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Machine learning-based prediction of survival and recurrence in patients with colon cancer

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Abstract

This article provides an overview of colorectal cancer statistics through the machine learning algorithm to gain insight into survival and mortality rates and relapse trends. In this study, three basic machine learning algorithms were used for prediction: support vector machine (SVM), genetic algorithm, and XGBoost decision tree. Additionally, some basic statistics were also used. By utilizing two different clinical datasets and the histopathology parameters, the prediction of metastasis and survival time of colon cancer was analyzed using machine learning (ML) in clinical research. The first dataset used in the study is the longitudinal dataset that comprises 929 patients and the clinical study results observed for approximately 6.5 years. The second dataset consists of a 90-person data set obtained from patients with APC level II tumors. With these data, the most appropriate model was selected using machine learning methods, and the survival and tumor recurrence predictions were made and evaluated. It was concluded that there was a notable difference in prognosis and a prominent difference in terms of gender between the early- and late-stage relapse groups. It should be emphasized that the most important factor affecting survival time in the study is the time to recurrence. Moreover, it was observed that the time to relapse and the time of death were the same in most of the study.

Keywords: Colon cancer, Genetic algorithm, Machine learning, Support vector regression (SVR), Survival analysis, XGBoost decision tree.

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1. Introduction

Worldwide, colorectal cancer is among the most frequently diagnosed cancers and the second leading cause of cancer-related death. Colorectal cancer (CRC) develops as a malignant tumor driven by complex genetic mutations in the stem cells of the colon or rectum [1]. The growing prevalence of malnutrition and sedentary lifestyles, particularly in developed countries, has contributed to an increase in colorectal cancer (CRC) cases. Improvements in treatment and early diagnosis have led to a significant reduction in mortality rates from this disease across highly developed countries. Additionally, lifestyle changes appear to have played a role in decreasing the incidence of colorectal cancer in these regions.

The term 'colorectal' refers to two distinct pathologies: colon cancer and rectal cancer. While these conditions share certain similarities, they are separate diseases with unique characteristics and diagnostic features [2].

Some studies highlight tumor size as a critical factor in determining the stage of colon cancer. Moreover, tumor size is regarded as a crucial predictive marker, not only for assessing the cancer stage but also for predicting patient survival time [3-5]. Survival of cancer patients with metastatic disease has increased significantly in recent years. Although colorectal cancer is related with environmental and hereditary factors, it is also closely related to the interaction between these factors in various ways.

The development of cancer is the result of not only cellular changes but also genetic and molecular-level interactions. Understanding the molecular basis of cancer can reveal how cellular abnormalities begin and how tumors grow and spread. This molecular understanding can help identify the biological factors that contribute to cancer progression from its initiation. As a result, treatment strategies and early diagnostic methods can be developed, as different molecular targets and biomarkers can be used depending on the stage of cancer. However, it is possible to increase the chances of success in treatment by determining the reaction or resistance to antitumor agents. Chromosomal aberrations are considered the most common form of genomic instability, leading to numerous changes in both chromosome number and structure.

Over the past few decades, there have been many genetic changes impacting genes involved in cell maturation and growth and they confirmed the existence of a genetic role in cancer development [6]. Although the majority of colorectal cancers are characterized by chromosomal instability (CIN), only a few genes have been identified as the cause of this instability.

Colorectal cancers are thought to have a high genetic heterogeneity. The data of these genes have led to new developments in tumor biology research by providing new perspectives for diagnosis and treatments [7]. The preservation of genomic stability is vital for maintaining cellular integrity. On the other hand, loss of genomic stability results in the development of new mutations linked to tumor formation.

In this study, the data set including APC gene mutations was also used in addition to the clinical data set, which consists of patients receiving chemotherapy treatment with the aim of providing additional information.

1.1. Colorectal Cancer (CRC)

We are living in an era marked by longer life expectancy and improved access to treatment systems, which have significantly enhanced medical diagnoses and disease treatment. These advancements have contributed to a rise in life expectancy in many parts of the world. However, cancer-related death rates have also risen by nearly 40% over the past few decades. Projections indicate that these rates will increase by 60% over the next 20 years, with an estimated 13 million cancer-related deaths expected in 2040 [8].

Detection of pre-cancerous lesions or early-stage malignancies is very important for the life span of patients. Therefore, the possibility of five-year survival is 10% in the patient diagnosed at the last stage, while it is 90% at the early stage [9]. The increase of colorectal cancer and its incidence in especially developed countries can be associated with a growing aging population, modern fast food-style dietary habits and the growing prevalence of risk factors such as smoking, insufficient physical activity, and obesity. Some studies have been systematically reviewed and they reported that increased physical activity in colorectal cancer patients improved the quality of life [10]. Dietary adjustments, such as increasing calcium and vitamin D intake through supplements or low-fat dairy, can substantially decrease the risk of CRC. As well as Fiber-rich foods, is thought to cause a reduction in CRC risk. Garlic, magnesium, fish, and vitamin B6 may also be considered as alternative supplements for potentially preventing CRC. Similarly, folate supplementation is thought to be effective in preventing tumor formation. Although dietary adjustments can help lower the risk of CRC, they may also promote the growth of pre-existing tumors, making them unsuitable for all individuals. Moreover, limiting alcohol, tobacco, and red meat consumption while boosting the intake of fiber-rich foods can reduce the risk of CRC by more than 50% [11-13]. Considering the higher rates of CRC incidence and mortality in developed countries, lifestyle changes that address the underlying risk factors could play a significant role in reducing both the incidence and death rates of this disease [14].

In some studies, CRC incidence is often thought to be a pathology related to diet, physical activity, alcohol, smoking, aspirin and lifestyle [15]. It shows that regular aspirin use is correlated with a notable reduction in the occurrence of CRC [16, 17]. There is evidence to suggest that regular aspirin intake is associated with a notable decrease in CRC occurrence.

Being overweight and insufficient physical activity are the most important behavioral factors that cause the development of CRC. This probably explains many of the different formations and variations between humans [18]. In stage II, cancer is typically localized to the organ where it started (e.g., colon for colorectal cancer). It may be larger than in stage I but has not spread to nearby lymph nodes or distant organs.

In stage III colon cancer, the disease has spread to adjacent lymph nodes, but it has not extended to other body parts. The evaluation of cancer recurrence in patients is primarily determined by findings observed when the disease has progressed to an advanced stage

Elements like tumor staging, spread to lymph nodes, weight loss and extent of metastatic disease spread to other organs provide important information that affects the aggressiveness of the cancerous tumor and the expected survival of patients.

With and without metastatic disease, based on the data obtained from clinical studies in stage II and stage III patients, the best predictive models have been developed with some Machine Learning (ML) analysis.

1.2. Treatment

As the data set utilized in the methodology and results sections includes information from one of the first successful adjuvant chemotherapy trials for colon cancer, a brief overview of these treatment protocols is provided in this section. This study is built upon the data and outcomes of patients who underwent these treatments.

Treatment for rectal cancer is often linked to long-term complications, with pelvic floor issues being more prevalent in patients who undergo neoadjuvant chemoradiotherapy or radiotherapy. It can be said that toxicity post-chemoradiotherapy is higher than that of radiotherapy alone. 5-Fluorouracil, used in chemotherapy, is generally well tolerated. FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOx (capecitabine and oxaliplatin) regimens are commonly used for chemotherapy. However, leucovorin or 5-FU alone is used in some patients, depending on the age group and general health status. The most important issue that needs to be evaluated in targeted treatments is to consider side effects. These drugs are often combined in pairs or more to enhance the effectiveness of treatment [16, 19-21]. This combination of chemotherapy regimens is used for the treatment of metastatic colorectal cancer. Each treatment method has its own side effects and complications specific to that treatment. One of the most feared surgical complications is the occurrence of problems such as anastomotic leakage after tumor removal. This event is usually associated with prolonged hospital stays and death.

Since the 1950s, 5-FU has an important place in the treatment of colorectal and other cancers. Response rates to 5-FU used in treatment are considered to be only 10% to 20% when used as a single agent [22, 23].

Rectal cancer patients receiving adjuvant chemoradiotherapy or radiotherapy are more likely to experience pelvic floor problems. The risk of post-chemotherapy toxicity is higher than that of radiotherapy alone.

Metastatic cancers such as anorexia, anemia, liver failure, biliary obstruction and impaired lung function, should be evaluated together with symptoms affecting the quality of life [24].

In stage II colon cancer treatment, performing surgery alone resulted in improved outcomes, however, the role of adjuvant chemotherapy remains a topic of debate. Patients with advanced cancer and high-risk features tend to have a poorer prognosis, and adjuvant chemotherapy is typically advised. In stage III colon cancer, the disease propagates to lymph nodes but does not affect other parts of the body. For individuals with stage III colorectal cancer, chemotherapy is often managed effectively as a viable treatment option [25-28].

Survival is very low in cases of early relapse. If both recurrence and spread of the disease are detected early, it is potentially suitable for a therapeutic surgical procedure and this will increase the patient's chances of survival [29, 30]. In patients with early recurrence, most frequently or locally recurrent tumors in the liver are seen and late recurrence mostly develops in the lung.

2. Materials and Methods

Ethical Approval: The use of publicly available datasets eliminates the need for ethical clearance

Support vector machines in machine learning function as models with algorithms that perform classification and regression analysis on data. As a regression technique, the Support Vector Machine retains all the essential elements that characterize the algorithm. The Support Vector Regression (SVR) method exhibits the same key features as SVM for classification.

Support Vector Regression has three types of applications: SVR, NuSVR, and LinearSVR. LinearSVR provides a quicker solution than the other application methods.

SVR(Support vector regression) allows us to define how much of the error is acceptable in our model to be applied and it creates the appropriate regression to fit the data [31].

In this study, in order to analyze the clinical research, we applied the SVR method using machine learning techniques. The SVR method was selected as the best model with the help of the genetic algorithm method. The LinearSVR method was chosen for analysis because the best result was obtained when the optimal machine learning model was searched using the TPOT (Tree-Based Pipeline Optimization Tool) library. TPOT is a machine learning tool that optimizes and automates the machine learning pipeline by using genetic programming. In order to determine the order of importance of variables, the XGBoost decision tree method was used. The XGBoost decision tree method can be defined as a machine learning technique developed to solve classification problems.

The treatments applied to the 929 patients with resected colon cancers that were very risky and locally invasive in the study were observed and recorded by NCCTG (The North Central Cancer Treatment Group) over a period of approximately 6.5 years. These data are the longitudinal data from one of the initial effective adjuvant chemotherapy approach trials for colorectal cancer. Recurrences are classified as local and remote if other organs involve the liver, lung, lymph nodes, or area [32, 33].

Treatment methods consist of Observation, Levamisole, Levamisole + 5-FU drug and compound chemotherapy drugs. Disparities in early clinical and pathological characteristics and subsequent relapses were analyzed by using artificial neural networks.

The aim of this study is to analyze and predict the efficacy and importance of the treatments applied to colon cancer patients using machine learning methods based on a real clinical data set. For all these purposes, the participation of stage II or III colon cancer patients across two different datasets in their clinical trial provided an exceptional opportunity to explore these questions within this patient population. With the help of two different data sets, this study focused on factors such as the subset of patients whose tumors returned after completing treatment, which organs the patients with recurrence mostly spread to, and whether there was a gender difference in this regard.

In addition, we tried to investigate whether the prognosis after tumor recurrence affects the survival rates of adjuvant chemotherapy administered after surgical removal of the tumor.

In addition, the role of genetics and familial predisposition in colon cancer was also included. We also investigated whether APC II and III improved outcomes in recurrent colon cancer patients over multiple decades and the variables impacting their longevity. For this purpose, in order to further elaborate on the study, stage II colon cancer data were obtained

from BioGPS according to the APC gene status retrospective study. This data set consists of the age, gender, metastasis status, location, first APC mutation, and second APC mutation data of 90 individuals.

The chemotherapy-based use of 5-fluorouracil (5-FU) is the cornerstone of treatment, although individual CRCs have unique genetic characteristics, especially for stage III and some stage II patients. Additional treatments have also emerged to treat CRC, based on specific genetic markers available. The adjuvant therapy of 5-FU-leucovorin-oxaliplatin (FOLFOX), which was also used as data in this study, has become the standard treatment for CRC.

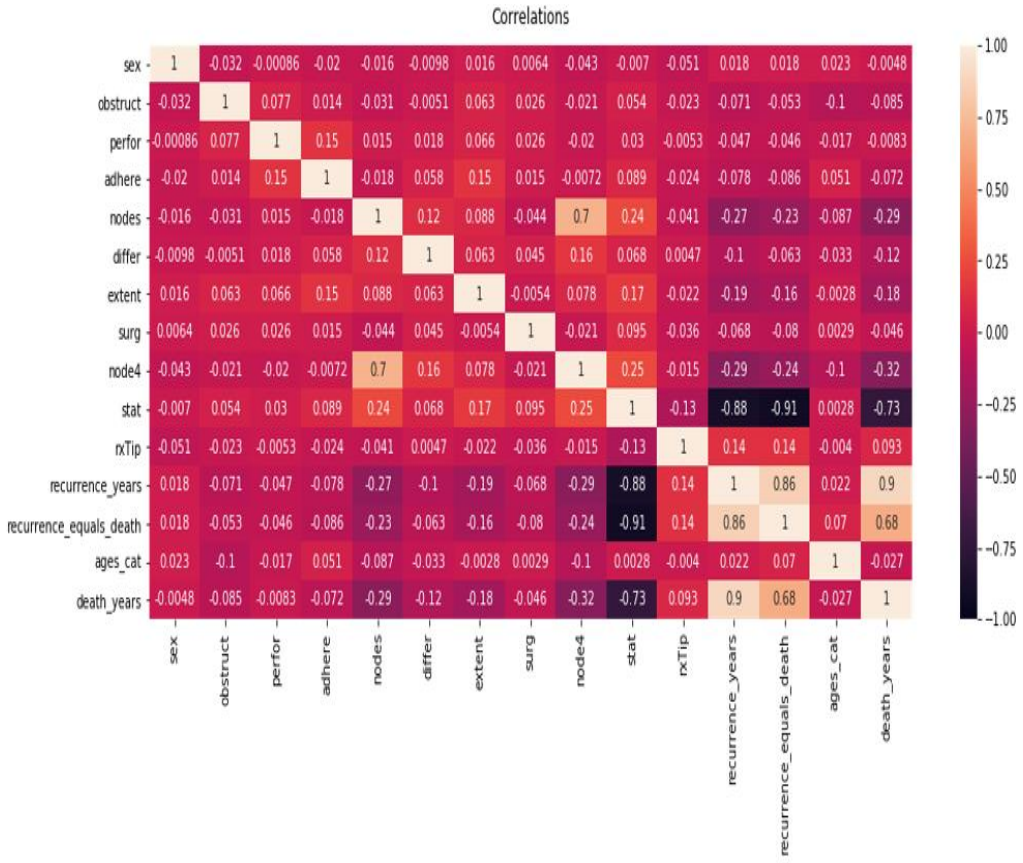

Figure 1.
Correlations between variables.

3. Results

Looking at Figure 1, some variables are shown in abbreviations. "Nodes" indicates the number of lymph nodes diagnosed. The variable indicated by "perfor" refers to the perforation of the column. "Stat" represents the state of sensing; "differ" is the differentiation of the tumor, i.e., its degree; the degree of propagation; "node4" refers to the spread to more than 4 lymph nodes. "Ages_cat" is the age variable expressed in categories. "Recurrence_equals_death" indicates the new variable we created in this dummy if there is equality between the recurrence state of the tumor and the time of death.

The results that can be deduced from the correlations are as follows: a value of 0.7 reflects a strong positive correlation with the tumor's spread to the lymph nodes and the variables showing spread to more than 4 lymph nodes. Similarly, a very high degree of positive correlation was found between time of death and time to relapse in patients. In other words, it can be said that the recurrence of tumor and death are highly correlated with 0.9.

Although there is a relationship between the treatment applied, relapse and time of death, it can be said that the degree of this relationship is very low.

In other words, it should be underlined that the most important factor determining the time of death with treatment is actually the recurrence state. Compared to non-recurrent patients, Stage II and Stage III patients diagnosed without regional lymph node metastasis exhibit reduced survival following tumor recurrence

We can say that stage II and III patients have very short survival following relapse. Therefore, it highlights the necessity of tailored plans for handling advanced disease, and the therapies to be applied may differ due to the different clinical behaviors of these patients.

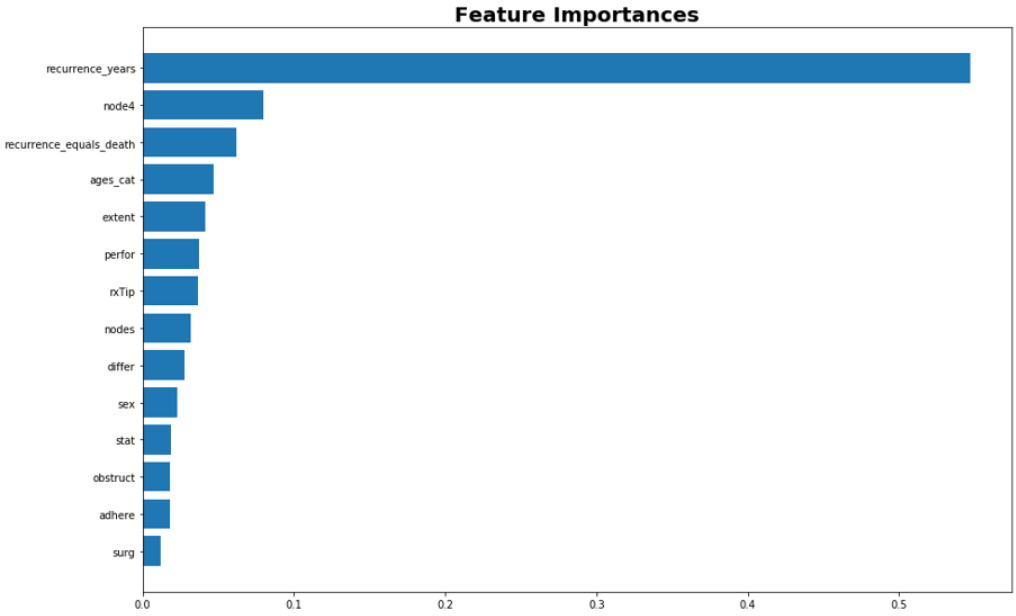

Figure 2.
The Order of importance for variables affecting life expectancy.

Figure 2 shows the order based on the results of the XGBoost decision tree method selected by a genetic algorithm and machine learning to determine whether the appropriate clinical treatments affect survival or not. According to these results, it is seen that the most important variable that affects the survival time of the patients is the time of relapse. The least important variable appears to be the variable indicated by the "surg", that is, the time after surgery. This situation can be considered as a problem that can be solved with prospective clinical studies. It can be said that the difference in survival between patients with stage II and stage III disease does not affect the treatment regimens for recurrent colon cancer. For this reason, these factors should be included in the assessment of emerging treatments and clinical trials.

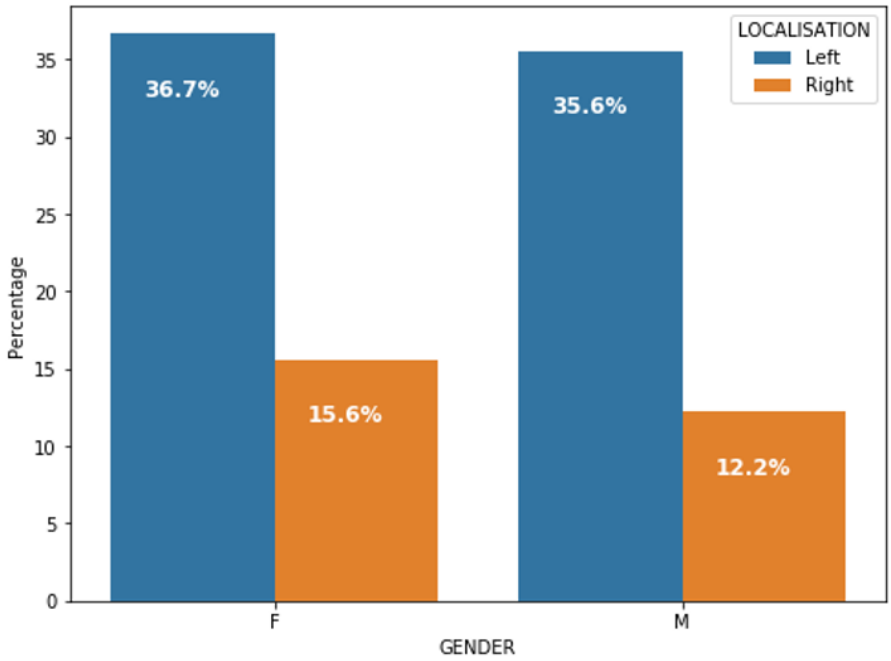

Figure 3.
The Distribution of tumors by location and gender.

When Figure 3 is evaluated in general, we can say that the location of the tumor is similar in women (36.7%) and men (35.6%) and is concentrated in the left colon. Similarly, in the patient group we analyzed, the rate of tumor location in the right colon was 15.6% in females, while it was 12.2% in males. When compared to the left colon, it can be said that the majority of the tumor site is located in the left colon.

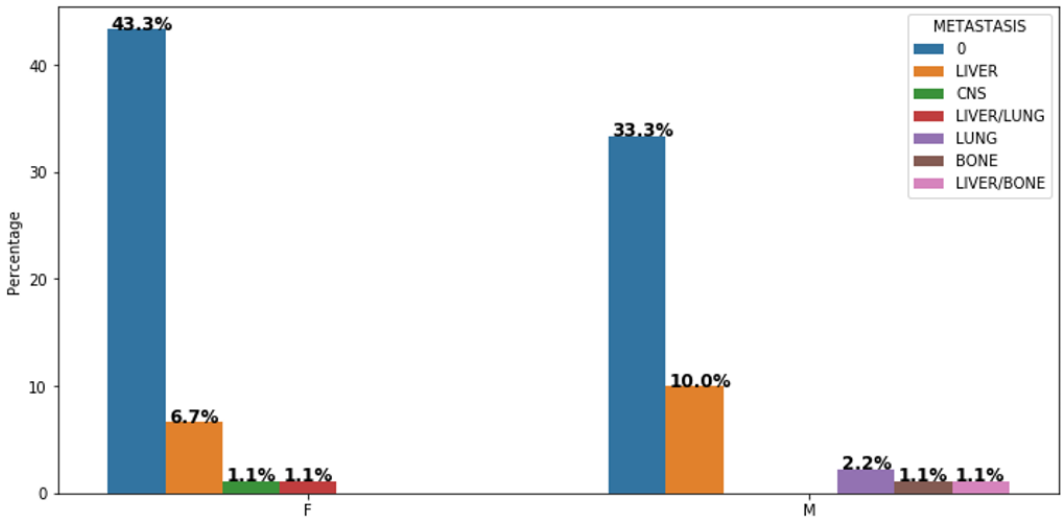

Figure 4.
The Distribution of tumors by location of metastasis and gender.

When Figure 4 is examined, we see the distribution of metastasis status by sex and organs. While the rate of not having metastasis in female patients was 43.3%, the rate of metastasis not being seen in male patients was 33.3%. However, it should be underlined that the organ that is affected most by the metastasis is the liver. This rate is 10% for men and 6.7% for women. After the liver, the rate of metastasis, in female patients is as follows: 1.1% of the CNS (central nervous system), 1.1% of the liver/lung spread is seen. In males, no spread was observed in the CNS, but it was found in 2.2% of the lung, 1.1% of bone and 1.1% of liver/bone spread.

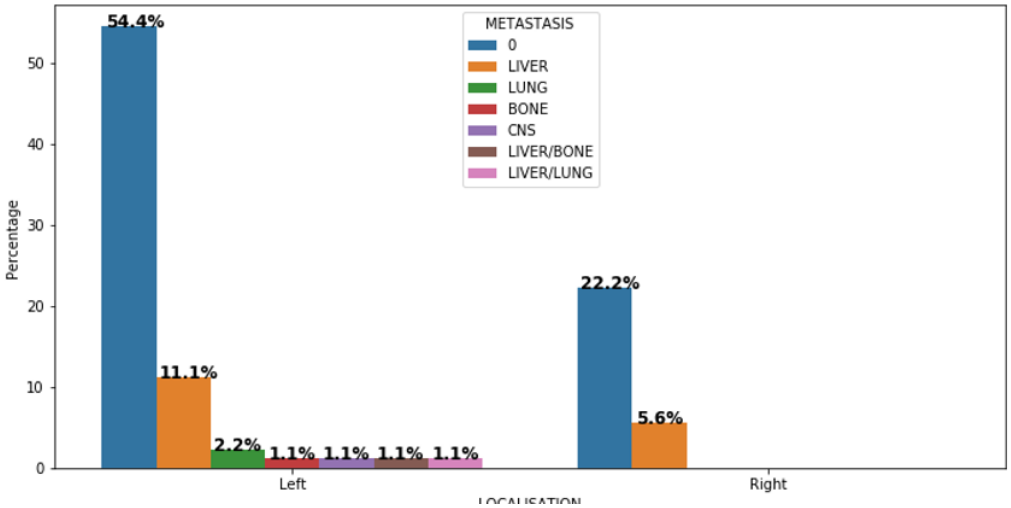

Figure 5.
Metastasis status according to the metastasis location of the tumor.

When Figure 5 is examined in detail, it is possible to see a comparison of the initial location of the tumor and its metastasis status. When the first location of the tumor is the left colon, metastatic organs are evaluated as follows: liver 11.1%, lung 2.2%, bone 1.1%, CNS (central nervous system) 1.1%, liver/bone 1.1%, liver/lung 1.1%, respectively.

When the first location of the tumor is the right colon, only liver metastasis (5.6%) is observed. In this sense, it can be interpreted that the left colon is a riskier area in terms of metastasis.

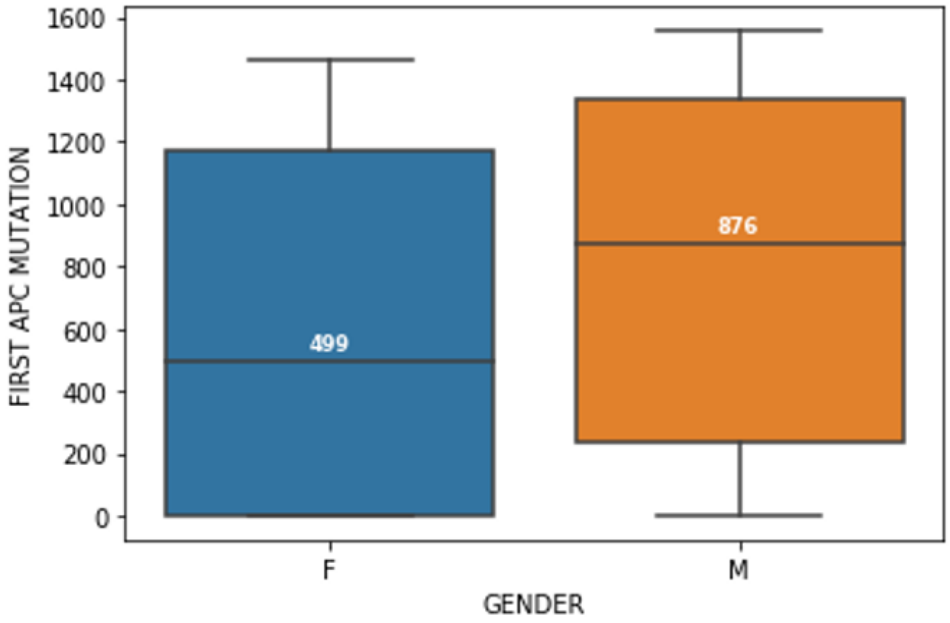

Figure 6.
The Box-Plot plot of the first APC mutation by gender.

When Figure 6 is examined, we investigated whether the APC mutation differs according to gender by Box-plot. Accordingly, we can say that female patients are more prone to mutation than men. The median value for female patients is 499 days and for males, it is 876 days. Therefore, it should be emphasized that the mutation occurs more rapidly for female patients and the monitoring of the patient follow-up accordingly during the treatment process is more important. In male patients, it should be considered that the number of mutation days occurs almost twice that of women.

The maximum number of days for mutation occurrence in females is 1465 days, and 1556 days in males, respectively. Supporting this result, Sargent et al. [34] in their analysis based on 18 clinical studies, found that patients had a recurrence rate of 80.

3.1. Key Message

In our study;

1. The XGBoost decision tree method, selected by genetic algorithm and machine learning, was used to determine whether appropriate clinical treatments affected survival.
2. It should be emphasized that the mutation occurs more rapidly for female patients and the monitoring of the patient follow-up accordingly during the treatment process is more important.
3. Also treatments, it makes a difference and contribute to the spread to other organs.

4. Discussion

Evaluating the role of genetic mutations and treatments in cancer patients' longevity has become essential as unique mutation patterns play a crucial role in identifying the best treatment options. This study aims to predict the prognosis of the disease, the relapse time and the survival times with the data of stage II and III colorectal cancer (CRC) patients by using machine learning (ML) technology and to bring a different perspective to treatment processes.

The liver has been found to be the most common site of relapse, and liver metastases are diagnosed in the majority of patients regardless of gender. This finding is very similar to the results of the study of Melli et al. [22]. Lung metastasis is the second most common region for the frequency of recurrence. These findings can help develop specific treatment programs and provide a different perspective for follow-up program.

Our results also emphasize that determining the lymphatic node invasion adequately for patients with early-stage colon cancer is more important than almost all treatment modalities.

It should be underlined that there is no notable distinction between the treatment groups of stage II or III colon cancer, divided into adjuvant FU, 5FU + Folfox and Observation after surgical removal of the tumor and they have worse survival rates following tumor recurrence compared to observation patients who did not receive chemotherapy. To put it more clearly, it is seen that the chemotherapy regimens applied are in the 7th place in Figure 2 in the ranking of factors affecting survival time and recurrence. These findings coincide with the findings in O'Connell et al. [35] and in Tsikitis et al. [36]. Trials treating colon cancer patients with stage 2 and 3 disease with adjuvant chemotherapy treatment, a number of clinical studies and observations that compare the therapy have shown little or no benefit for this group of patients [32, 33, 37-40].

According to the clinical study results and the findings we obtained through machine learning, when the number of lymph node spreads in patients is high it can be said to be associated with lower survival and worse outcomes. After surgical removal of the tumor, the clinical and pathological features of early or late recurrence are an issue that should be evaluated separately. However, early relapse was more common in female patients.

Therefore, a notable difference in prognosis was observed between the groups with early and late relapses, and a significant difference in terms of gender. In addition, it should be noted that female patients have a worse prognosis in cancer recurrence compared to men when evaluated in terms of recurrence and survival. When evaluated from this aspect, it may be suggested to develop a new perspective, such as determining follow-up protocols in order to intervene without recurrence in prolonging the lifespan of patients, following up female patients more closely, and recommending new treatment methods to prevent node spread.

It can be said that the available clinical information is insufficient to predict colon cancer recurrence after surgery for patients with stage II and III colon cancer. In order to improve the recurrence and prognosis of early-stage colon cancer, genetic markers should be used and evaluated together.

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