**Comparative Analysis of Integrated Multimodal CT/PET Imaging with CT and PET alone, with Deep Learning Techniques for Lung Cancer Sub-types** **Classification**

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**Abstract.** This study evaluates three convolutional neural network (CNN) architectures, VGG19, DenseNet121, and ResNet-50, to compare the performance of integrated CT/PET imaging with that of unimodal CT and PET modalities for lung cancer subtype classification. Three imaging strategies — integrated CT/PET, CT, and PET scans for lung cancer subtype classification. Three strategies (fused CT/PET, CT-only, and PET-only) were assessed using accuracy, precision, recall, and F1-score to determine their clinical utility in distinguishing between adenocarcinoma, squamous cell carcinoma, and small cell carcinoma. We analyzed a retrospective cohort of 355 patients (73.9% adenocarcinoma, 20.4% squamous cell carcinoma, and 5.7% Small cell carcinoma), of which 133 patients with paired CT/PET imaging were included in the analysis. Models were trained on 80% of the data (divided into 70% training and 30% validation sets) and tested on the remaining 20%, using identical parameters. The results demonstrate that integrated CT/PET consistently outperformed unimodal approaches. DenseNet121 achieved the highest performance with CT/PET (99.0%) accuracy, 99.0% precision, 98.0% recall, 99.0% F1-score) surpassing CT-only (78.) % accuracy, 81.0% precision, 75.0% recall, 78.0% F1-score) and PET-only (73.0% accuracy, 72.0% precision, 68.0% recall, 70.0% F1-score). The fusion strategy provided superior differentiation of adenocarcinoma, highlighting the complementary value of combining anatomical (CT) and metabolic (PET) data. While all architectures benefited from multimodal integration, DenseNet121's dense connectivity pattern particularly enhanced feature reuse and improved model robustness. The Class imbalance (73.9%) adenocarcinoma) was mitigated via augmentation for the rare subtypes. Multimodal deep learning, combined with fused CT/PET imaging, significantly enhances diagnostic accuracy for lung cancer classification, particularly for adenocarcinoma, compared to single-modality approaches. The integration of metabolic and structural data findings underscores the clinical potential of AI-driven multimodal frameworks; however, validation on larger, more diverse cohorts is needed to address dataset limitations. This approach could streamline oncology workflow, enabling earlier intervention and personalized treatment strategies.

# Introduction

Lung cancer remains a leading cause of cancer mortality worldwide, with about 2.5 million new cases and 1.80 million deaths annually. These figures represent 12.4% of all cancer diagnoses and 18.7% of cancer fatalities [1]. Despite modest declines in incidence rates, a persistently low 5-year survival rate, often attributed to late-stage diagnosis, highlights the urgent need for more precise diagnostic tools and targeted therapies.

As a heterogeneous disease, lung cancer is characterized by distinct pathological subtypes, which include small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), each with unique molecular profiles and metastatic behaviors. NSCLC accounts for 85% of cases [2]. NSCLC subtypes include adenocarcinoma (ADC), squamous cell carcinoma (SCC), and large cell carcinoma (LCC), all of which differ in molecular profile and treatment response [3]. Accurate classification often relies on immunohistochemical markers (e.g., p63 for SCC; TTF-1/Napsin A for ADC), to guide therapy selection [4].

Medical imaging, particularly CT and PET scans, is central to the detection, staging, and treatment planning of diseases. Integrated CT/PET combines CT’s high-resolution anatomy with PET metabolic mapping via fluorodeoxyglucose (18F-FDG) uptake, improving lesion characterization and optimizing biopsy targeting [5]. While CT reveals tumors size and invasion, PET identifies hypermetabolic foci [6]. However, CT can misclassify benign lesions as malignant; PET suffers from lower spatial resolution, inter-patient variability, and false positives (e.g., inflammatory uptake), which further challenge interpretation [7].

Deep learning (DL) and vision transformers have revolutionized computer vision, advancing medical image analysis, but they demand large, well-annotated datasets —a constraint compounded by data scarcity, privacy concerns, and annotation complexity [8, 9]. Despite these limitations, the AI-driven fusion of CT and PET innovations has markedly improved precise tumor localization, metabolic quantification, and automated classification of NSCLC subtypes, enhancing diagnostic accuracy and workflow efficiency [10].

Optimizing CT/PET-based workflows is therefore critical to improving patient outcomes. Integrating advanced AI techniques with multimodal imaging reduces diagnostic uncertainty, streamlines clinical pathways, and enables earlier intervention.

Given the facts, in this work, we present the following contributions: -

* **A DL framework for subtype classification**: The study leverages the strengths of three pre-trained CNNs (VGG, DenseNet, and ResNet) to classify ADC, SCC (NSCLC subtype), and distinguish them from SCLC.
* **A multimodal fusion method**: A fine-tuned ResNet-50 architecture, with an attention mechanism, aligns CT’s anatomical and PET’s metabolic features for robust fusion.
* **Comprehensive evaluation**: Three architectures (VGG19, DenseNet121, and ResNet50) are assessed in Single-modal (CT or PET only) and fine-tuned ResNet50-based fusion settings, demonstrating superior performance of multimodal (CT+PET) approaches.

# Related STUDY

Advanced neural network architectures are critical yet challenging, particularly in multimodal histopathological analysis for lung cancer diagnosis. Convolutional neural networks (CNNs) such as VGGNet [11], ResNet[12], and DenseNet [13] are the foundations for modern deep learning in extracting spatial features from multimodal image data. These architectures demonstrate significant performance gains in complex tasks, like histopathology subtype classification. For example, Chai et al. achieved 86% accuracy on lung cancer CT using VGG-16 [14]. Han et al. reported 84% accuracy for NSCLC subtypes [15]. However, these studies are constrained by small cohorts and high computational costs. In Loorutu et al., work, the effectiveness of DenseNet-121 and InceptionResNetV2 in prostate cancer histopathological classification is demonstrated, and the role of architecture selection in diagnostic accuracy [16].

Recent multimodal and radiomic approaches have further improved performance. Quin et al, 2020, [17] combined a 3D DenseNet with an attention mechanism to reach a 90% AUC, while Shen et al [18] used 3D radiomic features with SVM-RBF to achieve a 91% AUC on NSCLC subtypes. Similarly, Ma et al [19], it has been demonstrated that a DenseNet fusion strategy outperforms single-modal methods in multimodal analysis. Despite these advances, challenges remain, including limited data volume, modality-specific artefacts (e.g., CT motion vs PET’s noise), and model interpretability, which motivate the development of a more robust fusion framework.

# Materials and Methods

This study evaluates the performance of four deep learning models (VGG19, DenseNet121, ResNet50, and DenseNet201) as extended variants in both single-modal (CT-only, PET-only) and multimodal (CT+PET fused via fine-tuned ResNet50 with an attention mechanism) settings. The experimental pipeline includes dataset preparation, Image preprocessing, a multimodal fusion algorithm, data augmentation, and subtype classification. This framework compares single vs. multimodal approaches to optimize lung cancer subtype diagnosis. FIGURE 1 illustrates the framework of the proposed study.

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**FIGURE 1.** Process workflow of the study

**Dataset Description**

We utilized the Lung-PET-CT-Dx dataset from TCIA, which comprises paired CT and PET scans of 355 patients with lung cancer (189 men and 166 women; mean age, 61 years). Each case includes tumor localization verified by five radiologists and clinical metadata (e.g., TNM staging, histopathological grading). Patients are labelled by histopathological subtypes (A: Adenocarcinoma, B: Small Cell Carcinoma, E: Large Cell Carcinoma, and ‘G’ means Squamous Cell Carcinoma; subtype E (Large Cell Carcinoma) was excluded due to the limited sample size). For this study, 133 subjects with complete paired imaging and metadata were selected to enable consistent multimodal fusion of anatomical (CT) and metabolic (PET) biomarkers. FIGURE2 shows sample PET-CT images in the dataset, and FIGURE ***3*** displays a sample of patient clinical information in CSV format.

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A collage of x-ray images of a chest

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**FIGURE 2.** Sample Lung PET-CT-DX dataset **FIGURE 3.** Sample CSV, clinical data of the Lung PET-CT dataset

**Preprocessing**

DICOM files were converted to PNG format for pixel-level processing, with parameters such as resolution and slice thickness extracted for quality control purposes. CT (512x512 mm²/pixel) and PET (200x200 pixels, 4.07 mm²/pixel) scans were resized to 224x224 pixels using bicubic interpolation to balance detail and efficiency. Intensity values for CT images were normalized using the mean (0.485) and standard deviation (0.229) to align with the expectations of the pre-trained model. In contrast, PET images were normalized to the range [0, 1] using min-max scaling to reduce scanner variability and support model convergence. Batches of images are generated for training and fusion. This process ensured consistency across modalities for fusion.

**Image Fusion Methods: Overview and Proposed Framework**

Multimodal image fusion (e.g., CT+PET) combines structural and functional data to overcome the limitations of single-modality imaging [20]. Traditional spatial-domain techniques (e.g., weighted averaging blur edges [21]. While transform-domain methods (such as wavelet or shearlet) preserve features, they also risk introducing artefacts. Hybrid approaches balance performance and complexity [22]. Recent Deep learning (DL)-based methods, such as CNNs, capture spatial dependencies. GANs for photorealistic output [23], and transformers (e.g., AFTER-UNet) enhance feature extractions and fusion performance [24]. Frameworks like the ResNet-ZCA framework and VGG-based fusion address medical specificity but face challenges: small datasets, overfitting, and information loss during feature combination [25],

**Proposed Framework: Fine-Tuned ResNet-50 with Attention Mechanism**

We propose a Fine-Tuned ResNet-50 for the CT/PET Fusion framework, with three key innovations:

1. **Modality Setup: -**

**Backbone Models:** A ResNet-50 model (pretrained on ImageNet) is used, one for CT and one for PT. **Modification**: The first convolutional layer of each model is adjusted to accept single-channel (grayscale) input by averaging the weights of the original RGB channel.

1. **Fine-Tuning**: both models are fine-tuned on their respective datasets (CT and PT) using cross-entropy loss, optimizer, and training loop to run for an epoch with 70 batches per epoch, logging batch-wise and epoch-wise losses.
2. **Feature Extraction**: Features are extracted from layer 3 and layer 4 of the model using forward hooks. Features are normalized using L1 normalization to ensure comparable scales.
3. **Attention Mechanism**: CNN (AttentionModule) generates an attention map (W\_ct and W\_pt) from the normalized features. These maps highlight important regions in the CT and PT images. Attention weights are normalized to sum to 1(W\_ct +W\_pt+le-6) to balance contributions.
4. **Image Fusion**: The fused image is computed as a weighted sum:

***I*** *fused (x, y) =* ***W****CT (x, y).* ***I****CT (x, y) +* ***W****PET (x, y).* ***I****PET (x, y)---------------(1)*

Imagine a reconstruction to match the original image dimension.

1. **Output:** The fused image is saved as a grayscale PNG file. FIGURE 4 illustrates the overall fusion framework.

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**FIGURE 4.** Framework architecture of fine-tuned -ResNet50 with attention mechanism of CT/PET fusion

**Data enhancement**

Contrast-based augmentation of a balanced CT/PET dataset: for small cell carcinoma, we generated 10 variants by incrementing the contrast by 0.4 in 0.05 steps per image; for squamous cell carcinoma, we created 3 variants per image with a 0.4 contrast boost. Adenocarcinoma remains unchanged due to the availability of sufficient samples. This strategy enhanced diversity and robustness without compromising image quality.

**Proposed CNNs Classification Algorithm**

Pretrained convolutional neural networks (CNNs) have demonstrated exceptional performance in medical image classification tasks. However, selecting the most effective architecture requires rigorous comparative evaluation, as model performance can vary significantly depending on the dataset and application. In this study, we evaluated three widely used pre-trained CNN architectures—VGG19, ResNet-50, and DenseNet-121—for the classification of lung cancer subtypes (adenocarcinoma, squamous cell carcinoma, and small cell carcinoma). All models were trained under identical experimental conditions to ensure a fair comparison.

The training configuration for VGG-19 and ResNet-50 is summarized in Table 1. Performance results for VGG-19 and ResNet-50 are presented in Table 2 and Table 3, respectively. Detailed results for DenseNet-121, including per-class metrics and learning dynamics, are provided in Table 4 to 6 and Figure 5 to7.

**Table 1.** Model training parameters for VGG19 and ResNet-50

|  |  |
| --- | --- |
| Input image size | 224x224 |
| Batch size | 32 |
| optimizer | VGG19 Adam, ResNet-50 AdamW |
| Learning rate | Le 0.00001 |
| epoch | 20 |
| dropout | 224 |
| Dense layer | 64-unit |

**Table 2.** Average classification accuracy of ResNet-50 across imaging modalities

**Table 3.** Average classification accuracy of VGG19 across imaging modalities

|  |  |
| --- | --- |
| **Image Types** | **Average accuracy** |
| CT-Only | 0.82 |
| PET-Only | 0.76 |
| Integrated Multimodal CT/PET | 0.96 |

|  |  |
| --- | --- |
| **Image Types** | **Average accuracy** |
| CT-Only | 0.96 |
| PET-Only | 0.90 |
| Integrated  Multimodal CT/PET | 0.98 |

## DenseNet121

The DenseNet 121 model, pretrained on ImageNet with frozen weights, was adapted for classifying lung cancer subtypes (adenocarcinoma, squamous cell carcinoma, and small cell carcinoma). Using CT, PET, and CT/PET scans. The dataset was split into 60% training (including 15% validation) and 40% testing. Input images were resized to 224x224 pixels, preprocessed via Keras ImageDataGenerator, and augmented with a custom classification head (global average pooling, 64-unit ReLU dense layer, 3-unit SoftMax output). Model training was performed using the Adam optimizer (learning rate 1e-4) for up to 20 epochs. Early stopping (with a patience of 2 epochs) and model checkpointing were employed to retain the best optimal weights based on validation accuracy. The classification performance of DensNet121 on CT-only scans is presented in Table 4, with corresponding validation accuracy and loss trends shown in Figure 5. Similar evaluations for PET-only and fused CT/PET modalities are provided in Tables 5 and 6, along with corresponding learning curves in Figure 6 and 7.

**Table 4.** Performance metrics for Densenet121 on CT-Only scans

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|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type** | **Performance Metrics %** | | | |
|  | **Precision** | **Recall** | **F1-score** | **Support** |
| Adenocarcinoma | 0.81 | 0.75 | 0.78 | 1339 |
| Squamous Cell carcinoma | 0.69 | 0.78 | 0.73 | 920 |
| Small Cell carcinoma | 0.77 | 0.75 | 0.76 | 1103 |
|  | | | | |
| Accuracy |  |  | 0.78 | 3362 |
| Macro avg | 0.76 | 0.76 | 0.76 | 3362 |
| Weighted avg | 0.76 | 0.76 | 0.76 | 3362 |

Figure 5 (a) Model validation accuracy plot, (b) Model Loss

**FIGURE 5.** (a) Validation accuracy, and (b) Model loss over epochs

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**Table 5.** Performance metrics for Densenet121 on CT-Only scans

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type** | **Performance Metrics %** | | | |
|  | **Precision** | **Recall** | **F1-score** | **Support** |
| Adenocarcinoma | 0.72 | 0.68 | 0.70 | 1333 |
| Squamous Cell carcinoma | 0.65 | 0.65 | 0.65 | 894 |
| Small Cell carcinoma | 0.57 | 0.62 | 0.60 | 1106 |
|  | | | | |
| Accuracy |  |  | 0.73 | 3333 |
| Macro avg | 0.76 | 0.76 | 0.76 | 3333 |
| Weighted avg | 0.76 | 0.76 | 0.76 | 3333 |

ResNet-50

**FIGURE 6.** (a) Validation accuracy, and (b) Model Loss over epochs

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**TABLE 6.** Performance metrics for Densenet121 on fused

CT/PET scans

**FIGURE 7.** (a) Validation accuracy (b) Model loss over epochs

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type** | **Performance Metrics %** | | | |
|  | **Precision** | **Recall** | **F1-score** | **Support** |
| Adenocarcinoma | 0.99 | 0.98 | 0.98 | 1339 |
| Squamous Cell carcinoma | 0.98 | 0.98 | 0.98 | 920 |
| Small Cell Carcinoma | 0.99 | 1.00 | 0.99 | 1103 |
|  | | | | |
| Accuracy |  |  | 0.99 | 3362 |
|  |  |  |  |  |
| Macro avg | 0.99 | 0.99 | 0.99 | 3362 |
| Weighted avg | 0.99 | 0.99 | 0.99 | 3362 |

**Performance Metrics in the Study**

The study evaluated models using accuracy, precision, recall, and F1-score to assess the classification of lung cancer subtypes. These metrics were calculated per subtype (adenocarcinoma, squamous cell carcinoma, small cell carcinoma) and averaged macro/weighted. To address class imbalance. Integrated CT/PET achieved the highest scores (e.g., 99% accuracy/F1 for DenseNet-121), reflecting the robust fusion of anatomical and metabolic data. Precision emphasized correct subtype identification, while recall prioritized minimizing the number of missed cases. Critical for clinical decision-making. Despite strong results, class imbalance (73.9% adenocarcinoma) and small sample size (133 patients) may skew metrics, necessitating cautious interpretation.

**Discussion**

Integrated CT/PET imaging outperformed unimodal approaches by synergizing anatomical (CT) and Metabolic data, enhancing subtype differentiation. The Fine-Tuned ResNet-50 fusion method improved feature alignment and reduced redundancy, thereby addressing modality-specific limitations. DenseNet-121 achieved 99% accuracy, likely due to its dense connectivity, which enables robust feature reuse. However, the small, imbalanced dataset (133 patients) and low-resolution PET may risk overfitting and limit generalizability. Computational complexity and dependence on paired scans pose significant challenges to real-world scalability.

**Conclusion**

Multimodal deep learning with CT/PET fusion significantly improves the accuracy of lung cancer subtype classification compared to single-modality approaches. The fine-tuned ResNet-50 framework effectively integrates complementary imaging data. Aiding precise adenocarcinoma detection. Despite high performance, dataset imbalance and retrospective design necessitate validation on larger, diverse cohorts. Future work should focus on optimizing lightweight architecture and addressing data scarcity to facilitate clinical adoption. These approaches hold promise for reducing diagnostic uncertainty and enhancing personalized oncology care.

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