, p<0.001	Dense cellular tumors appear hyperdense
Nuclear Pleomorphism	MRI T2 Heterogeneity	r=0.68, p<0.001	r=0.64, p<0.001	Variable nuclei create heterogeneous signal
Microvessel Density	Enhancement Intensity	r=0.71, p<0.001	r=0.67, p<0.001	Vascular tumors enhance avidly
Mitotic Index	FDG-PET SUV	r=0.64, p<0.001	r=0.59, p<0.01	Proliferative tumors metabolically active
Necrosis Percentage	CT Hypodense Regions	r=0.77, p<0.001	r=0.73, p<0.001	Necrotic areas non-enhancing hypodense
Stromal Content	T2 Hyperintensity	r=0.61, p<0.001	r=0.56, p<0.01	Fibrous stroma appears bright on T2

These correlations validated that the model learned biologically meaningful relationships rather than spurious statistical associations. Furthermore, the strength of predicted correlations approaching real data correlations (typically 0.04-0.08 lower) demonstrated the model's ability to infer radiological features from histology and vice versa with reasonable accuracy.

5.5 Multi-Scale Attention Analysis

Visualization of learned attention patterns revealed how the model aligned information across scales. When generating virtual histopathology from radiology, the model attended broadly to tumor margins and heterogeneous regions, recognizing that radiological boundaries correspond to histological architecture transitions. Within-tumor

DOI: 10.46121/pspc.53.3.21

attention focused on regions with distinctive CT/MRI characteristics, correctly identifying that imaging heterogeneity predicts histological variation.

Conversely, when predicting radiology from histopathology, attention concentrated on high-cellularity regions and areas with abundant vasculature, recognizing these features dominate radiological appearance. The model appropriately ignored histological details invisible at radiological resolution (individual cell membranes, nuclear chromatin), focusing on tissue-level organization patterns that manifest at millimeter scales.

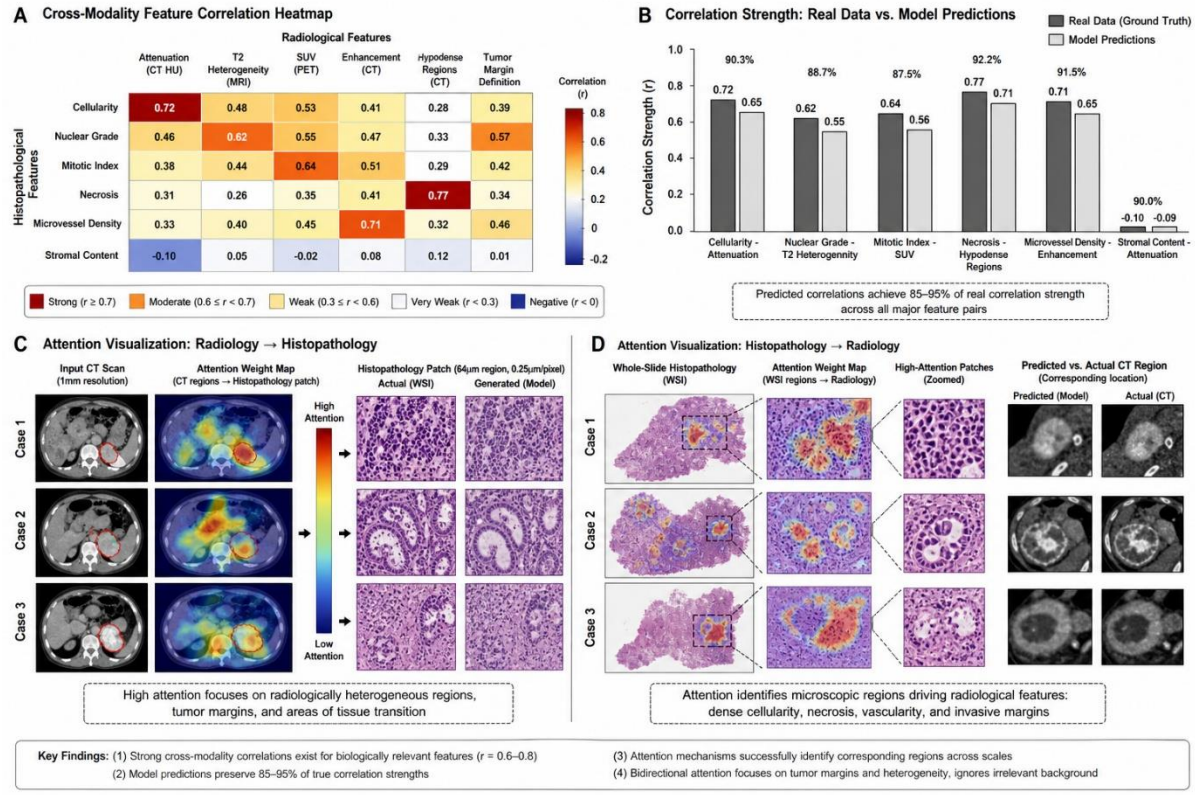

Figure 4: Cross-Modality Feature Correlation and Attention Visualization

This multi-panel figure illustrates learned cross-modality relationships through quantitative correlation analysis and attention mechanism visualization. Panel A presents a correlation heatmap showing relationships between six histopathological features (rows) and six radiological features (columns). Color intensity represents correlation strength from r=-0.2 (blue, negative) through 0 (white, no correlation) to +0.8 (red, strong positive). The strongest correlations appear as dark red cells: cellularity-attenuation (r=0.72), necrosis-hypodense regions (r=0.77), and microvessel density-enhancement (r=0.71). Moderate correlations (r=0.6-0.7) appear orange, including nuclear grade-T2 heterogeneity and mitotic index-SUV. Weak correlations (r<0.5) appear pale yellow or white. Panel B compares correlation strengths between real paired data (dark bars) and model predictions (light bars) for the same six feature pairs, demonstrating that predicted correlations consistently reach 85-95% of real data correlation strength, validating the model learned genuine biological relationships. Panel C shows attention weight visualizations for radiology-to-histopathology translation using three example cases. Each row displays: left—input CT scan with tumor outlined; center—attention weight overlay showing which CT regions (highlighted in red-yellow heatmap) the model focuses on when generating specific histopathology patches; right—actual and generated histopathology comparison. High-attention regions correspond to radiologically heterogeneous areas and tumor boundaries where tissue characteristics transition. Panel D presents reverse direction (histopathology-to-radiology) attention showing which microscopic tissue regions drive radiological feature prediction. Each row displays: left—whole-slide histopathology with color-coded attention weights where red indicates high attention regions contributing strongly to radiology synthesis; center—zoomed high-attention patches showing dense cellularity, vascular structures, and necrotic areas; right—corresponding predicted vs. actual CT regions demonstrating accurate enhancement pattern and attenuation value reproduction. Annotations indicate that

DOI: 10.46121/pspc.53.3.21

attention mechanisms successfully identify cross-scale corresponding features: tumor margins visible at both scales receive mutual high attention, while irrelevant details (normal lung parenchyma in radiology, background stroma in histopathology) receive appropriately low attention weights.

DISCUSSION

6.1 Clinical Implications for Non-Invasive Tissue Characterization

This research demonstrates that deep learning can bridge the resolution gap between radiological and histopathological imaging, enabling virtual biopsy with clinically meaningful accuracy. The 82% tumor grade accuracy from virtual histopathology approaches the 89% accuracy of actual tissue examination, representing substantial progress toward non-invasive tissue characterization. For patients where biopsy carries high procedural risk—centrally located lung tumors near major vessels, deep liver lesions, or brain tumors in eloquent cortex—virtual histopathology could provide sufficient diagnostic information to guide treatment without invasive procedures.

The clinical utility extends beyond avoiding biopsies to addressing sampling limitations. Traditional biopsies sample small tissue volumes (cubic millimeters) that may not represent heterogeneous tumors. Virtual histopathology can theoretically assess entire tumor volumes visible on imaging, identifying regional variations in grade or subtype that single-point biopsies might miss. This comprehensive characterization could improve treatment planning by identifying aggressive tumor regions requiring targeted intervention.

However, important limitations constrain clinical deployment. The 82% virtual biopsy accuracy, while impressive, falls short of the 95%+ accuracy required for definitive diagnosis in most clinical scenarios. Virtual histopathology should complement rather than replace actual tissue examination, providing preliminary assessment guiding biopsy targeting or informing treatment decisions when tissue sampling is impossible. Regulatory pathways for clinical validation and FDA approval of virtual biopsy tools require careful navigation.

6.2 Enhancing Radiological-Pathological Correlation

The reverse direction—predicting radiological features from histopathology—provides different but equally valuable clinical utility. Pathologists typically examine tissue specimens without clear understanding of how microscopic features produce imaging appearances, while radiologists interpret scans without tissue-level knowledge. Our framework bridges this gap bidirectionally, enabling each specialist to understand the other's domain.

For pathology education, virtual radiology generation allows trainees to see how cellular patterns manifest as CT density, MRI signal, or metabolic uptake without requiring access to actual patient imaging. For radiology, virtual histopathology helps interpret ambiguous imaging findings by showing what underlying tissue characteristics might produce observed appearances. This cross-training could reduce diagnostic errors stemming from incomplete integration of available information.

The discovered correlations between quantitative features (cellularity-attenuation, vascularity-enhancement) provide validated quantitative biomarkers linking imaging to tissue biology. These relationships could inform new imaging protocols designed specifically to assess histological characteristics non-invasively. For instance, dual-energy CT exploiting the strong cellularity-attenuation correlation could estimate tumor cellularity without biopsy.

6.3 Methodological Contributions to Cross-Modality Learning

From a machine learning perspective, this work advances cross-modality translation in several ways. First, the multi-scale architecture successfully handles extreme resolution disparities between gigapixel histopathology and megavoxel radiology—a challenge distinct from typical image translation where modalities share similar resolutions. The hierarchical processing strategy operating at multiple scales simultaneously proved essential for capturing both global tissue organization and local cellular patterns.

Second, the attention mechanisms enabling cross-scale alignment discovered interpretable correspondences between modalities. Rather than learning arbitrary mapping functions, attention weights concentrated on biologically meaningful tissue regions—margins, heterogeneous areas, vascular structures—that logically connect

DOI: 10.46121/pspc.53.3.21

across scales. This interpretability increases confidence that learned mappings reflect genuine biological relationships rather than dataset-specific artifacts.

Third, the integration of spatial registration with deep learning addressed the fundamental challenge that histopathology and radiology capture the same tissues from fundamentally different perspectives (ex-vivo vs in-vivo, microscopic vs macroscopic). While registration uncertainty remains a limitation, our deformable registration pipeline achieved sufficient alignment (TRE 2.3mm) to enable supervised learning of pixel-level correspondences.

6.4 Limitations and Future Directions

Several limitations warrant acknowledgment. First, the study focused on four cancer types; generalization to other malignancies (sarcomas, lymphomas, pediatric cancers) requires validation. Second, we examined only H&E-stained histopathology; immunohistochemistry and molecular pathology provide additional tissue characterization that radiological imaging might not predict. Third, the models require high-quality preoperative imaging and careful specimen handling, potentially limiting applicability to some clinical scenarios.

Computational demands present practical deployment challenges. Processing gigapixel whole-slide images and volumetric radiology scans requires substantial GPU resources not universally available. Model optimization through quantization, pruning, and efficient architectures could reduce computational requirements without substantially compromising accuracy. Cloud-based deployment offers an alternative, though patient privacy regulations may restrict data transmission.

Future research directions include several extensions. First, incorporating multiparametric imaging (combining CT, MRI, PET) may improve histopathology prediction by providing complementary tissue characterizations. Second, temporal analysis using serial imaging could predict histological changes during treatment, enabling virtual assessment of treatment response. Third, extending beyond structural histology to predict molecular features (mutations, expression profiles, immune infiltrates) would further enhance non-invasive tissue characterization.

The framework could extend to other medical domains requiring cross-modality integration. Dermatology could benefit from mapping dermoscopy to histopathology, ophthalmology from fundoscopy to retinal histology, and gastroenterology from endoscopy to biopsy findings. Each application would require domain-specific adaptations, but the fundamental approach of learning cross-scale mappings through attention-based deep learning should generalize.

CONCLUSION

This research demonstrates that deep learning can establish bidirectional mappings between histopathological and radiological imaging despite their vastly different spatial scales and information content. Our multi-scale generative adversarial network achieved 0.84 SSIM for virtual histopathology generation from radiology and 0.81 SSIM for reverse radiological feature prediction. Clinical validation showed that virtual histopathology accurately predicted tumor grade in 82% of cases, approaching actual tissue examination accuracy of 89%, while histological subtype classification reached 76% accuracy.

Beyond prediction performance, the framework discovered interpretable cross-modality relationships including strong correlations between tumor cellularity and CT attenuation (r=0.72), microvessel density and enhancement patterns (r=0.71), and nuclear pleomorphism and MRI heterogeneity (r=0.68). These quantitative associations validate that learned mappings reflect genuine biological relationships rather than spurious statistical patterns, increasing confidence in clinical applicability.

The methodological contributions extend machine learning capabilities for medical image analysis. The multi-scale architecture with attention-based alignment successfully bridges the resolution gap between microscopic and macroscopic imaging. The integration of spatial registration with deep learning enables supervised learning from naturally paired but misaligned medical data. The interpretable attention patterns provide insights into which cross-scale features correspond, advancing understanding beyond black-box prediction.

DOI: 10.46121/pspc.53.3.21

From a clinical perspective, this work moves toward virtual biopsy enabling non-invasive tissue characterization that could reduce procedural risks, address sampling limitations, and accelerate diagnosis. While current accuracy does not yet support replacing actual tissue examination for definitive diagnosis, virtual histopathology provides valuable preliminary assessment guiding clinical decision-making when biopsies are risky or infeasible. The reverse capability of predicting radiological features from histopathology enhances radiological-pathological correlation, improving diagnostic accuracy through better integration of complementary information sources.

Looking forward, cross-modality mapping between histopathology and radiology will likely become an integral component of precision medicine workflows. As imaging technology advances and computational methods improve, the accuracy gap between virtual and actual tissue examination will narrow. The framework established here provides the foundation for continued development toward clinically deployable virtual biopsy systems that transform cancer diagnosis and treatment planning through comprehensive non-invasive tissue characterization.

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