Artificial Intelligence and Cancer Staging in Upper Gastrointestinal Malignancies

Study protocol with statistical analysis

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INTRODUCTION

Esophageal and stomach cancers, which constitute cancers of the upper region of the digestive system, are cancers that are frequently observed and unfortunately have a low rate of cured patients [1]. Due to the fact that the esophagus and stomach are hollow organs and their capacity to stretch, patients' complaints about nutrition usually occur when the tumor grows and occludes the lumen. Naturally, the tumor is at an advanced stage when diagnosed [2]. The stage of cancer at diagnosis is very important for two reasons; First, the stage of the cancer is directly related to the survival time. Secondly, treatment is planned according to the stage. Different treatments are applied to patients at different stages [3,4].

Currently, the TNM staging (Tumor, Lymph Node and Metastases) system is the accepted one worldwide. According to this system, the depth of the cancer in the tissue (T), spread to lymph nodes and spread to distant organs (M) are evaluated and categorized from stage 1 to stage 4[5]. Despite many advanced technology tools used in staging (Computed Tomogrphy, Magnetic Resonance Imaging, Endoscopic Ultrsonograph), there are still difficulties in correct staging before surgery or before-after neoadjuvant therapy[6]. The Endoscopic Ultrsonograph (EUS) gives the best accuracy (71 - 99%) in “T” staging of esophageal and gastric cancers [6]. However, the number of centers where EUS is located and the number of experienced gastroenterologists who will perform EUS are low. Computed Tomography (CT), Magnetic Resonance Imaging (MRI) are used frequently, but the accuracy rates are reported to be 55-91% [6]. It is certain that the diagnosis and treatment will be better with the increase in the accuracy of cancer staging.

Artificial intelligence techniques are increasingly used in the field of health, especially in the diagnosis and treatment of cancers [7-9]. Obtaining cancer details in radiological images, which cannot be noticed by the human eye, by analyzing big data with the help of algorithms gave rise to the application area of "radiomics" [10]. It is stated that with Radiomiks, there will be improvements in both the diagnosis and staging of cancers and, accordingly, in the treatment.

While there are studies on the use of endoscopic methods with artificial intelligence for the early diagnosis of esophageal cancers, a limited number of studies have been conducted on stage estimation from radiological images [11,13]. In particular, there are not enough studies on the investigation of changes in tumor size after chemotherapy with artificial intelligence and the estimation of staging.

In this study, it was aimed to investigate the predictive efficiency of staging by processing tomography images in a region where esophageal cancers are endemic.

METHOD-MATERIAL

Design

The study, which included patients with histopathological proven diagnosis of esophageal cancer, was designed prospectively between the years 2021-2022. This research is the first pilot study of an ongoing project of artificial intelligence applications in the staging of upper gastrointestinal tract cancers. The study was carried out in 2 different centers, which are 3rd level training and research hospitals.

Approval was obtained from two separate local ethics committees (Van Training and Research Hospital Ethics Committee 26/12/2019, 2019/22 and Van Yuzuncu Yıl University Ethics Committee 15.12.2021, 2021/17).

In both centers participating in the study, all cancer patients are evaluated weekly by the oncology council. Tomography images of esophageal or stomach cancers that come to these councils are recorded. During the council, the “T” stage of the tumor is specified and recorded by the radiologist. According to this pre-treatment clinical staging, which is also confirmed by oncology and general surgery specialists, the treatment protocol that the patients will receive is determined.

In this study, tumors were marked on tomography images of patients who were admitted to the council at the time of new diagnosis or after neoadjuvant therapy (Figure-1). After marking, these images were taught to algorithms developed with the technique described in detail below. Thus, algorithm training is completed with these images.

Duration of study/number of patients

This study, in which artificial intelligence applications are planned to be developed through tomography images of patients, is planned to last two years. The more data inputs into the study, the better the training of algorithms will be, and the admission of patients will continue throughout the study period. After the last patient is recruited, the final revision of the developed algorithms will be made. The current pilot study was evaluated with data from 50 patients.

Inclusion criteria:

Each patient meeting the following criteria will be included in the study.

1- Being diagnosed with esophageal cancer (adenocarcinoma or squamous cancer) histopathologically

2- Being over 18 years old

3- Having a tomography image before or after chemotherapy.

4- Giving informed consent to participate in the study.

5- Having final pathological staging after surgery.

Exclusion criteria:

A participant with any of the following criteria will be excluded from the study:

1- Previous thoracic surgery.

2- Having a recurrent tumor

3- Inability to perform clinical staging due to technical reasons

4- Drawings cannot be made due to poor tomography quality.

Primary outcomes:

The accuracy of the algorithm developed with artificial intelligence to predict the “T” staging in esophageal cancer

Secondary outcomes:

In addition to the demographic data of the patients, post-treatment mortality, morbidity rates, complication rates.

Tomography shooting technique and drawing technique of images:

CT examinations were performed with a 128 slice CT [Siemens Definition AS +(Plus)), Siemens AG, Munich, Germany] device. The acquisition parameters (mAs, Kv, slicetickness) were as follows, respectively: ThoraxCT (110, 120, 3 mm) and abdomen CT (210, 120, 3 mm). CT scans were performed after 12 hours of fasting, and 1500 ml of water was drunk within 60 minutes of all patients before the extraction to distend the esophagus, stomach and intestines. Iokexol (Omnipaque or Opaxol), which is a non-ionic contrast agent, was administered 100 ml with an automatic injector at a rate of 3 ml/s by IV route. In ThoraxCT, imaging was performed from the distal neck to the upper abdomen, and in abdominal CT, from the diaphragm to the

symphysispubis level. All images are available in our PACS system and were evaluated by consensus by two radiologists with 15 and 17 years of thoracoabdominal CT experience. Tumors were also drawn on images by two radiologists. Readers were blind to both the pathology result and the AI prediction result.

Pathological evaluation:

The specimens were fixed in 10% formalin solution for 24 hours. Tissue sections taken after routine tissue macroscopic examination embedded in paraffin blocks. Then, from the prepared paraffin blocks, 4 mm thick sections were taken and stained with hematoxylin-eosin (HE). Microscopic examination of the primary tumor in the evaluation. Pathological staging was done according to American Joint Committee on Cancer as TX, T0, Tis, T1(a/b), T2, T3 and T4(a /b [14].

Predicting “T” stage of esophageal and gastric cancers in computed tomography images

Measurements parameters:

1- Patient’s CT images
2- Patient’s pathology “T” stages

Details:

We will collect all CT images, start from cervical region to upper abdomen. Images from DICOM will be converted to JPEG. Then these images will be classified with help of artificial intelligence (AI) algorithms. Training of algorithm will be performed with data previously collected and testing with new patients when available. New patient images will be evaluated for "T" stage by artificial intelligence algorithms. Then these predictions will be compared with pathological results and parameters below will be measured:

1- positive prediction value
2- false positive value
3- accuracy rate
4- sensitivity and specificity

Outcome measures:

1- prediction of "T" stage: there are 5 stages

T_0 → sensitivity, specificity, accuracy

T_1 → sensitivity, specificity, accuracy

T_2 → sensitivity, specificity, accuracy

T_3 → sensitivity, specificity, accuracy

T_4 → sensitivity, specificity, accuracy

Comparing AI success to pathology results:

	PATHOLOGY T_0	**PATHOLOGY T_1**	**PATHOLOGY T_2**	**PATHOLOGY T_3**	**PATHOLOGY T_4**	**TOTAL**
AI-T_0	A	B	C	D	E	A+B+C+D+E
AI-T_1	F	G	H	I	J	F+G+H+I+J
AI-T_2	K	L	M	N	O	K+L+M+N+O
AI-T_3	P	Q	R	S	T	P+Q+R+S+T
AI-T_4	U	V	W	X	Y	U+V+W+X+Y
TOTAL	A+F+K+P+U	B+G+L+Q+V	C+H+M+R+W	D+I+N+S+X	E+J+O+T+Y	A+B+C+…+X+Y

- Sensitivity of AI-T_1 = $\frac{G}{B+G+L+Q+V}$
- Accuracy of AI-T_1 = $\frac{G+(A+M+S+Y)}{A+B+C+\cdots+X+Y}$
  - for us 5% prediction precision will be important
- Sample size formula = $\frac{Z^2_{1-\alpha/2} \times S_N \times (1-S_N)}{L^2 \times Prevalence}$

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