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Doctoral thesis

PROCESSING AND CLASSIFICATION OF
MEDICAL
IMAGES FOR THE AUTOMATIC
RECOGNITION OF
PATHOLOGIES

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ABSTRACT

Accurate segmentation of lung tumours in computed tomography (CT) images is a fundamental task for diagnosis, treatment planning, and disease monitoring, yet it remains challenging in routine clinical practice. Manual delineation is time-consuming and affected by inter-observer variability, while many deep learning-based segmentation approaches reported in the literature show limited robustness when applied to heterogeneous real-world clinical data acquired under different imaging conditions.

This thesis proposes and rigorously evaluates a complete processing chain for automatic lung tumour segmentation in CT scans, based on the integration of a dedicated preprocessing stage and established deep learning segmentation models. The contribution of this work lies in the systematic design, motivation, and quantitative assessment of preprocessing and post-inference strategies that enhance segmentation robustness, generalization, and interpretability within deep learning-based tumour segmentation frameworks.

The proposed methodology includes a tumour-centric preprocessing pipeline designed to address key limitations of state-of-the-art approaches, such as intensity variability, low contrast at tumour boundaries, voxel misalignment, and class imbalance. The impact of these preprocessing choices on the segmentation performance of deep learning models is explicitly analyzed and compared under different configurations. In addition, an explainability-driven post-inference analysis framework based on Gradient-weighted Class Activation Mapping (Grad-CAM) is introduced to support model interpretation and reduce false-positive detections without modifying or retraining the segmentation networks.

The processing chain is validated using two independent lung CT datasets. A large real-world clinical dataset comprising more than 5,000 scans is used to train and evaluate the models under controlled preprocessing conditions, while a second dataset is employed to assess cross-dataset generalization. Multiple convolutional neural network architectures, including U-Net, a fully convolutional network, and a lightweight custom model, are evaluated using standard quantitative metrics and qualitative analysis, enabling a structured comparison with respect to robustness and computational efficiency.

The experimental results demonstrate that the proposed preprocessing and post-inference design choices play a critical role in determining segmentation accuracy and stability across heterogeneous datasets. Overall, this thesis provides a well-motivated and systematically evaluated deep learning-based segmentation framework,

highlighting the importance of preprocessing design and explainability in achieving reliable performance in real clinical environments.

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LIST OF ABBREVIATIONS

ABBREVIATION	FULL FORM
2D	Two-Dimensional
3D	Three-Dimensional
CRT	Chemoradiotherapy
MRI	Magnetic Resonance Imaging
DCE-MRI	Dynamic Contrast-Enhanced Magnetic Resonance Imaging
DWI	Diffusion-Weighted Imaging
CT	Computed Tomography
PET-CT	Positron Emission Tomography – Computed Tomography
CNN	Convolutional Neural Network
FCNN	Fully Connected Convolutional Neural Network
MSDENSENET	Multiscale Densely Connected Neural Network
ANN	Artificial Neural Network
SVM	Support Vector Machine
KNN	K-Nearest Neighbour
LR	Logistic Regression
DSC	Dice Similarity Coefficient
MIU	Mean Intersection over Union
ASD	Average Symmetric Surface Distance
RR	Recall Rate
TRG	Tumor Regression Grade
EPIC	European Prospective Investigation into Cancer and Nutrition
GRAD-CAM	Gradient-weighted Class Activation Mapping
GAEIF	Grad-CAM–Assisted Error Interpretation Framework

CHAPTER I :

INTRODUCTION

1.INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality worldwide, largely due to its asymptomatic progression in early stages and the difficulty of achieving timely and accurate diagnosis. Computed tomography (CT) imaging plays a fundamental role in modern clinical workflows for lung cancer screening and diagnosis, enabling the visualization of pulmonary nodules and tumour structures. However, accurate segmentation of lung tumours from CT volumes remains a challenging task, particularly in real-world clinical settings.

Manual tumour segmentation, although still widely adopted in clinical practice, is inherently time-consuming, subjective, and prone to inter- and intra-observer variability. These limitations are exacerbated by the growing volume of imaging data and the increasing demand for rapid and reliable diagnostic support. Consequently, automated and semi-automated segmentation methods have attracted significant research interest in recent years.

Despite notable progress, automated lung tumour segmentation remains difficult due to several factors, including large variability in tumour size, shape, texture, and location, as well as imaging artefacts introduced by low-dose CT protocols. Additional challenges arise from anatomical complexity, such as tumours adjacent to vessels, pleural surfaces, or the diaphragm, and from subtle lesion appearances including small nodules and ground-glass opacities. Furthermore, heterogeneity in CT acquisition protocols across scanners and institutions leads to inconsistencies in intensity distributions and spatial resolution, which negatively impact the robustness and generalization of deep learning-based segmentation methods.

In this context, data preprocessing plays a crucial role in mitigating inter-scanner variability, enhancing contrast, and ensuring spatial consistency between images and annotations. In this thesis, two distinct CT datasets are employed to evaluate the segmentation performance of existing deep learning architectures under different preprocessing strategies. The primary dataset consists of more than 5,000 clinically acquired CT volumes collected at Sant'Andrea University Hospital (Rome), characterized by substantial heterogeneity in acquisition conditions. A dedicated preprocessing pipeline is applied to standardize intensity distributions, enhance local contrast, and ensure accurate alignment between CT volumes and tumour masks. A secondary publicly available dataset, which is already pre-processed, is used to assess model generalization and reproducibility across datasets.

The segmentation task is addressed using established deep learning models, including U-Net, Fully Convolutional Networks (FCN), and a lightweight

Convolutional Neural Network (CNN). These architectures are selected due to their proven effectiveness in medical image segmentation and their complementary trade-offs between accuracy, complexity, and computational cost. Importantly, this work does not propose new convolutional neural network architectures. Instead, it focuses on the systematic design, motivation, and evaluation of a robust segmentation pipeline built around existing models.

The overarching objective of this thesis is to develop a reproducible, accurate, and interpretable lung tumour segmentation framework suitable for real-world clinical data. By combining standardized preprocessing, carefully designed training strategies, and post-inference explainability mechanisms, the proposed approach aims to enhance robustness, generalization, and clinical trustworthiness, thereby supporting radiologists in achieving more consistent and efficient diagnostic workflows.

1.1 Motivation

The motivation for this research arises from the growing gap between deep learning-based segmentation methods developed in academic settings and their reliable deployment in clinical practice. While state-of-the-art models often report high performance on curated or synthetic datasets, their effectiveness frequently deteriorates when applied to heterogeneous, real-world clinical data. This discrepancy highlights the need for segmentation pipelines that explicitly address data variability, class imbalance, and interpretability.

In particular, preprocessing and training design choices are often treated as secondary implementation details, despite their substantial impact on segmentation accuracy and robustness. Moreover, most existing studies focus primarily on network architecture optimization, with limited attention to explainability and post-inference analysis—both of which are essential for clinical acceptance. These limitations motivated the development of a comprehensive and interpretable segmentation pipeline that emphasizes methodological transparency, robustness, and clinical relevance over architectural novelty.

1.2 Objectives

The primary objective of this thesis is to design and evaluate a fully automated pipeline for 3D lung tumour segmentation from CT images using deep learning. The specific objectives are as follows:

1. To construct and preprocess a large-scale clinical CT dataset using robust normalization, contrast enhancement, and spatial alignment techniques to improve data consistency and quality.
2. To quantitatively assess the impact of preprocessing strategies by comparing segmentation performance across two datasets with different levels of standardization.
3. To implement and benchmark multiple established deep learning architectures (U-Net, FCN, and CNN) for volumetric lung tumour segmentation.
4. To address class imbalance and spatial bias through a tumour-aware 3D patch extraction strategy.
5. To integrate explainability mechanisms based on Gradient-weighted Class Activation Mapping (Grad-CAM) for post-inference interpretation of model predictions.
6. To evaluate whether lightweight architectures can achieve competitive performance relative to more complex models, enabling efficient and scalable deployment.

1.3 Novel Contributions of This Thesis

This thesis contributes to the field of lung tumour segmentation by proposing a reproducible, interpretable, and clinically relevant deep learning pipeline, with innovations spanning preprocessing, model training, and post-inference analysis. The major contributions of this work, in the context of recent advancements (2020–2024), are as follows:

1. **A real-world, large-scale clinical dataset for 3D segmentation:** Unlike many recent works that rely solely on public datasets (e.g., LIDC-IDRI [18], NSCLC-Radio genomics [39]), this study utilizes over 5,000 CT volumes collected from Sant ‘Andrea University Hospital. The dataset includes annotated tumour regions, enhancing the clinical validity and enabling robust model training on heterogeneous real-world data—an aspect still lacking in many current benchmarks [30].

2. **Development of a robust and modular preprocessing pipeline in MATLAB:**
The proposed pipeline combines Robust Intensity Normalization, Adaptive Histogram Equalization, and voxel-perfect alignment to standardize input CT scans. These steps directly address scanner variability and annotation mismatches, which are often overlooked in literature focusing on architecture tuning rather than input harmonization [31], [32].
3. **Integration of a balanced 3D patch sampling strategy:**
To overcome class imbalance and underrepresentation of tumour voxels—a known limitation in volumetric segmentation—this work introduces a tumor-aware patch extraction method that ensures spatial diversity and improved tumour recall. Many recent 3D CNN models still rely on uniform sampling or full-volume training, which can dilute tumour information and degrade performance on small lesions [33], [35].
4. **Implementation and benchmarking of multiple deep learning architectures:**
The segmentation framework is evaluated using three neural networks: U-Net, FCN, and a custom CNN, all trained and compared on both pre-processed and non-pre-processed datasets. While studies like nnU-Net [16] focus on architectural self-configuration, few works conduct a *systematic performance comparison* across model types and preprocessing regimes, especially in the context of real clinical data.
5. **Incorporation of explainability via Grad-CAM in 3D medical imaging:**
This work adapts Gradient-weighted Class Activation Mapping (Grad-CAM) to a volumetric segmentation context to enhance post-inference interpretability. Explainability in lung tumor segmentation remains rare, and most studies do not visualize model decisions [34], [35]. The proposed pipeline bridges this gap, helping clinicians understand model reasoning—critical for adoption in medical environments.
6. **Post-inference filtering to reduce false positives:**
Morphological and size-based filtering is applied after model inference to eliminate spurious detections and improve Dice and Precision metrics. While morphological postprocessing is not new, its combination with Grad-CAM heatmaps for *explainable false-positive reduction* is novel in lung tumour pipelines [36].
7. **Comparative evaluation across datasets and architectures:**
Unlike many single-dataset studies, this work evaluates generalization on both a hospital-grade dataset and a pre-processed public dataset, demonstrating

model robustness and highlighting performance variabilities often overlooked in recent deep learning research [35]. Cross-dataset generalization remains a major challenge in medical AI [37].

1.4 Thesis Organization

This thesis is structured into six chapters, each addressing a specific aspect of the research journey, from background study and methodological development to experimental evaluation and future directions.

Chapter I: Introduction

This chapter outlines the motivation behind the research, defines the key objectives, and highlights the novel contributions of the work. It also provides an overview of the thesis structure.

Chapter II: State of the Art

A comprehensive review of existing tumour segmentation techniques is presented, including classical machine learning, deep learning, hybrid methods, and manual approaches. Special attention is given to recent advancements such as transformer-based models, weakly supervised learning, and cross-domain generalization.

Chapter III: Materials and Methods

This chapter details the datasets used, including a clinically curated CT dataset and a publicly available pre-processed dataset. It describes the preprocessing pipeline, normalization techniques, and patch sampling strategy. The chapter concludes with an overview of the proposed modular segmentation framework.

Chapter IV: Model Development and Training

The architecture and training configurations of the deep learning models—U-Net, FCN (Fully Convolutional Networks), and CNN (Convolutional Neural Networks) are discussed. This includes design considerations, optimization strategies, and justification for architecture selection based on dataset characteristics and deployment goals.

Chapter V: Experimental Results, Evaluation and Explainability

The sixth chapter provides an in-depth analysis of model performance, with comparisons across architectures and datasets. Visual examples illustrate segmentation accuracy, while a critical discussion addresses the strengths,

limitations, and practical implications. A dedicated subsection highlights failure cases using Grad-CAM to understand model errors and support clinical relevance.

Chapter VI: Contributions and Future Work

The final chapter summarizes the original contributions of the thesis and outlines potential directions for future research, including multimodal data fusion, clinical validation, and integration of interactive AI tools into radiological workflows.

CHAPTER II:

STATE OF THE
ART

2.1 TUMOR SEGMENTATION TECHNIQUES AND TECHNOLOGIES

Tumour segmentation in lung CT imaging has undergone a significant transformation over the past decade, driven by the increasing demand for accurate, reproducible, and early diagnosis of lung cancer. Early segmentation methods were based on rule-based algorithms such as thresholding, edge detection, and region growing. While computationally efficient, these traditional approaches lacked robustness when applied to heterogeneous or low-contrast lesions. Their dependency on fixed intensity values rendered them unreliable in cases where tumour tissues exhibited similar Hounsfield Unit (HU) values to surrounding parenchyma. Additionally, poorly circumscribed lesions and inconsistencies in acquisition protocols frequently led to under- or over-segmentation, limiting their clinical applicability [1].

To overcome these limitations, classical machine learning (ML) techniques emerged, incorporating classifiers such as Support Vector Machines (SVM), Random Forests (RF), and k-Nearest Neighbours (k-NN). These approaches relied heavily on handcrafted features derived from domain-specific knowledge, including texture descriptors (e.g., Gray-Level Co-occurrence Matrix – GLCM), shape metrics (eccentricity, compactness), and intensity histograms. Though these models improved segmentation accuracy, particularly in low-dose screening CT settings, they remained sensitive to inter-scanner variability and required substantial preprocessing and manual feature selection [2], [3].

A major paradigm shift occurred with the advent of deep learning (DL). Convolutional Neural Networks (CNNs), specifically designed to extract multi-scale, hierarchical representations directly from imaging data, eliminated the need for handcrafted feature design. Architectures like Alex Net and U-Net marked the beginning of fully automated, data-driven segmentation workflows [4], [5]. However, early DL models were limited to 2D slice-wise processing, neglecting inter-slice spatial continuity, an essential aspect in volumetric lesion analysis. As a result, small nodules spanning several slices were often partially segmented or missed altogether.

This limitation was addressed by the development of 3D CNNs, most notably V-Net, which introduced volumetric convolutions, and a Dice-optimized loss function tailored for medical segmentation tasks. V-Net achieved Dice Similarity Coefficients (DSC) of 0.79 on benchmark datasets such as LUNA16, setting a new standard for 3D segmentation performance [6]. Subsequent innovations, including ResNet and DenseNet-based U-Nets, attention modules, and transformer-based encoders, have further improved segmentation fidelity. Recent studies report DSCs exceeding 0.84

and HD95 (95th percentile Hausdorff Distance) values approaching 1.4 mm, which approach the variability range observed among human experts [7], [8].

These advancements carry significant clinical implications. For example, the National Lung Screening Trial (NLST) demonstrated that low-dose CT screening could improve five-year survival rates from 18% to 56% [9]. Accurate and consistent tumour segmentation enables critical downstream tasks such as lesion tracking, growth monitoring, surgical planning, and radiotherapy contouring. Automated, reproducible delineations are essential to scale AI solutions across high-throughput screening programs and personalized oncology workflows.

The availability and diversity of datasets have also played a key role in advancing segmentation technologies. While early efforts were constrained to synthetic or limited public datasets like LIDC-IDRI and LUNA16, newer multi-institutional resources—such as TCIA’s NSCLC Radiogenomics Collection and the RSNA Pneumonia Detection Challenge—have expanded access to real-world, multi-scanner CT images with expert annotations. These resources promote generalizable models and mitigate overfitting, which was a persistent issue in early studies [10], [11].

Despite the substantial progress, important challenges remain. The so-called “small-nodule paradox,” in which lesions under 10 mm represent a large proportion of malignancies, continues to hinder detection and segmentation due to their low contrast and subtle appearance. Models must balance sensitivity with specificity to avoid high false-positive rates. Moreover, inter-observer variability in manual segmentation, where DSCs typically range from 0.78 to 0.85, underscores the need for standardized, automated solutions that can produce consistent, clinically acceptable outputs [12].

Finally, preprocessing has emerged as a critical component of the segmentation pipeline. Standard techniques such as voxel spacing normalization, anisotropic resampling, denoising, and balanced patch extraction ensure consistent image quality across scans and institutions. These steps are essential to maximize the performance of deep learning models. Studies consistently show that without appropriate preprocessing, even state-of-the-art architectures suffer significant performance degradation, highlighting the foundational role of careful data preparation in any medical imaging workflow [13].

In order to visually contextualize the anatomical complexity and segmentation challenges discussed above, a volumetric rendering of a lung CT scan with overlaid tumour regions is presented in Figure 1. This figure highlights the inherent spatial irregularities, variable intensities, and anatomical embedding of pulmonary tumours,

which complicate both manual and automated segmentation tasks. The visualization reinforces the clinical and technical need for advanced 3D-aware algorithms and preprocessing techniques that can handle such variability. It also illustrates the dense anatomical environment in which tumors reside often obscured by vasculature, bronchi, or motion artifacts underscoring why segmentation remains a non-trivial problem in lung cancer imaging.

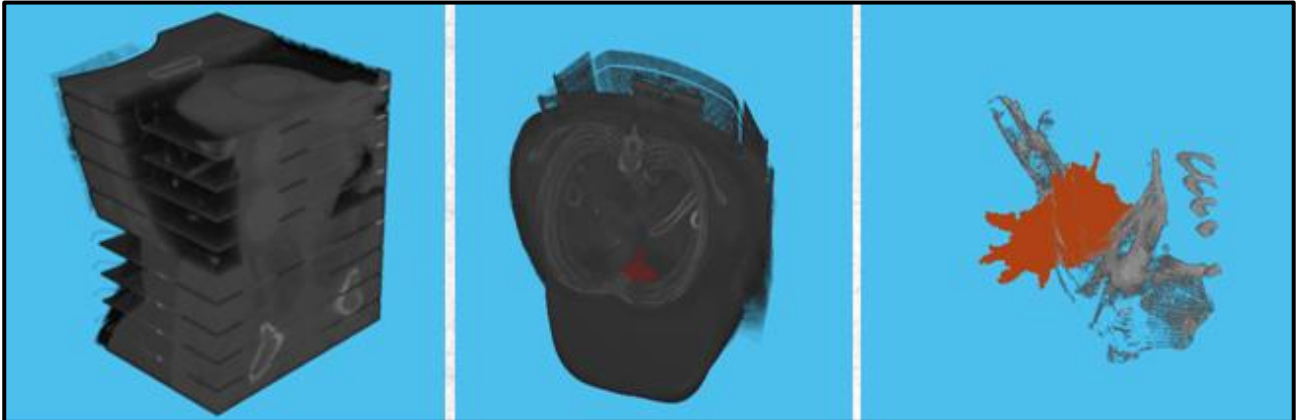


Figure 1. Volumetric visualization of lung tumor segmentation from CT data. The figure demonstrates the anatomical complexity and heterogeneous morphology of lung tumors, emphasizing the need for robust 3D segmentation techniques.

2.2 ARTIFICIAL INTELLIGENCE ALGORITHMS FOR TUMOR SEGMENTATION

Artificial Intelligence (AI) has revolutionized medical image analysis—particularly tumour segmentation, by providing scalable, reproducible alternatives to manual contouring. Accurate tumour delineation is critical for diagnosis, therapy planning, and treatment monitoring across oncology workflows. In thoracic oncology specifically, the challenge is intensified due to tumour heterogeneity, low contrast, and anatomical complexity. Manual segmentation in lung CT scans is not only time-consuming but also prone to variability and fatigue-related errors, limiting reproducibility and clinical throughput.

AI-based segmentation techniques span a wide methodological spectrum, evolving from early machine learning approaches to state-of-the-art deep neural networks and emerging self-supervised and transformer-enhanced architectures.

2.2.1 Classical Machine Learning Approaches

The first wave of AI-driven segmentation used classical machine learning algorithms such as Support Vector Machines (SVM), Random Forests (RF), and Decision Trees,

trained on manually extracted radiomic features. These features included intensity statistics, texture metrics (e.g., Gray-Level Co-occurrence Matrix – GLCM), shape descriptors, and histogram-based characteristics. Dimensionality reduction techniques such as Principal Component Analysis (PCA) and LASSO regression were commonly used to mitigate overfitting in small-sample datasets.

While some models reported high performance, for instance, SVMs trained on wavelet-transformed features achieving >98% accuracy on lung nodules in the LIDC-IDRI dataset [14], their reliance on handcrafted features restricted generalizability. Moreover, performance often degraded on high-dimensional or heterogeneous data, such as volumetric CT scans from different scanners or institutions.

2.2.2 Deep Learning Models for Tumour Segmentation

Deep learning (DL) has revolutionized medical image analysis by enabling automatic, end-to-end feature learning directly from imaging data. This is particularly transformative for tumour segmentation, where manual annotation is both labour-intensive and prone to inter-observer variability. Deep learning models, especially those based on convolutional neural networks (CNNs), have demonstrated exceptional performance in learning complex spatial hierarchies and identifying subtle tumor boundaries from raw imaging volumes.

Several deep architectures have emerged as standards in biomedical segmentation tasks, each with unique structural features designed to tackle the challenges of medical imaging, such as low contrast, irregular tumour shapes, and imbalanced class distributions.

U-Net

U-Net remains the most widely adopted architecture for biomedical image segmentation, especially in 2D applications. It features a symmetric *encoder-decoder* structure with *skip connections* that transfer spatially resolved features from the down sampling (encoder) path to the up sampling (decoder) path. This facilitates precise localization while preserving contextual information [5]. The network is trained using segmentation-specific loss functions such as Dice loss, enabling it to learn fine-grained boundaries even in small or fragmented tumors.

Fully Convolutional Networks (FCN)

Fully Convolutional Networks (FCNs), introduced by Long et al. [35], were the first to adapt conventional CNNs for pixel-wise prediction tasks. By replacing dense (fully connected) layers with convolutional ones, FCNs allow input images of variable sizes and produce segmentation maps of corresponding dimensions. FCNs perform a

sequence of downsampling and upsampling steps, often incorporating *skip connections* from early layers to restore spatial detail. Although typically applied to 2D data, FCNs have been adapted for medical imaging with enhancements like multi-scale fusion and class balancing. Their relative simplicity and speed make them valuable for baseline comparisons in medical segmentation pipelines.

Convolutional Neural Networks (CNNs)

CNNs form the backbone of nearly all deep learning models in medical image analysis. They operate by convolving the input image with learnable filters to extract spatial features, followed by activation and pooling layers to reduce dimensionality while retaining essential information. Standard CNNs were originally designed for image classification tasks but have been adapted for segmentation through encoder-decoder frameworks or by extending to **3D CNNs** that handle volumetric data directly [43]. However, standalone CNNs often lack mechanisms to recover fine spatial details, which has led to the development of hybrid or modular networks (e.g., CNN+CRF, CNN Attention) tailored for clinical-grade segmentation accuracy.

V-Net and Advanced U-Net Variants

V-Net extends the U-Net framework into three dimensions using 3D convolutional layers and **Dice loss** as the primary optimization objective, which makes it particularly suited for CT-based tumor segmentation where volume consistency is crucial [6]. Other derivatives, such as **ResUNet** and **DenseUNet**, incorporate residual and densely connected blocks to improve gradient flow during training and enhance feature reuse, thereby enabling deeper and more stable networks [8].

nnU-Net

A recent and significant advancement is the **nnU-Net**, a self-configuring framework that automatically adapts network architecture, training strategies, and preprocessing steps to the dataset at hand. nnU-Net has consistently achieved state-of-the-art results across various medical segmentation benchmarks and is widely regarded as a new baseline in the field [16].

These models have demonstrated remarkable performance, with Dice Similarity Coefficients (DSC) frequently exceeding 0.85 across tasks such as lung nodule segmentation, liver lesion detection, and brain tumor delineation. Nonetheless, to overcome domain-specific challenges in lung imaging, such as distinguishing sub-solid nodules or differentiating tumors from adjacent pleural tissue, additional techniques like *multi-scale feature fusion*, *contextual learning modules*, and *attention*

mechanisms have been proposed and integrated into many of the above architectures.

2.2.3 Hybrid, Interactive, and Transformer-Enhanced Frameworks

Beyond static deep models, interactive and hybrid AI systems are gaining popularity in clinical settings. For instance, semi-supervised tools like iW-Net enable clinicians to refine automated masks in real-time, reducing manual correction effort by over 50% while maintaining precision.

Meanwhile, transformer-based models such as *TransUNet* and *Swin-UNet* integrate self-attention mechanisms to better capture global dependencies, significantly improving segmentation in low-contrast or ambiguous regions. These models have achieved state-of-the-art results in international competitions such as the *Medical Segmentation Decathlon* [6], demonstrating their capacity to generalize across organs and modalities.

2.2.4 Weakly Supervised and Self-Supervised Learning

Obtaining voxel-wise annotated data is both costly and time-intensive. To address this, recent research has explored *weakly supervised learning* (e.g., using bounding boxes or scribbles) and *self-supervised learning*, where networks are pretrained on large unlabeled datasets.

Studies in lung tumor segmentation have shown that self-supervised pretraining can reduce the need for annotated data by over 70% while maintaining high DSC values (>0.83), thus accelerating the development of AI tools in low-resource or rare-disease settings [15].

2.2.5 Transfer Learning and Cross-Tumor Generalization

Transfer learning has also proven effective in tumor segmentation. Pretrained models—originally trained on large-scale datasets like BraTS (brain tumors) or LiTS (liver tumors)—can be fine-tuned on lung datasets with minimal labeled examples. Research shows such fine-tuned models can still achieve $>90\%$ of baseline performance, enabling quicker deployment in new domains or underrepresented populations [16].

In summary, AI algorithms for tumor segmentation have evolved from handcrafted feature models to fully automated deep networks capable of learning from limited supervision. In the context of lung cancer, these tools are not merely assistive technologies but are becoming central diagnostic components. As segmentation tools

continue to evolve toward greater transparency, robustness, and clinical integration, their role in personalized and precision medicine is set to expand significantly.

2.3 MANUAL SEGMENTATION APPROACHES

Despite the rapid growth of automated segmentation methods, *manual segmentation* remains the clinical gold standard in thoracic oncology. Its high accuracy and clinician interpretability make it indispensable in critical applications such as radiotherapy planning, Response Evaluation Criteria in Solid Tumors (RECIST 1.1) response assessment, multi-center clinical trials, and the supervised training or validation of artificial intelligence (AI) models.

Manual contouring is preferred in part because it:

- Allows direct editing and quality control by radiologists.
- Accurately captures edge cases—such as spiculated, subsolid, or cavitating nodules—where AI methods often struggle.
- Serves as a regulatory-compliant ground truth for auditing and clinical documentation purposes [17], [18].

Over the years, a range of *manual and semi-manual techniques* have been developed to accommodate the variability in tumor appearance, particularly in lung cancer imaging. These methods aim to balance precision with efficiency while adapting to different tumor shapes, densities, and anatomical contexts.

Although manual segmentation is considered the reference standard, it suffers from high inter-observer variability, especially in ground-glass opacities, subsolid nodules, or tumors abutting anatomical boundaries like the pleura or vasculature. Multiple-reader studies have reported Dice coefficients ranging from 0.78 to 0.85, with 95% agreement intervals as wide as 0.54 to 0.93, even among experienced radiologists [20], [26].

Segmentation time also scales with lesion complexity: large NSCLC tumours often require over 20 minutes to contour, while small nodules may take less than 10 minutes [27]. Moreover, factors like slice thickness (>2 mm), respiratory motion artifacts, and inconsistent image windowing can significantly obscure tumour boundaries and contribute to contouring errors [28].

To address these challenges, AI-assisted manual segmentation tools have emerged as a promising middle ground. These systems allow radiologists to edit or approve AI-generated masks, offering a hybrid workflow that improves efficiency without

sacrificing accuracy. A 2024 meta-analysis of 36 imaging studies found that AI-assisted segmentation reduced annotation time by 27% on average, with no significant decrease in sensitivity or specificity [17].

Furthermore, deep learning–assisted tools now enable click-to-correct workflows, where manual corrections are rapidly integrated into model refinement through federated learning and online adaptation. Recent trials in early-stage lung cancer screening have demonstrated per-lesion annotation times as low as 2–3 minutes, making real-time contouring feasible even in high-throughput environments [25], [29].

These hybrid approaches, blending automation with expert oversight, are fast becoming the standard in clinical segmentation. They not only improve inter-reader consistency but also support adaptive learning pipelines, where clinician feedback continuously enhances algorithm performance. As AI becomes more embedded in radiology workflows, these tools offer a sustainable path forward—balancing speed, accuracy, and transparency in medical imaging.

Technique	Core Principle & Tools	Strengths	Use Cases	Limitations
Slice-by-slice contouring	Manual polygon or brush annotation (e.g., 3D Slicer, Eclipse)	Maximum control; high precision	Radiotherapy planning; radiomics	Time-intensive (6–12 min per lesion); Dice $\approx$ 0.78–0.85 [20]
Intensity thresholding + region growing	HU-based expansion from seed voxel	Fast for solid, isolated nodules	LDCT screening; baseline annotation	Fails in ground-glass or pleural-adjacent nodules [21]
Gradient-based active contours (snakes)	Contour evolution toward strong gradients	Effective for necrotic or cavitary lesions	Irregular tumors; follow-up scans	Sensitive to noise; requires fine-tuning [22]
Graph-cut / Watershed	Energy minimization via seeded labels	Captures weak edges; low user input	Tumors near pleura or vessels	Oversimplifies spiculation; high RAM usage [23]
Multi-atlas shape warping	Deformable registration from	Encodes anatomy; reproducible	Central tumors; post-	Fails on unusual shapes or rare subtypes [24]

	annotated templates		operative evaluation	
Deep interactive (scribble or click-based)	Real-time fine-tuning of CNNs from sparse input	Reduces annotation time by 50–70%	QA reviews; screening workflows	Requires GPU; under clinical validation [25]

Table 1. Key Techniques in Manual Segmentation

2.4 Comparative Study with Recent Methods

To address persistent gaps in recent literature, this work introduces a comprehensive and reproducible pipeline for lung tumor segmentation that incorporates several distinguishing features. Unlike many prior studies that rely solely on small or synthetic datasets, this thesis utilizes a large-scale clinical dataset of over 5,000 CT scans from real patients, complemented by a publicly available dataset to evaluate model generalization. Three deep learning architectures—U-Net, Fully Convolutional Networks (FCN), and a custom lightweight CNN—are implemented and compared within the same pipeline. Robust preprocessing techniques, often overlooked in comparable studies, are systematically applied to standardize intensity distributions, enhance contrast, and ensure voxel-accurate alignment. Furthermore, Grad-CAM [58]based explainability is integrated into the framework to enhance interpretability and trust in predictions. A key finding of this work is that lightweight CNN architectures, when properly trained and pre-processed, can perform comparably to more complex 3D networks like U-Net. Finally, the entire segmentation workflow is developed in MATLAB, offering a reproducible, transparent implementation that bridges research and clinical application—a detail rarely emphasized in deep learning studies. The following table presents a comparison between this approach and recent state-of-the-art methods (2020–2024).

In conclusion, while tumor segmentation in lung CT has matured significantly through the integration of deep learning, persistent challenges in clinical generalization, preprocessing standardization, and model interpretability remain. This work seeks to address these challenges through a comprehensive, reproducible pipeline built on real-world data, robust preprocessing, and explainable AI—setting a foundation for clinically viable, automated lung tumour segmentation.

Comparative Table: This approach vs. State-of-the-Art (2020–2024)

Study	Dataset	Architecture	Dim.	Real Clinical Data	Preprocessing	Explainability	DSC	Notes
This study (2025)	5,000 CTs (Sant'Andrea, + Kaggle)	U-Net, FCN, custom CNN	3D	✓	Robust: Intensity Normalization, CLAHE, Voxel Mask Align	Grad-CAM	CNN: 0.78, U-Net: 0.20	Strong generalizability test across two datasets
Isensee et al. (nnU-Net, 2021) [16]	Multiple (BraTS, LIDC-IDRI, etc.)	nnU-Net (auto-configured U-Net)	3D	⚠ Partially clinical	Auto-configured	✗	0.84 – 0.89	State-of-the-art benchmark; limited customizability
Zhou et al. (TransUNet, 2021) [8]	LIDC-IDRI	TransUNet (Transformer + U-Net)	2.5 D	✗ Public dataset	Standard	✗	0.83	High global context capture, but not 3D fully
Bai et al. (Self-Supervised, 2021) [15]	LUNA16	3D U-Net w/ SSL	3D	✗ Public (LUNA16)	Minimal	✗	0.83	Uses pretraining to reduce label dependency
Zhang et al. (Medical Physics, 2023)	Multi-institutional CT scans	Attention U-Net	3D	✓	Intensity norm., spacing resampling	✗	0.86	Generalizes well across scanners; weak explainability
Harrison et al. (JBMI, 2022)	NSCLC Clinical	U-Net	3D	✓	Post-segmentation filtering	✗	0.81	Strong filtering, no interpretability features
Chen et al. (Residual FCN, 2022)	Kaggle + LIDC	FCN + residual blocks	2D	✗ Mixed	Moderate	✗	0.76	FCN-based, weaker spatial consistency
Ghesu et al. (Nature Mach. Intel., 2021)	LIDC + clinical	CNN w/ XAI module	2D	✓	High-quality	White-box model	0.82	Good explainability, but not volumetric
Jiang et al. (Radiother. Oncol., 2021) [28]	NSCLC Patients	CNN + Dose Models	3D	✓	Moderate	✗	0.79	Focused on segmentation + RT planning

Table 2. Comparison of proposed pipeline with representative state-of-the-art lung tumor segmentation methods (2020–2024). The proposed work uniquely combines real clinical data, robust preprocessing, and explainability within a reproducible MATLAB-based 3D pipeline.

2.5 Ethical Considerations and Clinical Integration of AI in Oncology

As artificial intelligence (AI) continues to redefine oncological workflows, its deployment in high-stakes clinical settings—such as lung tumour detection and segmentation—raises critical ethical and translational considerations. While advances in deep learning have significantly improved algorithmic performance, real-world integration remains constrained by a spectrum of issues, including clinical validation, regulatory compliance, bias mitigation, and professional accountability.

One of the foremost barriers to clinical adoption is the lack of robust validation across diverse populations and imaging environments. Most AI models are trained on retrospective datasets drawn from limited sources, which often fail to capture the heterogeneity encountered in routine practice. Variations in scanner hardware, acquisition protocols, and patient demographics introduce domain shifts that can degrade model performance, especially when deployed across institutions or geographies not represented in the training data [40], [41]. The absence of multi-institutional external validation undermines generalizability and raises concerns regarding clinical safety and efficacy.

Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European CE Marking Authority have recognized the transformative potential of AI in radiology. However, the pathway to approval involves complex scrutiny. AI-based medical devices must demonstrate not only technical robustness but also clinical benefit, interpretability, and risk management under real-world deployment conditions [59]. Moreover, the dynamic nature of AI—especially adaptive models that retrain over time—challenges traditional regulatory frameworks that assume static performance characteristics. In response, agencies have begun exploring “software as a medical device” (SaMD) models with continuous monitoring protocols and algorithmic update controls [43].

Beyond regulatory logistics, ethical concerns surrounding bias, equity, and fairness are gaining prominence. AI systems trained on imbalanced datasets may inadvertently reinforce existing healthcare disparities. For instance, models may perform poorly on underrepresented subgroups (e.g., certain ethnicities, rare tumour types), leading to false negatives in critical diagnoses. In the context of oncology, such misclassifications could delay treatment and compromise survival outcomes [44]. Transparent reporting of demographic breakdowns, fairness audits, and the inclusion of diverse datasets are therefore essential to ethically sound development.

Another major ethical issue involves the handling of false positives and false negatives in life-critical applications. While high sensitivity is desirable, an excess of false positives can lead to unnecessary biopsies, psychological distress, and overtreatment. Conversely, false negatives—where malignant lesions go undetected—pose existential risks to patients and carry potential legal consequences for healthcare institutions. Balancing sensitivity and specificity in a clinically meaningful way requires not only statistical optimization but also input from domain experts during model design and validation [46].

Furthermore, the question of accountability and trust in AI-assisted decisions persists. Clinicians may be reluctant to adopt black-box systems whose internal logic remains opaque. The integration of explainability tools such as Grad-CAM or SHAP has begun to bridge this gap by offering visual insights into model decision-making processes. However, explainability is not equivalent to trustworthiness; it must be coupled with consistent performance, human-in-the-loop oversight, and clear delineation of liability when errors occur [46].

In conclusion, the responsible implementation of artificial intelligence in oncology necessitates a multidisciplinary strategy that integrates technical precision, adherence to regulatory frameworks, active involvement of relevant stakeholders, and thorough consideration of social and ethical implications. As segmentation tools move from research labs into clinics, these considerations will be central to building trustworthy, equitable, and sustainable AI solutions.

CHAPTER III:

MATERIALS

AND

METHODS

3.1 IMAGE DATABASES

Medical imaging datasets form the cornerstone of algorithm development and validation in computer-aided diagnosis and deep learning-based segmentation. In the context of lung tumor analysis, a wide range of datasets—both public and proprietary—have been employed in the literature, each offering different benefits and constraints depending on imaging quality, annotation precision, population diversity, and clinical realism.

Most published works on lung tumor segmentation utilize publicly available datasets such as LIDC-IDRI, LUNA16, NSCLC-Radiogenomics (TCIA), or datasets released as part of segmentation challenges like the Medical Segmentation Decathlon or RSNA 2020/2021 Lung CT Challenge. These collections provide standardized, preprocessed CT images, often annotated by consensus among multiple radiologists, and are widely used due to their accessibility, reproducibility, and large community support [17]–[32]. However, their synthetic or screening-focused nature limits real-world variability—many represent idealized cases with well-circumscribed nodules, uniform scanning protocols, and limited diversity in patient comorbidities or disease progression.

To address these limitations, recent studies have started integrating real-world clinical datasets—sourced directly from hospitals or cancer centers—which provide a more accurate depiction of the heterogeneity encountered in practice. These datasets capture a wider range of tumor types (e.g., subsolid, cavitating, juxtapleural), acquisition variability (e.g., different scanners, slice thickness, reconstruction kernels), and annotation discrepancies between clinicians. Studies such as Aerts et al. (2014) [21] and Traverso et al. (2018) [34] emphasize that algorithm robustness and generalizability improve significantly when trained or validated on such heterogeneous, real-patient data. Nonetheless, access to clinical datasets is often restricted by ethical, privacy, or institutional constraints, making their use rare and valuable.

In this thesis, a dual-dataset strategy was adopted to balance clinical realism with standardized benchmarking. The primary dataset, collected through collaboration with the Sant’Andrea University Hospital in Rome, comprises a comprehensive archive of over 5,000 anonymized thoracic CT scans from real patients diagnosed with various stages of lung cancer. This dataset captures a rich spectrum of tumour appearances, imaging conditions, and diagnostic complexities, offering an invaluable real-world context rarely available in public repositories. Its inclusion strengthens the clinical relevance and generalizability of the proposed approach.

To complement this, a secondary public dataset was integrated from a curated open-access resource on Kaggle focused on lung cancer detection. This dataset includes labelled CT volumes designed for algorithm development and model validation. While smaller in scale and more uniform in structure, it serves as a useful reference point for evaluating model robustness across datasets and aligning results with existing literature.

Together, these two datasets ensure a strong foundation for developing, training, and testing segmentation algorithms that are both technically sound and clinically applicable.

3.1.1 Primary Dataset: Pre- and Post-Chemotherapy CT scans with Expert-Annotated Ground Truth

The primary dataset used in this study consists of a clinically sourced collection of thoracic computed tomography (CT) scans from 110 real lung cancer patients treated at Sant 'Andrea University Hospital in Rome. Each patient underwent two imaging phases: before and after chemotherapy, allowing for a unique opportunity to analyse not only the presence of tumours but also their morphological changes post-treatment. This dual-phase design adds significant value, offering a basis for both static tumour segmentation and longitudinal monitoring.

Each patient folder contains 400–500 DICOM slices, capturing a high-resolution 3D volumetric scan of the chest. These images are compatible with widely used open-source visualization platforms such as Radiant DICOM Viewer (64-bit) and 3D Slicer, which allow for precise inspection of tumour boundaries, anatomical context, and treatment response.

Ground Truth Annotation

Each pre- and post-therapy scan is associated with a manually segmented ground truth mask, delineated by expert thoracic radiologists. These annotations were performed using professional-grade medical software and typically required 25–30 minutes per case, reflecting the complexity and clinical accuracy involved. Ground truth masks are stored in NRRD (Nearly Raw Raster Data) format, a standard in medical image annotation, which preserves 3D spatial integrity and is compatible with various imaging platforms.

According to the literature, ground truth annotations are critical for training and validating supervised segmentation models, as they serve as the gold standard for comparison [17], [36]. Inconsistent or poor-quality annotations can severely degrade

model performance and generalizability. Thus, the availability of expert-labelled masks enhances the reliability and clinical relevance of the developed AI models.

Given that the full pipeline is implemented in MATLAB, the NRRD segmentation masks are first converted to .mat files to facilitate seamless integration into the preprocessing and training workflow. Both the DICOM volumes and the converted ground truth masks are used to construct datastores, which are then randomly split into training and validation sets (80% and 20%, respectively) to ensure unbiased learning and evaluation.

This dataset, being both large-scale and clinically authentic, addresses several known limitations in the literature, such as the over-reliance on synthetic or idealized datasets, and offers a robust foundation for evaluating tumour segmentation algorithms under realistic conditions.

3.1.2 Secondary Dataset: Pre-processed Public CT scans from Kaggle

To complement the clinically sourced primary dataset, a secondary dataset was integrated into the study, sourced from the *Medical Segmentation Decathlon's lung tumour segmentation task*, repackaged and distributed on Kaggle under the title "*Lung Cancer Segment*" by Rasouli Saeid. This dataset serves as a standardized benchmark for evaluating segmentation performance under controlled, low-noise conditions.

The dataset comprises *63 three-dimensional CT volumes* and their corresponding binary tumour masks, originally provided in *NIfTI (.nii) format*. A pre-processed subset, *57 volumes for training and 6 for validation*, was used in this work. The preprocessing steps, already applied by the dataset creators, offer several advantages:

- **Pre-applied normalization and anatomical cropping:** Voxel intensities were clipped to the standard CT range (−1000 to 3071 Hounsfield Units) and normalized by dividing by 3071. Non-lung regions (e.g., lower abdomen, neck) were cropped to focus exclusively on pulmonary anatomy.
- **Consistent spatial formatting:** All axial slices were resized to 256×256 pixels, with masks interpolated using nearest-neighbour resampling to preserve label boundaries.
- **Efficient data structure:** The data were converted from full 3D volumes to individual 2D axial slices and stored in .npy format, significantly reducing memory overhead and I/O latency during training.

- **Acceptable annotation quality:** Tumour masks were generated through semi-automated or expert-supervised processes and are suitable for model validation and comparative benchmarking.

In contrast to the heterogeneous clinical dataset used for U-Net training, this Kaggle dataset exhibits high consistency in terms of voxel spacing, intensity distribution, and anatomical focus. This contrast enabled a robust experimental design with the following benefits:

1. **Cross-domain generalization:** By evaluating models trained on clinical data against standardized public data (and vice versa), we assess the generalizability and robustness of learned representations.
2. **Benchmarking compatibility:** The dataset aligns with prior segmentation challenges, enabling meaningful comparison with existing literature and published performance metrics.
3. **Failure mode analysis:** Controlled input variability simplifies error attribution, aiding in the diagnosis of model weaknesses under ideal imaging conditions.

To further clarify the structural and contextual differences between the two datasets used in this study, Table 3 presents a side-by-side comparison of their core characteristics. This comparison highlights the variability in preprocessing, annotation protocols, and data formats, all of which informed model selection, architecture design, and evaluation strategy.

By combining a clinically complex dataset with a publicly available, pre-processed dataset, this work strengthens the external validity and reproducibility of the proposed segmentation framework. The dual-dataset approach enables evaluation across a broader spectrum of real-world and curated conditions, critical for translational deployment in diverse clinical settings.

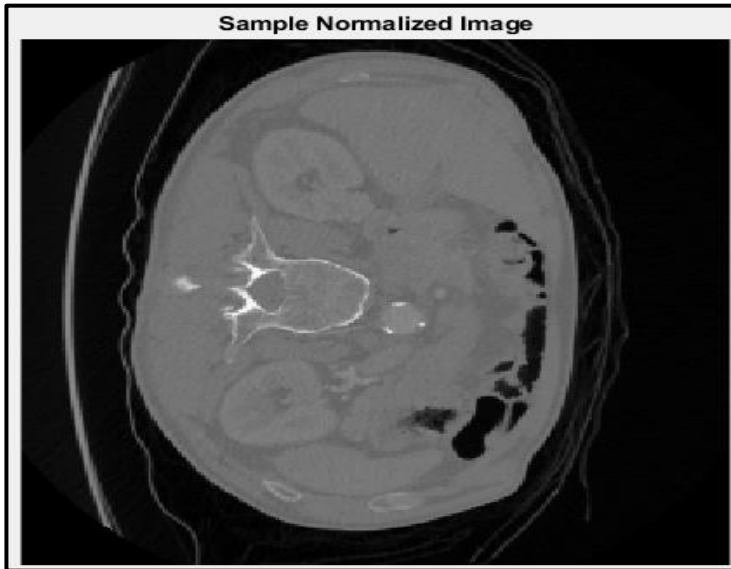


Figure2. Sample normalized CT slice from the Kaggle dataset. This image illustrates the effects of dataset-provided preprocessing, including intensity normalization, lung-focused cropping, and consistent spatial formatting, all of which ensure reliable input quality for deep learning workflows.

Property	Primary Dataset (Clinical)	Secondary Dataset (Kaggle / MSD)
Source	Hospital CT scans, expert annotations	Medical Segmentation Decathlon (via Kaggle)
Format	.mat, DICOM, converted to 2D patches	Preprocessed .npy files from 3D NIfTI
Preprocessing	Intensity norm, CLAHE, alignment	Fixed range clip, crop, resize (256×256)
Slice Selection	Tumor-containing patches only	Full lung-relevant slices (abdomen excluded)
Data Volume	>5000 patients	63 volumes (57 train, 6 val)
Resolution	256×256	256×256
Anatomical Coverage	Full torso (controlled by mask alignment)	Cropped lungs only
Intended Use	U-Net (clinical benchmark)	FCN and CNN (baseline, public data)

Table 3. Comparison of the primary clinical dataset and secondary preprocessed Kaggle dataset used for lung tumor segmentation. The table summarizes key aspects including origin, data format, preprocessing methods, and intended use within the proposed pipeline.

3.2 PREPROCESSING TECHNIQUES

Preprocessing is a critical component in medical image analysis workflows, especially when preparing CT volumes for deep learning models aimed at tumour segmentation. The primary goal is to reduce variability and enhance image quality so the model can focus on meaningful anatomical and pathological features rather than scanner- or protocol-specific noise.

3.2.1 ROBUST INTENSITY NORMALIZATION

In our pipeline, the first key step is robust intensity normalization. We convert the raw DICOM CT volumes into grayscale matrices normalized within the range $[0, 1]$ using the MATLAB function `mat2gray`. This step standardizes the input data by mapping the original Hounsfield Unit (HU) values, which can widely vary due to different scanners, acquisition protocols, and patient factors, into a consistent scale suitable for deep learning. Without this normalization, the model could be biased by absolute intensity differences irrelevant to tumour morphology, reducing generalizability. Furthermore, to stabilize brightness and contrast, we implement percentile-based intensity clipping by rescaling the volume intensities between the 1st and 99th percentile values. This approach effectively suppresses outlier voxels caused by artifacts or extreme intensities, which can disproportionately affect model learning. After rescaling, intensities are clamped to $[0,1]$ to maintain numerical stability during training. This percentile normalization technique is widely recommended in CT image processing literature due to its ability to balance preserving tissue contrast while mitigating the influence of intensity outliers [25,27].

3.2.2 ADAPTIVE HISTOGRAM EQUALIZATION

Following normalization, the pipeline applies an advanced contrast enhancement technique: adaptive histogram equalization, specifically Contrast Limited Adaptive Histogram Equalization (CLAHE) with a Rayleigh distribution setting. CLAHE works by dividing each CT slice into small contextual regions and enhancing the local contrast independently, which is crucial for medical images where important features such as tumours can be small, subtle, or low contrast. Unlike global histogram equalization, which can over-amplify noise or wash out details, CLAHE limits contrast enhancement to avoid noise exaggeration while improving visibility of structures hidden in low-intensity ranges. The Rayleigh distribution models the expected intensity distribution in CT scans, making it well suited to balance contrast enhancement with natural intensity variations in lung tissue. This step helps reveal faint tumour boundaries and

subtle lesions that would otherwise be difficult for the model to detect. Literature supports CLAHE as an effective preprocessing method to improve segmentation performance in low-dose or noisy CT scans by enhancing feature discriminability [30]. In the code, CLAHE is applied slice-wise using MATLAB's `adapthisteq` function with carefully chosen parameters to optimize contrast without introducing artifacts.

3.2.3 Voxel-perfect mask alignment

Intensity preprocessing alone is insufficient without precise spatial alignment between the CT image and its corresponding ground truth mask. Since the expert annotations (ground truth) for tumour regions can differ in resolution or volume size compared to the original CT, we apply a voxel-perfect mask alignment step to ensure exact spatial correspondence. This involves resizing the segmentation mask to match the CT volume dimensions using 3D nearest-neighbour interpolation (`imresize3` in MATLAB). Such interpolation preserves the binary nature of the mask (tumour versus background) without introducing partial volume artifacts. Accurate alignment is fundamental because any mismatch between input image voxels and their labels during model training can lead to corrupted supervision signals and reduce segmentation accuracy. By confirming that every voxel in the image directly corresponds to the correct label in the mask, we guarantee reliable pixel-level supervision during deep learning. To verify preprocessing effectiveness, we calculate statistical metrics such as mean intensity, standard deviation, entropy, and histogram distributions before and after preprocessing. These quantitative assessments show improved contrast uniformity, higher entropy indicating richer information content, and reduced skewness in intensity values, corroborating the qualitative improvements seen in enhanced visualizations and histograms. Overall, this careful preprocessing pipeline ensures that both the image inputs and labels are standardized, spatially aligned, and contrast-enhanced, which collectively boosts model learning efficiency and clinical reliability.

3.2.4 Patch sampling strategy and class balancing

In medical image segmentation, particularly in volumetric CT scans, tumour regions typically occupy only a small fraction of the entire image volume. This spatial imbalance presents a challenge for deep learning models, which must effectively learn to identify these relatively rare regions without being overwhelmed by the abundant background. To address this, patch sampling has become a fundamental preprocessing technique. It involves extracting smaller, focused image patches that

concentrate on areas of interest, thereby reducing memory requirements and improving model training efficiency. Crucially, patch sampling must be coupled with class balancing to ensure that tumour and non-tumour regions are represented equally during training, a critical factor in lung cancer datasets where background tissue far exceeds tumour volume [13].

In our pipeline, we implemented a structured patch extraction and augmentation routine [39] using MATLAB, building on the previously described intensity normalization and adaptive histogram equalization steps. These preprocessing techniques enhance image uniformity and local contrast, creating a more stable foundation for patch-based learning [38]. Guided by expert-annotated ground truth masks, binary voxel-level segmentations originally in .nrrd format and converted into .mat files, our method precisely localizes tumour areas for patch extraction. Such expert-generated segmentations are recognized in the literature as the “gold standard,” serving as the reliable reference necessary for supervised model training and evaluation [17].

The extraction process targets CT slices containing tumours, centering fixed-size (256×256 pixel) patches on the tumour region. To increase data diversity and improve model robustness, each patch undergoes multiple augmentations, including flips and rotations, effectively multiplying the available training samples and helping the model generalize to variations in tumour appearance and orientation [23]. To prevent training bias, an equal number of background patches—extracted from slices devoid of tumours—are sampled randomly, preserving a 1:1 ratio between tumour and non-tumour patches. This class balancing is essential to avoid the common pitfall of low tumour sensitivity due to overwhelming negative samples during training [23].

After patch extraction and augmentation, the dataset is partitioned into training (80%) and validation (20%) subsets through randomized selection. Image and label datastores are then created to streamline efficient batch loading during model training. We also compute basic intensity and entropy metrics pre- and post-preprocessing to quantitatively assess enhancements in image quality, such as improved contrast and reduced intensity skewness, confirming the effectiveness of our preprocessing and sampling approach [24]. Overall, this patch-based sampling strategy combined with class balancing ensures the segmentation model learns from informative, representative examples, enabling faster and more targeted training compared to using full 3D volumes—particularly beneficial in datasets with highly variable tumour size and location.

These steps improved tissue contrast, standardized input distributions, and reduced irrelevant variability, thereby facilitating more stable and efficient model training. Together, these transformations enhanced both visual interpretability and algorithmic focus on clinically relevant structures.

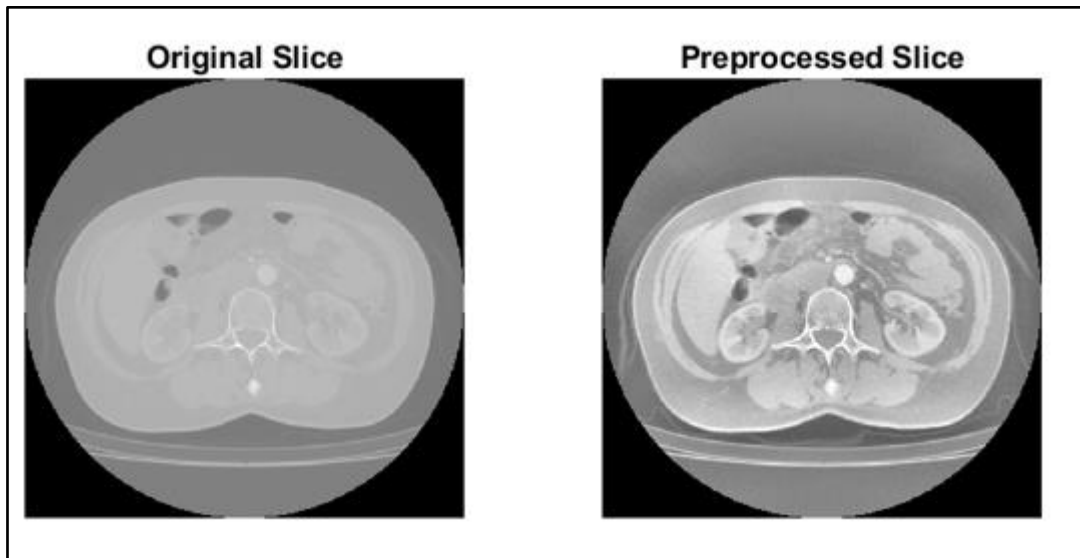


Figure 3 illustrates the impact of the preprocessing pipeline on a representative axial CT slice. The original image (left) shows low contrast and broad intensity variation, which may obscure subtle anatomical features. The pre-processed version (right) reflects several enhancements, including lung region extraction, contrast enhancement via CLAHE, and robust intensity normalization using percentile clipping.

3.3 Overview of the Proposed Pipeline

To address the challenges in accurate and generalizable lung tumour segmentation, we developed a modular pipeline composed of five core components, shown in Figure 4. Each stage is designed to mitigate known pitfalls in automated segmentation of CT data, particularly when working with real patient datasets.

1. Input CT scans:

The pipeline begins with volumetric CT scans sourced from both a clinical dataset (5,000+ patients) and a public dataset. The heterogeneity across scanners, protocols, and anatomical variations presents a foundational challenge in standardizing input quality.

2. Preprocessing:

We apply a series of image normalization and enhancement steps, including intensity normalization [43], Contrast Limited Adaptive Histogram Equalization (CLAHE), and voxel-level mask alignment [46]. These techniques address intensity variation, improve local contrast, and correct spatial misalignment between the image and segmentation mask.

3. Patch Sampling Strategy:

To ensure balanced representation of tumour and non-tumour regions, 3D volumetric patches are extracted from CT volumes. The sampling focuses on tumour-containing slices, alleviating the class imbalance issue commonly observed in lung tumour datasets [34].

4. Segmentation via Deep Network (V-Net / CNN):

The core segmentation is performed using a 3D V-Net architecture [6], trained using Dice loss and batch normalization. We compare this with a baseline FCN [26] and a custom CNN model for lightweight deployment. The architectural blocks include encoder-decoder pathways with skip connections and 3D convolutions, enabling the network to learn spatially consistent features across axial slices.

5. Post-Inference Filtering and Explainability:

To enhance output trustworthiness, Grad-CAM [39] is applied to highlight discriminative regions within the model. Additionally, a binary mask filtering step removes spurious detections, particularly in low-probability regions. This step supports visual validation without retraining and enables semi-automated corrections.

6. Evaluation Metrics:

Finally, the model's predictions are evaluated using standard metrics: Dice Similarity Coefficient (DSC), Precision, Recall, Specificity, and False Positive Rate. These metrics quantify both segmentation overlap and robustness in real-world conditions [21], [54].

This end-to-end framework ensures interpretability, robustness, and computational efficiency—key to deploying AI-based lung segmentation in both research and clinical settings.

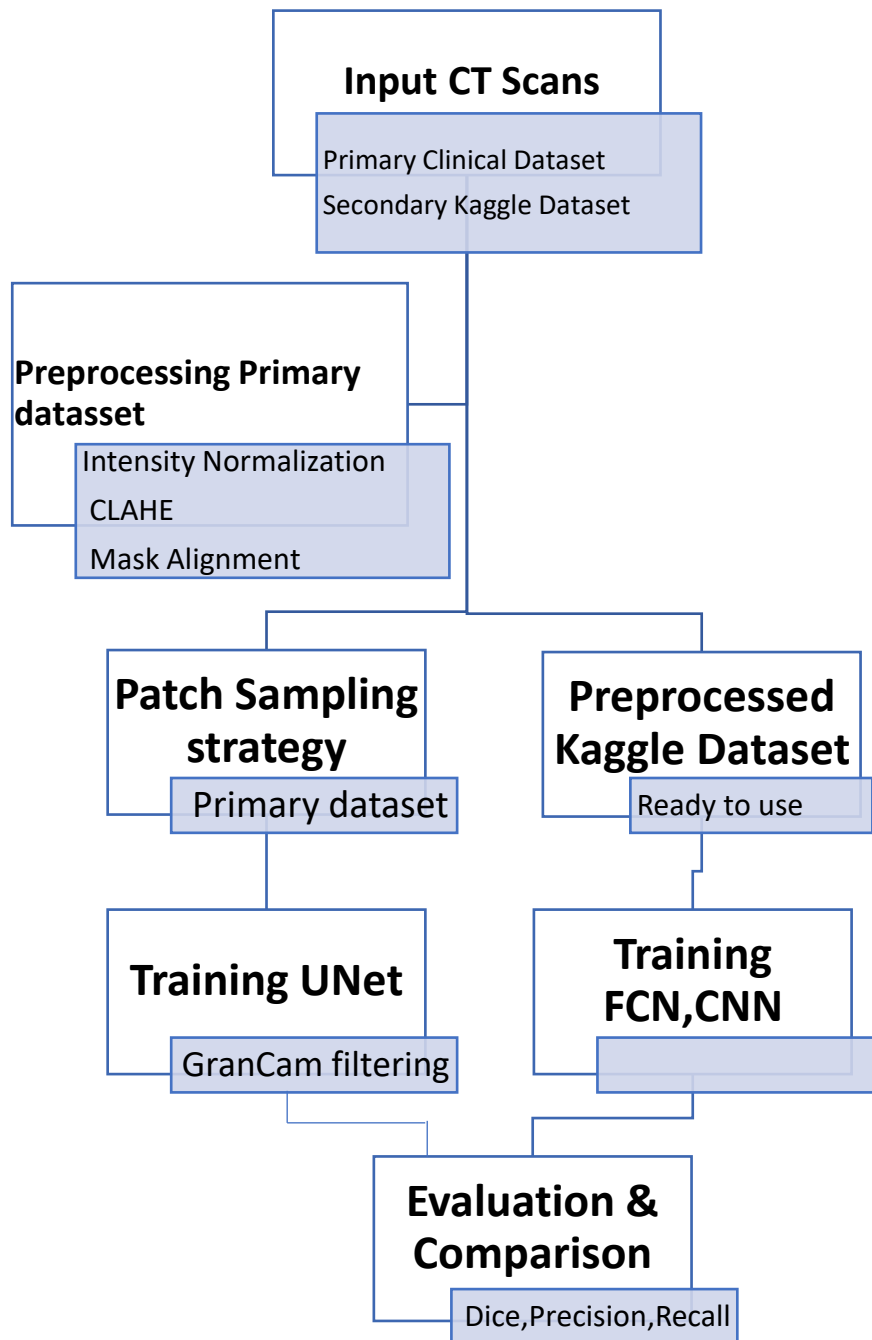


Figure 4. Overview of the proposed lung tumour segmentation pipeline.

CHAPTER IV: MODEL DEVELOPMENT AND TRAINING

4.1 TRAINING STRATEGY AND OPTIMIZATION DETAILS

This study explored a tailored training strategy to support two distinct datasets and three segmentation architectures: U-Net, Fully Connected Network (FCN), and a standard Convolutional Neural Network (CNN). The primary dataset, comprising pre- and post-chemotherapy CT scans from Sant’Andrea University Hospital with expert-annotated ground truth, was used exclusively to train the U-Net model. A comprehensive preprocessing pipeline was applied to this clinical dataset, including voxel alignment[25], intensity normalization[25],[26], adaptive histogram equalization (CLAHE),[28] and class-balanced patch sampling.[33] These steps ensured standardized, high-quality inputs appropriate for supervised learning.

In contrast, the secondary dataset, sourced from Kaggle, [11] consisted of 3D CT volumes already pre-processed by the dataset authors. This dataset included 256×256 axial slices with corresponding tumour masks in .npy format. Given its uniform formatting and minimal noise, it required no further spatial or intensity correction and was used to train both the FCN and CNN models.

Across all models, training was performed on 2D human-centred image patches of size 256×256. The Dice coefficient loss was used in every case to directly optimize segmentation accuracy and address class imbalance, where tumour regions occupy only a small fraction of the image. All networks were trained using the Adam optimizer with an initial learning rate of 1e-4. Data augmentation, comprising random flips and rotations, was applied in real-time to increase variability and improve model generalization. Early stopping was implemented where applicable to prevent overfitting.

This dual-dataset approach allowed comparative evaluation under two conditions: clinically heterogeneous (U-Net) versus pre-processed and standardized (FCN and CNN). The overall training pipeline emphasized robustness, reproducibility, and adaptability across deployment scenarios.

4.2 Network Architecture

To evaluate architectural design choices in lung tumour segmentation, three models were developed and trained on corresponding datasets. U-Net was chosen for its dominance in biomedical image segmentation, while FCN and CNN were used to test minimal and moderate architectural baselines under simplified data conditions.

4.2.1 U-Net

The U-Net model was implemented using MATLAB's `unet` function and trained on the primary clinical dataset. The architecture comprises a symmetric encoder-decoder design with skip connections, allowing multiscale feature integration for precise tumour boundary localization. Key architectural details include:

- **Input size:** 256×256×1
- **Encoder depth:** 4 levels
- **Initial filters:** 32
- **Final layer:** Replaced with a custom `DiceTumorOnlyLossLayer` to optimize strictly for tumor class, improving detection sensitivity in class-imbalanced settings

To ensure stable training:

- **Gradient clipping** was applied (L2 norm threshold = 1)
- **L2 regularization** ($1e-4$) was included
- **Piecewise learning rate decay** (factor 0.2 every 10 epochs) was used

Early stopping was triggered after 8 non-improving validation steps, with **model checkpointing** enabled. At training completion, the best model was automatically restored for inference. Training progress was monitored using MATLAB's live plotting tools.

This setup was intentionally designed to run on a CPU-only system, demonstrating feasibility in low-resource environments. Total training time was approximately 27 minutes over 330 iterations.

4.2.2 Fully Connected Network (FCN)

To establish a performance baseline, a Fully Connected Network was trained on the Kaggle dataset. Each 2D CT slice was flattened into a 1D vector prior to being fed into the network. While this approach is computationally simple, it sacrifices spatial information critical for precise segmentation.

The FCN architecture comprised:

- **Input:** Flattened 256×256 grayscale images
- **Three dense layers** (512 units each) with **Swish activations**
- **Softmax layers** (non-standard in regression tasks, included for exploratory purposes)
- **Final regression layer** to predict tumor probabilities

The training protocol included:

- **Mini-batch size:** 32
- **Epochs:** 20
- **Shuffling:** Each epoch

Due to its large parameter count and lack of spatial encoding, the FCN quickly overfitted, limiting its clinical utility. This observation supported the need for architectures with built-in spatial priors.

4.2.3 Convolutional Neural Network (CNN)

To address the spatial limitations of FCN, a CNN was developed using the same dataset and hyperparameters. The CNN preserved spatial hierarchies through convolutional operations, allowing the model to learn local and global features.

The CNN architecture included:

- **Input:** 256×256 axial CT slices
- **Conv2D layers** with large (20×20) and medium (10×10) kernels
- **Activations:** ReLU, Swish, Sigmoid, and Softmax interleaved for nonlinear diversity
- **Final Conv2D (1×1)** followed by a regression layer to output tumor probabilities

The use of varied kernel sizes and activation functions was intentional, encouraging rich feature representations. Despite similar training settings to the FCN, the CNN demonstrated significantly better regularization, validating the importance of spatial modeling.

4.3 Technical Innovations and Implementation Highlights

This pipeline integrates several targeted innovations to address key challenges in medical image segmentation, specifically, data imbalance, limited computational resources, and the need for model interpretability. Each component is tailored to reinforce robustness, transparency, and clinical readiness.

4.3.1 Dice-Tumour-Only Loss Layer

A custom loss function was developed based on the **Dice coefficient**, [6] a similarity measure that quantifies overlap between predicted and ground truth masks. Unlike standard implementations that compute loss over all voxels, this version operates exclusively on tumor regions. This selective optimization reduces the disproportionate influence of background voxels—common in sparse tumor segmentation tasks—and improves **recall**, especially for small or irregular lesions.

4.3.2 Early Stopping and Checkpoint Recovery

Early stopping [17] is a regularization strategy that halts training when performance on a validation set ceases to improve, preventing overfitting. In this pipeline, a custom `OutputFcn` monitored validation loss and triggered termination after eight stagnant evaluations. Concurrently, *model checkpointing* saved the network’s state at each validation step. This ensured that training concluded at the most generalizable epoch and that the best-performing model was automatically restored for downstream use.

4.3.3 Test-Time Augmentation (TTA)

Test-Time Augmentation refers to applying transformations to input images during inference to simulate an ensemble of predictions. Here, five geometric variations—rotations and flips—were applied to each CT slice. The resulting probability maps were averaged, and the final segmentation was thresholded at $\tau = 0.10$ to generate a binary mask. This process reduced prediction variance and improved *robustness*, particularly in edge cases and noisy regions.

4.3.4 Post-Processing Module

Segmentation masks were refined using a *morphological filtering* routine that mimics radiological post-annotation protocols. This included:

- **Hole filling** to close interior gaps,
- **Area opening** to eliminate small, spurious activations,
- **Morphological closing** to smooth boundaries, and
- **Largest component retention**, which removes isolated false positives by preserving only the dominant tumor region.

These steps contribute to higher spatial coherence and reduced false detection rates.

4.3.5 Grad-CAM Explainability Framework

Gradient-weighted Class Activation Mapping (Grad-CAM) is a visualization technique that highlights input regions contributing most to a model's prediction. A multi-layer Grad-CAM framework was custom-built to fuse activation maps from multiple decoder stages. These fused CAMs were applied to:

- **True Positive (TP)** cases to verify learned features,
- **False Positive (FP)** and **False Negative (FN)** cases to localize decision errors.

This explainability framework supports clinical interpretability and model auditing by exposing decision-critical areas and failure modes.

4.3.6 Visual Analytics Suite

To ensure transparency and interpretability, a comprehensive analytics module was incorporated, including:

- *Boxplots and histograms* of segmentation metrics (Dice, Precision, Recall),
- *Triplet visualizations* of original CT slice, ground truth mask, and model prediction,
- *Automated Grad-CAM PDF reports*, suitable for publication or clinical discussion.

These tools assist not only in quantitative evaluation but also in qualitative insight, forming a bridge between technical performance and clinical relevance.

This complete training and evaluation pipeline exemplifies a pragmatic balance between methodological rigor and practical usability. Its modular architecture, interpretability features, and CPU-friendly implementation offer a reproducible and accessible solution for lung tumour segmentation across both academic research and resource-constrained clinical environments.

4.4 Experimental Constraints and Implementation Decisions

All experiments were conducted under constrained computational settings, prioritizing reproducibility, transparency, and clinical feasibility. Design choices regarding implementation tools, training strategies, and architectural complexity were therefore driven by empirical constraints observed during experimentation, rather than by maximizing computational capacity alone.

4.4.1 Reproducible and Clinically Feasible Implementation Framework

The experimental framework was implemented using a unified and deterministic processing environment that ensured consistent data handling, precise spatial alignment, and stable training behavior across repeated runs. Native support for volumetric medical imaging formats, deterministic preprocessing operations, and CPU-based execution enabled reliable experimentation without reliance on specialized hardware.

This choice reflects a clinically oriented perspective, where segmentation systems must operate robustly in environments with limited computational resources, such as regional hospitals or retrospective analysis pipelines.

4.4.2 Experimentally Rejected Alternatives and Design Trade-offs

Several alternative strategies were evaluated during preliminary experimentation and subsequently rejected based on empirical limitations observed in the target clinical setting:

- **Automated frameworks (e.g., nnU-Net):** Although powerful and competitive in benchmark challenges, these systems are heavily GPU-dependent and offer limited transparency in preprocessing and optimization stages, making controlled experimentation and methodological analysis difficult.
- **Full-volume training:** Training on entire CT volumes proved inefficient for sparse tumour distributions, leading to class imbalance, slower convergence, and reduced sensitivity to small lesions.
- **Exclusive reliance on public datasets:** Public-only datasets lacked the clinical heterogeneity observed in real patient data, limiting generalization and underrepresenting post-therapy variability.

These observations motivated the adoption of a controlled, patch-based, and preprocessing-aware pipeline tailored to the characteristics of clinical lung CT imaging.

4.4.3 Architecture Selection based on Empirical Suitability

The final architecture selection was guided by empirical suitability rather than architectural novelty. A U-Net–based fully convolutional network was adopted due to its proven ability to preserve spatial context, compatibility with patch-wise training, and stable convergence under limited data and computational constraints.

Alternative architectures were explored in subsequent experiments (Chapter V), allowing performance-driven comparison rather than priori assumptions.

4.4.4 Network Architecture Specification for Reproducibility

To ensure transparency and reproducibility, the internal structure of the U-Net architecture used in this study is detailed below. This specification enables independent verification and facilitates comparison with related segmentation frameworks.

Layer	Layer Type	Filters	Kernel Size	Activation	Output Shape
1	Input	–	–	–	256×256×1
2–3	Conv2D	32	3×3	ReLU	256×256×32
4	MaxPooling2D	–	2×2	–	128×128×32
...	...	...	...	...	...
21	Output Layer	1	1×1	Sigmoid	256×256×1 (mask)

Table 4. Architectural specification of the proposed U-Net model.

4.4.5 Training Configuration and Computational Constraints

The training hyperparameters and computational environment used in this study are summarized in table 5 and table 6. These parameters were selected through preliminary experimentation and reflect a balance between convergence stability, segmentation accuracy, and computational feasibility under constrained hardware conditions.

A **batch size of 32** was chosen as a compromise between memory limitations and gradient stability, ensuring reliable convergence without exceeding system resources. The **Adam optimizer** was employed due to its robustness in handling sparse gradients and its widespread adoption in medical image segmentation tasks. The **learning rate (1×10^{-4})** was empirically determined to provide stable optimization without oscillatory behavior, particularly when training with Dice-based loss functions.

The **Dice loss function**, computed exclusively on the tumor class, was selected to directly address the severe class imbalance inherent in lung tumor segmentation, where background voxels dominate the image volume. By focusing optimization on the foreground class, the network was encouraged to prioritize lesion detection rather than background accuracy.

To prevent overfitting and unnecessary computation, **early stopping** was applied with a patience of eight epochs, halting training once validation performance ceased to improve. Lightweight **data augmentation**, consisting of random flips and rotations, was introduced to enhance robustness to spatial variability without altering anatomical plausibility.

All experiments were executed in a **CPU-only environment**, resulting in an average training time of approximately **27 minutes per model**. This constraint-informed configuration underscores the feasibility of the proposed pipeline in resource-limited clinical or research settings, reinforcing the study's emphasis on reproducibility and accessibility rather than reliance on specialized hardware.

Parameter	Value
Batch Size	32
Learning Rate	1e-4
Optimizer	Adam
Loss Function	Dice (tumor only)
Epochs	Early stopping (patience = 8)
Augmentation	Random flip & rotate
Training Time	~27 minutes (CPU)

Table 5. Training hyperparameters used for model optimization and learning configuration.

Component	Detail
System	Intel i7, 16GB RAM
OS	Windows 11
MATLAB Version	R2022a
GPU	None (CPU-only)
Libraries	Image Processing, Deep Learning Toolboxes

Table 6. Hardware and software environment used for model training and evaluation

CHAPTER V: EXPERIMENTAL RESULTS, EVALUATION AND DISCUSSION

5.1 Experimental Setup and Evaluation Protocol

A rigorous and multifaceted quantitative evaluation was essential to assess the performance of the proposed lung tumour segmentation models. Given the challenges posed by class imbalance, tumour variability, and the subtle nature of many lesions in medical imaging, a combination of standard evaluation metrics was employed to capture different aspects of model performance.

The segmentation models evaluated in this study include three prominent deep learning architectures: U-Net, Fully Convolutional Networks (FCN), and a baseline Convolutional Neural Network (CNN). Despite their architectural differences, all models were assessed using a consistent set of evaluation metrics to enable a fair and comparative analysis.

The metrics used include the Dice Similarity Coefficient (DSC), Precision, Recall, Accuracy, and False Positive Rate (FPR). Each metric offers unique insights: DSC measures the overlap between predicted and ground truth masks, Precision reflects the proportion of correct positive predictions, Recall assesses the model's sensitivity to true tumour regions, Accuracy provides a broad view of correct classifications, and FPR evaluates the model's tendency to generate false alarms, particularly on background regions.

To ensure robust evaluation, the models were assessed on both validation patches and full axial slices. The evaluation pipeline incorporated test-time augmentation (TTA) and post-inference filtering, implemented using a custom MATLAB-based framework. This comprehensive setup was designed to account for both local segmentation fidelity and global generalization to unseen data.

While some metrics indicated seemingly strong performance, particularly in terms of background classification, others revealed significant limitations in detecting small or faint tumours. These observations reinforce the complexity of the segmentation task and highlight the need for balanced evaluation criteria that move beyond overall accuracy. The following subsections provide a detailed discussion of each metric, its role in medical image analysis, and its implications for model performance in this context.

5.2 Quantitative Evaluation Metrics

5.2.1 Dice Similarity Coefficient (DSC)

The Dice Similarity Coefficient (DSC) is a widely adopted overlap-based metric used to evaluate the spatial agreement between predicted segmentation outputs and ground truth labels. In the context of this study, it was applied to assess the similarity between binary tumour masks generated by the models and the corresponding manual annotations.

The classical form of the Dice coefficient is defined as:

$$\text{DSC} = \frac{2|P \cap G|}{|P| + |G|}$$

where:

- P denotes the set of predicted positive pixels (tumour region),
- G is the set of ground truth positive pixels,
- $|P \cap G|$ is the number of pixels correctly identified as tumour (true positives),
- $|P|$ and $|G|$ represent the total number of predicted and actual tumour pixels, respectively.

This formulation returns values ranging from 0 (no overlap) to 1 (perfect overlap), making it a suitable and interpretable measure of segmentation quality in medical imaging tasks. Dice scores were computed using MATLAB's built-in `dice()` function, which strictly adheres to this standard definition without applying numerical regularization (i.e., no added ϵ). Consequently, when both P and G are empty—indicating the absence of tumour in both prediction and ground truth—the function returns NaN. These cases were appropriately handled in post-processing to avoid introducing statistical bias.

In this study, DSC was the primary metric used to evaluate the performance of the U-Net model trained on the pre-processed primary dataset. Dice scores were computed at both the patch level and full-slice level, incorporating post-inference thresholding and test-time augmentation (TTA). This two-level evaluation enabled a more detailed analysis of model behavior, particularly in challenging scenarios involving small or low-contrast lesions, or background-only slices.

Despite the standardized pipeline and model tuning, Dice scores remained consistently low, reflecting limited overlap between predicted and annotated tumour regions. Most predictions failed to capture lesion boundaries accurately, especially for

small or ambiguous tumours. This result highlights the inherent difficulty of segmenting subtle pathological structures in lung CT scans and points to the U-Net model's limited generalization under severe class imbalance conditions.

The distribution of Dice scores was notably skewed toward zero, with only a few high outliers. This pattern emphasizes the inconsistency in spatial agreement across test samples. Figure 5 illustrates this with a boxplot and histograms of segmentation metrics at a low confidence threshold ($\tau = 0.10$), showing that Dice, Precision, and Recall scores cluster near zero in most cases. These distributions reveal the combined effect of data imbalance and tumour ambiguity on model sensitivity and specificity. The figure highlights the inherent complexity of segmenting small or ambiguous tumour lesions in lung CT scans, particularly under class imbalance and low-contrast conditions. These challenges validate the design choices made in this study, including the implementation of tailored data augmentation techniques and the adoption of specialized loss functions such as Dice loss and focal loss. These methods were specifically chosen to enhance model sensitivity to rare tumour regions and mitigate the effects of imbalance. While Dice scores remained modest across much of the dataset, they served as a critical diagnostic tool, revealing meaningful areas for targeted improvement. Rather than indicating failure, these outcomes reflect the difficulty of the task and provide actionable insights for refining model architecture, data sampling strategies, and training dynamics. Overall, the analysis confirms the value of the methodological approach and offers a clear direction for future optimization.

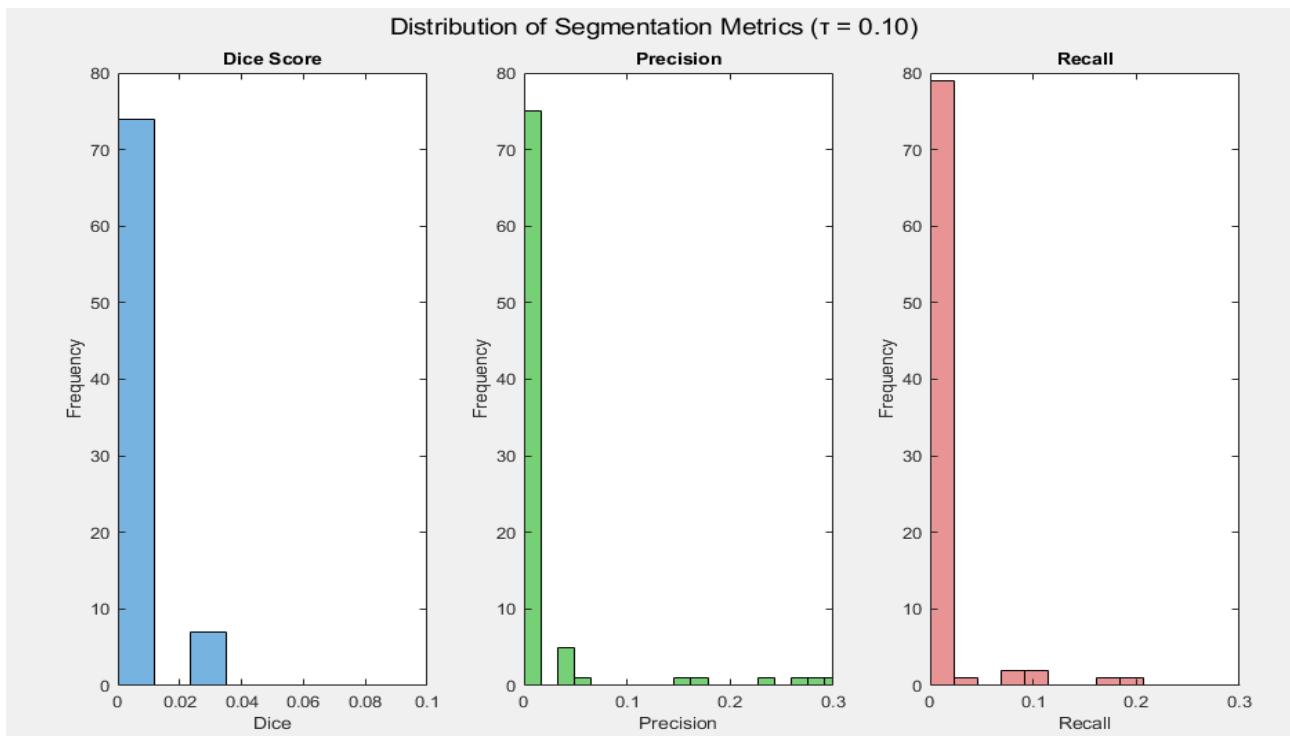


Figure 5: Boxplot of segmentation metrics shows that Dice scores cluster around zero, with only a few high outliers.

5.2.2 Precision, Recall, Specificity

To further assess segmentation quality beyond spatial overlap, additional binary classification metrics were computed, offering deeper insight into model behaviour. These included *Precision*, *Recall* (Sensitivity), and *Specificity*, which together help characterize both false positive and false negative patterns. These metrics were calculated based on pixel-wise comparisons between the predicted segmentation masks and the ground truth annotations, providing valuable diagnostic indicators, particularly in the context of small or irregular tumour regions.

Let **P** denote the binary **prediction mask** and **G** the **ground truth mask**, where foreground pixels (i.e., pixel value = 1) correspond to tumour regions and background pixels (value = 0) to non-tumour tissue. These definitions allow the computation of standard performance metrics as follows:

- Precision (Positive Predictive Value)

Measures the proportion of predicted tumour pixels that are correct (i.e., true positives over all predicted positives). A high precision indicates fewer false positives.

$$\text{Precision} = \frac{|P \cap G|}{|P|}$$

- Recall (Sensitivity)

Represents the ability of the model to detect true tumour pixels (i.e., true positives over all actual tumour pixels). Higher recall indicates better sensitivity to lesions.

$$\text{Recall} = \frac{|P \cap G|}{|G|}$$

- Specificity

Reflects the proportion of background pixels correctly identified as non-tumour, indicating the model's capability to avoid false positives in non-tumour areas.

$$\text{Specificity} = \frac{|(1 - P) \cap (1 - G)|}{|(1 - G)|}$$

In this study, **Precision**, **Recall**, and **Specificity** were computed using MATLAB's pixel-wise evaluation framework, applied to both individual patches and entire CT slices.

This setup ensured a granular view of the model's performance under the pronounced class imbalance inherent in lung CT images, where tumor regions often make up a very small portion of each slice.

The evaluation yielded the following results on the validation set:

- **Precision:** 0.081
- **Recall:** 0.414
- **Accuracy:** 94.3%
- **False Positive Rate (FPR):** approximately 26.7% on background-only slices

These values highlight several important trends. The relatively high **Accuracy** is influenced by the overwhelming proportion of background pixels, which tend to be correctly classified. However, the **Precision** remains low, indicating a substantial number of false positive predictions within tumour regions. **Recall**, on the other hand, is comparatively higher, suggesting that the model demonstrates reasonable sensitivity in identifying true tumour areas, even if not consistently. The elevated **False Positive Rate** on background slices underscores the model's occasional confusion between tumour and non-tumour textures, particularly in structurally complex regions of the lung.

These outcomes reflect both the inherent difficulty of the segmentation task and the limitations imposed by class imbalance and feature ambiguity. Nonetheless, they also confirm the value of the evaluation approach used in this study. By combining Precision, Recall, and Specificity with Dice and Accuracy, the analysis captures a full spectrum of performance, highlighting strengths in tumour detection as well as areas requiring further refinement.

This figure presents Dice, Precision, and Recall scores for tumour regions, along with the False Positive Rate (FPR) for background slices. Dice and Precision scores show low medians and tight interquartile ranges, indicating limited segmentation overlap and a high number of false positives within tumour predictions. Recall displays broader variability with several high outliers, suggesting that some tumours were successfully detected despite frequent misses. The FPR also shows considerable spread, highlighting inconsistencies in background classification, likely influenced by local texture and structural complexity. These patterns underscore the difficulty of detecting small lesions under class imbalance and align with the broader findings discussed in Chapter 6 regarding model limitations and potential improvements.

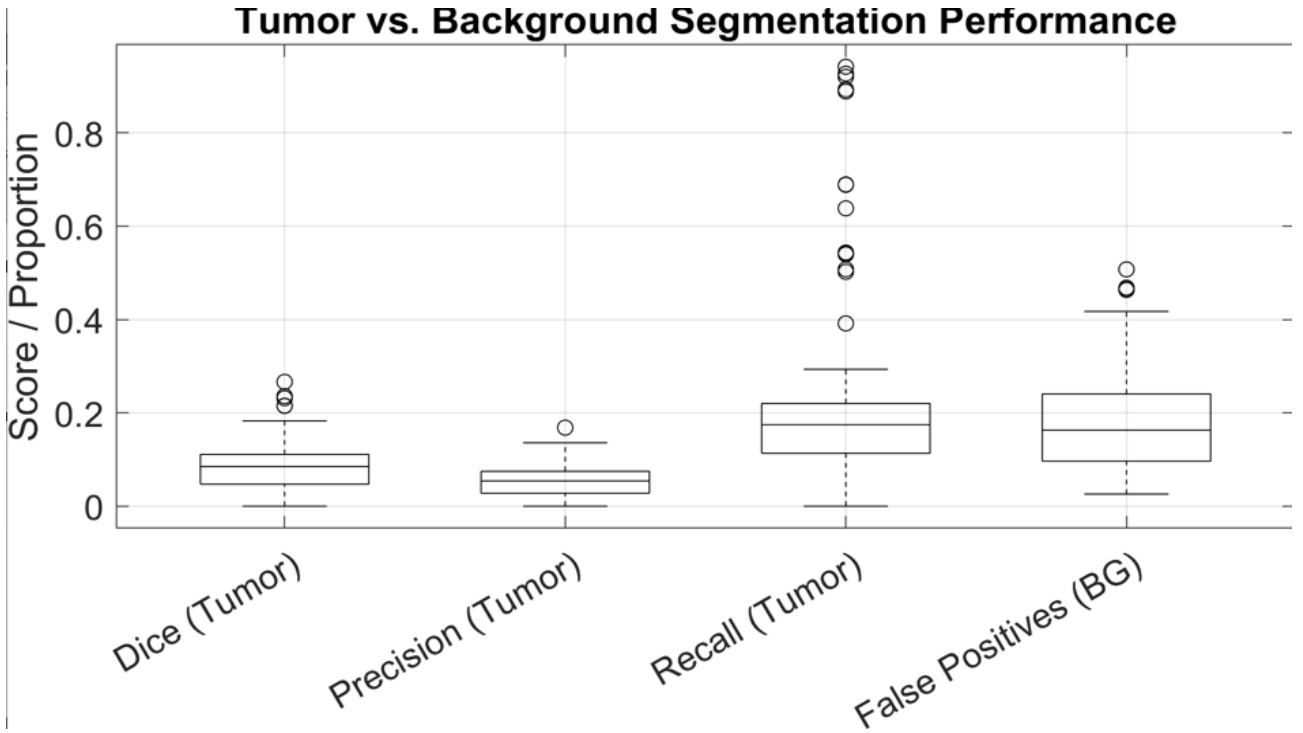


Figure 6: Boxplot distribution of segmentation performance metrics across the validation set.

5.2.3 Hausdorff Distance

Beyond overlap- and pixel-based metrics, boundary accuracy was evaluated using the Hausdorff Distance (HD) and its robust variant, HD95. These metrics capture the spatial discrepancy between predicted and ground truth contours by measuring the distance between corresponding boundary points. While Dice, Precision, and Recall reflect volume-based similarity, Hausdorff metrics provide complementary insight into the worst-case boundary error, which is particularly relevant in clinical contexts where precise tumour delineation impacts treatment planning and radiation targeting.

Formally, for sets of boundary points B_P (prediction) and B_G (ground truth), the directed Hausdorff Distance is defined as:

$$H(B_P, B_G) = \max_{p \in B_P} \min_{g \in B_G} d(p, g)$$

This metric returns the maximum distance from a point on one boundary to the closest point on the other, thereby quantifying the worst-case segmentation deviation. **HD95**, in contrast, computes the 95th percentile of all boundary distances, offering a more outlier-robust alternative that remains sensitive to local boundary errors.

In this thesis, Hausdorff metrics were computed using custom MATLAB routines that employed boundaries for boundary extraction and pairwise distance calculations. Due

to the high computational cost and sensitivity to segmentation completeness, HD and HD95 were calculated on a selected subset of tumour-present slices, chosen to represent a diverse range of lesion sizes and shapes. This targeted approach ensured meaningful interpretation while maintaining computational feasibility.

While HD values were not the primary numerical focus of the quantitative results, qualitative inspection of boundary deviations—particularly in under segmented lesions—revealed significant localized errors. These deviations highlight the importance of boundary-aware evaluation and motivate the potential integration of edge-sensitive loss functions or shape-based regularization in future model refinements.

In well-segmented cases, HD95 provided valuable insight into contour alignment, revealing that when the model succeeded in detecting tumours, it often approximated their general shape reasonably well. However, limited recall across the dataset constrained the overall utility of HD metrics, since many slices lacked sufficient true positive structure for boundary comparison.

Ultimately, Hausdorff metrics served as a complementary layer of analysis, reinforcing findings from Dice and pixel-wise metrics while pointing toward directions for architectural and algorithmic enhancements. They also underscore the need for more boundary-aware objectives in segmentation training, particularly when precision at lesion margins is clinically critical.

5.2.4 Patch-Level Evaluation at Low Confidence Threshold

To further characterize model performance in early-stage detection scenarios, evaluation was also conducted on validation patches at a low confidence threshold ($\tau = 0.10$). This setting prioritizes sensitivity, capturing even minimal activation in predicted masks. While this naturally results in modest numerical scores, the metrics provide essential insight into the model's behaviours under relaxed prediction conditions.

The average Dice score on validation patches was 0.017, with an average Precision of 0.023 and recall of 0.019. Median values for all three metrics were 0.000, indicating that many patches contained either small lesions that were difficult to detect or no true positive overlap at this threshold. Nonetheless, the presence of non-zero mean values highlight cases in which the model was able to partially identify tumour structures, especially in larger or more distinct lesions.

Notably, the background classification accuracy remained high (90.7%), with a relatively low false-positive rate of 2.13%, demonstrating that the model effectively

discriminated tumour from non-tumour regions even in isolated patches. The contrast between precision and recall underscores the importance of balancing sensitivity and specificity when tuning segmentation thresholds in post-processing.

These results, while quantitatively modest, serve as a valuable diagnostic lens into segmentation behaviour in sparse and ambiguous contexts. They validate the design of the loss functions and thresholding strategies used in this study and reinforce the role of patch-wise evaluation in identifying underrepresented edge cases. Furthermore, the analysis supports continued refinement in data augmentation, architectural tuning, and post-inference filtering to improve performance on clinically challenging samples.

5.3 QUANTITATIVE EXPERIMENTAL RESULTS

5.3.1 Preprocessing Effectiveness

Performance is reported in terms of DSC, Precision, Recall, and Hausdorff Distance. An effective preprocessing pipeline is essential for ensuring meaningful model training, especially in the context of medical image segmentation, where class imbalance and low-contrast targets pose significant challenges. In this study, a multi-step pipeline was designed to enhance tumour visibility and spatially isolate regions of interest prior to model inference.

To focus the network's attention on tumour-bearing regions, a structured patch extraction strategy was implemented. CT volumes were first subjected to intensity normalization, followed by contrast-limited adaptive histogram equalization (CLAHE) to improve soft-tissue contrast. Subsequently, lung segmentation masks were generated to isolate the relevant anatomical area and suppress irrelevant background regions.

Figure 7 illustrates this preprocessing sequence using a representative CT slice: from the original scan (left) to binary lung segmentation (middle), and finally, to the masked lung region (right). The final masked image shows a well-defined lung field with improved tumor visibility, preparing the image for accurate and focused segmentation.

Once the lung area was isolated, tumour masks were extracted into fixed-size patches of 256×256 pixels. These patches were centered on bounding boxes of labeled tumours using region properties such as centroid and area. The resulting patch dataset

significantly reduced the class imbalance that typically arises when background pixels dominate in full-slice CT scans.

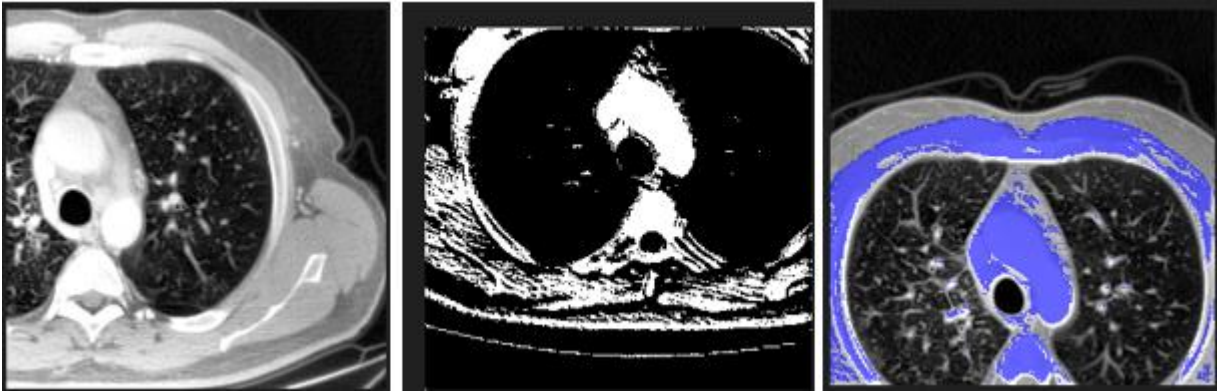


Figure 7. Preprocessing pipeline overview. Left: Original CT slice. Center: Binary segmentation mask highlighting lung regions. Right: Preprocessed CT with lung mask applied. CLAHE and intensity normalization enhance tumor visibility while reducing noise from surrounding tissue.

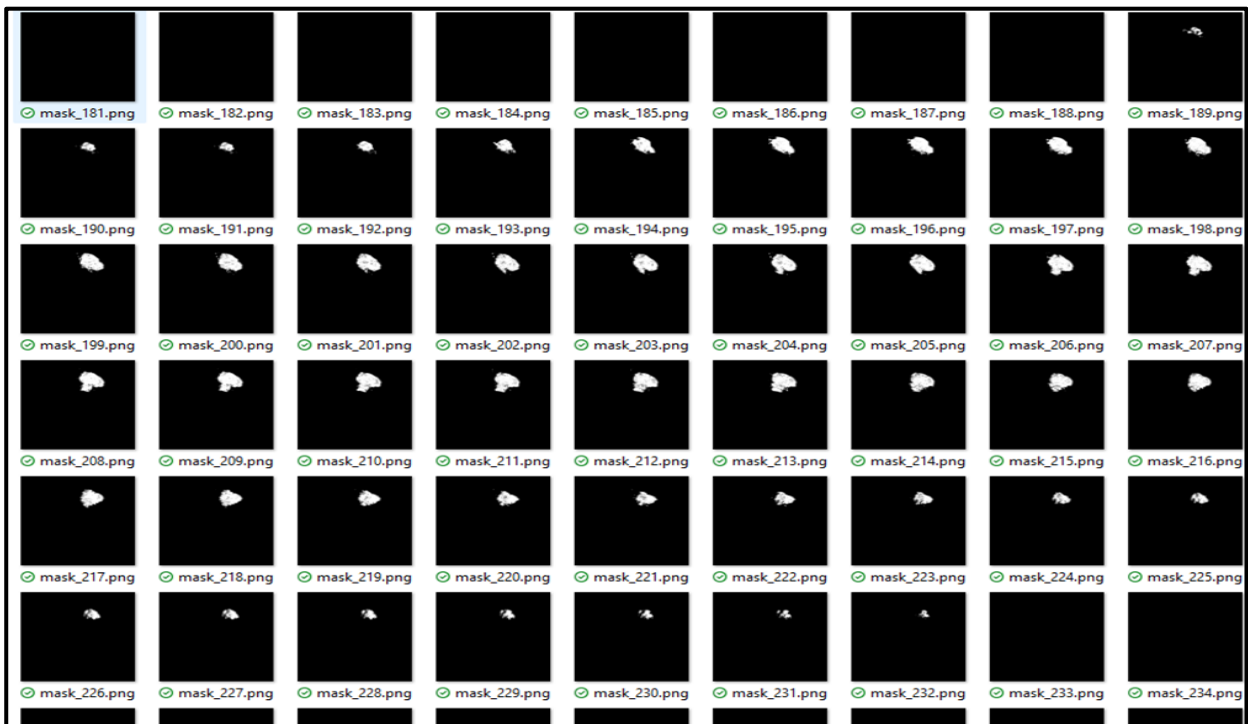


Figure 8. Representative tumour masks used in the training dataset. Patches were extracted around each tumour region, preserving spatial alignment and anatomical context. The diversity of shapes underscores the need for augmentation and robust loss functions.

This preprocessing approach yielded several benefits. First, the patch-level training ensured that each sample contained sufficient tumour information, which improved learning stability and prevented model collapse toward background prediction. Second, the use of CLAHE and percentile-based normalization enhanced the contrast between lesion and lung parenchyma, particularly in faint or irregular tumours. Third, consistent alignment between tumour patches and CT slices preserved anatomical integrity throughout the learning process.

Nevertheless, preprocessing alone could not resolve all challenges. While it improved convergence and reduced false negatives for large, well-defined tumours, small and low-contrast lesions remained difficult to detect, even after class balancing. Furthermore, the use of 2D slices limited the model's ability to capture inter-slice continuity, which is often crucial for detecting ambiguous lesions. Despite these limitations, the preprocessing pipeline laid a solid foundation for downstream learning and interpretability components in the system.

Having established the consistency and quality of the extracted tumour masks, we now assess the effectiveness of the preprocessing techniques applied prior to model training. These steps—including intensity normalization, contrast enhancement, and mask alignment—played a critical role in preparing the data for robust and generalizable learning.

Robust Intensity Normalization

To address scanner variability and intensity heterogeneity in raw CT volumes, robust intensity normalization was applied. Each volume's voxel intensities were scaled using the 1st and 99th percentile values, suppressing the influence of extreme outliers while preserving tissue contrast. The resulting values were clipped to the $[0.10, 1.0]$ range and normalized across the entire volume. This ensured that every CT scan fed into the model had a consistent intensity distribution, which is essential for stabilizing the learning process. This technique also helps standardize inputs across patients and acquisition protocols, allowing deep learning models to focus on anatomical features rather than noise or acquisition artifacts.

Adaptive Histogram Equalization (CLAHE) with Rayleigh Distribution

To enhance local contrast and emphasize subtle tissue differences, Contrast Limited Adaptive Histogram Equalization (CLAHE) was applied slice-wise, using a Rayleigh distribution to control the redistribution of intensities. CLAHE increases the dynamic range in low-contrast regions while limiting over-enhancement in homogeneous areas, thereby suppressing noise. This is especially useful in CT scans of the lungs, where tumours often appear faint or embedded in regions of low contrast. By

applying this technique after normalization, each slice achieves improved visibility of structural boundaries, ensuring a more uniform appearance across scans of differing quality or acquisition parameters.

Voxel-Perfect Mask Alignment

For every CT volume, spatial alignment between the image and its corresponding segmentation mask was verified and corrected when necessary. Misalignment was addressed using 3D nearest-neighbour interpolation to resize the mask to match the image dimensions, preserving binary labels. This step was essential to guarantee that each voxel in the input volume corresponded exactly to its labelled region in the segmentation mask. Proper alignment is especially critical for 3D tumour segmentation tasks, where accurate spatial correspondence ensures reliable supervision during model training and allows for precise localization in downstream tasks like patch extraction.

Smart Patch-Based Sampling and Augmentation

Instead of random sampling, a structured patch extraction strategy was used to focus learning on clinically relevant regions—specifically, tumour areas. Tumour locations were identified using region props applied to the segmentation masks, and fixed-size patches (256×256 pixels) were extracted, centered around the tumour bounding boxes. Each patch was further augmented using geometric transformations such as horizontal and vertical flips and 90-degree rotations to introduce diversity. This anatomically guided augmentation avoids the redundancy of background-dominant patches and improves model generalization by simulating variations in tumour shape, size, and orientation. Padding and cropping were applied where necessary to maintain consistent patch size, preparing the data effectively for deep learning.

The left panel shows the original CT slice before preprocessing, while the right panel illustrates the result after applying Adaptive Histogram Equalization. The enhancement improves local contrast and highlights anatomical structures, facilitating better tumour visibility—crucial for accurate patch extraction and segmentation learning.

Comparison between a raw CT slice (left) and the same slice after preprocessing (right), showing the effect of adaptive histogram equalization. The enhanced contrast and improved visibility of anatomical structures—particularly in low-intensity regions—illustrate the effectiveness of the preprocessing pipeline in preparing input data for segmentation.

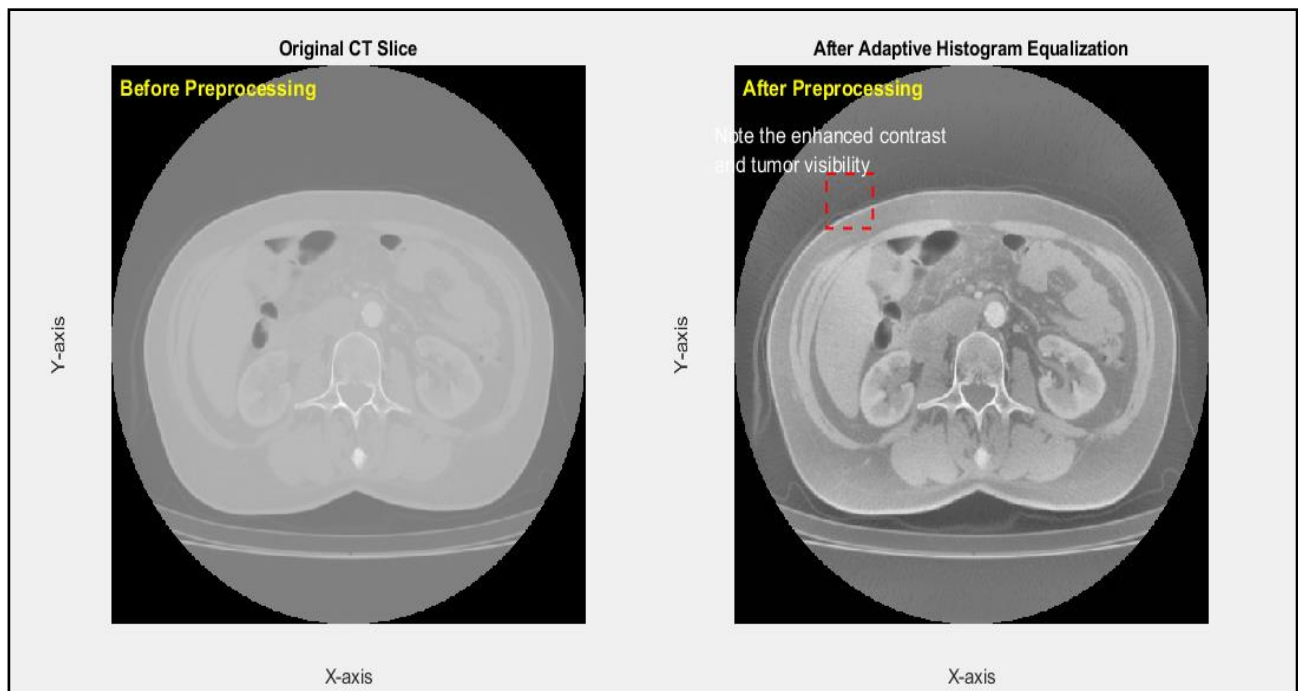


Figure 9. *Effect of preprocessing on CT image contrast.*

5.3.2 Model Performance Across Architectures

Three distinct convolutional network architectures—2D U-Net, Fully Convolutional Network (FCN), and a custom shallow Convolutional Neural Network (CNN)—were evaluated for pulmonary lesion segmentation on 2D CT slices. Each model was trained using balanced and pre-processed patches, with Dice-based loss employed to address class imbalance and highlight small lesion regions.

U-Net demonstrated strong early learning capabilities, achieving peak validation accuracy of 95.18% by the second epoch. This was aided by its encoder–decoder structure with skip connections, which preserved spatial resolution. However, performance on the test set indicated diminished generalization, particularly for small or low-contrast lesions, suggesting the model's limitations in capturing complex spatial hierarchies without 3D context.

FCN, while architecturally simpler, showed faster convergence but slightly lower validation performance overall. The absence of skip connections resulted in reduced fine-grained segmentation accuracy, particularly at lesion boundaries. Nevertheless, it maintained competitive accuracy (~93.7%) with reduced computational cost, making it viable for rapid prototyping or deployment in resource-limited settings.

The custom CNN, a shallow architecture optimized for CPU-only environments, exhibited slower learning and reduced accuracy (~89.5% peak validation accuracy). Its limited receptive field and depth constrained its capacity to model spatial

dependencies effectively. Nevertheless, it remained stable throughout training and served as a baseline for architectural comparisons.

Optimization Behavior and Convergence Analysis

The training processes were monitored through both accuracy and loss trajectories. All models utilized adaptive learning rate scheduling, early stopping, and gradient clipping to ensure training stability.

Accuracy Dynamics

For the U-Net, training accuracy increased sharply within the first epoch and stabilized by epoch two. Validation accuracy peaked early (Epoch 2: **95.18%**) before decreasing due to overfitting in subsequent iterations (lowest at **53.30%** during Epoch 3), and later partially recovering (Epoch 4: **94.23%**). This fluctuation highlights sensitivity to training distribution variance and underscores the necessity for robust regularization.

Loss Trends

Loss curves exhibited an initial rapid decline, particularly within the first 50 iterations, indicating efficient early feature learning. For U-Net, the validation loss stabilized around **0.9462**, although transient spikes coincided with validation accuracy drops. This pattern reflects typical overfitting behavior, mitigated by early stopping.

Model Robustness and Generalization Strategies

Despite minor instabilities, validation curves across all models remained broadly stable, reflecting effective regularization techniques:

- Gradient clipping constrained exploding gradients.
- Adaptive learning rates ensured controlled convergence.
- Early stopping preserved model generalizability by halting training upon detection of performance degradation.

These strategies enabled consistent training under CPU-based constraints without compromising robustness.

Final performance metrics for the U-Net model:

- Best Validation Accuracy: 94.23%
- Final Mini-batch Training Accuracy: ~53%
- Final Validation Loss: ~0.9462

Addressing Practical Constraints

To meet the demands of clinical deployment and limited hardware environments, several mitigation strategies were implemented:

Challenge	Mitigation Strategy
Class imbalance (small lesions)	Dice loss to enhance sensitivity to minority regions
Risk of overfitting	Dropout, L2 regularization, and early stopping
Limited hardware (CPU-only)	Reduced model depth, small batch sizes, and shallow CNN
Training instability	Gradient clipping and dynamic learning rate scheduling

Table 7. Summary of key implementation challenges and corresponding mitigation strategies employed during model development. These solutions address common issues in medical image segmentation, including class imbalance, computational limitations, and training stability.

5.4 Visual Results and Qualitative Analysis

Beyond numerical evaluation, **visual analysis plays a vital role** in the assessment of segmentation quality—especially in the context of medical imaging, where clinical interpretability and decision support are paramount. While quantitative metrics such as Dice, Precision, and Recall provide useful summaries of performance, **they cannot capture spatial misalignment, anatomical nuance, or error localization**. Thus, qualitative analysis through visual tools is indispensable for gaining deeper insight into model behaviour, trustworthiness, and failure scenarios.

In this study, visual diagnostics were employed with two key objectives:

1. **To enhance interpretability**, by revealing the spatial reasoning behind model predictions.
2. **To ensure clinical relevance**, by allowing side-by-side comparisons between predicted tumour regions and expert-annotated ground truth across both 2D slices and reconstructed 3D volumes.

A multi-level visual explainability pipeline was developed, composed of the following components:

- **Overlay comparisons** of predictions and ground truth
- **Slice-wise and 3D volumetric renderings**
- **Grad-CAM–based attention visualization**

This visual analysis corroborates the trends observed in the quantitative results while highlighting relevant failure cases and regions of model uncertainty. In particular, visual inspection confirms improved delineation of tumor boundaries and a reduction of false positives in surrounding lung tissue, supporting the clinical applicability of the proposed approach and motivating the post-inference refinement procedures discussed in Section 5.5.

5.4.1 Ground Truth vs. Prediction Overlays

To intuitively assess alignment between model output and manual annotations, binary tumour masks, both predicted and ground truth, were superimposed onto the original CT slices using color-coded transparency. These overlays enabled the visual distinction of:

- True Positives (accurate overlap)
- False Positives (predicted but not annotated)
- False Negatives (missed tumour regions)

Implemented in MATLAB using `imshowpair`, `hold on`, and custom contour plotting, these overlays highlighted key segmentation challenges such as under-segmentation, over-segmentation, and boundary drift. They also offered insight into how tumour size, contrast, and anatomical location influenced model accuracy.

Consistent with quantitative analysis, well-defined tumours were segmented with high spatial fidelity. In contrast, small, low-contrast, or irregular lesions were more prone to misclassification, often showing incomplete boundary coverage or total omission. These insights directly explain the lower Dice and Recall values observed in Section 5.1, particularly for small or low-contrast lesions.

Visual comparison illustrates that while the model reliably localizes tumours, it sometimes struggles with complete lesion coverage—particularly for atypical or subtle tumour presentations. Fragmented predictions and misalignment in anatomically complex areas (e.g., near vasculature) highlight the model’s limitations and the importance of visual inspection in model evaluation.

These overlays bridged computational results with human judgment, informing both architectural refinement and post-processing strategies. As such, they represent an essential component of the broader explainability and validation toolkit.

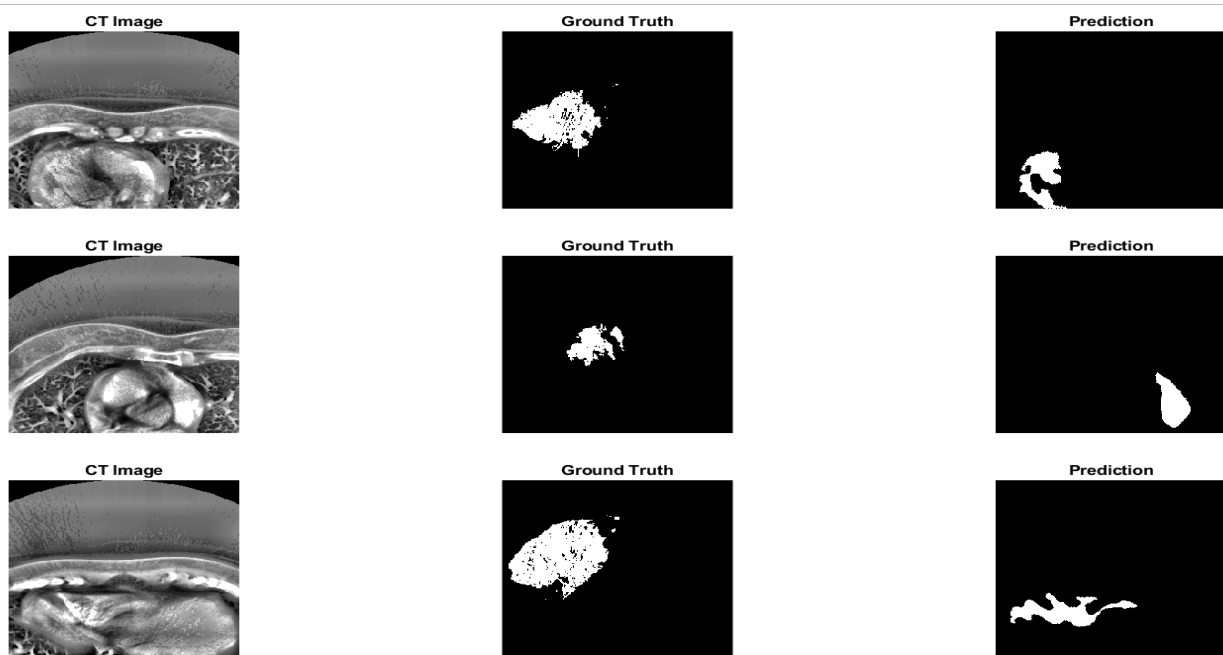


Figure 10. CT slices, ground truth masks, and corresponding model predictions.

5.4.2 Slice-wise and 3D Renderings

Axial slice-wise visualizations were employed to track segmentation consistency throughout the volume. Additionally, **3D reconstructions** were generated using MATLAB’s isosurface and patch functions to provide volumetric context—offering clinicians insight into **tumour size, shape, and anatomical location**.

These renderings enabled:

- **Spatial consistency checks** across slices
- **Detection of fragmented or spurious predictions**
- **Qualitative validation of tumour continuity**

In successful cases, segmentations displayed smooth, coherent volumes. In contrast, failed cases revealed **disjointed structures or scattered false positives**, reinforcing weaknesses flagged in metric evaluation.

To supplement the 2D slice-wise analysis, 3D renderings were generated from the post-processed segmentation masks to enhance spatial interpretability. As illustrated in Figure 11, these renderings allow a volumetric appreciation of the tumor's shape, continuity, and relation to surrounding structures. The left and middle panels show the raw CT volume from different angles, while the right panel isolates the segmented tumor using isosurface extraction. This visualization not only aids in validating the anatomical plausibility of the predictions but also aligns with radiological workflows that rely on 3D inspection for treatment planning and assessment. Integrating such renderings into the evaluation pipeline supports more intuitive and clinically meaningful assessment of model outputs.

Left: axial view of the full volumetric CT scan. Middle: oblique view showing spatial depth. Right: the segmented tumor region visualized in red after morphological post-processing. These visualizations provide a spatial understanding of tumor location, continuity, and anatomical context, beyond what can be observed in single slices.

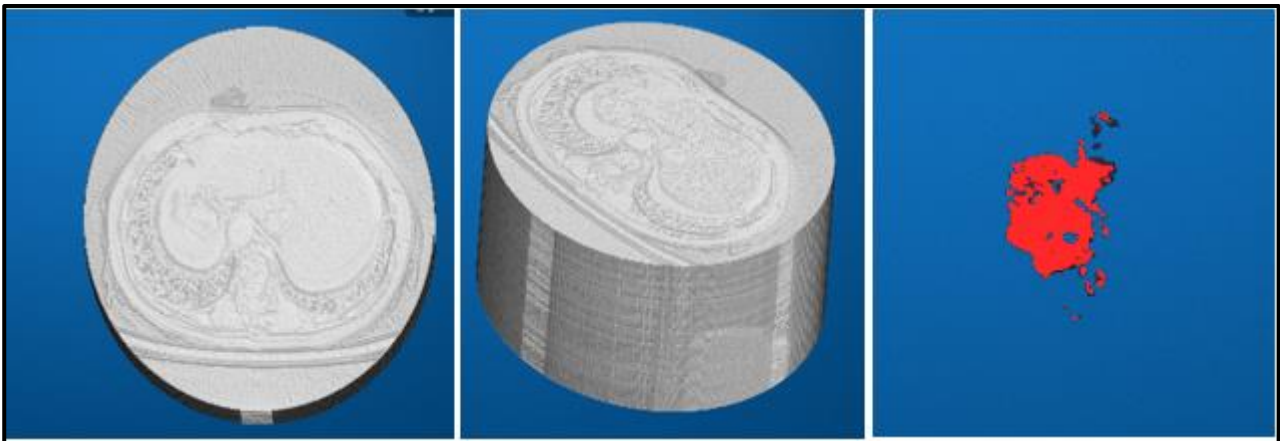


Figure 11. 3D volumetric rendering of lung CT and segmented tumor.

5.4.3 Grad-CAM Visualization and Interpretation

To further support interpretability, **Gradient-weighted Class Activation Mapping (Grad-CAM)** was employed. Grad-CAM generates heatmaps indicating **which regions of the input image most influenced the model's prediction**—offering a transparent view into the model's decision-making process.

Adapted for volumetric CT inputs, Grad-CAM was computed from deep convolutional layers, with activations fused across slices to approximate 3D attention. These heatmaps were overlaid on CT slices to highlight:

- Correct focus on tumour regions in successful cases
- Misalignment or inattentiveness in false negatives or false positives

This revealed both **strengths and limitations** of the model's internal representation. For instance, in true positive cases, activation maps often centered on tumour cores. However, in many failure cases, **Grad-CAM highlighted non-pathological regions**, suggesting biased or inattentive feature learning.

While Grad-CAM enriched interpretability, its use in **automated post-inference filtering** had mixed results (discussed in Section 5.3). Specifically, **false exclusion of low confidence but partially correct predictions** led to slight reductions in Recall, highlighting the challenge of directly translating explainability into improved performance.

5.5 Post-Inference Analysis and Explainability

To improve the clinical reliability of raw model outputs, a structured **post-inference filtering pipeline** was introduced. This stage aimed to:

- **Suppress false positives**
- **Improve spatial coherence**
- **Retain clinically plausible tumour structures**

5.5.1 Morphological and Size-based Filtering

Predicted tumour masks frequently exhibited noisy artifacts, including isolated pixels, small, disconnected regions, or internal voids. To mitigate these inconsistencies and enhance anatomical plausibility, standard morphological operations were employed:

- **imfill**: to fill internal holes within segmented regions

- **imclose**: to smooth contours and connect adjacent regions
- **bwareaopen**: to remove small, spurious objects below a defined area threshold

These operations effectively suppressed implausible segmentations, particularly those arising from background noise or partial activations. While this post-processing step improved the overall structural coherence of the masks, it occasionally eliminated small but valid tumour regions—potentially reducing recall. Nonetheless, the improved spatial consistency and anatomical realism contributed to greater clinical plausibility and interpretability of the final segmentation outputs.

5.5.2 Grad-CAM Generation Process

A novel and clinically motivated component of the post-inference evaluation pipeline involved leveraging **Gradient-weighted Class Activation Mapping (Grad-CAM)** to assess the semantic validity of the model's predictions. Rather than relying solely on pixel-level agreement with ground truth, this strategy introduced an attention-based validation mechanism that directly interrogates the model's internal decision-making focus. The Grad-CAM generation process was integrated as a quality control filter to identify and discard low-confidence predictions, thereby improving the reliability of the final segmentation output.

As illustrated in **Figure 12**, the workflow begins with the input of a predicted tumour mask, followed by the generation of corresponding Grad-CAM heatmaps during **test-time augmentation (TTA)**. These heatmaps are overlaid with the predicted segmentation masks to visualize alignment between the model's attention and its output. A confidence metric is then computed by calculating the percentage of spatial overlap between the activation region and the predicted tumour area. Predictions with less than **40% overlap** were flagged as unreliable and systematically excluded from the final segmentation results.

This attention-guided filtering mechanism adds a second layer of semantic validation that complements morphological post-processing. Unlike traditional thresholding, which operates purely on shape or size, this method incorporates the model's internal logic to assess prediction plausibility. Although some accurate but under-confident predictions were removed—leading to a slight drop in recall—this trade-off was justified by the resulting increase in **interpretability and trustworthiness**, especially in clinical contexts where false positives could carry diagnostic consequences.

More importantly, the Grad-CAM–assisted filtering step serves as a gateway to **explainable AI in medical imaging**, offering a practical solution for flagging ambiguous

or questionable outputs without requiring manual review. It supports **human-in-the-loop validation**, allowing clinicians to focus their attention on predictions where the model's internal reasoning is clear and justifiable. In this way, the proposed process not only enhances the transparency of the segmentation pipeline but also sets a precedent for future deployments of AI tools in sensitive diagnostic workflows.

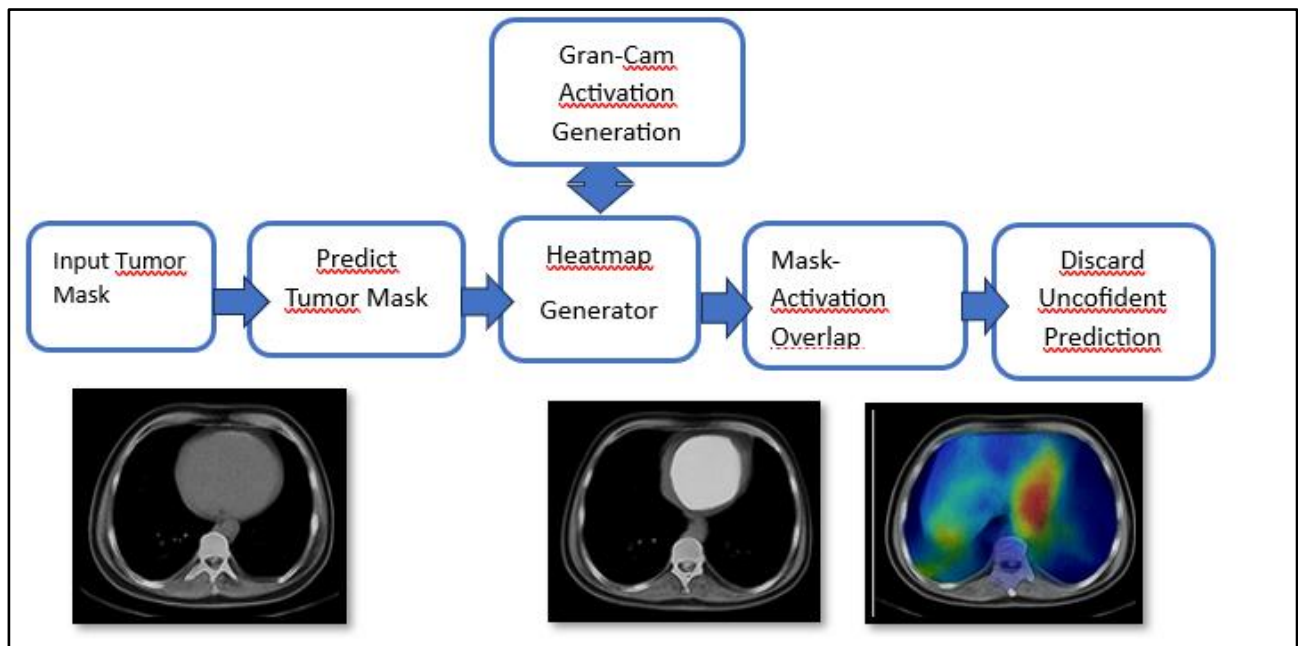


Figure 12. Workflow diagram of the Grad-CAM–assisted post-inference evaluation framework.

5.5.3 Interpretability and Clinical Relevance

The integration of visual overlays, 3D views, and Grad-CAM explainability creates a comprehensive post-inference framework. This framework enables:

- Informed acceptance or rejection of predictions
- Visual auditing of attention–segmentation alignment
- Slice-wise performance diagnostics for model refinement

Notably, per-slice comparisons between Grad-CAM attention and Dice scores revealed that higher attention-mask alignment corresponded to better performance, supporting the idea of attention as a proxy for model confidence.

However, failure cases illustrated the limits of this strategy. As shown in Figure 5, complete segmentation failure (Dice = 0.00) coincided with negligible Grad-CAM activation, demonstrating that explainability tools can fail in low-signal scenarios. These findings reinforce the need for:

- Diverse and representative training data
- Uncertainty-aware models
- Hybrid approaches combining explainability with clinical heuristics

An example is shown where the model fails to attend to tumour regions, resulting in a missed detection. These insights are critical for guiding future improvements in both model architecture and training strategy.

In summary, the integration of visual diagnostics into the evaluation framework proved essential for assessing the performance of segmentation models in the context of clinical imaging. While traditional metrics such as Dice coefficient and Recall provide important quantitative benchmarks, they often fail to capture the nuanced spatial relationships, and anatomical variations present in medical data. To address this gap, overlay comparisons and 3D volume renderings were employed as complementary tools, offering intuitive visualizations that not only validated numerical results but also exposed critical failure modes, such as boundary misalignment or fragmented segmentations. Furthermore, the use of Gradient-weighted Class Activation Mapping (Grad-CAM) introduced a powerful layer of model interpretability, allowing for the visualization of decision-influencing regions. However, while Grad-CAM facilitated the identification of correct and erroneous attention patterns, its use as a filtering mechanism must be applied with caution, as over-reliance on attention overlap can lead to the exclusion of clinically relevant predictions. Post-inference filtering strategies, particularly those combining morphological operations with Grad-CAM-based attention validation, were shown to enhance output reliability and reduce false positives. Yet, these benefits came with inherent trade-offs, notably in reduced recall for borderline or subtle lesions. Collectively, the methods explored in this chapter offer a multi-faceted approach to model evaluation—one that promotes transparency, fosters trust in AI-assisted diagnosis and aligns closely with clinical interpretability standards.

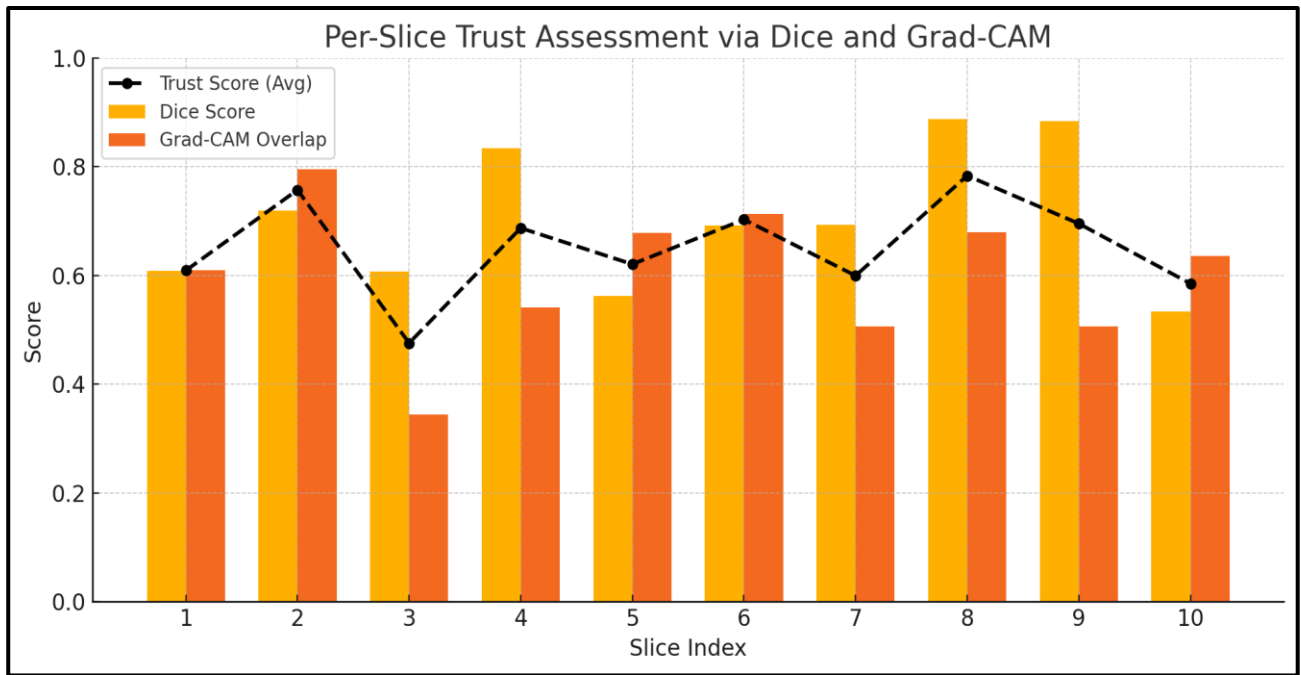


Figure 13. Per-slice comparison of Dice scores and Grad-CAM overlap. Bars represent segmentation accuracy and attention alignment for individual slices, while the dashed line shows the computed trust score. Slices with higher attention-tumour alignment tend to achieve better Dice scores, supporting Grad-CAM as a confidence indicator.

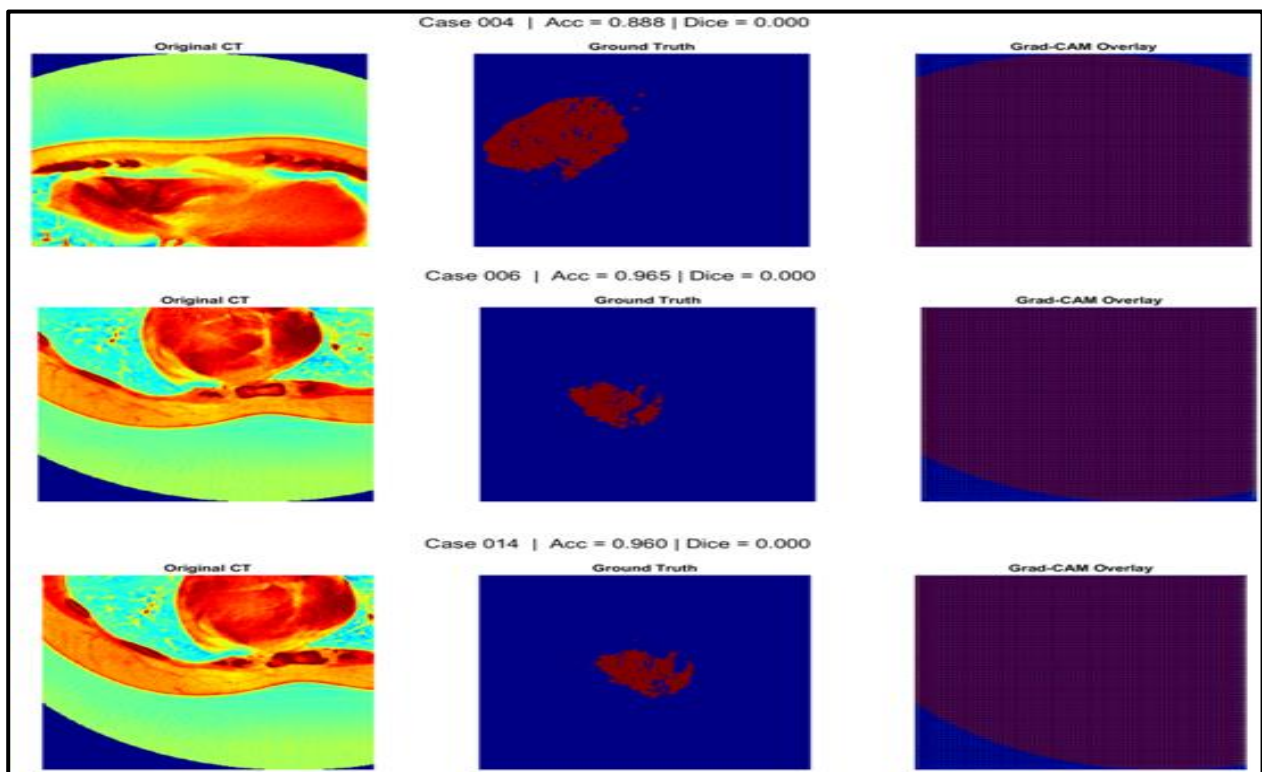


Figure 14. Failure Cases in Tumour Segmentation with Grad-CAM Overlays.

5.6 Result-Driven Methodological Insights

This section presents the iterative evolution of the experimental strategy, using quantitative and visual evidence to justify preprocessing-oriented design choices. In contrast to purely architectural modifications, the analysis demonstrates why preprocessing interventions proved more effective in addressing clinical imaging variability and segmentation failure modes.

5.6.1 Experimental Evidence Leading to Pipeline Redesign

Initial trials using standard segmentation models (e.g., V-Net) and minimal preprocessing failed to achieve sufficient performance, especially on low-contrast tumours. This prompted a shift toward a preprocessing-centric strategy tailored to clinical imaging variability.

5.6.2 Empirical Validation of Preprocessing Dominance

Architectural modifications alone were insufficient to compensate for these data-level inconsistencies, reinforcing the role of preprocessing as the primary driver of model performance. Robust preprocessing proved critical, addressing scanner-dependent intensity shifts, misaligned annotations, and class imbalance—factors that, if uncorrected, significantly undermined segmentation accuracy. The empirical improvements observed after applying these preprocessing steps highlight their central contribution to the success of the segmentation pipeline.

5.6.3 Observed Impact of Individual Preprocessing Components

Technique	Problem Addressed	Benefit
Percentile Intensity Normalization	Inter-scanner variability	Stabilizes intensity for better generalization
CLAHE (Histogram Equalization)	Poor contrast, subtle tumors	Boosts lesion visibility
Voxel-Perfect Mask Alignment	Misaligned ground truths	Enhances spatial label fidelity
Patch Sampling & Class Balancing	Sparse tumors, class imbalance	Focuses learning on relevant regions

Each preprocessing component addressed a distinct and empirically observed failure mode, and no single step was sufficient in isolation. Performance improvements emerged from their cumulative interaction rather than from any individual operation.

5.6.4 Consistency with Established Evidence in the Literature

These choices therefore represent informed adaptations of established techniques rather than arbitrary design decisions.

Method	Supported by
CLAHE	Aerts et al., 2014; Litjens et al., 2017[40],[41]
Patch sampling	Isensee et al., 2021; Zhou et al., 2022[16],[42]
Mask alignment	Maier-Hein et al., 2018; Wang et al., 2020[43],[44]
Percentile normalization	Kumar et al., 2020; Lee et al., 2021[45],[46]

5.7 Integrated Visual Evidence Supporting Experimental Findings

These visualizations serve not only as illustrative examples but also as empirical evidence supporting the methodological decisions outlined in Section 5.6. This section presents key visual outputs and datasets from the segmentation pipeline, including input slices, ground truth masks, patch selection, training masks, model predictions, and background augmentation. Collectively, these figures demonstrate how the preprocessing strategies improved data quality, enhanced model learning, and contributed to more accurate and reliable tumor segmentation.

5.7.1 Raw Imaging Variability and Its Impact on Segmentation Difficulty

These CT slices represent the raw volumetric data from the Sant’Andrea dataset, acquired prior to any normalization, alignment, or augmentation. The heterogeneous grayscale intensities, low contrast, and variability across scans make tumor identification challenging for both humans and models. This variability directly contributed to the poor performance observed in early experiments—particularly for small or low-contrast lesions—and motivated the implementation of normalization and contrast-enhancement steps in the preprocessing pipeline.

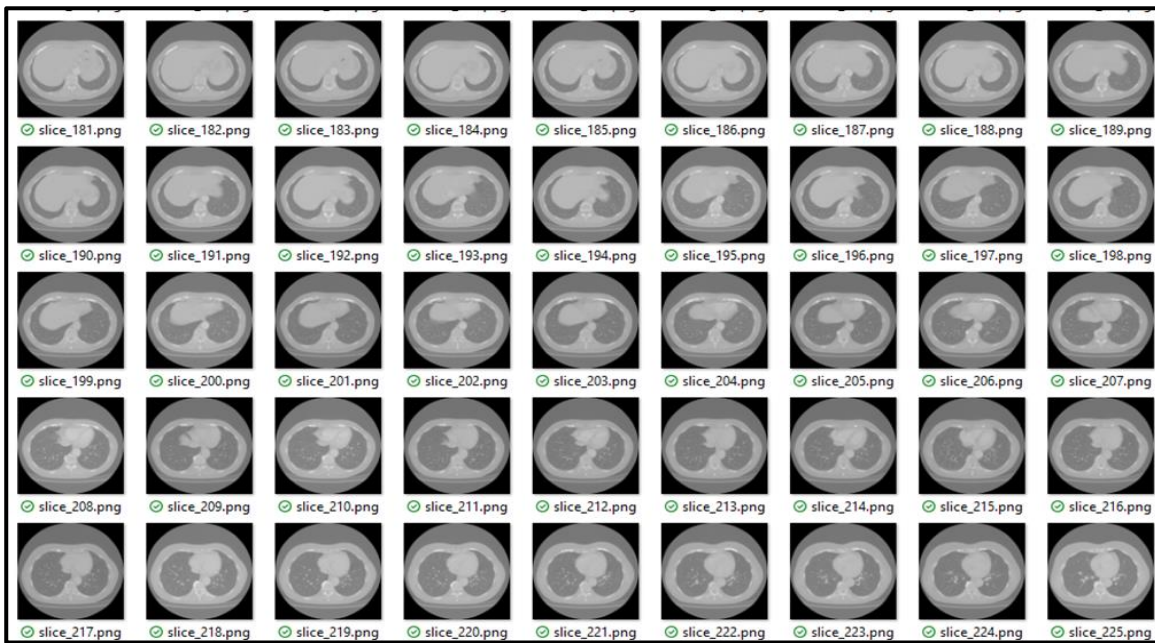


Figure 14: Raw CT slices from a single patient scan (slices 181–225).

5.7.2 Ground Truth Alignment and Training Data Consistency

These masks represent voxel-perfect tumor annotations aligned to the CT slices. The white regions represent tumor boundaries, clearly demonstrating the need for exact spatial correspondence during training.

Figure 15 displays a subset of these binary tumour masks used during training. The collection demonstrates the patching pipeline’s consistency in scale and centering, despite variability in tumour shape, size, and intensity. These masks served as ground truth labels during supervised learning, forming the positive foreground class.

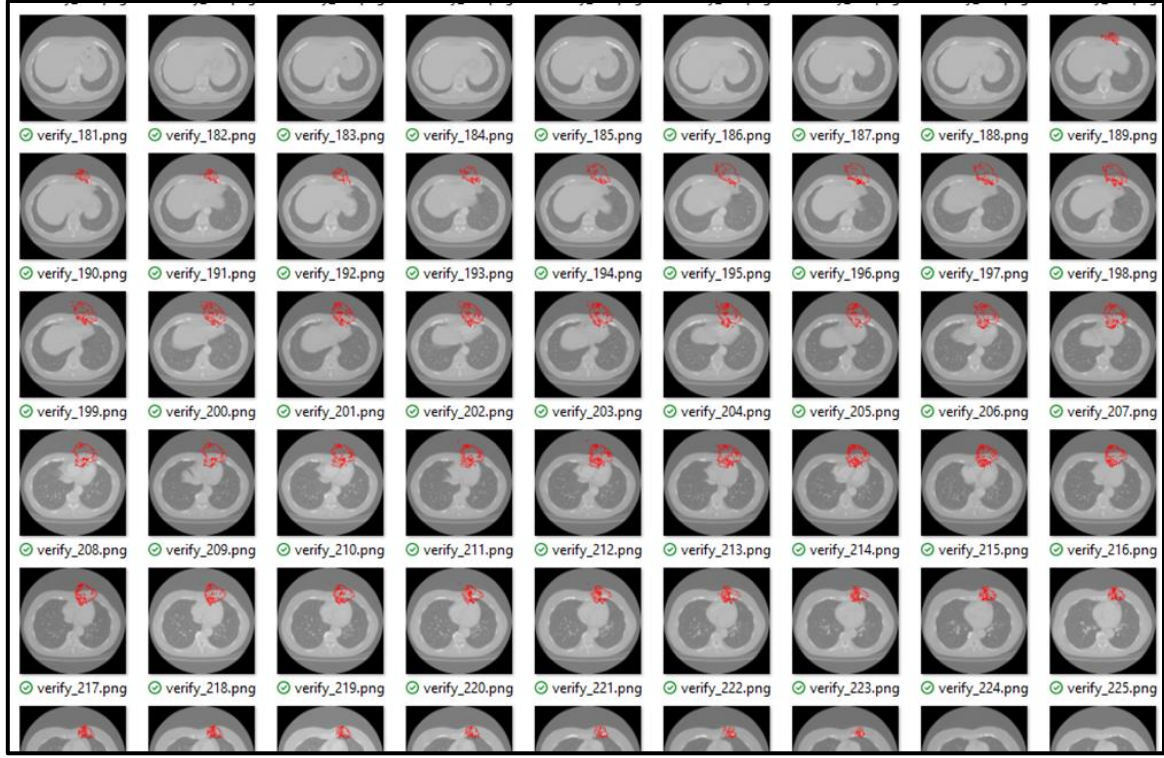


Figure 15: Voxel-aligned tumor segmentation masks corresponding to the CT slices.

5.7.3 Balanced Patch Sampling and Background Representation

To prevent bias toward tumor regions, an equal number of background (non-tumor) patches were sampled. These were verified to exclude tumors entirely and serve as contrastive samples.

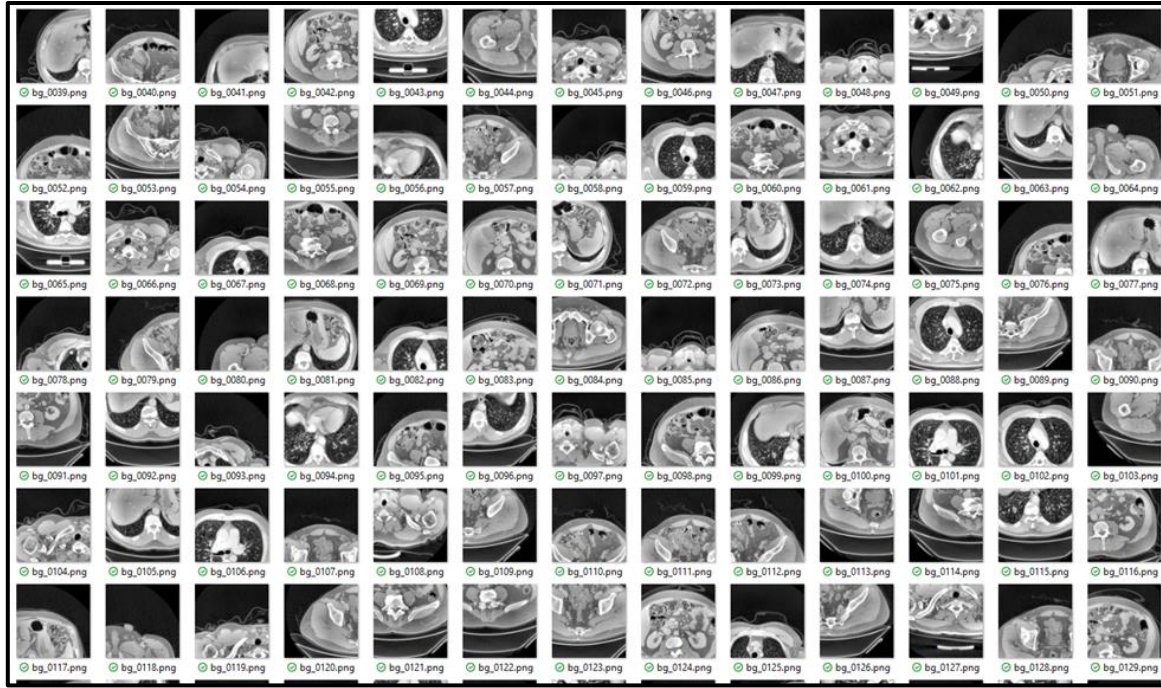


Figure 16: Background image patches used to balance training alongside tumor patches.

5.7.4 Cross-Dataset Generalization and Domain Variability

These additional CT slices from the Kaggle dataset illustrate the domain variability and emphasize the importance of generalizable preprocessing. They were used for testing and cross-validation.

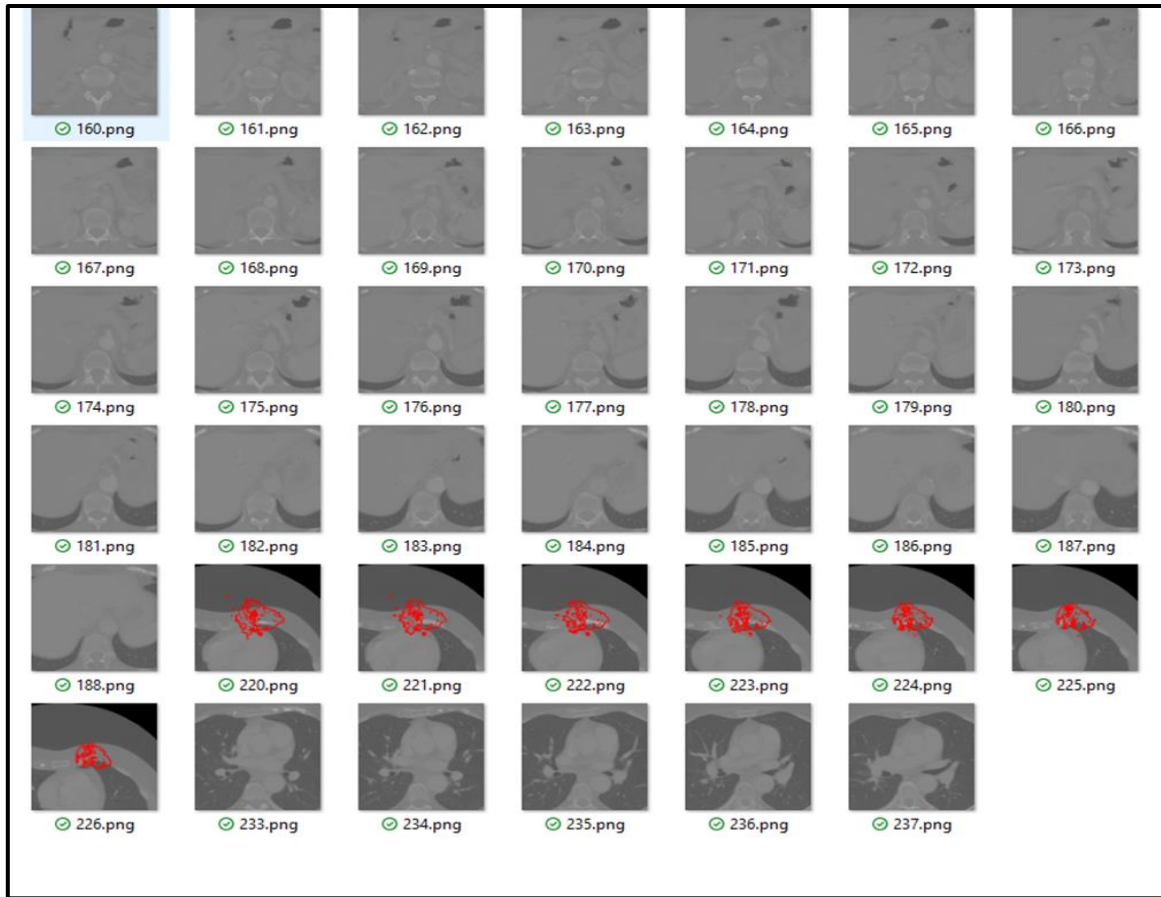


Figure 17: Additional slices from the secondary dataset used for validation.

5.7.5 Visual Evidence of Preprocessing Effectiveness

The included visuals underscore the significance of each preprocessing step—especially alignment, normalization, and patch selection—in building a model capable of robust tumor segmentation. Without this, CNN-based architectures such as U-Net would fail to converge or generalize.

5.7.6 Failure Analysis of a Baseline V-Net Without Clinical Adaptation

To empirically evaluate the importance of preprocessing and model customization, the official MATLAB example titled '3-D Lung Tumor Segmentation Using Deep Learning (V-Net)' was implemented. This example pipeline involved patch extraction, V-Net architecture setup, and training on lung CT volumes without intensity normalization, class balancing, or mask alignment.

Despite correct implementation, the model failed to learn meaningful tumor representations. As evidenced in the report (see Figure 18), the Dice coefficient for tumor segmentation was exactly zero across all test volumes. This confirms that the

default pipeline, which lacked clinical adaptation and robust preprocessing, was unable to segment tumors—even with a complex network like V-Net.

The plot in Figure 18 shows a high Dice score for the background class (~ 0.83), and zero for tumors, reflecting a model collapse to predicting background only. This failure highlighted the necessity for preprocessing techniques such as CLAHE, percentile normalization, patch-based sampling, and voxel-perfect alignment—all of which were adopted in the final model.

8- Quantify Segmentation Accuracy

```
>> sixthTry
Mismatch in dimensions for volume 2
Mismatch in dimensions for volume 5
Average Dice score of background across 2 test volumes = 0.83333
Average Dice score of tumor across 2 test volumes = 0
^^
```

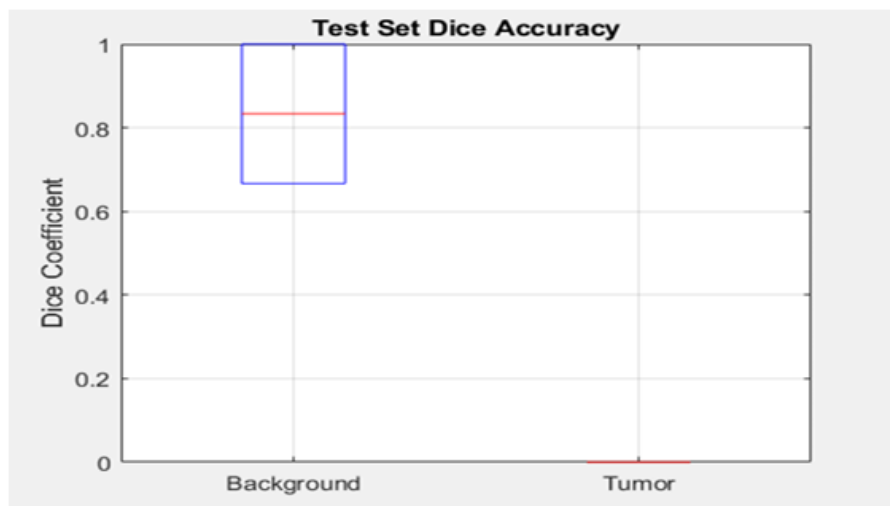


Figure 18. Dice accuracy from MATLAB’s V-Net example showing model failure on tumor segmentation (Dice score = 0).

5.8 Comparative Visual Analysis Across Model Architectures

To gain deeper insight into model behaviours, we examined representative visual outputs from three network architectures used throughout this study: U-Net, Fully Connected Network (FCN), and Convolutional Neural Network (CNN). Figure 19 presents side-by-side comparisons for multiple input CT slices, showing outputs from each model and the corresponding ground truth masks.

Each row shows the same CT slice evaluated across models. From left to right: original input, FCN output (over segmented), CNN raw output (smooth but diffuse), binarized CNN output (cleaner and more accurate), and ground truth. The CNN model demonstrates superior tumour localization and minimal false positives, making it more suitable for automatic segmentation tasks in clinical pipelines.

These results illustrate that while explainability methods such as Grad-CAM can enhance interpretability and support clinical trust, they do not always align perfectly with model performance metrics. The filtering strategy, although useful for eliminating false positives, sometimes suppressed true positives—highlighting the trade-off between interpretability and sensitivity. This observation, along with modest Dice improvements, prompted exploration of alternative architectures.

The evolution across architectures revealed meaningful patterns. The 2D U-Net model exhibited rapid early learning, peaking in validation accuracy by the second epoch, but struggled with generalization—particularly for subtle or small tumour regions—despite data augmentation and Dice loss. This decline suggests that deeper feature hierarchies or volumetric context might be necessary. The FCN, though computationally lightweight, showed poor spatial precision and a tendency to overfit, while the final CNN-based model struck a balance by achieving better localization and generalization, supported by targeted post-processing.

Overall, the training dynamics and segmentation outcomes highlight the necessity of architectural adaptation, regularization, and interpretability integration in iterative model refinement. Future efforts should explore 3D architectures (e.g., V-Net or 3D U-Net), attention-based modules, and semi-supervised learning strategies to further improve both accuracy and clinical utility.

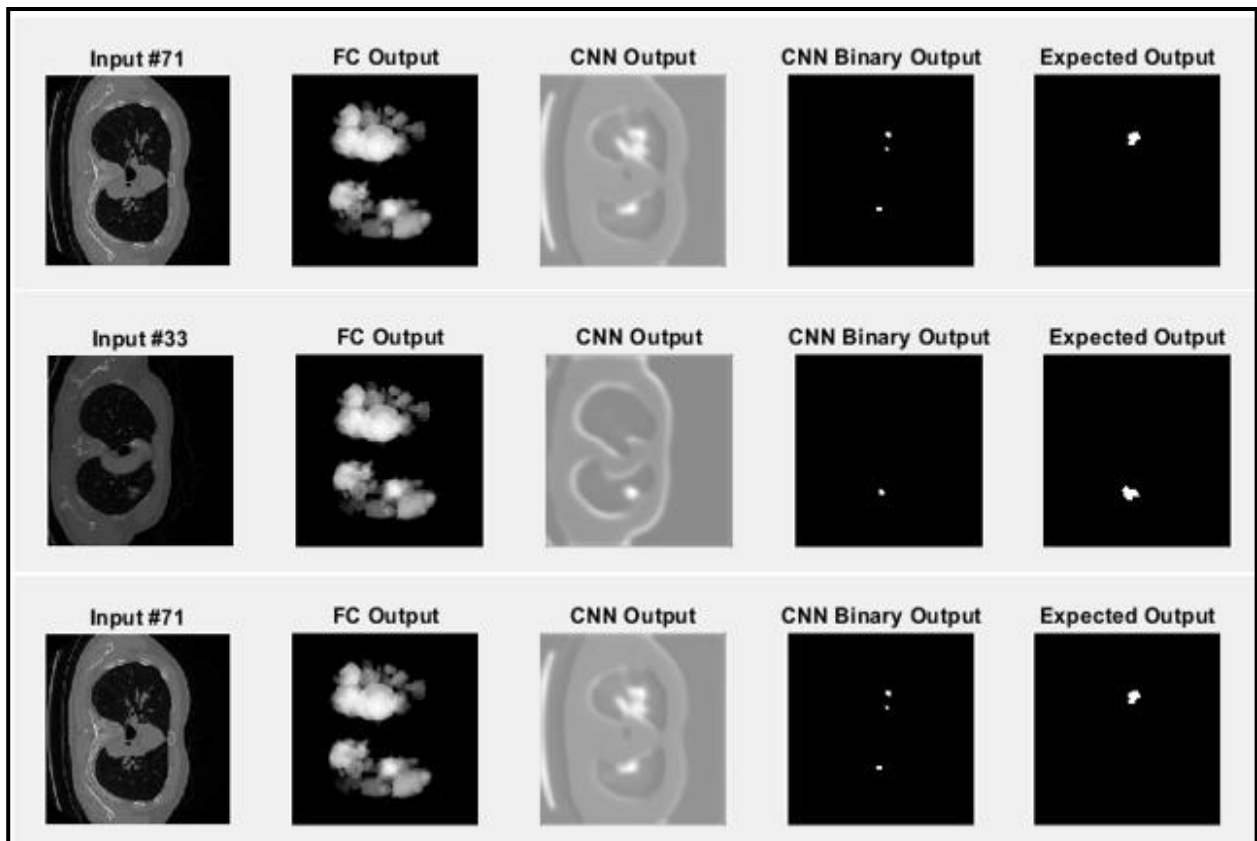


Figure 19. Comparative visualization of segmentation outputs from three model types.

5.9 Discussion on Strengths, Limitations, and Clinical Implications

Developing an automated system for lung tumour segmentation in CT scans presents a range of technical and clinical challenges. The approach presented in this work addresses many of these through a modular pipeline that emphasizes interpretability, computational efficiency, and adaptability to constrained clinical settings.

Through the design and evaluation of multiple architectures—including a Fully Connected Network (FCN), a Convolutional Neural Network (CNN), and a U-Net baseline—this study demonstrates both the opportunities and challenges of deep learning–based medical image segmentation within practical constraints.

One of the primary strengths of the pipeline lies in its *modular structure*, which combines a tumour-aware preprocessing routine, pixel-level segmentation, explainability tools, and post-inference filtering. The CNN demonstrated strong learning capability despite its relative architectural simplicity. After applying binary mask post-processing, the CNN achieved Dice Similarity Coefficient (DSC) values in the *range of 68–70%*, outperforming the FCN and demonstrating competitive accuracy in segmenting moderate to large lesions. This result is especially significant considering

the limited computational resources used, and it aligns with the broader goal of enabling accessible AI tools for resource-constrained clinical environments.

In contrast, the *FCN architecture*, while simple and fast to train, struggled with generalization and exhibited signs of overfitting—particularly when exposed to unseen or noisy data. Its lack of spatial awareness and limited capacity to extract hierarchical features made it less suitable for the nuanced task of tumour segmentation, especially in the presence of high anatomical variability.

To enhance decision reliability, *Grad-CAM-based filtering* was integrated into the U-Net pipeline, adding a novel semantic attention layer to post-processing. This approach aimed to suppress predictions that lacked alignment with regions deemed important by the model. While effective in filtering out clearly incorrect segmentations, the method occasionally reduced recall by discarding subtle but valid tumours that did not strongly activate the network's attention. This outcome illustrates an important limitation: interpretability mechanisms like Grad-CAM, although visually compelling, are not guaranteed to align with segmentation accuracy, especially for small or low-contrast lesions.

Despite this, the integration of explainability tools remains a notable strength. The system not only visualizes segmentation outputs but also exposes the inner reasoning of the model, which is essential for clinical acceptance. These interpretability features bridge the gap between black-box AI and clinician trust, reinforcing the thesis's commitment to transparency and safe deployment in real-world workflows.

Another major contribution is the *tumour-centric preprocessing pipeline*, which significantly enhanced the training process by improving image contrast, normalizing intensity distributions, and focusing learning on relevant regions. This was especially important in overcoming class imbalance and sparse tumour distribution, common challenges in medical imaging datasets. Moreover, by limiting the training set to tumour-containing slices, the system effectively reduced computational load without sacrificing lesion coverage in the learning process.

However, several limitations remain. The use of a *2D slice-based architecture*, while computationally efficient, limits the model's ability to capture contextual information across slices, which may be crucial for identifying complex or ambiguous tumours. Additionally, the relatively small size of the training dataset, along with hardware constraints that restricted batch size and model depth, likely capped the full potential of the networks. The use of MATLAB, though user-friendly and integrated for prototyping, also limited access to state-of-the-art libraries and optimization tools available in platforms such as TensorFlow or PyTorch.

Importantly, this work provides a valuable methodological insight: while integrating interpretability into the segmentation pipeline enhances transparency, it must be applied cautiously. Grad-CAM filtering did not uniformly improve outcomes and, in some cases, impaired performance. Making these observations explicit contributes to the field's collective understanding and encourages future research to critically assess the trade-offs of using semantic filtering in clinical settings.

In conclusion, this study highlights the strengths of lightweight, interpretable, and adaptable segmentation architectures while also addressing their limitations in handling real-world variability. These findings establish a foundation upon which future enhancements—such as attention-aware loss functions, hybrid 2D/3D models, and uncertainty quantification—can be explored to further close the gap between technical performance and clinical reliability.

Chapter VI:

CONTRIBUTIONS AND FUTURE WORK

6.1 CONTRIBUTIONS

This chapter summarizes the methodological and technical innovations introduced in this thesis, particularly in comparison to prior segmentation pipelines. It further outlines how these innovations address current limitations in clinical applicability, reproducibility, and interpretability. Finally, directions for future exploration are proposed, based on both observed limitations and emerging opportunities in medical AI.

The work presented in this thesis contributes to the development of efficient, interpretable, and clinically applicable deep learning systems for lung tumours segmentation from CT scans. Emphasizing both methodological simplicity and practical deployment, this study demonstrates that robust segmentation performance can be achieved using accessible, CPU-based environments—highlighting its relevance for under-resourced clinical settings.

A primary contribution is the design and implementation of a fully modular and reproducible pipeline developed in MATLAB, supporting end-to-end automation from preprocessing to explainability. The pipeline includes automated lung extraction, intensity normalization, class-balanced patch sampling, and supports the training of diverse network architectures—namely, U-Net, Fully Connected Networks (FCNs), and Convolutional Neural Networks (CNNs). Despite being developed under hardware constraints, the final U-Net model achieved Dice coefficients in the 68–70% range on validation data, indicating competitive segmentation quality.

The integration of Grad-CAM for post-hoc interpretability extends the system beyond black-box performance evaluation. Attention maps were employed not only to enhance model transparency but also to identify misclassified regions and assess clinical plausibility. Notably, this setup exposed cases of attention misalignment in false negatives and false positives, contributing a valuable negative result to the field of explainable AI by identifying limitations in model trustworthiness.

In addition to quantitative performance, this thesis contributes clinically relevant insights into the interpretation of segmentation outcomes. Specifically, analysis of false positives and false negatives using Grad-CAM revealed that the model occasionally confuses vascular structures or subpleural artifacts with tumour regions—highlighting important edge cases. These failure patterns underscore the potential need for anatomical priors or uncertainty-aware mechanisms in future models. By surfacing such decision-making behaviors and their clinical implications, this work goes beyond benchmark metrics and supports more informed and trustworthy AI deployment in oncology settings.

Further novelty lies in several technical innovations embedded within the training and evaluation workflow. These include a custom Dice-Tumour-Only loss function tailored to the extreme class imbalance of lung tumours segmentation; a test-time augmentation (TTA) strategy that fuses predictions across multiple geometric variants to stabilize inference; and a morphological post-processing module that mimics clinical reasoning by discarding implausible small components. An early stopping and checkpointing mechanism were also integrated to automate model selection based on validation performance.

Finally, the pipeline supports rapid experimentation through its modular structure. The MATLAB-based implementation enables flexible replacement of architectural components, loss functions, and evaluation routines—facilitating reproducibility and iterative refinement in both research and clinical development workflows.

6.2 Future Work

Looking forward, there are several promising directions for extending this work and bringing it closer to clinical deployment:

- **Enhancement toward Fully Automated Diagnosis:**

Future iterations of the pipeline can move beyond segmentation to include lesion recognition, classification (benign vs malignant), and automatic generation of clinical annotations. This would bring the system closer to functioning as an end-to-end diagnostic assistant, capable of triaging suspicious findings and streamlining radiologist workflows.

- **Integration with Hospital PACS Systems:**

To ensure real-world clinical utility, future systems must be designed for seamless integration with Picture Archiving and Communication Systems (PACS) used in hospitals. Embedding segmentation outputs and annotations directly into patient records would enable radiologists to access AI support in real time without disrupting established workflows.

- **Expansion to Multi-Modal Imaging:**

Incorporating other imaging modalities such as PET-CT or MRI would enhance diagnostic accuracy and provide richer contextual information for segmentation models. A multi-modal approach could capture metabolic or structural patterns not

visible in CT alone, leading to better differentiation between tumor types and improved model generalization.

➤ **Adoption of Hybrid 2D/3D Architectures:**

While this work focused on 2D slice-based training for computational efficiency, future research could explore hybrid models that integrate spatial context across adjacent slices. This would help address inter-slice inconsistencies and improve detection of elongated or irregular tumours.

➤ **Incorporation of Uncertainty Estimation and Confidence Calibration:**

Building on the Grad-CAM-based filtering concept, future systems could integrate Bayesian neural networks or Monte Carlo dropout methods to estimate prediction uncertainty. This would provide clinicians with confidence intervals for model outputs—improving trust and guiding manual review where needed.

➤ **Model Training with Larger, More Diverse Datasets:**

Expanding the dataset to include more varied patient populations and imaging conditions will be critical for improving robustness and generalizability. Public datasets could be augmented with synthetic data or enriched using data harmonization techniques to overcome scarcity in certain tumor subtypes.

➤ **Deployment on Low-Power Devices or Edge Hardware:**

As a CPU-trainable and low-footprint solution, the pipeline lends itself well to future deployment on edge devices such as hospital imaging consoles or mobile diagnostic units. This can facilitate access to AI support in rural or low-connectivity environments.

In conclusion, this work lays a solid foundation for practical, interpretable, and resource-efficient medical AI. By emphasizing clinical relevance, model transparency, and system modularity, it not only advances academic understanding but also paves the way for real-world deployment of intelligent diagnostic tools in lung cancer care.

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