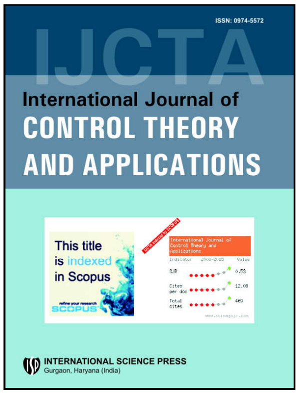

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An Automated System for the Detection of Lung Cancer in CT data at Early Stages: Review

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Abstract: The severity of lung cancer presented the challenging tasks to the researchers for the development of efficient automated systems or Computer-aided diagnosis (CAD) systems to detect of lung cancer in primary stages. Due to this reason, automated systems for the detection of lung cancer have been explored in large number of research articles. This paper emphasizes the general CAD systems for the diagnosis of lung cancer which consist of major steps like preprocessing, lung segmentation, nodule detection in the lung area, nodule segmentation and analysis based on volume & shape, growth, texture & appearance followed by classification as malignant or benign and diagnosis. This paper focuses the current technical issues, existing methodologies, various referred databases and validation with ground truths and finally the description of achieved performance and its analysis & comparisons with some popular metrics.

Keywords: Computer aided diagnosis (CAD) systems, Medical Image Processing, Lung cancer, Lung segmentation, Nodule Detection and Computed Tomography.

1. INTRODUCTION

According to the statistical analysis of American Cancer Society [1] in 2016, there are 224,390 new cases of lung cancer in the United States, and deaths from lung cancer are estimates around 158,080. Among all kind of cancer, lung cancer is the leading cause of cancer death which includes both men and women, i.e. lung cancer causes about one cancer death out of four. The total of colon, breast and prostate cancer are less than the Lung cancer each year. The survival rate of lung cancer is five year, which is very poor because the diagnosis of lung cancer is usually done in later stages. Earlier the evaluation of CT scans was generally done through manually resulting very exhaustive tasks. So the clinical identification and handling of diseases in managed way are required that would lead to enhancement of survival rates [2]. Thus a computer-aided diagnosis (CAD) system can be extremely useful to reduce the manual overhead and to detect the lung cancer in early stages so that it can improve the survival rate of lung cancer patient and provide the better healthcare services in this field. These facts attracted the attention of many researchers to develop an effective and efficient automated CAD system that involves steps of image processing into the patient's CT image to detect the cancerous cell and do the required analysis to diagnose [3].

The various common non invasive imaging modalities are computed tomography (CT), contrast enhanced computed tomography (CE-CT), low-dose computed tomography (LDCT) and Positron emission tomography (PET) for detection and diagnosis of lung cancerous cell. The block diagram of General CAD system for the detection of lung cancer is as shown in Figure 1. The input to the CAD systems is the image acquired by specific imaging modalities. The preprocessing step may contain transformation and DICOM specific operations, format and window size identification finally thorax part extraction. The lung segmentation is crucial and essential step; it basically extracts the portion of lungs from CT chest image for finding the accurate ROIs. The next step is to detect and segment the nodules in segmented lungs and finally the detected nodules are classified into malignant (cancerous) and benign (non-cancerous) on the basis of shape, growth and texture & appearance analysis followed by diagnosis.

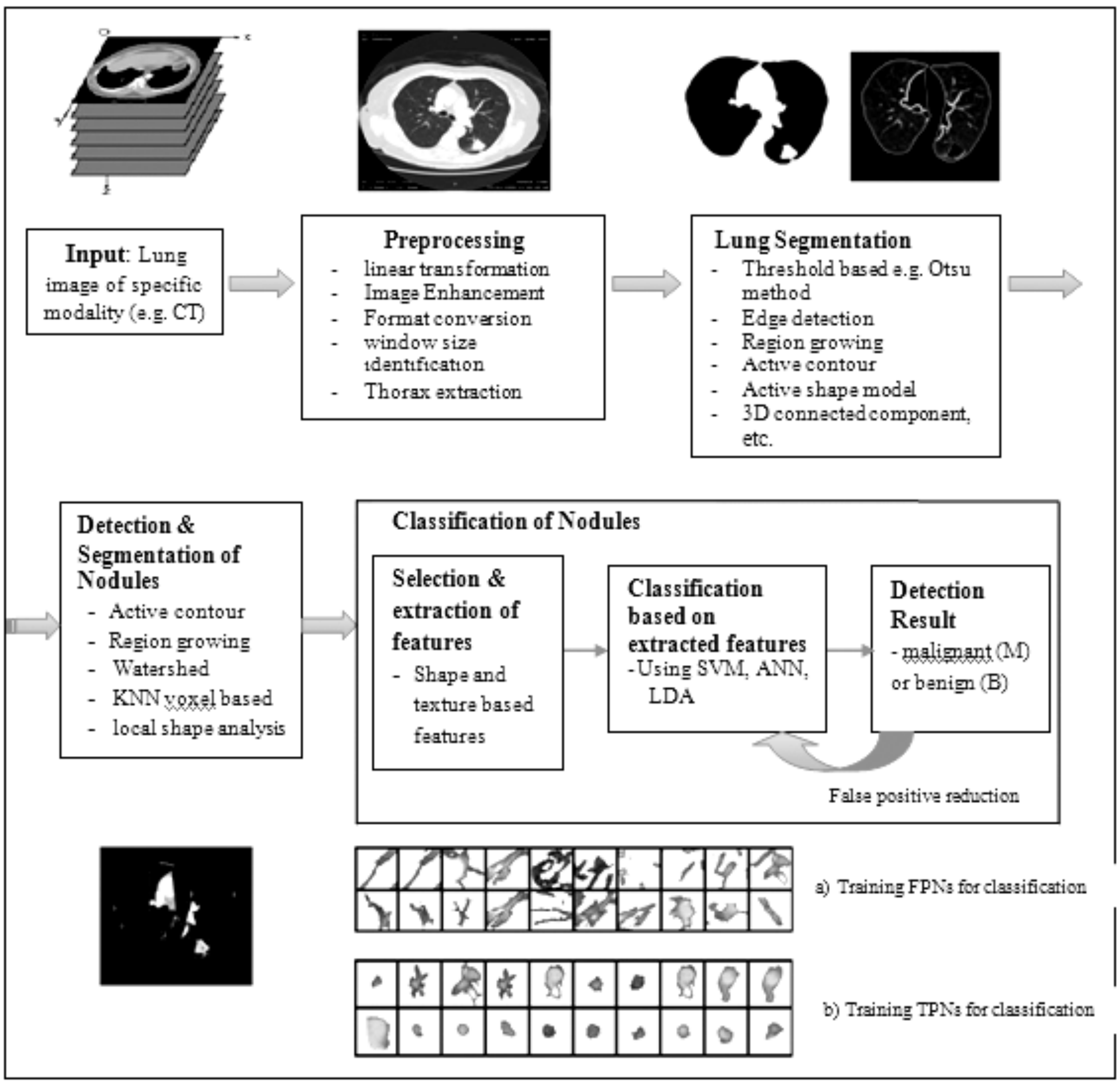

Figure 1: General CAD System for Lung Cancer

In CADe systems, a system for lung nodules detection comprises image acquisition, preprocessing, lung segmentation, nodule segmentation & detection of segmented candidates into nodules and non-nodules (normal components like vascular organs, etc.). However in CADx systems, the lung nodules detected in CADe systems or by radiologists are identified whether these are malignant or benign.

In the remaining section of paper, the different processing steps of CAD systems are discussed such as lung segmentation and its various investigations by researchers, nodule segmentation, detection and classification with some performance metrics.

2. LUNG SEGMENTATION

The lung segmentation is an essential and preprocessing step that reduces the search space and decreases the overhead for further process i.e. detection of the nodules. It is process of extraction of the lungs in CT chest images and separates the ROIs from muscles, fats, and other attached pulmonary structures like veins, arteries, bronchi, and bronchioles. The accuracy of segmentation is very important and well stated by S. G. Armato and W. F. Sensakovic that due to poor and inaccurate lung segmentation approximately 4.9 % to 17% true lung nodules are not detected and missed [2]. Though, the presence of noise, low contrast and intensity inhomogeneity and in CT images makes the lung segmentation a difficult task but the most challenging problem for researcher is to recognize the nodules attached to pleural surface (i.e. juxtapleural) and to include these regions in the segmented lungs. Numerous algorithms have been anticipated in the literature, such as thresholding based segmentation, region growing based segmentation, segmentation based on fuzzy c-means (FCM) clustering approach, active contour models based segmentation, Intensity-based segmentation, Level set image segmentation, Texture-based image segmentation, and so forth. The widely used lung segmentation techniques are:

Active contour based Segmentation: Minimization of the energy function in each iteration using some dynamic contour is the central idea behind active contour model (ACM). The problem in accurate segmentation is due to lack of organ tissue homogeneity in texture and shape of various slices of CT image. Initialization and poor convergence related problem also limit the effectiveness of active contour method, which has been addressed in many research studies [5, 6 and 7]. One of the approaches for convergence has been given by Laurent D Cohen [6], to the object's boundary, an external force will apply to guide the snake which is similar like inflates or deflates a balloon. When snake initialized far from the desired boundary then the convergence is improved, but weak edges boundary may not be detected if the strength of the balloon force is too high. The introduction of Gradient vector flow (GVF) as an external force has been given as an important solution by Chenyang Xu and Jerry L Prince [5] where both the problems initialization and convergence has been addressed. In this direction further improvement has been done by Wang et al. [8] with approach called normally biased GVF (NBGVF) as an external force. This method keeps existing desired property of GVF with weak edges and smoothen the noise. The related work for improving the convergence has been also addressed in [10, 11, and 14]. Another reason for the poor convergence is the smaller searching space. For the initialization issue Chan et al.[11] adopted a ACM that exploit techniques of curve evolution. Mumford–Shah function [5] skipped the need of precise boundary and doesn't even require for smoothening of the initial image to detect the object. Cui et al.[12] defined energy function to draw contour toward object boundaries with local intensity distribution for flexible initialization and effective noise handling. Athertya et al.[13] has shown fully automatic method for ACM that avoids the human interaction.

Thresholding Based segmentation: Lungs portion are darker as compared to other anatomical structure in the thorax region so with the selection of optimum threshold the segmentation of lungs have been utilized in number of research studies. Hu et al.[15] adopted the iterative threshold with some morphological operations. Gao et al.[16] proposed the threshold based approach with some preprocessing, region growing and morphological smoothing. Wei et al.[17] used threshold to segment the lung region using histogram analysis, Ye et al.[18] used adaptive fuzzy thresholding for the lung segmentation from CT data. Baniani et al. [19] has given the approach

Table 1
Current methodologies review for lung segmentation

Authors, Year	*Technique/Method*	*Database & Dimension*	*Image Size*	*Performance Accuracy*	*Ground Truth*
Hu et al., 2001 [15]	Iterative threshold, dynamic programming, morphological Operations	24 dataset from 8 Subjects, 3D	512x512, 3 mm thin	RmsD = 0.54 mm (0.8 pixel)	229 manual traced images
Yim et al., 2005 [34]	Region growing, connected component	10 subjects, 3D	512x512, 0.75 - 2.0 mm thin	RmsD =1.2 pixel	10 manual traced data
Gao et al., 2007 [16]	Thresholding	8 subjects, 2D	512x512x240	DSC=0.9946	8 manual traced datasets
El-Baz et al., 2008 [35]	statistical MGRF model	10 image datasets, 3D	512x512x182, 2.5 mm thin	Segmentation Accuracy = 0.968	1820 manual traced images
Kockelkorn et al., 2010 [28]	Prior training, statistical classifier	22 scans, 3D	512x512, 0.9 - 1.0 mm thin	OM=0.96AD= 1.68mm	12 manual traced data
Sofka et al., 2011 [30]	Active Shape Based	260 scans, 3D	512x512, 0.5 - 5.0 mm thin	SCD = 1.95	68 manual traced data
Hua et al., 2011 [36]	Graph Search	15 scans, 3D	512x512, 0.3 - 0.9 mm thin	HD=13.3 pixel Sen.=0.986 Spec.= 0.995	12 semi-automated traced data
Nunzio et al., 2011 [37]	Threshold, Region Growing, Morphological operation	130 HRCT Scans, 3D	512x512, 1.25 mm thin	OM=0.96±0.02, AD=0.74±0.05, RmsD =0.57±0.04	36 manual traced data
Pu et al., 2011 [31]	Threshold & Geometric modeling, shape based analysis	230 scans, 2D & 3D	NA	RmsD=0.15±0.092 Max error =7.82± 3.37 OM=95.1+2.0%	20 manual traced data
Sun et al., 2012 [32]	Active shape based	30 MDCT scans, 3D	512x512x424-642, 0.6-0.7 mm thin	DSC=0.975 AD=0.84 mm SPD=0.59 mm HD=20.13 mm	30 manually corrected traced data
Abdollahi et al., 2012 [38]	statistical MGRF model	11 scans, 3D	512x512x390, 2.5 mm thin	DSC =0.960	11 manual traced data
Cortez et al., 2013 [39]	3D region growing & Threshold	11 subjects, 3D	512x512, 0.5 - 2.0 mm thin	2 pulmonologists qualitatively evaluated seg. results 64.78 % & 68.18% satisfactory	11 manual traced data
Keshani et al., 2013 [40]	Adaptive Fuzzy Thresholding, Active contour	63 subjects (4 groups: 4, 4, 5 & 50 subjects of LIDC), 3D	512x512, 0.625 - 5.0 mm thin	Segmentation Accuracy = 0.981	8 manual traced data I & II group and all annotations provided from III & LIDC
Kuruvilla et al., 2014 [41]	Otsu Threshold, Morphological operation	155 subjects, 3D	512x512, 0.75-1.25 mm thin	RmsD =0.0942	LIDC annotated and manually traced data
Orkisz et al., 2014 [42]	Threshold, Morphological operation	20 scans, 3D	512x512, 0.6-1.0 mm thin	differentiated vessels from bronchial	20 manual traced data

(contd...Table 1)

Authors, Year	*Technique/Method*	*Database & Dimension*	*Image Size*	*Performance Accuracy*	*Ground Truth*
	& region growing			walls spec. = 0.848	
Zhou et al., 2014 [43]	Preprocessing, FCM and adaptive thresholding	20 MDCT scans, 3D	512x512x210-540, 0.6-1.0 mm thin	OM=95.81±0.89% AD=0.63±0.09mm	20 manual traced data
Shen et al., 2015 [44]	Preprocessing, adaptive Threshold	233 scans, 3D	512x512	Re-inclusion rate= 92.6%, over seg = 0.3% and under seg=2.4%	10 manually traced data
Wang et al., 2016 [45]	Principal component, Morphological op, Connected reigion based and contour segmentation	45 scans, 3D	512×512×275 - 512×512×502, 0.55-1.0mm. thin	RmsD=1.6957± 0.6568 mm , AD= 0.7917± 0.2714 mm VOE=3.5057± 1.3719mm VD=11.15±69.63 cm^3	45 manually traced data

Abbreviations: DSC - Dice similarity coefficient; OM - overlap measure = TP/(TP + FP + FN); Sen. - sensitivity = TP/(TP + FN).

Spec- specificity = TN/(TN + FP); RmsD - root mean square difference = distance between the segmentation and the ground truth; AD - mean absolute surface distance; HD - Hausdorff distance = mean maximum distance of a set to the nearest point in the other set; SPD -mean signed border positioning error; SCD - symmetrical point-to-mesh comparison error; VOE – volume overlap error; VD – volume difference,

LIDC – Lung Imaging Database Consortium (https://imaging.cancer.gov/programsandresources/informationsystems/lidc)

to determine single or more threshold value based on histogram. An optimal multilevel thresholding has been proposed by Maitra et al. [21] an enhanced particle swarm optimization (PSO) variant, the approach decomposed multidimensional swarm into numerous one-dimensional swarms, to estimate overall fitness swarms exchange information among themselves. Multilevel thresholding method termed as maximum entropy based artificial bee colony thresholding (MEABCT) anticipated by Ming-HuwiHorng [20], for selecting the passable thresholds this method simulates the behavior of Artificial bee colony algorithm. Xu et al. [22] proposed an improved discrete quantum particle swarm optimization (IDQPSO) algorithm, based on 2D threshold particle swarm binary-encoded method for accelerating the converging and local searching. Otsu thresholding technique is one of the frequently used thresholding methods, but is having the drawback of complexity in computation and processing time. Otsu adaptive thresholding segmentation has been proposed by Kim et al. [23] based on bimodal histogram which inspect the bimodality of each region and shown the better performance. Helen et al. [24] improved the performance of 2D Otsu-based thresholding segmentation using PSO. Banimelhem et al. [25] proposed memetic algorithm (MA) for image segmentation in order to speed up the searching process and generating faster solution.

Shape based segmentation: This technique uses the prior shape information of lungs. Some previous shape parameters like edges and points are analyzed and used to formulate the variational energy framework for segmentation. This energy framework guide and help to deformable models for the segmentation of lung fields. Shi et al.[26] proposed the population based and patient specific shape statistics to constraints the deformable model. The earlier segmentation results and shape statistics have been collected online and updated when some new segmentation results available and thereby used to refine and improve the segmentation accuracy. Annangi et al.[27] used prior shape and some low level features for lung segmentation in x-ray images. Kockelkorn proposed user interactive techniques for lung segmentation in CT image with severe abnormalities where prior shape are trained using k-nearest-neighbor classifier and on the basis of classification results can be corrected. Kumar et al.[29] presented two stage approach for automatic lung lobes segmentation where fissure region are found then fissure location and curvatures are identified within these regions. Sofka et al. [30] combined statistical shape model with anatomical information based pattern recognition technique for the robust lung segmentation. Pu et al. [31] proposed an approach with geometric modeling and shape based "break-and-repair" strategy for segmentation of a medical image. Sun et al. [32] proposed novel approach robust active shape model to roughly segment the outline of lungs, then optimal surface finding method is used to further adapt the initial segmentation result. Gill et al. [33] given the feature based atlas approach for initialization of active shape models for segmentation.

The research studies of some current techniques in lung segmentation are reviewed in Table-1 along their technical issues and effectiveness with different data sets and modalities.

3. NODULE SEGMENTATION AND CLASSIFICATION

The lung nodules are white spherical (circular) matter having lower contrast found in lung region. The most challenging tasks for the segmentation of such nodules are their unfavorable locations i.e. if attached to wall of parenchyma called as "juxtapleural nodules"; nodules attached to vessels of blood called as "juxtavascular nodules". The other type of nodules which are sub-solid in nature and usually having lower HU values as compared to other nodules are called as "ground-glass opaque" (GGO) nodules. Also some nodules are small in size but having critical role for the prior detection of cancer in lung region. For the juxtapleural cases, a number of research studies have been addressed the solution and the most common method used is "pleural-surface-removal" (PSR) given by [46, 47, 49, 50, 51, 55]. This method can be implemented in global scenario where firstly complete segmentation of lung from CT slices then the outcome is adopted as negative mask to avoid the non-targeted wall portion to be considered in segmentation results. For the juxtavascular cases of nodules the most popular method given by [46-49, 55] is morphological operations i.e. filtering based on erosion, dilation, opening, etc. GGO nodules offer the challenging task to draw the exact boundaries and modeling of the irregular contours. The widely used method addressed by [48, 52, 53] is based on probabilistic classification of voxels. For dealing with small nodules the common method called "partial-volume-effect" (PVE) and its variants given by Ko et al.[54] and Kuhnigk et al.[55] respectively. Summarizing about the nodules all authors cited here have their opinion that juxtapleural and sub-solid nodules are very hard to characterize and offered most challenging task for accurate segmentation.

The classification of nodules to be malignant or benign in an automated systems the common approach followed by various authors in number of research studies are based on domain specific features. The most common features considered for lung nodules are depend upon the nodules shape, appearance, textures, etc. The steps followed for the classification are: i) selection and extraction of useful features, ii) extracted features are organized, analyzed and processed by some specific classifier algorithms e.g. SVM, LDA, ANN, etc., iii) classifier algorithms are designed and implemented based on features, iv) sampled data sets are trained (iteratively with some defined limiting conditions) using classifier algorithm considering the extracted important features and the outcome are validated with some benchmarks or ground truths, v) finally in testing phase entire data sets are processed and nodules are classified into malignant or benign and further the results are observed with ROC analysis and subsequently criteria may be followed for the performance enhancement i.e. reduction of false positives. Kwata et al.[56] used shape based features of 3D nodules such as surface curvature and ridge line. El-Baz et al. [57] proposed a novel approach based on 2D visual appearance features where HU values of malignant nodule appearance were modeled with rotational invariant second order Markov-Gibbs random field (MGRF). Han et al. [58] investigated the 2D texture features like linear binary pattern (LBP), haralick and gabor and further extended these features to 3D spaces and observed that haralick feature achieved greatest area under curve (AUC) values. Recently for the irregularities in nodules shape Dhara et al. [59] had given diagnostic parameters like sphericity, spiculation and lobulation.

Table 2
Review of current methodologies for nodule segmentation and classification

Authors, Year	*Technique/Method*	*Features Used classification*	*Database*	*Performance Accuracy*	*Clinical Validation*
Antonelli et al., 2011 [60]	RFCM, Region growing, Thresholding, Multiclassifier systems aggregated from statistical, NN and decision tree.	3D geometrical features: volume, sphericity, radius, max compactness, max circularity and max eccentricity	30 scans	Sen.= 0.925 Spec.= 0.835	10 manual traced datasets
Keshani et al., 2013 [40]	Adaptive Fuzzy Thresholding, Active contour, classification by SVM	2D stochastic and 3D anatomical features	63 subjects (4 groups: 4, 4, 5 & 50 subjects of LIDC)	Detection rate= 89%, Fp/scan = 7.3	8 manual traced data I & II group and all annotations provided from III & LIDC and ANODE09 challenge
Filho et al., 2014 [61]	Threshold & region growing and SVM	Shape features: spherical disproportion, density, sphericity, weighted radial distance and radial shape index	800 exams (640 for validating and 160 for testing)	Sens = 85.91%, Spec = 97.70% , accu = 97.55%,	LIDC-IDRI
Choi et al., 2014 [62]	Threshold, 3 D connected component and SVM	3D shape based features	84 CT scans	Sens = 85.91%, Fp/scan = 6.76	Manual traced data; LIDC datasets
Kuruvilla et al., 2014 [41]	Otsu Threshold, Morphological operation, Statistical method: mean, SD, skewness, kurtosis, fifth & sixth central moment; feed forward BPN	Statistical features	155 patients	Train. Func 1: Accu = 91.1 %, Spec =100%, Sens=91.4% , MSE = 0.998 Train. Func 2: Accu =93.3 %, MSE = 0.0942	LIDC datasets
Alilou et al., 2014 [63]	Region growing, Morphological operation, Rule based & SVM classifiers	3D features: volume, min dimension size, max dimension size, eccentricity, compactness, min intensity, dist to center2D features: area, circularity, intensity, dist to center, max & min intensity	60 CT scans	Sens = 0.80 Fp/Scan= 3.9	LIDC datasets
Tasci et al., 2015 [64]	Morphological operation, Threshold, generalized linear model regression (GLMR)	Shape and texture based features	24 CT scans	With 33 features nodule recog AUC value = 0.9679	LIDC datasets
Farahani et al., 2015	Region growing,	Roundness,	60 CT Scans	MLP – Accu =	LIDC datasets

(contd...Table 2)

Authors, Year	*Technique/Method*	*Features Used classification*	*Database*	*Performance Accuracy*	*Clinical Validation*
[65]	Threshold, For classification : combination of multilayer perceptron (MLP),k-nearest neighbor (KNN) and SVM classifiers	Circularity, Compactness, Ellipticity, Eccentricity		90.41, Sens = 73.55 KNN – Accu = 91.20, Sens = 81.76.SVM – Accu = 90.60, Sens = 73.44.	
Aggarwal et al., 2015 [66]	Threshold, morphological operation, Linear discriminate analysis (LDA), GLCM for computing features.	Geometrical & Statistical features.	90 images Cancer Imaging Archive	Accu = 84 %, Sens= 97.14 % Spec = 53.33 %	Cancer Imaging Archive online database
Golan et al., 2016 [67]	Deep Convolutional Neural Network (CNN), BPN	Volumetric features	NA	Sens = 78.9% with Fp/scan = 20 Sens =71.2% with Fp/scan = 10	LIDC datasets
Qi et al., 2016 [68]	3D convolutional neural networks (CNNs)	Shape , Intensity and gradient features	888 CT scans	Sens = 94.4%	LIDC datasets, Manual traced data and LUNA 16 challenge

Abbreviations: Sen. - Sensitivity = TP/(TP + FN); Spec - specificity = TN/(TN + FP); Accu - Accuracy = (TP + TN)/(TP + TN + FP + FN); AUC =Area under curve; MSE = mean square error; Fp/scan = no. of false positive per scan. LIDC-IDRI : Lung Imaging Database Consortium – Image Database Resource Initiative (https://wiki.cancerimagingarchive.net/display/Public/LIDC-IDRI)

The research studies of some current trends used by various authors in nodule segmentation and classification are reviewed in Table-2.

4. DISCUSSION AND CONCLUSIONS

Development of effective and efficient automated (CAD) systems that can detect the cancerous matter or nodules in primary stage is very useful and important because early detection and diagnosis may lead to the better and appropriate treatments and thereby decrease the mortality from the lung cancer and enhance our healthcare services too. In this paper we have addressed 68 publications on various phases of automated systems. The recent trends, technological aspects and methodologies have been focused with their limitations and strengths. In the major phase of lung segmentation the technical issues and challenges have been discussed with number of research articles and the common techniques are categorized such as threshold, active contour, prior shape model, etc. based approaches are reviewed with their proper validations. In nodule segmentation and classification phase the complexities related to various nodule types are discussed. Then the suggested solutions to each type of nodules in recent studies proposed by different authors have been explored with their clinical validations. The investigations made in this paper are based on the referred articles but being a demanding area of research, the automated systems of lung cancer need more attention and studies toward this emerging field.

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