Microsatellite Instability in Gastrointestinal Cancer Using Deep Learning: A Review

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Abstract. Currently, the health management is a foremost concern all over the world. Particularly in India, due to lack of physical activity, overweight, stress and unhealthy eating habits, various diseases like heart disease, diabetes and cancer disease are increasing at a very rapid rate. The common problem which is affecting all age generation is a gastrointestinal disorder which includes various conditions like colitis, colon polyps, perianal infection and cancer. Microsatellite Instability (MSI) in gastrointestinal (GI) cancer is the second leading cause of death worldwide. However, this cancer can frequently be asymptomatic during the early stages and stay undetected until the later stages of tumor advancement. Deep Learning has the capacity to detect MSI in gastrointestinal cancer at an early stage, which is very helpful for the patients. There are number of research papers, focusing on different techniques used for detection of MSI in gastrointestinal cancer. In this paper, we focus on the recent trends of deep learning methods in this field. The main goal of this review paper is to provide a detailed discussion from technological perspective. This article discusses various challenges, molecular subtypes, pathologist approach and computer aided approach for gastrointestinal cancer detection. Also, this article brings into light the existing literature and state of art with their contribution in different aspects of detection of microsatellite instability in gastrointestinal tract with the help of deep learning techniques.

Keywords: Machine Learning, Deep learning, Microsatellite Instability (MSI), Microsatellite Stability (MSS), Gastrointestinal Tract.

1. Introduction
The gastrointestinal tract is an organ within human body which takes in food, digest it, absorb nutrients, provides energy and removes the remaining waste from the body. The gastrointestinal tract includes various organs like esophagus, stomach, small intestine, large intestine, colon etc. The gastrointestinal disorder can lead to various types of cancer [1]. Cancer is the foremost cause of death in various countries. Gastrointestinal cancer is the second most common reason for death in the world which is affecting both men and women of all age groups. Gastrointestinal cancer refers to the dangerous conditions of the gastrointestinal tract and embellishment organs of absorption like esophagus, stomach, pancreas, small intestine, large intestine and rectum [2]. The various parts of gastrointestinal tract which can be affected by cancer are stomach, gallbladder, liver, duodenum, colon, rectum and pancreas.
1.1 Molecular Subtypes

There are four molecular subtypes of gastrointestinal cancer according to The Cancer Genome Atlas (TCGA) namely Epstein-Barr-Virus (EBV), Genomically-stable (GS), Microsatellite-instability (MSI) and Chromosomal-instability (CIN). TCGA is a project which was started in 2005 to categorize genetic mutation for cancer. Mutation is an alteration in DNA sequence which makes a gene. TCGA clinically elaborated four molecular subtypes which have different reasons for their occurrence. EBV is the common virus which is found mostly in children and spreads via oral transfer of saliva and genital secretion. People adapt immunity against this virus easily and can survive. GS is associated with less genomic alteration, so survival rate is high. CIN is the form of genetic cancer which may be cancerous or not [3]. All molecular subtypes are harmful but the cancer is mostly categorized according to MSI because of its higher mutable rate which is mostly cancerous. MSI is further classified into MSI-High (MSI-H), MSI-Low (MSI-L) or Microsatellite Stability (MSS) according to biomarkers which are the indicator of some disease. The National Cancer institute agreed on five microsatellite markers to determine MSI which include two mononucleotide-BAT 25, BAT 26 and three dinucleotide markers D2S123, D5S346 and D17S250. If two or more marker shows instability then it is known as MSI-H else MSI-L or MSS.

1.2 Microsatellite Instability (MSI)

MSI means instability in cancer cells which are the repeated sequences of DNA. MSI is a condition of impaired DNA Mismatch Repair (MMR). MMR consists of a family of proteins that detect DNA replication error. The important genes which are responsible for the MMR factors are MLH1, MSH2, MLH3, MSH6 and PMS2. Any mutation that occurs to these genes will lead to non-functional MMR which leads to increase or decrease of microsatellite which is the basis for MSI. It is associated with colon cancer, gastric cancer, ovarian cancer and endometrium cancer. But it is most predominant in affiliation with colon cancer. But it is most predominant in affiliation with colon cancer. In MSI, MMR is deficient which increases the mutation rate and is an alteration in the DNA sequence that makes up a gene. Due to deficient MMR, DNA replication go unrepaired leading to high mutation tumor. MSI can be detected with the help of automatic techniques like machine learning and deep learning very easily. By using histological images of tissue slide we can detect MSI status easily. The histological images of MSI and MSS are represented by Figure 1(a) and 1(b) respectively.

![Figure 1. Histological Images of [6] (a) MSI Tissue Slide (b) MSS Tissue Slide](image-url)
1.3 Microsatellite Stability (MSS)
Microsatellite Stability means, there is no instability in tumor. It is just the opposite of MSI and tissues are found same as normal tissue which does not confirm any instability in biomarkers. In MSS, MMR is proficient which leads to low mutation rate. In the presence of functional MMR system, the replication error occurs at a very low mutation rate which slows down the process of growth of cancer cell replication. The cancer detection measures are required to differentiate between MSI and MSS gastrointestinal cancer. The procedure used for cancer detection is elaborated in the upcoming section.

2. GI Cancer Detection Process by Pathologist
The process used for detection of cancer is represented by Figure 2. The slide scanner as shown in Figure 2 (a) is used to scan the tissue slides images like MSI and MSS, then after scanning, images are used for tissue mapping where different magnification tissues are converted into same size and are mapped with each other as represented by Figure 2 (b). After mapping tissues are analyzed according to their structure as shown in Figure 2 (c). Finally, the tissue area is divided into different rectangles according to region of interest (ROI) where structural and nuclear features are analyzed as shown in Figure 2 (d) and according to the given slides results are predicted as shown in Figure 2 (e).

3. Computer Aided Design for GI Cancer Detection
Computer aided design is proposed for the identification of gastrointestinal cancer. It is further divided into three steps such as pre-processing, processing and post-processing as described in Figure 3.

3.1 Pre-processing
In the pre-processing part, input data of gastrointestinal cancer prediction is read in the form of colored RGB images and can be resized. After that, image enhancement methods like filtering, contrast methods can be used. It refers to all the changes which are performed on the raw data before it is fed to machine or deep learning algorithm.

3.2 Processing
In the processing part, features of the images are extracted with the help of machine learning and deep learning algorithm such as Convolutional Neural Network (CNN). It also includes classification operation which is used to categorize the images.
3.3 Post-processing
Post processing is the process which is used to refine the knowledge to get some desirable results. In post processing part, various measures will be evaluated for checking the performance of developed algorithm. Various performance metrics such as precision, recall and F-score will be used to evaluate the performance of the algorithm.

4. Convolutional Neural Network
CNN is a deep learning algorithm which takes an input image, assign weights to the object and classify them according to features. It is also known as ConvNet, and is type of artificial neural network. CNN can be used in image processing, Natural Language Processing etc. It is basically four layered concept which consists of Convolutional layer, oooling layer, Flattening layer and Fully Connected layer. The description of each layer is given below.

4.1 Convolutional Layer
It is a basic building block of CNN and is also known as Kernel or filter (for example 5*5 filter with a Kernel size of 3 *3) as shown in Figure 4, used to pass over the image. Convolution operation is performed to reduce the size of the image. After that the resulting output image is passed to the Pooling layer.
4.2 Pooling Layer
The main function of this layer is to reduce the spatial size of the matrix. In this, filter is passed over the results of convolutional layer. There are max, min and average pooling approach which can be applied to the matrix. The most common approach used is max pooling because this allow network to train faster as shown by Figure 5. Stride of 2*2 is used on the image to access the maximum features from image and formed a new matrix known as pooled feature map which is then passed to Flattening layer.

![Figure 5. Pooling layer](image)

4.3 Flattening Layer
It is used to convert the pooled feature map into a single column which is used as an input for the next layer as shown by Figure 6. In this, output is flattened into a single long feature vector which is connected to Fully Connected layer.

![Figure 6. Flattening layer](image)

4.4 Fully Connected Layer
The flattened feature map is passed to neural network for processing. This layer consists of input layer, fully connected layer and output layer as shown in Figure 7. In this, every node in the first layer is connected to second layer of every node and gives the final probability to classify the images.
5. Publically Available Dataset

Dataset is known as the collection of data or information which is useful in training the model. The various ways of dataset collection are survey, questionnaires, direct observations or publically available dataset. The dataset which is publically available is known as free dataset. Various publically available dataset used for detection of gastrointestinal cancer are represented in terms of number of images and size by Table 1.

| Source | Dataset Used | No. of Images | Image Size | Types of Cancer |
|--------|--------------|---------------|------------|-----------------|
| [8]    | Hiroshima University Hospital (Hiroshima, Japan) and Hardoi Hospital (Japan) | 4,128 stomach WSIs and 4,036 colon WSIs | 512x512 pixel | Gastric and Colon Epithelial Tumours |
| [19]   | Datasets from multiple Laboratories | 548 images | 299x299 pixel | Gastric Cancer |
| [23]   | LIDC-IDRI Database | 18,408 images | 28x28 pixel | Lung Cancer |
| [5]    | TCGA MSI-MSS Kaggle Dataset | 192312 images | Images of different size | Gastrointestinal Cancer MSI and MSS. |
6. Literature Review

In this section, a review of last seven years ranging from 2014 to 2020 has been done in gastrointestinal cancer detection with the help of Machine Learning and Deep Learning. Various authors reviews have been collected to analyse the different techniques used for gastrointestinal cancer detection as shown by Table 2.

| Year of Publication | Author/s       | Source | Summary |
|---------------------|----------------|--------|---------|
| 2020                | Lizuka et al.  | [9]    | Proposed an AI based computational technique for classification of gastric and colon cancer. CNN is used for feature extraction and RNN model is used to classify data under time constraints into Adenoma, Non-neoplastic and Adenocarcinoma. |
| 2019                | Fu et al.      | [10]   | Proposed a prediction model for MSI status of right-sided Colon Cancer (RCC) based on the qualitative transcriptional signature. RCC samples is used for the relative expression orderings of gene pairs and based on the feature selection with RCCs authors achieved F-scores is near to 1, 0.9630, 0.9412 and 0.8798, respectively. |
| 2019                | Chen et al.    | [11]   | LncRNAs model is developed to predict MSI status of tumour patient with the help of SVM and PCA Algorithm. MATLAB (2018 a) is used for implementation. TCGA TANRIC database is used for the study which is available publically. |
| 2019                | Kim et al.     | [12]   | Predicted data from a Hospital named as Severance. The data is analysed using various methods such as Kaplan Meier method, long rank test and Cox model. The main aim of the paper is to classify MSI-H with MSS. |
| 2019                | Wan et al.     | [13]   | Proposed an expert system is developed to detect cancer at an early stage. Various machine learning algorithm like SVM, KNN, EB, RF are compared with deep learning algorithm like CNN, RNN1 and RNN2.It is found that machine learning algorithm worked well because the dataset was very small in size. |
| 2019                | Nakahira et al.| [14]   | Proposed a deep neural network for gastric cancer detection. Computerized system is developed to analyse |
the images of cancer prediction. In this the system detected gastric cancer risk in three different groups low, moderate and high. CNN algorithm is used for detection purpose with gradient booster.

| Year | Authors            | Reference | Description |
|------|--------------------|-----------|-------------|
| 2019 | Siegel et al.      | [15]      | Presented an analysis of gastric cancer according to the American Society of Cancer, the amount of new cases of cancer instances and the deaths rates resulting from cancer and the latest cancer information collected. |
| 2019 | Muhammed et al.    | [16]      | Proposed Artificial Neural Network (ANN) has been implemented to tackle early detection of pancreatic cancer. Two data sources are used for this purpose. The results can be further improved by using another technique. |
| 2018 | Yoshida et al.     | [17]      | Proposed an automated image analysis in the field of surgical pathology to achieve the desired results. In this research 3062 gastric specimen were used. The main focus of the research to perform classification of e-pathologist software of images. Histopathological study of images can be done further. |
| 2018 | Kim et al.         | [18]      | Collected cases with slide level and region-level labels and trained deep neural network for tissue classification. To improve the tissue classification performance, they exploited slide-level weak label for training the model with patches without region-level label. For whole slide classification, they extracted features representative for whole slide characteristics |
| 2018 | Drost et al.       | [19]      | Presented the previous research work done for the model of cancer, such as preclinical models are compulsory to translate cancer research more efficiently translation into newer therapy schemes for cancer patients. In a setting that reaches the behavioural atmosphere, genetic manipulation of organoids enables modelling of disease. They have evaluated organoid tumour protocols and how they can be used in cancer research as an alternative model. |
| Year | Authors            | Reference | Summary                                                                                                                                                                                                 |
|------|-------------------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2018 | Islami et al.     | [20]      | Proposed a model to estimate the percentage and amount of invasive cancer instances and fatalities in 2014 non-melanoma skin cancers has been exclude here and 26 kinds of cancer in individuals 30 years of age and younger in the United States attributable to significant, possibly modifiable exposures. |
| 2018 | Razmjooy et al.   | [21]      | Proposed a novel efficient methodology to detect melanoma cancer. Firstly, the scales that are not needed are removed through the edge detection and smoothing technique. After getting extracted and optimized outcomes this method become able to segment the cancer images. |
| 2018 | Silva et al.      | [22]      | Proposed a methodology to detect lung cancer with the help of CNN using PSO algorithm with the help of CT (computed tomography) images. 18,408 samples were collected for analysis of lung cancer. For this purpose, LIDC-IDRI database is used. |
| 2017 | Sharma et al.     | [23]      | Proposed an automatic Classification of gastric carcinoma using whole slide images in digital histopathology. Deep learning is used to detect gastric cancer with the help of CNN Architecture. The classification results are compared with the traditional analysis methods used for histopathological images. |
| 2017 | Liu et al.        | [24]      | Proposed the various parameters of histopathological images of gastric cancer with the help of CT texture analysis. The main focus is to analyse the correlation between these two by using t-sample test. |
| 2016 | Esfahani et al.   | [25]      | Proposed a Complex computational technique on the basis of deep learning has introduced using medical images. This scheme was able to detect melanoma instances from benign ones. In proposed scheme, clinical input pictures, which could contain lighting and noise impacts, are pre-processed to decrease such artefacts. |
### 2016
**Alshamlan et al.** [26]
Proosed a model using Artificial Bee colony algorithm (ABC) along with Support Vector Machine (SVM) to measure the accuracy of the selected genes. The data set comprises of two classes namely six binary and multiclass microarrays. Also, the comparison between previously existing techniques such as ABC, GA, and PSO along with ABC-SVM has been provided.

### 2015
**Goto et al.** [27]
Proposed a new technology names as hyperspectral imaging. The study is done to differentiate gastric tumor and normal mucosa with the help of hyperspectral camera.

**Wang, J., & Watada, J.** [28]
Proposed a few feature point detection techniques and panoramic mosaic images by using Open CV. SURF (Speeded up Robust Feature) algorithm is used in this study. Image Mosaic King with transformation matrix is used to carry out the work.

### 2014
**Tao et al.** [29]
Proposed different methods like magnifying endoscopy and chromo endoscopy are used for enhancement of gastric cancer. 643 specimens are used as sample for analysis. Data is collected from Peking Union Medical College Hospital of two years and then study is performed.

**Chen et al.** [30]
Presented an innovative genetic selection method using swarm optimization in conjunction with a classifier known as decision tree. Mathematical analysis demonstrates that the proposed method performs better than other common optimization algorithms by conducting research on 11 datasets of cancer expression of genes.

### 7. State of Art
After the analysis of above existing work, comparison of previous work on the basis of different performance parameters and dataset used is summarized in the Table 3. Along that, author wise comparative analysis of Area Under Curve (AUC) is represented by Figure 8. AUC is an evaluation metrics to distinguish various models. Higher the AUC, better will be the performance of the model. It has been proposed that in the comparative analysis of AUC graph by different authors, Lizuka et al. [9] shows highest value for AUC (97% approximately).
| Reference       | Number of Images /Patient Dataset | Image Size | Disease Detected                                   | Techniques Used                                                                 | Results                                                                 |
|-----------------|----------------------------------|------------|---------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Lizuka et al. [9] | 4,128 stomach WSIs and 4,036 colon WSIs | 512 × 512 pixel | Stomach and Colon adenoma, adenocarcinoma Cancer | Convolutional Neural Network (CNN). Recurrent Neural Network (RNN) have been used. | ➢ AUC=0.977 and 0.99 for gastric adenoma and adenocarcinoma               |
|                 |                                  |            |                                                   |                                                                                | ➢ AUC = 0.966 and 0.99 for colon adenoma and adenocarcinoma                 |
| Fu et al. [10]  | 57 MSI, 154 MSS patients meta data | patients meta data | MSI and MSS prediction in right-sided Colon Cancer | A qualitative transcriptional signature technique has been used.               | ➢ F-score=0.9348, Sensitivity=0.93                                         |
| Chen et al. [11] | 285 tumor sample, 33 normal patient’s sample | patients meta data | MSI detection in stomach adenocarcinoma | Support Vector Machine (SVM) algorithm has been developed using MATLAB (version 2018 a) tool | ➢ AUC=0.976, Sensitivity=0.9; 8, Specificity=0.963                             |
| Kim et al. [12] | 1156 tumors patient’s metadata | patients meta data | MSI status of gastric tumor | Kaplan Meier method. long rank test. Cox model has been used for tumor detection. | ➢ AUC =0.933                                                                   |
| Muhammed et al. [16] | 800,114 patients meta data | patients meta data | Pancreatic Cancer | Artificial Neural Network has been used | ➢ AUC=0.85, Sensitivity=0.87, Specificity=0.87                              |
| Kim et al. [18] | 548 images 299 x 299 pixel | Gastric Cancer | CNN has been used | Accuracy=0.92, AUC=0.98 | ➢ AUC=0.955, Sensitivity=0.92, Specificity=0.98                             |
| Silva et al. [22] | 18,408 images 28 x 28 pixel | Lung Cancer | Swarm optimization algorithm with CNN has been used | Accuracy=0.95, AUC=0.98 | ➢ AUC=0.955, Sensitivity=0.92, Specificity=0.98                             |
| Tao et al. [29] | 508 patient’s metadata | patients meta data | Gastric Cancer | Enhanced magnifying endoscopy used | ➢ Accuracy=0.95, AUC=0.98 |
8. Conclusion
As the health is an important aspect, the concept of AI as deep learner can be helpful in finding the MSI in gastrointestinal cancer detection at an early stage. The main objective of this paper is to find out the best techniques for gastrointestinal cancer detection. Deep Learning has proven boon to this aspect, it gives accurate and generalized results on the large datasets. In this paper, various techniques are described for gastrointestinal tract cancer detection. After the comparative analysis of AUC graph, it has been analysed that CNN technology has been proved best technique till now. Further improvements can be done in CNN to improve the accuracy of gastrointestinal cancer detection.

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