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The Story of Cigarettes and Tobacco That Captured the World with Radiation

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Review

History

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ABSTRACT

Cigarettes, which are scientifically proven to cause diseases and deaths, have radiation effects in addition to many toxic substances. In this review, we aimed to talk about the radioactive content of cigarettes, which is known by a small number of people and which we think may be one of the most effective efforts to prevent the cigarette epidemic that affects everyone, men, women, young, old and children, especially in developing countries. We aimed to support the fight against smoking with this review article.

Keywords: Cigarette, tobacco, radiation, lung cancer, Polonium 210

Dünyayı Esir Alan Sigara ve Tütünün Radyasyonla Hikayesi

Derleme

Süreç

Geliş: 07/04/2025
Kabul: 09/05/2025

ÖZ

Hastalıklara ve ölümlere neden olduğu bilimsel olarak kanıtlanan sigaranın birçok toksik madde içeriği dışında radyasyon etkisi de bulunmaktadır. Biz de bu derlemede, özellikle gelişmekte olan ülkelerde olmak üzere kadın, erkek, genç, yaşlı, çocuk herkesi etkileyen sigara salgınının önüne geçmek için gösterilen çabaların en etkinlerinden biri olabileceğini düşündüğümüz ve az sayıda kişi tarafından bilinen radyoaktif içeriğinden bahsetmeyi amaçladık. Biz bu derleme makale ile sigaraya karşı savaşa destek olmayı amaçladık.

Anahtar Kelimeler: Sigara, tütün, radyasyon, akciğer kanseri, Polonyum 210

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Introduction

The harmful effects of cigarette smoke and tobacco on health have been known for years because they contain many toxic substances such as nicotine, tar, carbon monoxide and arsenic.[1] In this review, we would like to talk about the relationship between smoking and radiation in addition to this classical information. Perhaps explaining the radiation effect of cigarettes may be the most effective method to prevent the epidemic of smoking, which is sweeping the whole world, especially in developing countries, affecting everyone, men, women, young, old and children, and to make them quit smoking. We aimed to support the fight against smoking with this review article.

Discovery of Cigarettes

Although the date of the first use of tobacco is not known, it is known that it was brought to Europe by Christopher Columbus and his friends as a gift from the natives during their discovery of America at the end of the 1400s. Tobacco, which was accepted as a spiritual inspiration in Africa, became widespread, especially in England and France with propaganda that it was beneficial and even a medicine.[2] In fact, in 1559, Jean Nicot, the ambassador of France to Portugal, presented tobacco to the French Queen by mentioning that it was good for cough, asthma, headache, stomach diseases and gynecological diseases; for this reason, tobacco was called "Queen's weed" or "Ambassador's weed" and Nicot became the unforgettable ambassador of tobacco history.[3] It is astonishing that the first edition of the Merck Manual, which is considered one of the basic books of medical sciences, published in 1889, included a suggestion that cigarettes could be used in the treatment of bronchitis and asthma "with today's knowledge".[4]

The Relationship Between Smoking and Radiation

Let us now look at how tobacco leaves are exposed to radiation during tobacco production. Radon (Rn) is a colorless, odorless, tasteless and completely radioactive gas with atomic number 86 and atomic weight 222, which is formed by the natural decay of uranium and radium found in almost all rocks and soils. During its decay, it is converted into polonium, which emits alpha radioactivity ($^{222}_{86}Rn \rightarrow {}^{218}_{84}Po + {}^{4}_{2}He_2$). Radon moves upwards through soil and rocks. For this reason, it accumulates especially in basements in contact with the ground and can even enter buildings through openings in the walls. Polonium 210 (Po-210) and lead 210 (Pb-210), which are released by the breakdown of radon, a naturally occurring radium product in the soil, can be taken up by the roots of tobacco plants. In addition, fertilizers rich in polyphosphates used to increase productivity in tobacco plants also contain Pb-210 and Po-210. As the plant grows, these radioactive products stick especially to the sticky hairs on the underside of tobacco leaves, called trichomes. It is also very difficult to wash off with rain. Tobacco growers have been aware of the presence of this alpha radioactivity in tobacco smoke since about 1960. And even in 1980, it was discovered that acid washing was highly effective in removing Po-210 from tobacco leaves. Unfortunately, however, the cigarette industry has avoided the use of acid washing because the acid environment would ionize nicotine into a poorly absorbable form in smokers' brains, thus depriving them of the much sought-after instant "nicotine hit" sensation, as well as "economic costs to farmers" and "unknown environmental consequences of acid leaching into the soil".[5]

Polonium 210, known to be present in cigarettes, shows a radiation effect 4 times higher than uranium due to its alpha radioactivity ($^{210}_{84}Po_{126} \rightarrow {}^{206}_{82}Pb_{124} + {}^{4}_{2}He_2$). It has a 138-day physical half-life. The characteristic of alpha radiation is that it can be stopped even by a thin layer of paper or skin. However, when inhaled, it enters the body and lodges in the airways (especially in bifurcations of segmental bronchi). Polonium was discovered by Marie Sklodowska Curie and her husband Pierre Curie in 1898 and named "Polonium" in honor of Marie Curie's native Poland. Although its discovery is old, the assassination of former Russian agent Alexander Litvinenko with Po-210 in November 2006 drew attention to how lethal this radioactivity can be.[6] In the literature, there is very striking data on the amount of radioactivity exposed by smoking. According to Scott et al., ingestion of as little as 1 µg of Po-210 can be fatal.[7] Ingestion (or inhalation) of a few milligrams is expected to be fatal for everyone. Ingestion (or inhalation) of a few milligrams would be expected to be fatal for everyone. Fatal ingestion of Po-210 causes severe damage leading to tissue necrosis in the bone marrow, spleen, liver, kidney, skin, lymph nodes and possibly other areas of the body. According to their study, Little and Radford estimated that people who smoked for 25 years would receive a radiation dose of 2 Sv due to Po-210 in the bronchial epithelium of the bifurcation region of the inferior lobes of the lungs.[8] The annual carcinogenic risk of a smoker who smokes 20 cigarettes per day is equivalent to having 300 chest X-rays.[9] According to the results of a review by Karagueuzian et al., the annual radiation dose to a person who smokes 2 packs of cigarettes per day for 20 years is 330 mSv due to the radioactivity in them.[5] This radiation dose is thought to accumulate cumulatively after 20 years of smoking. To understand how high this dose is, it is necessary to state one of the basic principles of radiation safety rules: "The highest allowable dose value to which a radiation worker can be exposed is 20 mSv per year".

Cigarette, Lung Cancer and Radiation

According to WHO data, more than 8 million people die each year due to tobacco use.[10] Lung cancer is the leading cause of cancer-related deaths (18.7%).[11] The incidence of lung cancer among lifelong nonsmokers falls within the National Cancer Institute's (NCI) definition of "rare" cancer (less than 40,000 cases per year, age-standardized incidence rate <15 per 100,000).[12] The argument that most smokers who cannot quit take refuge behind is that

"smoking is not the only etiology of lung cancer." However, it must be admitted that this information does not change the fact that tobacco exposure is by far the greatest risk factor for lung cancer worldwide.

Although it varies according to the filters used, some of the Po-210 content in cigarettes is inhaled by the smoker (5-37%) and the other part is released into the atmosphere.[13] These released radioactive decay products bind to smoke particles.[14] Some of them are so small that they can remain suspended in the air almost indefinitely. As a result, some of these airborne particles can be inhaled by passive smokers and smokers themselves. According to a study by Begy et al., the average radiation dose from active smoking was estimated to be 8.36 ± 0.91 μSv/year, while the dose reaching the respiratory system from passive smoking was estimated to be 5.92 ± 0.49 μSv/year.[15] In other words, it is clear that "if you are in an environment with active smokers, you are as much as if you smoke". Even though the radiation doses calculated in this study may seem low at first glance, the long half-life of the exposed radiation and the fact that it cannot be excreted out of the body in continuous smokers due to its accumulation in the place where it is located cause an increase in radiation exposure.

Effective attempts to reduce tobacco use are being made all over the world. According to a study conducted by Malvezzi et al. in the five most populous European Union countries, it is predicted that a 35% reduction in cancer mortality rate could be achieved by 2035 with a reduction in the risk of lung cancer through tobacco control and further efforts to control overweight and obesity, alcohol consumption, infection and related neoplasms, as well as improvements in screening, early detection and treatment.[16] However, the prevalence of tobacco use among adults and adolescents in Europe is increasing, especially among young people.[17] Three cost-effective interventions are attempted to be implemented for tobacco control banning/restricting smoking in public and workplaces; direct health warning labels on cigarette packs and other tobacco products; and increasing the price of cigarettes and tobacco products through higher taxes.[17] Of these, the increase in the average tobacco tax is considered to be one of the most effective methods tried to be implemented by WHO. However, only the European region has reached the 75% tax criterion recommended by the WHO.[18] In Turkey, smoking was banned in all indoor areas (except restaurants, bars and cafes) with the "Smoke-Free Air Zone" campaign in May 2008 and this ban was extended to restaurants, coffee houses, bars and cafes in July 2009. Although there is no precise data, it is thought that this ban has also raised awareness in terms of reducing passive exposure in homes.

In the past, men were more likely to smoke than women, but in recent years it is clear that women are increasingly becoming smokers. Perhaps as a result of this situation, according to GLOBOCAN 2018 data, lung cancer was the 3rd most common cancer in women (8.4% of all cancers), but according to 2022 data, it is now the 2nd most common cancer in women (9.4% of all cancers).[11,19] Cigarettes, which were considered a serious taboo for women in Europe until the first half of the last century, became an expression of women's emancipation as women's demands increased, it was frequently written and said that it was not a product exclusively for men, and the desire for social equality increased. In a study conducted, 58.5% of the respondents answered "to try cigarettes out of curiosity", 46.6% answered "for friendship (friends, schoolmates, colleagues) and imitation", and 15% answered "to face a difficult period" when asked why they started smoking.[20] Unfortunately, in today's society, tobacco companies have succeeded in recruiting women as smokers, perhaps even more than men, through their efforts to make smoking a "symbol of modern femininity and freedom". The visual media's emphasis that smokers are financially and professionally successful, emphasized in popular movies, and television shows, and even showing improved social status, has been skillfully implanted in the subconscious of all young people. In fact, the most important factor for both sexes to start smoking is social acceptance and admiration. Smoking seems to be the most unifying part of social activity today. Friends and family smoking are the most predisposing factors for smoking. According to Oh et al., the risk of starting smoking is 12 times higher in individuals with half or more of their friends who smoke.[21] It is obvious that young people with lower socio-economic conditions and lower education levels are also more vulnerable to increased tobacco smoking. Why is smoking more common in developing countries with low socioeconomic levels? Although this may seem like a paradox, perhaps the most important factor in the increase in the prevalence of cigarette use in the past years was its low price. It was even distributed to soldiers free of charge in our country. Due to reasons such as a lack of information about the harmful effects of cigarettes on health and the lack of attention given to this issue by the policies in developing countries, smoking has become increasingly common in underdeveloped countries.

There are different studies evaluating the relationship between smoking, gender and cancer. According to Bain et al., tobacco exposure does not effect risk differences between men and women.[22] It is suggested that factors such as the depth of inhalation during tobacco use, cigarette type and tar content and differences in population sampling in the studies have an effect. According to an analysis by May et al., the overall mortality rate from lung cancer and tumor grade at the time of diagnosis is higher in men than in women.[23] However, they also reported that this situation is not related to tobacco use alone, but may be affected by many conditions such as other environmental exposures, especially asbestos, the higher immune system in women compared to men and their tendency to respond better to cytotoxic and targeted therapies, the effect of estrogen, etc.

Conclusion

As a result, although people are attracted to its pleasurable effect, tobacco and cigarettes, apart from their chemical toxins, are undeniably harmful to our body, especially the lungs, due to their alpha radioactivity content, which is known to have a very high ionizing effect. Unfortunately, while cigarette companies continue to earn at ever-increasing rates thanks to this epidemic, the health of millions of people who continue to smoke, knowing, unknowing or unwilling to know the harm to their health, is under threat. The best advice to smokers is to quit smoking, and if they are unable to do so, to reduce the risk by smoking outdoors where the radioactivity suspended in the air will not be inhaled by passive smokers and themselves. I think that the most effective solution to this issue would be for politicians to make plans to reduce radiation content, such as making acid washing mandatory for cigarette manufacturers and monitoring the content of fertilizers used in tobacco production. I also think that it would be much more effective to write warnings such as "Caution: Contains Radioactivity" on cigarette packages or to have radiation warning signs on cigarette packages.

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Rectal Foreign Body Management: 22 Years Of Experience

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ABSTRACT

Rectal foreign body (RFB) is a clinical picture rarely encountered in the emergency department, but the majority of them are men. It is known that the most common reason for these objects taken orally and anally is for voluntary sexual stimulation. These patients are usually sexually active patients between the ages of 20-40. In this study, we aimed to evaluate only rectal foreign bodies placed in the anal region and to present a management strategy for these patients with our own experience and literature. A total of fifteen RFB cases that applied to the emergency department between 2002-2024 and were placed only in the anal region were included in our study. The objects removed were; 6 cosmetic objects, 4 soda bottles, 3 vegetables, and 2 glasses. The reason for approximately ¾ of our patients was sexual stimulation. 9 (60%) of RFB were removed anal, 5 (33.3%) were removed anal with laparotomy and bowel milking by bringing the object closer to the anus. In 1 (0.66%) patient, the object was removed by performing laparotomy and colotomy primary repair. Although RFB retention is an unusual clinical presentation, colorectal surgeons should be familiar with different extraction methods. It should also be kept in mind that patients experience psychological trauma and a nonjudgmental approach should be followed with patients.

Keywords: Rectum, foreign body, exraction, colonic perforation, Management

Rektal Yabancı Cisimlerin Yönetimi: 22 Yıllık Deneyim

Araştırma Makalesi

Süreç

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ÖZ

Rektal yabancı cisim (RFB) acil serviste nadir karşılaşılan bir klinik tablodur ancak çoğunluğunu erkekler oluşturmaktadır. Bu nesnelerin ağızdan ve anal yoldan alınmasının en yaygın nedeninin istemli cinsel uyarılma olduğu bilinmektedir. Bu hastalar genellikle 20-40 yaş arası cinsel açıdan aktif hastalardır. Bu çalışmada sadece anal bölgeye yerleştirilen rektal yabancı cisimleri değerlendirmeyi ve bu hastalara kendi tecrübelerimiz ve literatürümüzle bir yönetim stratejisi sunmayı amaçladık. Çalışmamıza 2002-2024 yılları arasında acil servise başvuran ve sadece anal bölgeye yerleştirilen toplam 15 RFB vakası dahil edildi. Kaldırılan nesneler; 6 kozmetik obje, 4 soda şişesi, 3 sebze ve 2 bardak. Hastalarımızın yaklaşık ¾'ünün nedeni cinsel uyarılmaydı. RFB'nin 9'u (%60) anal, 5'i (%33,3) laparotomi ve bağırsak sağımı ile anüse yaklaştırılarak anal çıkarıldı. 1 (%0,66) hastada laparotomi ve kolotomi primer onarımı yapılarak cisim çıkarıldı. RFB tutulması alışılmadık bir klinik tablo olmasına rağmen kolorektal cerrahlar farklı ekstraksiyon yöntemlerine aşina olmalıdır. Hastaların psikolojik travma yaşadığı da akılda tutulmalı ve hastalara yargılayıcı olmayan bir yaklaşımla yaklaşılmalıdır.

Anahtar Kelimeler: Rektum, yabancı cisim, ekstraksiyon, kolon perforasyonu, Yönetim

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Background

Rectal foreign bodies (RFB) are usually inserted transanally for sexual stimulation, concealment of illegal substances and medical purposes, while foreign bodies can also be seen after oral ingestion. Anorectal foreign bodies are more common in men than in women .[1] When looking at the studies on RFB in the literature, the majority of them are male (male/female=6/1). The age range varies between 11 and 88. It is also reported that a large portion of these objects are inserted into the rectum for sexual stimulation.[2-4] Rectal object insertion is categorized as voluntary, involuntary and sexual. Involuntary ones mostly occur in children as a result of ingestion of medical instruments such as thermometers or oral objects, while voluntary ones include the insertion of cocaine and other illegal objects known as "body-packing" into the rectum to conceal them. The most common cause of RFB is objects inserted into the rectum for sexual purposes, with 75% .[5-7] Most patients do not seek medical attention at first, they wait for the RFB to pass spontaneously or they usually present to the emergency department (ED) days later with complaints such as abdominal pain, anal pain, and rectal bleeding because they try to remove it themselves. If a mucosal injury or perforation occurs due to trauma and/or a direct object while trying to remove it themselves, they may present with fever, abdominal pain, vomiting, and even septic symptoms. When RFB is suspected during the initial evaluation of the patient in the emergency department, especially in mentally retarded and incarcerated patients, it is necessary to thoroughly question whether the foreign body has a sharp surface before performing the rectal digital examination and, if necessary, to perform a rectal examination after imaging. Depending on the distance of the foreign body from the anus, it is classified as mid-distal rectum, high rectum, and colon localization. If there is no mucosal injury or perforation in laboratory findings, no pathology is usually detected. Radiolucent object may be seen in imaging, and pneumoperitoneum may be seen if there is perforation.[8-10] Although RFB constitutes a very small portion of patients presenting to the emergency department, it is a condition that involves medical and social difficulties. This condition, which is difficult to manage for both the patient and the doctor, requires an approach that does not cause the patient to be embarrassed, ashamed or blamed. In this study, we aimed to evaluate only rectal foreign bodies placed in the anal region and present a management strategy for these patients based on our own experience and the literature.

Materials and Methods

A total of 22 RFB cases admitted between 2002-2024 were included in the study. The patients' diagnosis was confirmed according to anamnesis, physical examination and radiological imaging methods. 7 patients were excluded from the study because RFB occurred as a result of oral intake. Only fifteen patients with RFB placed through the anal route were included in our study. Patient information was obtained from hospital records and recorded. Patient demographic data, hospital arrival times, reasons for RFB placement, RFB shape, laboratory results, imaging, location according to the anal region, extraction method and complication status were examined. Personal information of the patients was kept confidential. We divided the object location into three classes as distal mid-rectum low location (L), proximal rectum middle location (M) and colon location high location (H). Different extraction methods were recorded with pictures and videos. No statistical method other than standard average was used for statistical analysis.

Results

All patients were male and the mean age was 33.1. The marital status, causes of RFB and other characteristics of the patients are given in Table 1. When the patients applied to the ED, the object could be palpated in only 8 (53.3%) patients with digital rectal examination in the first evaluation and was recorded as L localization. No object was palpated in any patient during the abdominal examination. As a result of imaging, the object was detected as M localization in 4 patients and H localization in 3 patients. All patients underwent surgical intervention under spinal or general anesthesia. 9 (60%) of RFB were removed anal, 5 (33.3%) were removed by laparotomy and intestine milking and the object was removed from the anal region by approaching the anus. In 1 (0.66%) patient, the object was removed by laparotomy and colotomy primary repair. The removed objects were; 6 were cosmetic objects, 4 were soda bottles, 3 were vegetables and 2 were glasses. No patient required follow-up imaging or sigmoidoscopy after the operation. No complications were observed in any of our patients after the treatment. When the patients were examined according to their causes, it was seen that they were grouped into three groups as sexual stimulation (SS) 11 (73.3%), therapeutic (T) 1 (0.66%) and humiliating punishment method (HP) 3 (2%). In the first evaluation of the patients, history collection, physical examination and laboratory tests were performed. This information is shown in Table 1.When removing vegetables from the rectum, successful results were obtained by using a Kelly clamp for carrots, an over clamp for cucumbers, and two spoons as forceps for apples. The computerized tomography image of the apple in axial section is shown in Figure 1 and the extraction of the apple in the form of forceps using two spoons is shown in Figure 2. When a Foley catheter is used to remove the cups, when the cup is pulled towards the anal region, in cases where the cup mouth diameter is larger than the colon diameter, mucosal damage may occur in the colon due to the plane difference between the cup mouth and the colon wall. To eliminate this situation, a long twisted balloon is used instead of a Foley catheter Figure 3.In imaging methods, the cup mouth diameter is determined approximately and the amount of air that inflates the balloon to the cup mouth diameter outside the body is determined. A long balloon placed on a tube is placed into the cup with an anoscope and the determined amount of air is given, and since the cup mouth and the colon wall are on the same plane, and the rectosigmoid fold is corrected, mucosal damage is prevented, and the extraction process becomes easier.

Figure 1: Apple image in axial section

Figure 2: Extraction of apple with two spoons

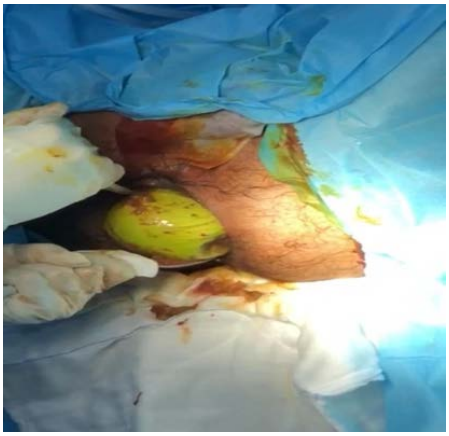

Table 1: Characteristics of patients, causes of RFB, characteristics and extraction methods

No	Age (years) Marital status	Cause	Day after insertion	Reason for ED	FB/size (cm)	RFB location	Extraction method	Complication
1	42/M	T	2	Constipation	Carrot/17	L	Transanal extraction	No
2	45/M	SS	4	Constipation	Cosmetic object/20	L	Transanal extraction	No
3	38/W	HP	2	Anal pain	Soda bottle/ 16	L	Transanal extraction	No
4	51/NA	SS	3	Fear/confess	Apple/11	L	Transanal extraction	No
5	47/W	SS	2	Rectal bleeding	Glass/10	M	Laparotomy-Milking Transanal extraction	No
6	34/NA	SS	1	Rectal bleeding	Cosmetic object/19	L	Transanal extraction	No
7	26/W	HP	2	Fear/confess	Cucumber/ 19	L	Transanal extraction	No
8	49/M	SS	3	Constipation	Glass/11	L	Transanal extraction	No
9	31/W	SS	2	Fear/confess	Soda bottle/23	H	Colotomi extraction and primer repair	No
10	25/NA	SS	4	Fear/confess	Cosmetic object/18	M	Transanal extraction	No
11	40/M	SS	1	Anal pain	Soda bottle/17	M	Laparotomy-Milking Transanal extraction	No
12	46/W	HP	5	Fear/confess	Soda bottle/16	H	Laparotomy-Milking Transanal extraction	No
13	22/W	SS	2	Abdominal pain	Cosmetic object20	L	Transanal extraction	No
14	42/M	SS	1	Anal pain	Cosmetic object	H	Laparotomy-Milking Transanal extraction	No
15	35/NA	SS	3	Fear/confess	Cosmetic object	M	Laparotomy-Milking Transanal extraction	No

M:Married, W:Widowed, NA:Not available, T:treatment, SS:Sexual pleasure, HP: Humiliating punishment, ED:Emergency Department L:Lower, M:Middle, H:High

Discussion

Despite the existence of management guidelines and algorithms for rectal foreign bodies, management challenges remain. It has been reported that the majority of these foreign bodies are self-implanted. Patients are often unable to openly accept this information during their history-taking visits to the ED. Cultural differences and attitudes of these patients may affect the incidence of rectal RFB in clinical practice.The causes of RFB inserted in the anal region are diverse; they include relief from hemorrhoids or constipation, concealment of

medications, secondary gains in patients with psychiatric disorders, assault and sexual gratification or anal eroticism. Autoeroticism for sexual gratification appears to be the most

clues. A detailed physical examination, including imaging and digital rectal examination, should be performed. Plain radiography provides important information to determine the size, shape and location of RFB. However, radiolucent RFBs such as fish bones, plastic objects, and vegetables may not be easily visualized. Plain radiography may be sensitive to bowel perforation in only up to 50% of cases. Although the indications for CT in these cases have not been clearly established, CT may be needed to demonstrate perforation that cannot be confirmed by plain radiography or complications due to high-lying RFBs.[4,7,11-13] RFB insertion for sexual gratification is considered taboo; due to the shame associated with this practice, many patients do not provide a truthful history. Patients may fabricate a history and may not provide accurate information about the reasons for RFB insertion. It is imperative to establish and maintain a nonjudgmental relationship and respect for the patient's privacy. It is important for physicians to consider suspected cases of sexual abuse. Involuntary RFB insertion has been reported in children, the elderly, and individuals with intellectual disabilities. In cases of sexual abuse, special attention should be paid to addressing both the mental and physical well-being of the patient. Many sexual abuse victims may be reluctant to undergo examination. Therefore, it is recommended that physicians also perform an assessment of general trauma when interviewing and examining potential sexual assault victims. The incidence of RFB perforation in these patients is approximately 10% .[14,15] In the vast majority of cases, rectal foreign bodies may be inserted during erotic activity. Objects are typically seen in dildos, vibrators, light bulbs, candles, shot glasses, soda bottles, beer bottles, and similar objects of unusual or unusual size. In our study, the reason for this was sexual stimulation in approximately three-quarters of our patients. Concealed foreign objects may be inserted rectally. Typically, these objects are drug packets, and less commonly, objects such as knives or guns. No concealed RFB was detected in our patients. Some psychiatric patients intentionally conceal sharp objects in their rectums in order to harm the examiner performing the rectal examination. Finally, in older patients, rectal foreign objects used for prostate massage or to break up stool particles may be lost during this activity. Some rectal foreign bodies are initially swallowed and then pass through the gastrointestinal tract. Examples of the latter include toothpicks, popcorn, bones, sunflower seeds, and, in recent years, camera pills used in gastrointestinal studies .[16,17] Patients may cause anal sphincter damage while trying to remove the RFB before reaching the ED. RFB removal may become easier in these patients. Care should be taken when removing the RFB in patients who use the rectum to store illegal objects. Because it should be kept in mind that there may be substances in the package that are toxic to the body in excessive doses. Therefore, care should be taken not to tear the RFB sheaths in order to prevent them from tearing and developing systemic effects of the toxic substance inside. Oral intestinal motility enhancing drugs can be given to bring RFBs located high closer to the lower level, and in cases where these drugs are ineffective, the object can be milked downwards by laparoscopic or laparotomy, and then the RFB can be removed transanally. In cases where it is not possible to common reason for RFB insertion. Most patients are sexually active men between the ages of 20 and 40, as observed in this study.Patients' accurate history provides important diagnostic milk from the colon, colotomy, extraction and primary repair can be performed. It is accepted that glass-like FBs are a potential indication for laparotomy [18,19]. There is no consensus among the authors regarding RFB placements in the literature. In our study, the number of objects located at the lower level was found to be 8 (53.3%), objects located at the middle level were found to be 4 (26.7%) and objects located at the high level were found to be 2 (20%).Studies have shown that the rate of RFB removal in the emergency department is 51.3%. In addition, vaginal spatulas, wire and plastic forceps, rubber-coated bone-holding clamps, and tenaculum forceps have all been described as grasping foreign bodies for extraction. In this context, intraoperative proctoscopy can be used to grasp and pull out bulky foreign bodies. In our study, two spoons were used as forceps for an apple, which yielded successful results. Precautions should be taken to avoid damaging the anal sphincter during these procedures. It has been described that posterior sphincterotomy can be performed, especially for the removal of large objects. Transanal extraction is the most common approach used in patients with RFB, and 60–75% of FBs can be successfully removed transanally.[20–23]If the foreign body is small in diameter and there is no suction effect, enemas or oral cathartic (magnesium sulfate) agents can be used, but these treatments may have risks such as bleeding, further mucosal damage, and intestinal perforation. Occasionally, the object may be too high in the recto-sigmoid to be grasped. In such cases, it is recommended that the patient be sedated and hospitalized for monitoring to allow peristalsis to lower the foreign body to the lower level within 12 hours .[24,25]

Sigmoidoscopy is usually recommended after RFB removal to assess the anorectal mucosa and the extent of injury. Although a few authors have advocated sigmoidoscopy as a mandatory procedure, it may not be mandatory because it may predispose to complications and close clinical observation is sufficient for post-extraction care. In our study, none of our patients required sigmoidoscopy during close follow-up and had sphincter damage that could cause anal incontinence. In conclusion, although RFB retention is an unusual clinical presentation, colorectal surgeons need to be familiar with different extraction methods. It should also be considered that patients experience psychological trauma and a non-judgmental approach should be followed with patients.

Declaration of competing interest

The authors declare no conflict of interest.

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Preoperative and Early/Late Postoperative Evaluation of Endocrine Functions of Patients who Underwent Pituitary Surgery

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ABSTRACT

Introduction and Aim: Pituitary masses may lead to hormonal insufficiencies due to compression or postoperatively. Endocrine functions in patients with postoperative pituitary insufficiency may eventually improve. Monitoring endocrine functions in these patients is crucial to avoid lifelong replacement therapy. In our study, we assessed preoperative and "early/late postoperative" endocrine functions of the patients in our clinic and aimed to emphasize the importance of endocrinologic evaluation.

Material and Method: In our study, a total of 103 patients aged 18 years and older who underwent transsphenoidal pituitary surgery and were followed up in our clinic were included. Patients' preoperative endocrine functions, as well as endocrine functions during early postoperative period (first 3 months), at the postoperative year 1 and at the final visit were recorded to be analyzed.

Results: Among the patients, 54 (52.4%) were male and 49 (47.6%) were female, with a mean age of 46.6±13.4 years. Of the patients included in the study, 85 (82.5%) were found to be diagnosed with pituitary adenoma. Of the patients, the mean tumor diameter was determined to be 2.21±1.07 cm and the mean duration of follow-up was determined to be 2.6±1.5 years. Median number of pituitary insufficiency in our patients was found to be 1 during the preoperative period, 3 within first 3 postoperative months, 2 at postoperative year 1, and 2 at the final visit. DI developed during preoperative period in 7 patients (6.8%), at postoperative week 2 in 80 (77.7%), and at postoperative month 3 in 56 (54.4%) patients. At final visits, 33 patients (32%) were found to have DI. Hypothyroidism was observed in 14.6% during preoperative period and in 59.2% at the 3rd month. Adrenal insufficiency was observed at a rate of 12.6% during preoperative period, whereas the rate was 56.3% at the 3rd month. Hypogonadism, however, was observed at a rate of 35.9% preoperatively, whereas the rate was 65% at the 3rd-month visit. No significant difference was determined when preoperative and postoperative rates of pituitary insufficiency in functional and nonfunctional pituitary adenomas were compared.

Conclusion: In our study, we observed that rates of particularly DI and adrenal insufficiency significantly increased at the postoperative month 3 compared with the preoperative period and tended to decrease at at the 12-month follow-up. Our rates of pituitary hormone insufficiency following pituitary surgery, which were higher than those reported in most previous studies, were the most important result of our study. Thus, considering a better understanding of the complications and eventual recovery of hormonal deficiencies, postoperative monitoring of endocrine functions is crucial for treatment management.

Keywords: Pituitary Adenoma, Pituitary Surgery, Pituitary Insufficiency, Diabetes insipidus,

Hipofiz Ameliyatı Olan Hastaların Preoperatif ve Postoperatif Erken/Geç Dönemde Endokrin Fonksiyonlarının Değerlendirilmesi

Araştırma Makalesi

Süreç

Geliş: 03/01/2025
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ÖZ

Giriş ve Amaç: Hipofiz kitlelerinde bası bulgularına bağlı veya cerrahi sonrası hormonal yetmezlikler gelişebilir. Post-op hipofizer yetmezlik gelişen hastalarda endokrin fonksiyonlar zamanla düzelebilir. Bu hastaların endokrin fonksiyonları açısından takibi; hastanın ömür boyu replasman tedavisi almaması açısından önemlidir. Çalışmamızda kliniğimizde takip olan hastaların preoperatif ve postoperatif erken/geç dönem endokrin fonksiyonlarını değerlendirdik ve endokrinolojik değerlendirmenin önemini vurgulamayı amaçladık.

Materyal ve metod: Çalışmamıza hipofiz operasyonu geçirmiş olan ve kliniğimizde takipli 18 yaş ve üzeri 103 hasta dahil edildi. Hastaların preoperatif ve postoperatif erken dönem (ilk 3 ay), postoperatif 1. yıl ve hastanın son vizitindeki endokrin fonksiyonlar kaydedildi ve analizler gerçekleştirildi.

Bulgular: Hastalarımızın 54 (%52,4)'ü erkek, 49 (%47,6)'u kadındı ve yaş ortalamaları 46,6±13,4 yıl olarak belirlendi. Çalışmaya dahil edilen hastalardan 85 (%82,5)'inin hipofiz adenomu tanısı aldığı tespit edildi. Hastaların ortalama tümör çapları 2,21±1,07 cm ve takip süreleri 2,6±1,5 yıl olduğu saptandı. Hastalarda hipofiz yetmezlik sayısı medyan değerleri preoperatif dönemde 1, postoperatif ilk 3 ayda 3, postoperatif 1. yılda 2, son vizitte ise 2 olarak tespit edildi. Preoperatif dönemde 7 hastada (%6.8) DI mevcutken, postoperatif 2. haftada 80 (%77,7), postoperatif 3. ayda 56 hastada (%54.4) DI mevcuttu. Hastaların son takiplerinde ise 33 hastada (%32) DI tespit edildi. Preoperatif hastaların %14,6'sında 3. ayda %59,2'sinde hipotiroidi mevcuttu. Adrenal yetmezlik, preoperatif dönemde %12,6 olarak görülürken 3. ayda %56,3 düzeylerinde tespit edildi. Hipogonadizm ise

preoperatif dönemde %35,9 oranında görülürken 3. ay kontrollerinde %65 düzeylerindeydi. Fonksiyonel ve nonfonksiyel hipofiz adenomlarında cerrahi öncesi ve sonrasında gelişen hipofizer yetmezlik oranları karşılaştırıldığında aralarında anlamlılık bulunmadı.

Sonuç: Çalışmamızda özellikle DI ve adrenal yetmezliğin hastalarda görülme yüzdesinin postoperatif 3. ayda preoperatif döneme göre ciddi oranda arttığını, daha sonra ise 12. ay kontrollerinde de azalma eğiliminde olduğunu gözlemledik. Hipofiz cerrahi sonrası gelişen hipofiz hormon yetmezliği oranlarımız literatürdeki çoğu çalışmadan fazla olması çalışmamızın en önemli sonucuydu. Bu nedenle postoperatif dönemde endokrin fonksiyonların takibi, komplikasyonların daha iyi anlaşılması ve hormonal yetmezliklerde zamanla düzelme olacağı göz önüne alındığında tedavi yönetimi açısından önemlidir.

Anahtar Kelimeler: Hipofiz Adenomu, Hipofiz cerrahisi, Hipofizer yetmezlik, Diabetes insipidus,

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Introduction

Pituitary masses account for 15-20% of all intracranial tumors. The most common cause of pituitary masses is adenomas (%90), other, less common causes include it may result from less common causes including craniopharyngiomas (5-15%), carcinomas, meningiomas, metastases, abscesses, aneurysms, pituitary apoplexy, pituitary sarcoidosis, and Rathke pouch cysts[1]. Pituitary adenomas can be functional and/or cause compression due to mass effect. As a result of mass effect of adenomas, impaired vision and neurological deficits, as well as pituitary symptoms including secondary adrenal insufficiency, central hypothyroidism and hypogonadotropic hypogonadism may occur[2].

The first treatment option for functional pituitary adenomas other than prolactinoma and pituitary masses causing compression is transsphenoidal surgery. Following pituitary surgery, endocrine functions may improve due to hypersecretion after removal of functional adenomas or hormone levels may normalize in patients with pituitary insufficiency caused by compression. Furthermore, postoperative pituitary insufficiency may occur as a surgical compression in patients who have undergone pituitary surgery. Endocrine functions may recover in patients developing postoperative pituitary insufficiency as well. Monitoring of endocrine functions of these patients is crucial to avoid life-long replacement therapy[3].

Since there is limited number of studies on this issue in the literature, we evaluated preoperative and "early/late postoperative" endocrine functions of the patients in our clinic and aimed to emphasize the importance of endocrine evaluation.

Material and Method

In our study, patients who had underwent endoscopic endonasal transsphenoidal pituitary surgery at the University of Health Sciences Adana City Training and Research Hospital and were followed in Department of Endocrinology and Metabolic Diseases were included. The study was initiated after an ethics committee approval with decision number 1517 from our hospital's Ethics Committee on Clinical Research was obtained.

Medical records of 1078 patients with pituitary masses were examined retrospectively. Patients aged 18 years and older whose pituitary hormone levels during preoperative period, at postoperative month 3, at postoperative year 1 and at the final visit were available; preoperative and postoperative pituitary MRI results were available; immunohistochemical staining was performed; additionally those with other cellar lesions diagnosed by a pathologist were included in the study. A total of 103 patients with eligible records were included in the study. These patients' age, gender, date of diagnosis, age at diagnosis, date of surgery, postoperative treatments received, pituitary hormone levels, and MRI reports were recorded. Patients' preoperative endocrine functions, as well as endocrine functions during the early postoperative period (first 3 months), at the postoperative year 1, and at the final visit were evaluated. The total duration of follow-up was addressed as to cover the time from the date of operation to the present time. Whether improvement in endocrine functions was observed or not was determined.

For diagnosis of male hypogonadism, normal or low-normal gonadotropin levels in the presence of low-normal baseline testosterone levels were required. For diagnosis of gonadotropin deficiency in premenopausal women, normal or low-normal estradiol and gonadotropin levels in addition to menstrual irregularity in peripheral blood samples was required[4-5].

For diagnosis of central hypothyroidism, normal or below-normal TSH levels with below-normal free T4 levels were required[6].

For the diagnosis of adrenocorticotropic hormone insufficiency, patient files were examined; at the first step, baseline cortisol levels collected at 8 am were examined. A cortisol level ≥18 µg/dL was considered normal, but ≤3 µg/dL was considered adrenal insufficiency. When the cortisol level was 3-18 µg/dL, dynamic test results were examined. Those with a peak cortisol level below 18 µg/dl

in the ACTH stimulation test or insulin tolerance test were considered to have ACTH deficiency[6].

For diagnosis of GH deficiency, the presence of low IGF-1 levels together with more than 3 accompanying hormone insufficiencies was considered GH deficiency (6).

ADH deficiency was diagnosed from patient files based on serum and urine osmolarity results in patients with polydipsia and polyuria (≥3lt/24 hours)[7].

The number of pituitary hormone deficiencies per person was scored from 0 to 5.

Laboratory Data

Hormone levels from peripheral blood samples were studied using the chemiluminescence method (Beckman Coulter, DXI 800, Brea, CA, USA), complete blood count was performed on a Sysmex XN 9000 device, and measurements of other biochemical parameters were performed on a Cobas C 701 biochemistry autoanalyzer (Roche, Germany).

Specimens of 103 operated cases were kept within 10% formalin solution for 24 hours, and then 0.4-micron paraffin-embedded tissue slices were prepared, after which these slices were stained with H-E and then examined under an Olympus microscope.

Statistical Analysis

Statistical analysis of the data was performed by using SPSS (Statistical Package for the Social Sciences) 25.0 software program. Categorical variables were expressed as number and percentage, whereas continuous variables were summarized as mean and standard deviation (as median and minimum-maximum when necessary). Categorical variables were compared using Chi-squared test. Normality of distribution of the study parameters was determined using Shapiro-Wilk test. For paired group comparisons of non-normally distributed parameters, Mann Whitney U test was used. Wilcoxon test was used for examination of the differences between postoperative and preoperative findings. For all analyzes, level of statistical significance was considered 0.05.

Results

A total of 103 patients were included in the study. Of the patients, 54 (52.4%) were male and 49 (47.6%) were female. The mean age was determined to be 46.6±13.4 years (Table 1).

Of the patients included in the study, 85 (82.5%) were found to have pituitary adenoma (table 2).

Of the patients, mean tumor diameter was determined to be 2.21±1.07 cm and mean duration of follow-up was determined to be 2.6±1.5 years.

DI developed during preoperative period in 7 patients (6.8%), at postoperative week 2 in 80 (77.7%), at postoperative month 3 in 56 (54.4%) patients, 33 at final visits (32%). During preoperative period, 15 (14.6%) had hypothyroidism, while 61 (59.2%) had hypothyroidism at the postoperative month 3. Adrenal insufficiency was found in 13 (12.6%) patients during preoperative period and in 58 (56.3%) patients at the postoperative month 3.In the 3rd month posoperatively,in 40 patients evaluated , the cortisol level was below 3, and in20 patients, the basal cortisol level was above 18.Since the basal cortisol levels of 43 patients were between 3-18 , a 1mcg ACTH stimulasyon test was performed. In 25 of these patients who underwent the stimulation test , ınsufficiency was excluded because the cortisol level rose above 18 , while in 18 patients ,the stimulation test result was accepted as insufficiency .In the 3rd month postoperatively a total of 58 patients were diagnosed with secondary adrenal ınsufficiency , and all of these patients were started on treatment. Hypogonadism was observed in 37 (35.9%) during preoperative period, in 67 (65%) patients at the postoperative month 3, and in 63 (61.2%) patients at the postoperative month 12. GH deficiency was determined in 6 (5.8%) patients during preoperative period and in 10 (9.7%) patients at the postoperative month 3 (Table 3, Figure 1). Median number of pituitary hormone insufficiencies was determined to be 1 during preoperative period, 3 at the postoperative month 3, 2 at the postoperative year 1, and 2 at the final visit. Number of pituitary hormone insufficiencies was 0.81±0.9 during preoperative period, whereas it was 2.5±1.4 , 2.2±1.4 , and 2.1±1.4 at the postoperative month 3, at the postoperative year 1 and at the final visit, respectively (table 3).

Comparative analysis of preoperative and postoperative rates of pituitary insufficiency in functional and nonfunctional pituitary adenomas revealed no statistically significant difference (p>0.05) (Table 4).

Table 1. Patients' Demographic Characteristics and Baseline Laboratory Results

	Number (n)	Percentage (%)
Gender		
Male	54	52,4
Female	49	47,6
	Mean±sd	**Med (Min-Max)**
Age	46.6±13.4	47 (19-80)
Fasting blood glucose	120.3±60.7	100 (57-404)
BUN	25.5±12.3	23 (7-84)
Creatinine	0.68±0.24	0.62 (0.06-2.0)
ALT	22.9±15.8	18.1 (6.7-127.2)
AST	21.9±9.3	20 (11-61)
Na	139.8±4.4	140 (119-153)
K	4.52±2.9	4.2 (3.1-33)
Ca	9.1±0.6	9 (7.7-10.3)
Hgb	12.6±1.3	12.6 (10-16)

Table 2. Patients' Diagnosis

	Number (n)	Percentage (%)
Diagnosis		
Pituitary adenoma	85	82.5
Pineocytoma	2	1.9
Craniopharyngioma	8	7.8
Oligodendroglioma	1	1.0
Rathke cleft cyst	3	2.9
Spindle cell oncocytoma	1	1.0
Arachnoid cellar cyst	1	1.0
Meningothelial meningioma	2	1.9

Table 3. Hypothyroidism, adrenal insufficiency, hypogonadism, GH deficiency and diabetes insipidus findings during preoperative period, at the postoperative month 3, at the postoperative year 1 and at the final visit in patients with pituitary insufficiency

	Preop		Postop month 3		Postop year 1		Final visit	
	n	%	n	%	n	%	n	%
Hypothyroidism								
No	88	85.4	42	40.8	45	43.7	50	48.5
Yes	15	14.6	61	59.2	58	56.3	53	51.5
Adrenal insufficiency								
No	90	87.4	45	43.7	48	46.6	49	47.6
Yes	13	12.6	58	56.3	55	53.4	54	52.4
Hypogonadism								
No	66	64.1	36	35.0	40	38.8	40	38.8
Yes	37	35.9	67	65.0	63	61.2	63	61.2
GH deficiency								
No	97	94.2	93	90.3	94	91.3	93	90.3
Yes	6	5.8	10	9.7	9	8.7	10	9.7
Diabetes insipidus								
No	96	93.2	47	45.6	60	58.3	70	68.0
Yes	7	6.8	56	54.4	43	41.7	33	32.0
	Preop		**Postop month 3**		**Postop year 1**		**Final visit**	
	Mean±sd Med (Min-Max)		**Mean±sd Med (Min-Max)**		**Mean±sd Med (Min-Max)**		**Mean±sd Med (Min-Max)**	
The number of pituitary hormone deficiencies per person	0.81±0.9 1 (0-4)		2.5±1.4 3 (0-5)		2.2±1.4 2 (0-5)		2.1±1.4 2 (0-5)	

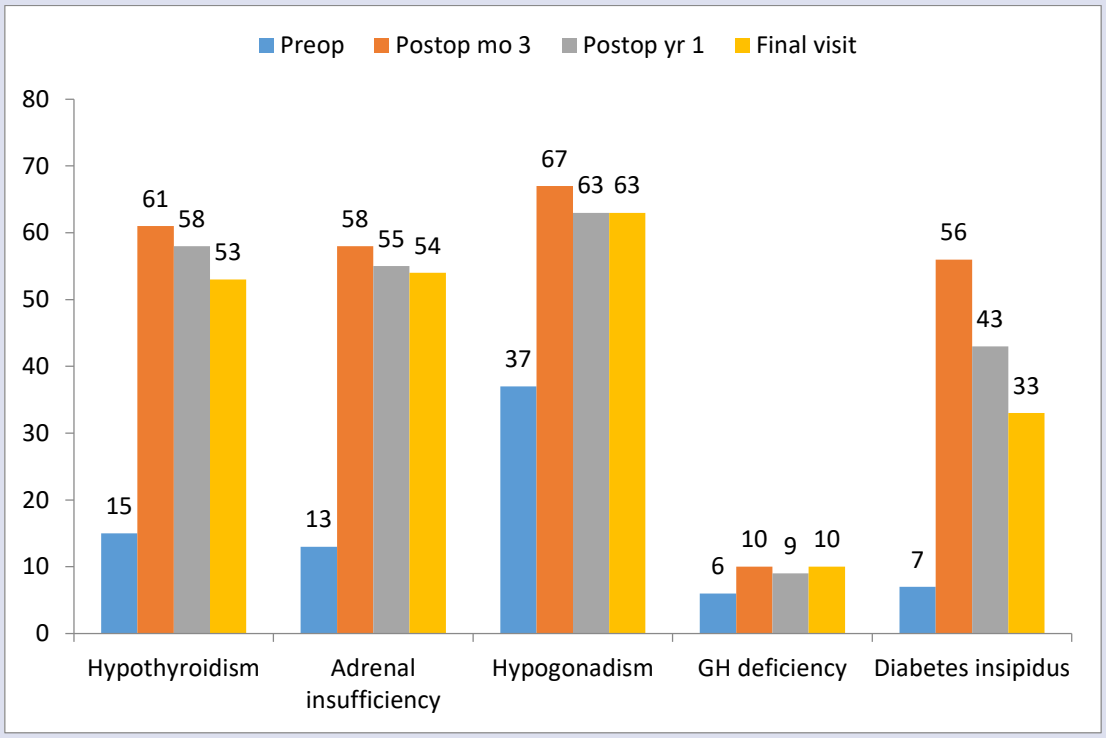

Figure 1. Number Of Patients with Pituitary Surgery Who Developed Pituitary Insufficiency During Preoperative Period, At the Postoperative Month 3, At the Postoperative Year 1 And at The Final Visit

Table 4. Differences between findings during preoperative period, at the postoperative month 3, at the postoperative year 1 and at the final visit between functional and nonfunctional adenoma groups

		Preop		Postop month 3		Postop year 1		Final visit	
		n	%	n	%	n	%	n	%
Hypothyroidism									
Functional		2	7.4	14	51.9	13	48.1	11	40.7
Nonfunctional		10	17.2	33	56.9	31	53.4	28	48.3
	p[c]		0.225		0.663		0.649		0.516
Adrenal insufficiency									
Functional		3	11.1	11	40.7	11	40.7	10	37.0
Nonfunctional		7	12.1	32	55.2	30	51.7	30	51.7
	p[c]		0.898		0.215		0.345		0.207
Hypogonadism									
Functional		8	29.6	18	66.7	17	63.0	18	66.7
Nonfunctional		21	36.2	37	63.8	34	58.6	34	58.6
	p[c]		0.552		0.796		0.704		0.479
Gh deficiency									
Functional		1	3.7	1	3.7	2	7.4	3	11.1
Nonfunctional		5	8.6	8	13.8	6	10.3	6	10.3
	p[c]		0.410		0.159		0.666		0.915
Diabetes insipidus									
Functional		1	3.7	16	59.3	13	48.1	9	33.3
Nonfunctional		5	8.6	29	50.0	21	36.2	16	27.6
	p[c]		0.410		0.426		0.295		0.588
			Preop Mean±sd		**Postop month 3 Mean±sd**		**Postop year 1 Mean±sd**		**Final visit Mean±sd**
Number of Pituitary Hormone insufficiencies									
Functional			0.77±0.9		2.29±1.5		2.14±1.6		2.00±1.5
Nonfunctional			0.82±0.9		2.39±1.4		2.10±1.4		1.96±1.4
	p[b]		0.745		0.791		0.897		0.977

p<0.05

Discussion

The most common cause of pituitary masses are pituitary adenomas. The primary goal of surgical treatment is to remove the tumor in nonfunctional tumors before hormonal insufficiency develops. In the case of functional tumors, the aim is to achieve hormonal control without causing insufficiency[8-9]. Preoperative hormonal deficiencies due to compression may resolve postoperatively, and endocrine function in patients who develop postoperative hormonal deficiencies may improve over time. In a previous study involving 150 patients, the patients were followed up for complications for 36 months. Pituitary insufficiencies were observed to begin within the first weeks after surgery and remitted in patients within a mean duration of 2-4 months[10]. In order to evaluate effect of surgery on endocrine functions, in our study we evaluated our patients during preoperative period, at the postoperative months 3-12 and at the final visit for development of hypothyroidism, adrenal insufficiency, hypogonadism, GH deficiency and diabetes insipidus. Moreover, we created a pituitary insufficiency score by scoring number of deficient hormones. As a result of the analyzes we performed by scoring each insufficiency from 0 to 5, number of pituitary hormone insufficiencies was 0.81±0.9 during preoperative period, whereas it was 2.5±1.4 , 2.2±1.4 , and 2.1±1.4 at the postoperative month 3, at the postoperative year 1 and at the final visit, respectively. In regard with median values, there was 1 hormonal insufficiency during preoperative period, whereas there were 3 hormonal insufficiencies during early postoperative period and 2 at the first year and at the final visit. In conclusion, we observed that pituitary insufficiencies of our cases began during early postoperative period and maintained similar at the long term, with minimal reductions after the 3rd month.

A study investigating hormonal remission following pituitary surgery reported that the most common hormonal insufficiency following transsphenoidal surgery was diabetes insipidus and that the risk of transient DI was 15-60%, particularly in suprasellar adenomas. They also reported that persistent DI was less common [11]. In a study by Viries et al., they reported that the most common complication following pituitary surgery was DI and suggested that postoperative DI should be treated with multiple factors taken into consideration[12]. In our study, when the patients were evaluated for diabetes insipidus, DI was found in 7 (6.8%) patients during preoperative period, 80 (77.7%) patients at the postoperative week 2, and 56 (54.4%) patients at the postoperative month 3. At the final visits of the patients, 33 (32%) were found to have DI. Regarding early-term development of hormonal insufficiencies, the most common increase was observed for frequency of DI. In the long-term, however, recovery rate for DI was determined to be higher compared with those of other hormonal axes. In terms of proportion, the greatest increase in DI among hormonal insufficiencies we determined in our study and the greatest recovery in DI in the long term were consistent with the literature, although our rates of persistent DI were higher.

The most common cause of secondary adrenal insufficiency is tumors of the hypothalamic-pituitary region. It may result from compression due to mass effect or accompanies panhypopituitarism developing after surgery. A previous study reported that, following pituitary surgery, 10% of the patients developed adrenal insufficiency, 34% of which required external cortisol treatment for 1-3 months and then recovered[13-14]. In our study, 56.3% of the patients developed adrenal insufficiency postoperatively. Furthermore, adrenal insufficiency persisted at the final visit in 52.4% of the patients. In our study, our rates of early- and late-term adrenal insufficiency were much greater than those reported in the literature.

Hypothyroidism was determined in 14.6% of the patients during the preoperative period and in 59.2% of the patients at the postoperative month 3, and this increase was statistically significant. At 12-month and final visits, hypothyroidism persisted at similar rates. In the previous studies, prevalence of thyroid insufficiency following surgery has been reported to be 10-50%[15]. Our findings, however, were higher than those in the literature.

Rate of hypogonadism, however, was 35.9% during preoperative period and 60% at 3- and 12-month visits. In the literature, it has been reported that hypogonadism develops in approximately 68-83% of the patients who undergo pituitary surgery due to any reason and persists at a rate of about 10%[14].

In our study, rate of patients with GH deficiency was approximately 9%, with minimal increase during postoperative period. The rate of patients developing hormonal insufficiencies other than GH deficiency was higher than those reported in the literature [13-14,16]. The lower rate of GH deficiency was attributed to not performing dynamic tests to evaluate and to the fact that insufficiency was defined as low IGF-1 values with accompanying 3 additional hormonal insufficiencies. Comparative analysis of preoperative and postoperative rates of pituitary insufficiency in functional and nonfunctional pituitary adenomas revealed no significant difference.

Our higher complication rates may be due to the fact that majority of our cases were macroadenomas. Another important factor for development of complications is surgical experience. Complication rates decrease with increased experience of the surgeon. Although our study was single-center and only operations performed by one surgeon were included in the study, we could not determined whether complication rates eventually decreased or not, since number of surgeries and complications was not separately described by years. This is a limitation of our study, which might also be the reason for our higher rates.

In conclusion, as multiple hormone deficiencies can be encountered after pituitary surgeries, we are in thought of that attention should be paid on pituitary insufficiencies which may develop following pituitary surgeries and that patients should be closely monitored due to potential recovery in time.

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Psychiatric Diagnosis Received By Patients Diagnosed With Autism Spectrum Disorder In Childhood In The Adult Period

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Research Article

History

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ABSTRACT

Objective: ASD; It is a neurodevelopmental disorder whose symptoms persist throughout life. There are many studies investigating ASD in childhood, but there are few studies examining the adulthood of ASD patients. The aim of this study is to examine the psychiatric diagnoses received in adulthood by patients diagnosed with ASD in childhood.

Method: This study included 28 patients who were diagnosed with autism at the child and adolescent mental health outpatient clinic between 2006 and 2023, and who subsequently received psychiatric diagnoses at an adult psychiatry outpatient clinic

Results: When the diagnoses received by the patients in adulthood are examined; %35.6 of the patients had mental retardation (MR), %21.4 had childhood autism and MR, %7.2 had atypical autism and MR, %7.1 had atypical autism, %7.1 had MR and psychotic disorder, %7.1 with pervasive developmental disorder, %3.6 with pervasive developmental disorder and mild MR, %3.6 with anxiety disorder, %3.6 with childhood autism and anxiety disorder, %3.6 were diagnosed with conduct disorder, %3.6 with mild MR and attention deficit and hyperactivity disorder (ADHD), and %3.6 with autism, moderate MR and ADHD, It was found that.

Conclusion: ASD is a neurodevelopmental disorder characterized by symptoms that persist into adulthood and is frequently associated with comorbid psychiatric conditions. Clinical problems and diagnostic features of patients in adulthood vary. For these reasons, investigating adult symptoms and the clinical course of individuals with ASD may contribute to the development of more effective and appropriate treatment strategies.

Keywords: Autism Spectrum Disorder, Adult Autism Spectrum Disorder, Mental Retardation

Çocukluk Çağında Otizm Spektrum Bozukluğu Tanısı Olan Hastaların Erişkin Döneminde Aldığı Psikiyatrik Tanılar

Araştırma Makalesi

Süreç

Geliş: 15/03/2025
Kabul: 21/05/2025

ÖZ

Amaç: OSB; belirtileri ömür boyu devam eden nörogelişimsel bir bozukluktur. Çocukluk çağında OSB'yi araştıran çok sayıda araştırma bulunmaktadır ancak OSB hastalarının erişkinlik dönemini inceleyen az sayıda araştırma bulunmaktadır. Bu çalışmanın amacı çocukluk çağında Otizm Spektrum Bozukluğu tanısı olan hastaların erişkin döneminde aldığı psikiyatrik tanıları incelemektir.

Yöntem: Bu çalışma, 2006 ile 2023 yılları arasında çocuk ve ergen ruh sağlığı polikliniğinde otizm tanısı konan ve daha sonra erişkin psikiyatri polikliniğinde psikiyatrik tanılar alan 28 hastayı kapsamaktadır.

Bulgular: Hastaların erişkinlik döneminde aldıkları tanılar incelendiğinde; hastaların %35,6'sının mental retardasyon (MR), %21,4'ünün çocukluk otizmi ve MR, %7,2'sinin atipik otizm ve MR, %7,1'inin atipik otizm, %7,1'inin MR ve psikotik bozukluk, %7,1'inin yaygın gelişimsel bozukluk, %3,6'sının yaygın gelişimsel bozukluk ve hafif MR, %3,6'sının anksiyete bozukluğu, %3,6'sının çocukluk otizmi ve anksiyete bozukluğu, %3,6'sının davranış bozukluğu, %3,6'sının hafif MR ve dikkat eksikliği ve hiperaktivite bozukluğu (DEHB), %3,6'sının otizm, orta MR ve DEHB tanısı aldığı bulunmuştur.

Sonuç: ASD, belirtileri yetişkinlik dönemine kadar devam eden ve sıklıkla eşlik eden psikiyatrik bozukluklarla ilişkili olan bir nörogelişimsel bozukluktur. Hastaların erişkin dönemde klinik sorunları ve tanısal özellikleri farklılık göstermektedir. Bu nedenlerle, ASD'li bireylerde yetişkinlik dönemine ait belirtilerin ve klinik seyrin araştırılması, daha etkili ve uygun tedavi stratejilerinin geliştirilmesine katkı sağlayabilir.

Anahtar Kelimeler: Otizm Spektrum Bozukluğu, Erişkin Otizm Spektrum Bozukluğu, Mental Retardasyon

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Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder.[1] ASD is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), as a neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction, along with restricted, repetitive patterns of behavior, interests, or activities.[2] These symptoms may be severe enough to require lifelong assistance or mild enough to require little lifelong assistance.[3]

Although ASD is a common neuropsychiatric disorder, its cause has not yet been elucidated. Genetic and environmental factors are thought to play a role in its etiology.[4] The prevalence of ASD has increased in recent years.[5] According to research, autism spectrum disorder is thought to be seen in one in every fifty-nine people in the world.[6] This increase can be attributed to heightened awareness of autism among both the general public and clinical professionals, the broadening of diagnostic criteria, and advances in early diagnostic methods.[6]

Research has found that approximately 70% of people with autism have at least one psychiatric disorder.[7] The most common comorbid psychiatric diagnoses in individuals with ASD are attention deficit and hyperactivity disorder, behavioral disorders, anxiety disorder and depressive disorder.[8] It is emphasized that psychiatric symptoms may be masked by autistic features or that autistic features may be incorrectly labeled as a separate psychiatric illness. This situation may lead to inadequate identification and assessment of adults with autism, as well as inadequate recognition and treatment of comorbid mental health problems.[9]

Autism spectrum disorder symptoms usually begin in childhood, and patients are diagnosed with autism during this period. ASD symptoms often persist into adulthood. .[10] During the first year of life, lack of eye contact and reduced response to their name are commonly observed. Between 12 and 24 months, in addition to these signs, delays in fine motor development and the emergence of repetitive behaviors are frequently noted. Between the ages of 2 and 5, symptoms such as speech delay, preference for solitary play, difficulties in social interaction, and challenges in forming friendships are commonly observed. During adolescence, behavioral issues including irritability, impulse control problems, depression, and suicide attempts may emerge. The most important criteria that show the course of the disorder in adulthood are the patient's intelligence level and whether he/she has received appropriate education.[11]

In studies on autism, childhood has generally been investigated, and studies investigating adulthood are less common. Therefore, there is no clear understanding of how autism symptoms change in adulthood.[12] The methods used in the treatment of autistic patients are behavioral methods, communication-oriented methods and pharmacotherapy. Special treatments should be planned for these patients and families.[13] For these reasons, ASD is one of the important public health problems.[14]

Despite the increasing interest in ASD, most studies have focused on childhood and adolescence, leaving a gap in our understanding of adult outcomes. In particular, psychiatric comorbidities in adults with a childhood diagnosis of ASD remain underexplored. In this study, psychiatric diagnoses in adulthood were analyzed in individuals who had been diagnosed with ASD in childhood.

Materials and Methods

This research is a retrospective study. Due to the retrospective nature of the study, comorbid diagnoses were identified through a review of diagnoses recorded in the hospital system. The study included 28 patients who were diagnosed with autism at the XXX Hospital Child and Adolescent Mental Health and Disorders Polyclinic between 2006 and 2023, and who were subsequently diagnosed at the Adult Mental Health and Disorders Polyclinic after the age of 18." Inclusion criteria for the study were being diagnosed with autism spectrum disorder between the ages of 3-17. Exclusion criteria for the study were the presence of genetic syndrome, being younger than 3 years old and older than 17 years old. The study was approved by the Clinical Research Evaluation Committee of the Faculty of Medicine, Cumhuriyet University on 16 November 2023, under approval number 2023-11/19.

In our study, SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA) version 21.0 was used for the statistical analysis of the data. In descriptive statistics, mean and standard deviation values were used for continuous variables, and number and percentage values were used for categorical variables.

Results

Among the 28 patients included in the study, 21 were male (75%) and 7 were female (25%). All patients were diagnosed with autism in childhood, and the mean age at diagnosis was 9.9±4.3 years. During childhood, 46.5%, 32.1%, and 21.4% of the patients were diagnosed with Childhood Autism, Pervasive Developmental Disorder, and Atypical Autism, respectively. (Table 1)

The mean age of the patients when they applied to the adult psychiatry outpatient clinic was 21.5±2.79. When adult diagnoses were examined, 35.6% of the patients were diagnosed with mental retardation (MR), 28.6% with both autism and MR, 7.1% with atypical autism, 7.1% with MR and psychotic disorder, 7.1% with pervasive developmental disorder, 3.6% with pervasive developmental disorder and mild MR, 3.6% with anxiety disorder, 3.6% with childhood autism and anxiety disorder, 3.6% with conduct disorder, 3.6% with mild MR and attention deficit hyperactivity

disorder (ADHD), and 3.6% with autism, moderate MR, and ADHD. Diagnoses and their respective sub-classifications are shown in Table 2.

Table 1: Types of Autism Diagnosis Received by Patients in Childhood and Average Age at Diagnosis

Age at which patients were diagnosed (ort±ss)		9,9±4,3	
		n	**%**
Childhood Diagnosis	Childhood autism	13	%46,5
	Pervasive developmental disorder	9	%32,1
	Atypical autism	6	%21,4

Table 2: Psychiatric Diagnoses Received by Patients in Adulthood

Current Age of Patients (ort±ss)		*21,5±2,79*	
		n	***%***
Adult Diagnosis	*Mental retardation (MR)*		
	MR(Untyped)	*3*	*%10,7*
	Mild MR	*1*	*%3,6*
	Moderate MR	*2*	*%7,1*
	Severe MR	*2*	*%7,1*
	Childhood autism and MR		
	Childhood autism and Borderline MR	*1*	*%3,6*
	Childhood autism and Mild MR	*1*	*%3,6*
	Childhood autism and Moderate MR	*2*	*%7,1*
	Childhood autism and Severe MR	*2*	*%7,1*
	Atypical autism and MR		
	Atypical autism and Mild MR	*1*	*%3,6*
	Atypical autism and Moderate MR	*1*	*%3,6*
	Atypical autism	*2*	*%7,1*
	MR and Psychotic Disorder	*2*	*%7,1*
	Pervasive developmental disorder	*2*	*%7,1*
	Pervasive developmental disorder and Mild MR	*1*	*%3,6*
	Anxiety disorder	*1*	*%3,6*
	Childhood autism and anxiety disorder	*1*	*%3,6*
	Behavioral Disorder	*1*	*%3,6*
	*Mild MRI and ADHD**	*1*	*%3,6*
	*Autism, MRI and ADHD**	*1*	*%3,6*

** ADHD: Attention Deficit Hyperactivity Disorder*

Discussion

In this study, we aimed to investigate the psychiatric diagnoses received in adulthood in patients diagnosed with Autism Spectrum Disorder in childhood.

It is generally accepted that around 40% of autistic individuals experience a diagnosable mental health disorder at some stage in their lives. The most commonly reported problems include depression, anxiety disorder, phobia and ADHD.[15] In addition, a significant proportion of individuals with autism are also diagnosed with mental retardation. Studies indicate that approximately 40% have an IQ between 40–50, and up to 70% fall within the 50–70 IQ range.[16]

Our findings showed that 35.6% of individuals diagnosed with ASD in childhood were later diagnosed with mental retardation during adulthood. Individuals with mental retardation are at increased risk for impulse control disorders, emotional dysregulation, and behavioral disturbances, including agitation and aggression. These behavioral symptoms may increase the likelihood of individuals with mental retardation seeking psychiatric care more frequently. In our study, it was seen that 3.6% of patients diagnosed with ASD were diagnosed with anxiety disorder and 3.6% with ADHD in adulthood. The low total number of patients received may have been effective in the low number of these rates.

Conclusions

As a result of our study, it was found that these patients received additional psychiatric diagnoses such as anxiety disorder, ADHD, and behavioral disorders, as well as mental retardation in adulthood. Based on our findings, we believe that further studies with larger sample sizes are needed in this area.

Follow-up studies of patients with ASD indicate that the diagnostic features, differential diagnosis, and clinical problems of adult autistics differ significantly from those of children with autism. Follow-up studies on autism are thought to be useful in determining the appropriate and most effective treatment programs for adult autism.[17]

Our study aims to reveal the rates of certain psychiatric diagnoses made in adulthood among patients diagnosed with Autism Spectrum Disorder during childhood, and to contribute to the literature by enhancing the understanding of the clinical presentation of adult ASD.

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Evaluation of Learning Preferences of Medical Faculty Students with VARK Questionnaire

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ABSTRACT

Aim: This study aims to evaluate the learning styles of Medical Faculty students using the VARK model.

Material and Method: The population of this cross-sectional quantitative study consists of volunteer students from years II, III, IV, and V who are currently studying. A census sampling approach was employed, and a total of 210 students participated in the study. The data collection instrument was structured into three distinct sections. The first section includes five items pertaining to students' sociodemographic characteristics; the second section contains six questions addressing study habits during the distance education period; and the third section incorporates the VARK Learning Preferences Inventory. Statistical analyses were performed using the SPSS version 22.0 software package. The normality of the numerical data distribution was assessed by examining the skewness and kurtosis coefficients.

Results: This study reveals that medical students' learning styles vary and that demographic characteristics can influence learning preferences. The fact that the majority of students prefer kinesthetic learning methods and unimodal learning styles indicates that individual differences should be considered in the educational process.

Conclusion: Male students demonstrated a greater preference for auditory and kinesthetic learning modalities, whereas female students showed higher scores in the read/write domain, suggesting that learning styles may vary by gender.

Keywords: Learning Preferences, Medical Students, Learning

Tıp Fakültesi Öğrencilerinin Öğrenme Tercihlerinin VARK Anketi ile Değerlendirilmesi

Araştırma Makalesi

Süreç

Geliş: 29/04/2025
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ÖZET

Amaç: Bu çalışmada, Tıp Fakültesi öğrencilerinin öğrenme stillerinin VARK modeli ile değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Araştırmamız kesitsel nicel tiptedir. Araştırma evrenini Dönem II, III, IV ve V'te öğrenim gören 885 öğrenci oluşturmuştur. Örneklem hesabı yapılarak örneklem seçilmiştir. Veri toplama aracı olarak kullanılan anket formu üç bölümden oluşmaktadır. Formun ilk bölümü öğrencilerin sosyodemografik özelliklerinin sorgulandığı beş sorudan oluşmakta, ikinci bölüm uzaktan eğitim dönemindeki çalışma düzeni ile ilgili altı sorudan oluşmakta olup, üçüncü bölüm ise VARK Öğrenme Tercihleri Envanterinden oluşmaktadır. Araştırmanın istatistiksel analizi SPSS 22.0 paket programı ile gerçekleştirilmiştir. Sayısal verilerin normal dağılıma uygunluğu çarpıklık ve basıklık katsayılarının analizi ile değerlendirilmiştir.

Bulgular: Araştırmaya katılmaya gönüllü olan 210 öğrencinin yaş ortalaması 21,1±2,8 idi. %60 (n=126)'ı kız öğrenciydi. Tıp öğrencilerinin öğrenme tercihleri incelendiğinde en sık kinestetik yolla (n=116, %55,2) öğrenmeyi tercih ettikleri görülmektedir. Öğrenimleri ise en sık unimodal (n=132, %62,9)'dir. Erkek öğrencilerin işitsel ve kinestetik öğrenme sıklığı kız öğrencilere göre anlamlı derecede daha fazlaydı. Kız öğrencilerin okuma yazma öğrenme tercih puanı erkek öğrencilerden anlamlı derecede daha yüksekti. Ayrıca klinik öncesi evre öğrencilerinin tüm öğrenme tercihlerinde puanı klinik öğrencilerine göre anlamlı derecede daha yüksekti (p<0,05).

Sonuç: Erkek öğrencilerin işitsel ve kinestetik öğrenme sıklığının daha yüksek olması, kız öğrencilerin ise okuma-yazma tercihinde daha yüksek puan alması, öğrenme stillerinin cinsiyete göre farklılık gösterebileceğini işaret etmektedir. Ayrıca klinik öncesi öğrencilerin tüm öğrenme tercihlerinde daha yüksek puanlar alması, erken dönem öğrenme süreçlerinde çeşitliliğin daha belirgin olduğunu göstermektedir.

Anahtar Kelimeler: Öğrenme tercihleri, Tıp Öğrencileri, Öğrenme

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Introduction

Learning styles refer to the methods of gathering, processing, interpreting, organizing, and thinking about information. diversity in knowledge acquisition is observed in classrooms regarding how students acquire knowledge. Claxton and Murrell categorized learning styles into four categories: personality models, information processing models, social interaction models, and instructional preference models.[1] The VARK (Visual, Auditory, Reading/Writing, and Kinesthetic) model, based on the instructional preference model, allows for the classification of individuals according to their learning preferences.[2] In the VARK model, which defines individual learning styles based on the four sensory modalities used by individuals to assimilate new information, it is stated that visual learners learn best by seeing, auditory learners by hearing, and reading/writing learners prefer printed material. In contrast, kinesthetic learners learn best through physical or practical experience.[2] This model helps determine how individuals perceive, process, store, and recall information most efficiently and effectively. Therefore, identifying students' learning styles enables educators to diversify their teaching methods, providing learning experiences tailored to each student's needs and aiming to maximize students' potential by offering diverse learning opportunities.[3] Today, one of the most important goals in education is to make learning easy, efficient, and appropriate for all students during their studies. To achieve this goal, it is important to know each student's learning style.[4]

With the help of developing and changing technology, it is necessary to follow and implement new approaches and contemporary teaching methods in learning-teaching activities[5]. By determining the personal characteristics of students, the most suitable learning model can also be created.[6] There are various studies showing that determining learning styles and using the correct model in the teaching process are important in improving the quality of education.[7,8] Evaluating individuals' learning styles is important for the teaching and learning process.[9] It is observed that knowing students' learning styles also helps educators in developing methods, techniques, and activities planned to be used in learning and teaching environments.[10] Many studies are showing that learning styles affect student achievement.[11]

Method

Participants

The exclusion criterion for the study was not having studied at this faculty during the distance education period. A total of 885 students were enrolled in the specified academic years. No sampling method was employed in the study, and an attempt was made to reach the entire population. After providing information about the research via a message in the phone application group used for communication, a participation link was sent to the students. Students were invited to participate in the research three times in 10-day intervals. The first page of the online survey contained an informed consent form, and questions were accessible only after participant consent. Incomplete surveys were not included in the study. Repeated entries were prevented through IP address monitoring. A total of 210 students volunteered to participate. A power analysis was conducted using a known population size (N = 885), a sample of 210 participants, and a margin of error of 5%, yielding a confidence level of 90%. Data collection for the study took place between April 1 and April 30, 2021..

Data collection form

The first five questions addressed students' sociodemographic characteristics, followed by six items concerning their study routines during the distance education period. The final section of the questionnaire was dedicated to the VARK Learning Preferences Inventory.

The VARK (Visual, Auditory, Reading/Writing, and Kinesthetic) learning inventory was originally developed by Hawk and Shah in 1987. It consists of 16 items, each presenting a distinct scenario in which respondents are asked to select their preferred response, reflecting their approach to learning in real-life situations. Rather than merely identifying how individuals exchange information, the VARK inventory provides insight into their preferred modalities for processing and internalizing information. The model categorizes learning preferences into four sensory modalities: visual, auditory, reading/writing, and kinesthetic. A Turkish adaptation and validation of the inventory was conducted by Düzgün in 2018, yielding a Cronbach's alpha reliability coefficient of 0.76. These four categories form the basis for understanding individual learning styles and are widely used in educational research and practice.

- Visual learning: Understanding information more easily through drawings, graphs, and visuals.
- Auditory learning: Acquiring information through listening or discussion.
- Reading/Writing learning: Preferring to acquire information by reading or writing.
- Kinesthetic learning: Learning through touching, feeling, and experiencing.

These learning styles are used to understand and support individuals' different approaches to information.[13]

Permissions

Ethical approval for the study was obtained from the Sivas Cumhuriyet University Non-Interventional Clinical Research Ethics Committee (Approval date/number: 10.03.2021. 2021-03/17). Permission to use the scale in our research was obtained via email from Dr. Serkan Düzgün.

Statistical analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). The normality of the

data distribution was assessed based on skewness and kurtosis values. Huck,[14] states that for data to show normal distribution, the skewness and kurtosis values should range between -1 and +1. First, descriptive statistical analyses of the data were performed. Frequencies were calculated for categorical data, and measures of central tendency (Mean ± Standard Deviation) were calculated for numerical data. Chi-square test was used for comparing categorical data. Independent samples T-test was used to analyze whether the means of normally distributed numerical data showed significant differences between two independent groups; One-Way ANOVA test was used to analyze whether they showed significant differences among more than two independent groups. At a 95% confidence interval, a p-value below 0.05 was considered significant.

Results

The mean age of 210 students who volunteered to participate in the study was 21.1±2.8 years. 60% (n=126) were female students. The frequency of students living in the city center was 81.9% (n=172), while those living in districts/villages were 18.1% (n=38). 95.2% (n=200) of the participants were Turkish students; 4.8% (n=10) were of foreign nationality. Their distribution according to classes was as follows: 37.6% (n=79) second year, 23.3% (n=49) third year, 26.7% (n=56) fourth year, and 12.4% (n=26) fifth year.

During the distance education period, 93.3% (n=196) of the students stayed at home with their families. 6.7% (n=14) stated that they stayed at home with friends. For studying during the distance education period, 61.4% (n=129) used computers, 4.8% (n=10) used tablets, 11.4% (n=24) used smartphones, and the remaining 22.4% (n=47) stated that they studied from course notes. 7.2% (n=15) of the students stated that they always participated in distance education classes online, while 18.8% (n=39) always watched the recordings. 65.4% (n=136) watched the classes sometimes online and sometimes offline, while 8.7% (n=18) said they never watched the classes. 47.1% (n=99) of the students stated that their frequency of studying decreased during the pandemic period. The resources they used for studying during the pandemic period, in order of frequency, were materials uploaded to the system (77.6%; n=163), previous term's course notes (14.8%; n=31), and textbooks (7.6%; n=16). The students' studying situations during the distance education period are shown in Table 1. The results of the students' evaluation of distance education and face-to-face education in terms of advantages and disadvantages are presented in Table 2.

Table 1. *Students' study habits during the distance education period*

Parameters related to studying habits	n	%
Place of residence during the pandemic		
At home with family	196	93,3
At home with friends	14	6.7
Device used for studying		
Computer	129	61.4
Tablet	10	4.8
Smartphone	24	11.4
From lecture notes	47	22.4
How classes were attended		
Always online	15	7.2
Sometimes online. sometimes recorded	136	65.4
Always from recordings	39	18.8
Did not watch classes	18	8.7
Change in frequency of studying		
Decreased	99	47.1
No change	81	38.6
Increased	30	14.3
Resources used for studying		
Materials uploaded to the system	163	77.6
Lecture notes from previous semesters	31	14.8
Textbooks	16	7.6

Table 2. *Students' opinions on educational methods*

	Distance education		Equal		Face-to-face education	
	%	n	%	n	%	n
Efficient	58.1	122	20.5	43	21.4	45
Instructive	58.6	123	27.1	57	14.3	30
Practical	63.3	133	1.9	4	34.8	73
Accessible	17.6	37	14.8	31	67.6	142
Easy communication	41.4	87	21.9	46	36.7	77
Engaging	66.2	139	23.3	49	10.5	22
Affordable	19.0	40	19.0	40	61.9	130
Knowledge retention	62.9	132	26.7	56	10.5	22
Repeatable	69.0	145	14.3	30	16.7	35

When examining the learning preferences of medical students, it is observed that they most frequently prefer to learn through kinesthetic means (n=116, 55.2%). Their learning style is most commonly unimodal (n=132, 62.9%). Learning preferences and learning preference scores of medical students shown at Table 3.

The comparison of students' learning preferences based on gender and educational stages is shown in Table 4. According to this, male students had significantly higher frequency of auditory and kinesthetic learning compared to female students. Female students' reading and writing learning preference scores were significantly higher than

male students. Additionally, pre-clinical stage students had significantly higher scores in all learning preferences compared to clinical students (p<0.05). When comparing learning preference scores based on the tools students use for studying, students who study by printing out lecture notes (7.3±2.9) had significantly higher kinesthetic scores than those who study from computers, tablets, or smartphones (6.1±2.6) (p=0.032). There were no significant differences between other learning preferences and educational stages (p>0.05). Students with kinesthetic learning preference (n=66, 56.9%) showed a significant decrease in study frequency during the distance education period compared to others (n=33, 35.1%) (p=0.007). When students were asked about the resources they used for studying during this period, 90.5% (n=57) of students who preferred visual learning stated that they studied from visual materials uploaded to the system, while this rate was 72.1% (n=106) for those who preferred other learning models (p=0.007). There were no significant differences between other learning preferences and the materials they used for studying (p>0.05). Figure 1 provides a visual representation of students' learning models.

Table 3. *Learning preferences and learning preference scores of medical students*

Learning Preference	n	%
V (visual)	61	29
A (auditory)	90	42.9
R (reading-writing)	98	46.7
K (kinesthetic)	116	55.2
Unimodal	132	62.9
Bimodal	29	13.8
Trimodal	15	7.1
Quadmodal	34	16.2
Learning Preference Score	**Mean**	**SD**
V (visual)	5.13	3.11
A (auditory)	6.07	2.74
R (reading-writing)	6.08	2.75
K (kinesthetic)	6.58	2.70

Table 4. Comparison of students' learning preferences by gender

Learning Preference	Female n (%)	Male n (%)	p	Preclinical stage n (%)	Clinical stage n (%)	p
V (visual)	39 (31)	24 (28.6)	0.416	39 (30,5)	24 (29,3)	0,490
A (auditory)	48 (38.1)	44 (52.4)	0.029	54 (42.2)	38 (46.3)	0.326
R (reading-writing)	66 (52.4)	34 (40.5)	0.060	57 (44.5)	43 (52.4)	0.164
K (kinesthetic)	63 (50)	53 (63.1)	0.042	69 (53.9)	47 (57.3)	0.366
Multiple learning	41 (32.5)	36 (42.9)	0.085	41 (32.1)	36 (43.9)	0.056
Unimodal	84 (66.7)	48 (57.1)		86 (67.2)	46 (56.1)	
Bimodal	15 (11.9)	14 (16.7)	0.251	15 (11.7)	14 (17.1)	0.071
Trimodal	6 (4.8)	9 (10.7)		5 (3.9)	10 (12.2)	
Quadmodal	21 (16.7)	13 (15.5)		22 (17.2)	12 (14.6)	
Learning Preference Score	**M ± SD**	**M ± SD**		**M ± SD**	**M ± SS**	
V (visual)	5.2±3.2	4.9±2.8	0.449	5.6±3.4	4.3±2.2	0.002
A (auditory)	5.9±2.7	6.2±2.7	0.473	6.6±2.7	5.2±2.5	<0.001
R (reading-writing)	6.4±2.7	5.5±2.7	0.016	6.6±2.8	5.2±2.2	<0.001
K (kinesthetic)	6.4±2.5	6.8±2.8	0.284	7.0±2.7	5.8±2.4	0.002

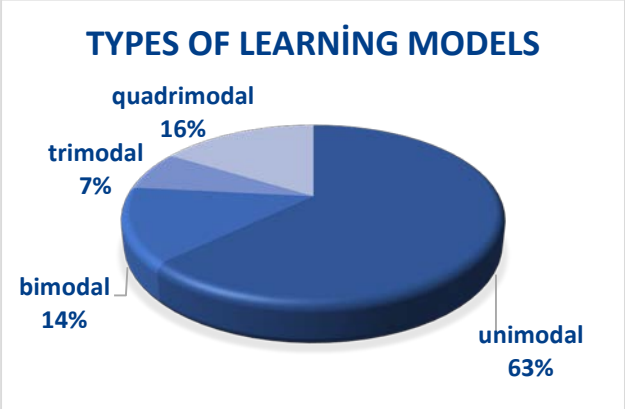

Figure 1. *Students' learning models*

Discussion

This study investigated the learning styles of medical students using the VARK Learning Preferences Inventory and explored how these styles influenced their learning experiences. Furthermore, students' sociodemographic characteristics and their study habits during the period of distance education were also examined.

The findings of this study revealed that medical students most frequently preferred kinesthetic learning (55.2%) and tended to adopt a unimodal learning style (62.9%). Similar results were reported by Chinnapun and Narkkul, who found that kinesthetic learning was the most commonly preferred style among medical students.[15]

Consistent with this, several other studies have emphasized the predominance of kinesthetic preferences and highlighted the importance of practical applications in enhancing academic performance[16]. However, in contrast to the current study's findings regarding the dominance of unimodal preferences, Ojeh et al. reported that most students favored multimodal learning and found no significant gender-based differences in learning preferences.[17] Similarly, Urval et al. found that among unimodal learners, auditory (45.5%) and kinesthetic (33.1%) modalities were most frequently preferred.[18] Another study focusing on the pre-clinical period noted that among both unimodal and multimodal learners, the most preferred style was reading/writing (33.8%), followed by kinesthetic (32.5%)[17].

It has been reported in various studies that the multimodal learning style is most frequently preferred among first-year medical students,[19] with 70% of students preferring this learning style, while the remaining 30% opt for a unimodal style. Auditory (A) and kinesthetic (K) styles were found to be the most preferred unimodal styles.[20] Additionally, a study including undergraduate medical and dental students indicated no significant difference between learning styles, with the majority preferring multimodal learning styles.[21] In our study, it was observed that students most frequently had a unimodal learning style; however, there are also studies concluding that the majority of medical students have multiple learning preferences.[22]

Our study also investigated the influence of gender and stage of education (pre-clinical vs. clinical) on students' learning style preferences. The findings indicated that male students showed a significantly higher preference for auditory and kinesthetic learning styles than their female counterparts. This result is partially supported by previous research, which also identified a higher prevalence of kinesthetic learners among male students, although the difference was not statistically significant[18]. Additionally, our study found that female students scored significantly higher in the reading/writing learning preference. A similar trend was observed in the study by Ojeh et al., which reported that female students tended to prefer reading/writing styles, whereas male students were more inclined toward kinesthetic learning; however, this difference did not reach statistical significance[17].

While some studies suggest gender differences in learning style preferences, others have not been able to demonstrate any difference.[20] One of the prominent findings in our study was that pre-clinical stage students scored significantly higher in all learning preferences compared to clinical students. When examining the literature, it is observed that most studies involve first-year medical school students.[19,20,23-25]

In this study, which also examined study habits and tools during the distance education period, prominent data revealed that most students (93.3%) attended classes from home with their families, primarily preferring computers (61.4%), followed by smartphones (11.4%) and tablets (4.8%). It was found that the majority of students (65.4%) participated in classes sometimes online and sometimes through recordings. When examining study frequency, results showed that it decreased for 47.1%, remained unchanged for 38.6%, and increased for 14.3%. Materials in the system were used most frequently (77.6%); course notes (14.8%) and textbooks (7.6%) were preferred to a lesser extent. Among the obtained results was that most students study at home with their families, using computers and preferring materials provided in the system. Class participation often occurred both online and through recordings, but study frequency generally decreased. Similar to our study, other research found that during the distance education period, a large portion of students participated in education at home with their families via computers and mobile devices,[26] with the majority of students attending classes online and following course materials through digital platforms.[27,28] When comparing learning preference scores based on the tools students used for studying, those who studied by printing course notes had significantly higher kinesthetic scores compared to students who studied using computers, tablets, or smartphones. No significant differences were found between other learning preferences and learning stages. It was observed that the study frequency of students with kinesthetic learning preferences decreased significantly during the distance education period compared to others.

Numerous studies have demonstrated significant variation in students' learning styles, underscoring the need for instructional programs to be tailored to accommodate these individual differences[29].

Knowing students' learning styles is considered a valuable skill in education. Knowledge of learning styles can help educators identify and solve learning problems among students, thus helping them become more effective learners. According to Fleming, a learning style expert and the author of perhaps the most widely used sensory modality preference assessment, there are four main sensory modalities. These four modalities are identified as visual (V), auditory (A), reading-writing (R), and kinesthetic (K). Students with a V preference learn best using pictures, graphs, diagrams, etc., those with an A preference learn best by listening to and discussing the material, those with an R preference learn best with textual materials, and finally, K students internalize information best when physically involved (e.g., touching and experiencing materials).[30] The results we obtained in our study also show that medical students most frequently prefer kinesthetic learning. In other words, with kinesthetic learning, students experience information hands-on and learn best through physical movements and learning by doing-experiencing. This result can be evaluated as consistent with the nature of medical education, which intensively includes practical work. For example, it is possible to express students working on a cadaver in an anatomy class or experiencing patient scenarios during a clinical simulation as typical

examples of kinesthetic learning. Students learn more effectively when they have the opportunity to directly apply theoretical knowledge, not just by reading or listening to it. At the same time, in kinesthetic learning preference, students achieve higher success in activities such as group work and one-on-one field experience. It is emphasized that students who learn kinesthetically prefer to be involved in physical experiences, touch, feel, and have practical hands-on experiences.[31]

This result emphasizes that medical education should not only utilize traditional methods but also make greater use of interactive and hands-on learning tools that support kinesthetic learning. This way, a learning environment that caters to students' natural learning styles can be provided. The VARK questionnaire can be used to identify and explain student sensory modality preferences, which is a critical step in optimizing learning.[32] Students have different learning styles, and it is the instructor's responsibility to address this diversity of learning styles among students and develop appropriate learning approaches.[33]

Conclusion

The findings from this study suggest that the VARK tool is useful in gathering information about different learning styles and can help educators design mixed teaching strategies to meet students' needs, as well as be important in helping students become aware of their learning style preferences to enhance learning. At the same time, the majority of students preferring the kinesthetic learning style emphasizes the importance of hands-on learning methods. Developing methods that suit students' learning styles can increase success in medical education.

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None

Authors' contributions

Concept/Hypothesis NS, EA, MBK, SK; Design, NS, EA, MBK, SK; Data Collection/Data Processing, NS, EA, SK; Data Analysis, EA; Manuscript Preparation, NS, SK.

The authors read and approved the final manuscript.

Conflict of interest statement

The authors deny any conflicts of interest related to this study.

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CRT Results: Patients Who Do Not Accept Radical Cystectomy But They Are Not Suitable For Bladder-Preserving Treatment

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ABSTRACT

Aim: This study aimed to evaluate overall survival (OS) and disease-free survival (DFS) in patients with muscle-invasive bladder cancer (MIBC) who refused radical cystectomy and were not eligible for bladder-preserving treatment, and to identify prognostic factors affecting these outcomes under chemoradiotherapy (CRT).
Materials and Methods:A total of 71 patients with non-metastatic MIBC who underwent definitive CRT between 2010 and 2024 were retrospectively analyzed. Clinical findings and survival outcomes following CRT were evaluated.
Results: Among the 71 patients with bladder cancer, 90% were male and 10% were female. The median age was 72 years. Local recurrence occurred in 23 patients (32%), and distant metastasis was observed in 52 patients (73%). Male gender, concurrent chemotherapy including a platinum-based regimen, and a radiotherapy dose ≥60 Gy were identified as independent favorable prognostic factors for both OS and DFS. In addition, performance status was found to be an independent prognostic factor affecting OS.
Conclusion: Definitive chemoradiotherapy appears to be a reasonable treatment option for appropriately selected patients with muscle-invasive bladder cancer, particularly in those who decline radical cystectomy or are ineligible for trimodal bladder-preserving therapy.

Keywords: Chemoradiotherapy, bladder cancer, radical cystectomy, bladder-preserving treatment, prognostic factors, overall survival

Radikal Sistektomiyi Kabul Etmeyen Mesane Koruyucu Tedaviye De Uygun Olmayan Hastaların KRT Sonuçları

Araştırma Makalesi

Süreç

Geliş: 27/05/2025
Kabul: 11/06/2025

ÖZ

Amaç: Bu çalışmada kas invaziv mesane kanserinde radikal sistektomiyi kabul etmeyen hastalarda koruyucu tedavi de uygun olmayan hastaların kemoradyoterapi (KRT) ile genel sağkalımı (OS) ve disease free survival (DFS) etkileyen prognostik faktörlerin araştırılması amaçlandı.
Gereç ve Yöntem: Çalışmaya, 2010-2024 yılları arasında metastatik olmayan kas invaziv mesane kanseri olan 71 hasta dahil edildi. Klinik bulgular ve KRT sonrası sağkalım analizi değerlendirildi.
Bulgular: Mesane kanserli 71 hastanın verileri incelendiğinde hastaların %90'ının erkek, %10'unun kadın olduğu saptanmıştır. Hastaların medyan yaşı 72 idi. 23 (%32) hastada lokal nüks ve 52 (%73) hastada uzak metastaz gelişmiştir. Erkek cinsiyet, eşzamanlı kemoterapi rejiminde platin kullanımı, RT dozunun ≥60 Gy olması hem OS'yi hemde DFS'yi etkileyen bağımsız iyi prognostik faktör olarak bulunmuştur. Ayrıca performans durumu da OS'yi etkileyen bağımsız iyi prognostik faktör olarak tespit edilmiştir.
Sonuç: Kas invaziv mesane kanseri özellikle radikal sistektomiyi reddeden ya da mesane koruyucu trimodal tedaviye uygun olmayan hastalarda uygulanan definitif kemoradyoterapi uygun hastalarda makul bir seçenektir.

Anahtar Kelimeler: Kemoradyoterapi, mesane kanseri, radikal sistektomi, mesane koruyucu tedavi, prognostik faktörler, genel sağkalım, hastalıksız sağkalım

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Introduction

Bladder cancer is the fourth most common cancer in men worldwide, accounting for approximately 6% of all new cancer cases and 4% of cancer-related deaths.[1,2] At diagnosis, about 70–75% of cases present as non–muscle-invasive bladder cancer (NMIBC), 20–25% as muscle-invasive bladder cancer (MIBC), and approximately 5% as metastatic disease.[3-6] Around 90% of bladder cancers are histologically classified as urothelial carcinoma.

While most patients with NMIBC can be successfully treated with intravesical therapy following transurethral resection (TUR) of the tumor, radical cystectomy remains the standard treatment approach for MIBC.[3] Radical cystectomy involves the surgical removal of the bladder along with pelvic lymph node dissection and carries a significant risk of morbidity and mortality. Therefore, bladder-preserving treatment strategies are considered as alternatives in appropriately selected patients.[5]

Bladder-preserving trimodal therapy consists of maximal TUR followed by CRT and systemic chemotherapy (CT). This approach has shown promising outcomes in patients with good performance status, unifocal T2–T3 tumors, preserved renal function allowing for cisplatin use, and no evidence of obstructive uropathy or carcinoma in situ.[6-8] Trimodal therapy offers both oncological control and functional preservation, serving as a viable alternative to surgery.[9]

However, some patients either decline radical cystectomy for personal reasons or are medically unfit for surgery. Additionally, not all patients are suitable candidates for trimodal therapy. In this group, therapeutic options are limited, and there is no well-defined clinical management pathway.

The present study aims to evaluate the effects of definitive chemoradiotherapy on OS and DFS in patients with MIBC who are not candidates for radical cystectomy or trimodal bladder-preserving therapy and to identify prognostic factors associated with these outcomes.

Materials and Methods

In this study, data from 71 patients with Bladder Cancer treated at the Oncology Center of Cumhuriyet University Faculty of Medicine between January 2010-December 2024 were retrospectively analyzed. Ethical approval for the study was granted by the Ethics Committee of Sivas Cumhuriyet University Faculty of Medicine (Date:15.5.2025, No: 2025-05/07). This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethical committee (Sivas Cumhuriyet University Ethical Committee). Written informed consent could not be obtained due to the retrospective nature and anonymous data.

Patient Selection

Female patients aged 18 years or older with histologically confirmed Bladder Cancer were included in the study. Patients with non-metastatic Bladder Cancer, Patients who had undergone radical cystectomy or were eligible for bladder-preserving trimodal therapy were excluded from the study.

A total of 71 patients diagnosed with invasive bladder cancer following TUR, who were either medically unfit for radical surgery or refused radical cystectomy, were included in the study. Relevant laboratory and pathology results were retrieved from hospital records, while treatment follow-up data were obtained from clinical files. Patients who were eligible for bladder-preserving trimodal therapy or who underwent radical cystectomy were excluded from the study. Additionally, patients with distant metastases or those who received palliative radiotherapy were not included in the analysis.

Data Collection

Clinicopathological data including age, sex, performance status, tumor stage, histopathological subtype, number of tumor foci, presence of hydronephrosis, lymph node status, treatment protocols, and survival outcomes were collected from the hospital information system and patient records. Performance status was assessed according to the Eastern Cooperative Oncology Group (ECOG) criteria. All patients were staged at the time of diagnosis according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system.[10-11]

OS was defined as the time from diagnosis to death or the last follow-up date. DFS was defined as the time from diagnosis to disease progression, recurrence, or death from any cause.

Treatment Protocol

All patients underwent maximal TUR following evaluation by a multidisciplinary tumor board. Patients were stratified into two groups based on their Eastern Cooperative Oncology Group (ECOG) performance status: good performance (0–1) and poor performance (≥2). Risk classification was based on tumor stage, tumor size, multifocality, presence of carcinoma in situ (CIS), and hydronephrosis, and was defined as follows:

Low risk: Stage T2–T3, tumor <5 cm, unifocal, no CIS, no hydronephrosis

High risk: Stage T4, tumor ≥5 cm, multifocal, presence of CIS and/or hydronephrosis

Radiotherapy and Chemotherapy

Radiotherapy was delivered using conventional fractionation with either a linear accelerator (LINAC, n=28; 78%) or TomoTherapy (n=8; 22%). Treatment planning was performed using either the Eclipse 3D-conformal radiotherapy system (version 8.6, Varian Medical Systems, USA) or the Tomo HD VoLO system for intensity-modulated radiotherapy (IMRT).

According to the treatment protocol, the pelvic region (including obturator, internal, and external iliac lymph nodes and the entire bladder) received a total dose of 40–45 Gy. A boost dose was administered to the bladder to reach a total radiation dose of 60–66 Gy, while respecting organ dose constraints.

Concurrent chemotherapy consisted of weekly cisplatin (35 mg/m²), gemcitabine (400 mg/m²) or a combination regimen (cisplatin 75 mg/m2 1. day + gemcitabine 400 mg/m² 1. and 8. day). None of the patients underwent radical cystectomy following CRT.

Statistical Analysis

All statistical analyses were conducted using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics (frequency, median, minimum, maximum) were used to summarize patient demographic and clinical characteristics.

Survival analyses were performed using the Kaplan-Meier method. Prognostic factors were assessed using univariate and multivariate Cox regression analyses. A p-value of <0.05 was considered statistically significant.

Results

Analysis of data from 71 patients with bladder cancer showed that 90% were male and 10% were female. The median age of the patients was 72 years (range: 53–89). Comorbidities were present in 68% of the patients. Regarding tumor histology, 94% had urothelial carcinoma. In terms of staging, 63% were diagnosed with stage 2 disease, while 37% had stage 3–4 disease based on cystoscopy evaluation. Recurrence was observed in 32% of patients, and distant metastasis was noted in 27%. The demographic and clinical characteristics of the patients are summarized in Table 1.

Overall Survival

Performance status (p = .001), gender (p < .001), radiotherapy (RT) dose (<60 Gy vs. ≥60 Gy; p = .041), and the type of concurrent chemotherapy regimen (cisplatin vs. gemcitabine vs. combination; p = .011) were found to be statistically significant factors affecting OS. In contrast, tumor stage, tumor focality (unifocal vs. multifocal), presence of hydronephrosis, degree of tumor resection during TUR (complete vs. incomplete), post-CRT chemotherapy, and the type of radiotherapy device used (LINAC vs. TomoTherapy) were not statistically significant. The prognostic factors affecting patient survival are presented in Table 2. Male gender, good performance status, use of platinum-based concurrent chemotherapy, and a RT dose of ≥60 Gy were identified as independent favorable prognostic factors for overall survival.

Disease Free Survival

Performance status (p = .049), gender (p = .001), radiotherapy dose (<60 Gy vs. ≥60 Gy; p = .041), and the type of concurrent chemotherapy regimen (cisplatin vs. gemcitabine vs. combination; p = .041) were identified as statistically significant factors influencing DFS. The prognostic factors affecting DFS are presented in Table 3.

Male gender, the use of platinum-based concurrent chemotherapy, and a radiotherapy dose of ≥60 Gy were found to be independent favorable prognostic factors for DFS.

Table 1. Clinical, and Pathological Characteristics of Patients

	Number of patients:n=71	%
Gender		
Male	64	90
Female	7	10
ECOG		
ECOG 0	37	45
ECOG 1	22	31
ECOG ≥2	12	14
Patolojik Subtypes		
Uroepitelyal	67	94
Others	4	6
Grade		
Grade I	4	6
Grade II	2	3
Grade III	62	91
The Number of Tumor		
Unifocal	38	54
Multifocal	33	46
Hydronephrosis		
No	31	44
Yes	40	56
Stage		
Stage II	45	63
Stage III-IV	26	37
Node		
N0	55	78
N+	16	22
Distant Met		
No	52	73
Yes	19	27
Recurrence		
None	23	32
Present	48	68

ECOG PS: Eastern Cooperative Oncology Group performance status.

Table 2. Overall survival outcomes of patients.

	3-year survival (%)	5-year survival (%)	Median survival (months)	*p* value
Gender				
Male	40	30	29	**<0.001**
Female	-	-	7	
ECOG				
ECOG 0	39	28	29	
ECOG 1	41	16	27	**0.001**
ECOG ≥2	14	15	8	
The Number of Tumor				
Unifocal	35	21	27	0.579
Multifocal	37	29	27	
Hydronephrosis				
No	53	39	46	0.118
Yes	20	11	19	
Treatment				
Only RT	21	11	19	0.097
CRT	43	29	32	
RT schedule				
Konvansiyonel	39	27	27	0.517
SIB	34	0	15	
RT doses				
<60 Gy	25	14	19	**0.041**
≥60 Gy	53	45	59	
KRT Scheme				
Platinum	61	41	46	
Gemcitabine	33	22	16	**0.011**
Combine	0	0	7	
Stage				
Stage II	34	25	27	0.657
Stage III-IV	31	11	16	
Multivariate analysis	**HR**		**95% CI**	***p* value**
Gender				
Male	RF			
Female	7,14		1.67-30.53	**0.008**
ECOG				
ECOG 0	RF			
ECOG 1	0.81		0.42-1.56	0.541
ECOG ≥2	3.49		1.56-7.81	**0.002**
RT doses				
<60 Gy	RF			
≥60 Gy	0.22		0.08-059	**0.002**
KRT Scheme				
Platinum	1			
Gemcitabine	3.46	1.41-8.55		**0.007**
Combine	5.79		1.78-18.77	**0.003**

ECOG PS: Eastern Cooperative Oncology Group performance status.

Table 3. Disease Free Survival Outcomes of Patients.

	3-year survival (%)	5-year survival (%)	Median survival (months)	*p* value
Gender				
Male	36	17	23	**0.001**
Female	-	-	7	
ECOG				
ECOG 0	35	21	27	
ECOG 1	35	7	23	**0.049**
ECOG ≥2	15	0	7	
The Number of Tumor				
Unifocal	32	11	20	0.931
Multifocal	32	14	16	
Hydronephrosis				
No	42	19	27	0.245
Yes	24	12	16	
Treatment				
Only RT	16	37	19	0.579
CRT	11	18	16	
RT schedule				
Konvansiyonel	33	15	19	0.638
SIB	28	-	15	
RT doses				
<60 Gy	24	14	15	0.089
≥60 Gy	44	18	32	
KRT Scheme				
Platinum	51	26	42	
Gemcitabine	27	13	14	**0.041**
Combine	0	0	7	
Stage				
Stage II	32	16	27	0.436
Stage III-IV	26	10	14	
Multivariate analysis	**HR**		**95% CI**	***p* value**
Gender				
Male	RF			
Female	3.82		1.04-13.97	**0.043**
RT doses				
<60 Gy	RF			
≥60 Gy	0.22		0.08-059	**0.002**
KRT Scheme				
Platinum	RF			
Gemcitabine	1.90		0.88-4.13	0.101 **0.012**
Combine	3.80		1.34-10.72	

ECOG PS: Eastern Cooperative Oncology Group performance status.

Discussion

In patients with muscle-invasive bladder cancer who either refuse radical cystectomy or are not candidates for bladder-preserving trimodal therapy, treatment remains challenging. This difficulty is further exacerbated by the fact that these patients are often diagnosed at an advanced age. Bladder cancer is more commonly diagnosed in older adults, and it has been reported to be more frequent in women than in men.[12] In our study, 90% of the patients were male, with a median age of 72, which aligns with global epidemiological data on bladder cancer.[12]

In our study, a good performance status (ECOG <2), the use of platinum-based chemotherapy, and a radiotherapy dose of 60 Gy or higher were significantly associated with better outcomes in both OS and DFS. These findings are consistent with previous studies that highlight the role of performance status and aggressive treatment in the success of CRT.[12-13]

The Radiation Therapy Oncology Group (RTOG) has been investigating bladder-preserving treatments since the 1980s.[14-17] The RTOG has conducted a series of CRT studies using various chemotherapy agents. These studies have reported 5-year OS rates ranging from 49.5% to 71.75% .[15-17] A retrospective analysis of 475 bladder cancer patients treated with TUR + CRT (cisplatin, 5-

fluorouracil, paclitaxel, gemcitabine radiation dose of 64 Gy) between 1986 and 2013 showed a 5-year OS 57% and a 5-year DFS 66%. Advanced age was identified as an independent adverse prognostic factor for overall survival.[16-17]

Wujanto et al. evaluated 45 bladder cancer patients taht 21 (47%) applied CRT and 24 (53%) RT. Forty-two patients (93%) completed the planned treatment. In this study, performance status was identified as an important prognostic factor for survival.[18]

The BC2001 study showed that adding concurrent chemotherapy to radiotherapy improves local control and DFS.[19] Similarly, the other retrospective series, 5-year OS rates ranged from 50% to 60%.[15-19]

Although tumor multifocality, hydronephrosis, and tumor stage are recognized as significant prognostic factors in many studies, these parameters did not reach statistical significance in our multivariate analysis. This discrepancy may be attributed to differences in patient selection criteria and variations in the chemoradiotherapy protocols used.[19]

Our findings suggest that CRT, particularly when combined with platinum-based chemotherapy, may serve as an alternative to radical cystectomy in carefully selected patient populations. The treatment was well tolerated by the majority of patients, including elderly individuals, aligning with previously reported data in the literatüre.[19]

In many studies on bladder cancer, RT doses above 60 Gy have been used. Lee et al. reported a median dose of 58.6 Gy (range: 54–62.8 Gy) Hsieh et al. used a median dose of 64.8 Gy, and Korpics et al. used 60–66 Gy.[20-22] Similar to these studies, we administered a median dose of 60 Gy and 64 Gy to the pelvic region and bladder. CRT was well-tolerated by all patients in our study.

Bladder cancer stage is an important factor influencing both the disease course and survival rates. Several studies have been conducted on the stage of the disease and its prognosis, with varying results.[12] In our study, there was no significant difference in survival rates based on stage. DFS and OS were highest in Stage II, as nearly all these patients received CRT.

Hsieh et al. evaluated the outcomes of 19 bladder cancer patients treated with IMRT (N=9) or helical TomoTherapy (N=10). The median age of the patients was 80 years (range: 65–90). Regardless of whether the patients received concurrent chemotherapy, a median RT dose of 64.8 Gy was applied. The median survival for all patients was 21 months (range: 5–26 months). The 2-year OS was 26.3% for IMRT and 37.5% for helical TomoTherapy.[21] In contrast to this study, we did not find any statistically significant difference in survival between 3D-RT and TomoTherapy in our study. The 2-year OS rates were 32% for 3D-RT and 54% for TomoTherapy. Additionally, the 2-year OS rates in our study were slightly higher than those reported by Hsieh et al.

Korpics et al. compared RT and CRT in elderly bladder cancer patients using data from the National Cancer Database. The study involved 1369 bladder cancer patients with clinical T2–4, N0–3, M0 disease, of whom 630 (46%) received CRT. The RT dose ranged from 60–70 Gy. The 2-year OS for patients who received CRT was 56%.[22]

In patients with locally advanced bladder cancer, concurrent cisplatin has been shown to enhance local control by acting as a radiosensitizer. In a study by Coppin et al., the complete response rate was 47% and the 3-year OS rate was also 47% in patients applied concurrent cisplatin with RT. The results were comparable to those of radical cystectomy.[9] In our study, patients treated concurrent cisplatin had better local control, distant recurrence-free survival, and overall survival outcomes compared to those treated with RT alone, concurrent carboplatin, or adjuvant chemoradiotherapy. In our study, age and gender did not show any prognostic impact on the target outcomes.

Most studies reporting definitive RT results in bladder cancer are retrospective. Therefore, it is difficult to obtain reliable data on the effect of performance status on treatment outcomes. However, even in studies based on chart reviews, performance status has been shown to be an important prognostic factor.[22] In our study, the statistical significance of performance status, gender, RT dose, and CRT regimen was demonstrated.

Conclusion

This study shows that definitive CRT is an effective and feasible treatment option for patients with muscle-invasive bladder cancer who are not suitable for or refuse radical cystectomy. In particular, survival outcomes were significantly improved in patients with good performance status, those treated platinum-based chemotherapy, and those applying radiotherapy at doses of ≥60 Gy. However, when making treatment decisions for this patient group, all prognostic factors must be carefully considered. Prospective studies are needed to support our findings and standardize treatment protocols.

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Development Of An Artificial İntelligence-Based Precision Medicine Decision Support System For Radiogenomics Data Sets

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Research Article

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ABSTRACT

Aim: This study aims to apply deep learning algorithms for superpixel segmentation, herbaceous thresholding, and disease reference position estimation from DICOM images and clinical data of Non-Small Cell Lung Cancer (NSCLC) patients. Quantitative imaging data was integrated with clinical information. Various machine learning algorithms were employed to identify biomarkers and evaluate classification performance based on clinical data, imaging data, and their combination, assessing the model improvement rates.

Materials and Methods: The clinical dataset included 43 patients with and 168 without an Epidermal Growth Factor Receptor (EGFR) mutation, and 38 with and 173 without a Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) mutation, totaling 211 NSCLC cases. A total of 2,231 images were analyzed. Using the VGG16 deep learning model, 25,088 features were extracted from each image. XGBoost, CatBoost, Random Forest, and Support Vector Machine (SVM) classification algorithms were used to predict mutation status.

Results: Clinical data revealed significant differences in mutation status among NSCLC patients. The Random Forest algorithm was employed for feature selection, identifying the 50 most important variables for model training. XGBoost and CatBoost achieved the highest classification performance, with results for accuracy, balanced accuracy, precision, sensitivity, F1-score, and ROC-AUC as follows: 0.965 ± 0.015, 0.954 ± 0.021, 0.953 ± 0.024, 0.994 ± 0.007, 0.973 ± 0.011, and 0.990 ± 0.005, respectively.

Conclusion: The study's findings demonstrate that XGBoost and CatBoost models were highly effective in predicting KRAS mutation status from imaging data. CatBoost also performed best in determining EGFR mutation status, outperforming other machine learning methods.

Keywords: Lung cancer, Biomedical, Digital imaging, Machine learning

Radyogenomik Veri Setleri İçin Yapay Zeka Tabanlı Bir Hassas Tıp Karar Destek Sisteminin Geliştirilmesi

Araştırma Makalesi

Süreç

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ÖZ

Amaç: Bu çalışma, küçük hücreli dışı akciğer kanseri (KHDAK) hastalarına ait DICOM görüntüleri ve klinik verilerden süperpiksel segmentasyonu, otsu eşikleme ve hastalık referans pozisyonu tahmini için derin öğrenme algoritmalarını uygulamayı amaçlamaktadır. Nicel görüntüleme verileri, klinik bilgilerle entegre edilmiştir. Klinik veriler, görüntüleme verileri ve bunların kombinasyonuna dayalı olarak biyobelirteçleri tanımlamak ve sınıflandırma performansını değerlendirmek için çeşitli makine öğrenmesi algoritmaları kullanılmış; model iyileşme oranları değerlendirilmiştir.

Gereç ve Yöntem: Klinik veri seti, Epidermal Büyüme Faktörü Reseptör (EGFR) mutasyonu olan 43 ve olmayan 168, Kirsten Rat Sarkom Viral Onkogen Homoloğu (KRAS) mutasyonu olan 38 ve olmayan 173 hasta olmak üzere toplam 211 KHDAK vakasını içermektedir. Toplam 2.231 görüntü analiz edilmiştir. VGG16 derin öğrenme modeli kullanılarak her bir görüntüden 25.088 özellik çıkarılmıştır. Mutasyon durumunu tahmin etmek için XGBoost, CatBoost, Random Forest ve Destek Vektör Makineleri (SVM) sınıflandırma algoritmaları kullanılmıştır.

Bulgular: Klinik veriler, KHDAK hastaları arasında mutasyon durumlarına göre anlamlı farklılıklar olduğunu ortaya koymuştur. Model eğitimi için en önemli 50 değişkeni belirlemek amacıyla Random Forest algoritması ile özellik seçimi yapılmıştır. XGBoost ve CatBoost, en yüksek sınıflandırma performansını elde etmiştir. Elde edilen doğruluk, dengelenmiş doğruluk, kesinlik, duyarlılık, F1 skoru ve ROC-AUC değerleri sırasıyla şu şekildedir: 0.965 ± 0.015, 0.954 ± 0.021, 0.953 ± 0.024, 0.994 ± 0.007, 0.973 ± 0.011 ve 0.990 ± 0.005.

Sonuç: Çalışmanın bulguları, XGBoost ve CatBoost modellerinin görüntüleme verilerinden KRAS mutasyon durumunu tahmin etmede son derece etkili olduğunu göstermektedir. Ayrıca CatBoost, EGFR mutasyon durumunun belirlenmesinde de diğer makine öğrenmesi yöntemlerinden daha iyi performans göstermiştir.

Anahtar Kelimeler: Akciğer kanseri, Biyomedikal, Dijital görüntüleme, Makine öğrenimi

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Introduction

Since the genomics revolution in the early 1990s, cancer research has concentrated on determining the genetic origins of illnesses in order to allow precision medicine therapies. Following the completion of the human genome project, the design of genes and proteins has progressed to functional levels of gene science and gene functions. Many cancer studies, such as the Cancer Genome Atlas (TCGA), have tried to acquire transcriptome, epigenomic, and proteomic data on genome type. [1,2] Consequently, protocols addressing the primary hazards and potential aggravating symptoms associated with genetic analysis technologies have been established.

Genetic analysis may fail to correctly represent genetic variations in tissue biopsy samples due to intra- and inter-group variability of tumor variables.[3] As precision medicine and big data research advance, several professionals in the area underscore the significance of "Radiogenomics". Radiogenomics facilitates the establishment of multi-scale correlations between medical imaging and genetic data, enhancing analogous linkages and integrating the overlooked elements of radiomics and genomics. [4] Radiogenomics is a commonly utilized approach for predicting gamete mutations known as phenotype or genotype. To apply the classification model, the radiogenomic structure is divided into two or more groups, and the classification models are used to generate the appropriate prediction model.

Model prediction for radiogenomics categorization is typically real-valued. The anticipated performance values are determined by considering true positive, true negative, false positive, and false negative values. [5-6] Lung cancer-related deaths are highly widespread over the World.[7] Medical imaging radiography or computed tomography (CT) is used to diagnose lung cancer, and the results are often the existence of a lesion in the lung and the interaction between this tumor and the surrounding tissues. The discovered lesions are often biopsied to determine the cancer diagnosis and histological symptoms of the tumor, such as small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), and so on. [7]

Deep Learning (DL) models are a valuable tool in medical image analysis. Models derived from deep learning network architectures are extremely useful in many fields of health sciences, particularly medical image identification and segmentation. It is commonly used in areas such as early diagnosis and therapy. [8] DL challenges advance at a slower rate than other real-world problems in medical imaging and medical services. By evaluating the variables influencing the rise in the development of DL architectures and in accordance with medical imaging investigations, the application fields of Computed Tomography (CT) technology were explored and the associated topics were highlighted. [9]

The fundamental method for detecting the radiogenomics of lung cancer using DL techniques involves assessing the alterations in genomic biomarkers obtained from CT scans. A convolutional neural network (CNN) model was developed to analyze the epidermal growth factor (cell division, cell growth, cell survival, etc.) for assessing the mutation status using CT devices and identifying the most effective tree-based technique for the ideal procedure.[10] Image analysis has demonstrated remarkable success employing CNNs in the medical industry for learning feature detection in lung nodes and mass segmentation applications. [11]

Although databases designed to compare data on publicly available biomedical images help to develop image analysis algorithms by providing resources for users to evaluate and compare previous models as well as generate new models, the fact that some datasets are distributed in multiple locations or indexed using different terminologies makes reliable model comparison and reproducibility difficult. The Lung Image Database Consortium (LIDC) image collection allows for a comparison of the fundamental accuracy of biological datasets to models.[12-13]

This study aims to develop a medical decision support system that preprocesses clinical and radiogenomic datasets for NSCLC and then builds Machine Learning (ML) based prediction models for lung cancer.

Materials and Methods

Dataset

This dataset comprises detailed medical records and imaging data from 211 NSCLC patients. The collection includes both well-reviewed descriptions of malignant tumors apparent on medical imaging and quantitative data on the related CT scan images. Tumor segmentation pictures from PET/CT scans are also presented.[14] The dataset included 211 samples, with 135 (64%) men and 76 (36%) females. There were 19 (14.10%) male patients having an Epidermal Growth Factor Receptor (EGFR) mutation. Male patients without EGFR mutation were 116 (85.90%), while male patients with Kirsten Rat Sarcoma viral oncogenic homolog (KRAS) mutation were 27 (20%) and male patients without KRAS mutation were 108 (80%). There were 24 (31.60%) female patients having an EGFR mutation. There were 52 female patients (68.40%) who did not have EGFR mutation. Female patients with KRAS mutation were 11 (14.50%), whereas female patients without KRAS mutation were 65 (85.50%).

Radiogenomics

Radiogenomics, which is developed by combining "Radiomics" and "Genomics" in the field of artificial intelligence(AI) health, has gained its position in the literature as the most recent technology science employed in the disciplines of precision medicine and cancer, as well as in other departments of science. Radiogenomics is the categorization of risk that combines precision medicine genetic data with large volumes of radiographic imaging data. Many AI studies involving patients in clinical settings have been used to develop models. In oncology research, life analytic forecasts and studies have demonstrated significant accomplishments using radiogenomic outcomes facilitated by AI.[15]

Substantial advancements have been achieved in lung cancer treatment, encompassing sophisticated screening techniques employed by specialists in conjunction with artificial intelligence, the implementation of minimally invasive diagnostic and therapeutic procedures, radiation modalities such as stereotactic ablative therapy, and the development of novel targeted therapies and immunotherapeutics.[16] The introduction of these novel therapy modalities has been linked

to enhanced survival rates, especially in patients with non-small cell lung cancer. The two-year relative survival rate for NSCLC rose from 34% in 2009-2010 to 42% in 2015-2016. [17]

Image Processing

Image processing techniques are employed to segment lung tissue and lesions. This procedure seeks to retrieve useful information by detecting and assessing the borders of lesions. Researchers underline the efficiency of this strategy by investigating the performance of automated lesion detection. [18] Lesions are classified using ML algorithms based on their shape and density. This approach is proposed to distinguish between malignant and precancerous lesions.[19] The outcomes of automated lesion recognition in CT scans were evaluated using sensitivity, specificity, and other metrics from image processing performance measurements. [20]

Artificial Intelligence (AI)

Machines can use AI algorithms to compare data, arrange patient follow-up in the health sector, learn data, communicate, perceive, interpret images, and move and displace items. It is also a science that aids physicians in their decision-making processes while diagnosing and treating patients, as well as diagnosing diseases. AI may be used to create systems that imitate certain human actions (such as picking up things and depositing them in specified areas) as well as human thought processes (such as data computation and medical diagnosis).

Although substantial improvements have been achieved, there is currently very little study in the subject of AI, and AI researchers are continually developing new technologies. The basic methodologies of AI include fuzzy logic, artificial neural networks, genetic algorithms, and expert systems. Computer systems can create, plan, diagnose, interpret, summarise, generalize, control, and provide suggestions [21].

DL techniques suggest that some illnesses can be identified using radiological data. Chest radiography, for example, is the most prevalent form of radiological examination in the world, with a vast dataset. DL models appear to be able to identify clinically significant anomalies in chest radiography such as pneumonia and pneumothorax [22].

Machine Learning (ML)

A machine learning (ML) algorithm is a subfield of artificial intelligence that investigates strategies for improving data set performance by developing skill in processing large amounts of data. ML explains the data set using Supervised, Unsupervised, Semi-supervised, and Reinforcement learning approaches based on the data set's output variables. It gives the researcher a broad variety of information regarding the correlations between input and output data. ML algorithms are capable of solving a variety of perceptual problems.

The basic objective of ML is to create predictive models capable of making data-driven assessments and choices while producing accurate and consistent forecasts. These models may be used to a broad range of tasks, including image recognition, model accuracy, natural language processing, and fraud detection. Its rising prominence may be attributed to the availability of vast volumes of data and increases in computer processing capacity [23,24].

Approaches to Preprocessing Clinical Data

Data mining and modeling is the process of preparing data and increasing data quality in order to make the data processing more efficient and accurate. This procedure often includes data cleaning, data transformation, data standardization, data reduction, RF and variable selection, and other activities necessary to prepare the data for future analysis. These stages fill in data gaps, fix discrepancies, and prepare the data for analysis [25]. This study employed “scikit-learn” for categorical data and utilized “TensorFlow” and “keras” libraries for picture normalization, since the “VGG16” model offers superior performance in data transformation.

Preprocessing Approaches for Image Data

Image preprocessing refers to a collection of tools and approaches used to analyze and meaningfully transform the raw data of digital photographs. This technique consists of multiple processes to increase picture quality, remove noise, and highlight certain characteristics.Image processing steps that make a picture suitable for analysis include adjusting the brightness, contrast, and color balance; cropping out unwanted areas; resizing the picture to make it a different size; applying filters to make the picture less noisy; identifying objects in the picture using edge detection methods; and finally, applying histogram equalization to make the picture more contrasty [26]. In this work, "OpenCV" was used for image normalization, "SciPy" from the python library for imge segmentation, and "OpenCV" was utilized for contour detection. Additionally, Image Thresholding Methods were employed.Additionally, Image Thresholding Methods were used.

Random Forest (RF)

Random Forest(RF) is one of the disciplines of research where it has been widely applied to image categorization. RF is recognized for its efficacy on datasets with numerous characteristics, has robust noise resilience, and attains elevated classification accuracy. The final classification outcome is determined by the majority vote of the decision trees inside the Random Forest model, which synthesizes the results from several trees trained on the data [27]. It is trained less frequently due to its enhancement of the RF algorithm's dependability and stability. The technique is highly resilient regarding generalization and model correctness, therefore offering a dependable solution for prediction and classification challenges [28]. The decision tree framework for the RF method, which generates a decision tree for each segment after partitioning the dataset into random subsets, is illustrated [29].

Extreme Gradient Boosting (XGBoost)

Chen and Guestrin created this effective ML algorithm for regression and classification procedures. It performs quite well, particularly on structured data. XGBoost is an improved version of the gradient boosting technique. This approach works by successively merging weak learners to fix model flaws, increasing the efficiency of these operations. XGBoost is widely employed across a variety of industries, including healthcare, finance, and clinical imaging. It works well with huge data sets and data with missing cells [30]. The "XGBClassifier" package for the XGBoost method was used in this work, and classification performance for models with 200 iterations was achieved.

Categorical Boosting Algorithm (CatBoost)

The CatBoost algorithm is a machine learning system capable of processing both numerical and categorical input. CatBoost mitigates overfitting, a characteristic aspect of this technique, by including the algorithm's prior values with low-frequency characteristics and regions of high density, so effectively handling points in noise. Gradient-assisted decision trees underpin the creation of the CatBoost methodology. CatBoost mitigates the bias in predicted values generated by the gradient descent method, hence enhancing data comprehension and outcome evaluation [31,32]. This study employed the "CatBoostClassifier" library for the CatBoost method, utilizing 200 iterations to get metrics on classification performance.

Support Vector Machines

The Support Vector Machines (SVM) method seeks to reduce the empirical error probability of traditional pattern recognition approaches by improving performance on the training dataset. SVM, on the other hand, is concerned with minimizing structural risk, which refers to the danger of inaccurately categorizing unseen patterns based on the data's fixed but unknown probability distribution. The concept of uniform convergence in probability led to the development of a new principle of induction, which aims to minimize an upper constraint on the generalization error [33].

Biostatistical Analyses

This study presented quantitative data using mean ± standard deviation and qualitative data using number (%). Prior to deriving conclusions from the data analysis, examinations were performed to detect absent values or severe outliers within the dataset. The data set was amended using suitable procedures, if required. The Shapiro-Wilk test was employed to assess conformity with the normal distribution assumption, hence informing the selection of hypothesis tests for data analysis. The statistical significance threshold was established at $p<0.05$. IBM SPSS Statistics for Windows Version 27.0 package program was used for statistical analysis [34].

Python programming language and "tensorflow, keras, preprocessing.image", "seaborn", "pandas", "OpenCv", "traceback", "os", "pydicom", "sklearn" for ML methods used in classification of biomedical data and image analysis.ensemble", "StratifiedKFold", "tqdm", "sklearn.metrics", "tensorflow, keras", "torch", "skimage.segmentation", "glob" libraries were used.

Result

The dataset for this study includes information on the presence and absence of EGFR and KRAS mutations. With 211 samples total, there are 135 males and 76 females, or 64% and 36% of the total, respectively. There were 19 male patients (14.10% of the total) who showed evidence of EGFR mutations. A total of 108 male patients (80%) lacked the KRAS mutation, 27 male patients (20%) possessed the EGFR mutation, and 116 male patients (85.90%) lacked the KRAS mutation. Among the patients, 24 had EGFR mutations, accounting for 31.60% of the total. Of the individuals analyzed, 52 were female and accounted for 68.40% without an EGFR mutation. We found 65 female patients (85.50%) without KRAS mutation and 11 female patients (14.50%) with KRAS mutation. [35]

The demographic characteristics of the categorical variables are presented in Table 1. When the descriptive statistics table of categorical variables related to EGFR mutation status was analyzed, According to Table 1, the variables of gender $p=0.002$, smoking status $p<0.001$, histology $p=0.002$, histopathologic grade $p=0.014$, and patient survival status $p=0.046$ ($p<0.05$) show a statistically significant difference between the groups in terms of EGFR mutation. In patients with EGFR mutation, 81.4% were connected with Stanford Health System/Hospital, and the proportion of female patients was 55.8%, which was greater than the proportion of male patients (44.20%).

The percentage of patients who had never smoked was 51.2%. Furthermore, all patients with the EGFR mutation exhibited adenocarcinoma histology, and their survival percentage was assessed to be 83.7%. However, there was no statistically significant difference in pathologic staging (T, N, M), lymphovascular invasion, pleural invasion, or adjuvant therapy characteristics ($p>0.05$). When analyzing the table based on KRAS mutation status, only the histology parameter showed a significant difference ($p<0.05$; $p=0.010$). Although 97.4% of patients with the KRAS mutation had adenocarcinoma histology, there was no statistically significant difference in all other demographic and clinicopathologic parameters (gender, ethnicity, smoking status, pathologic staging, histopathologic grade, lymphovascular invasion, pleural invasion, adjuvant treatment, and survival) ($p > 0.05$).

When Table 2 is analyzed according to EGFR and KRAS mutation status, there is no statistically significant difference between the groups in the variables of age at histologic diagnosis (68±10, 68±10, $p=0.924$) and (66±10, 68±10, $p=0.165$), weight (122±18, 123±22, $p=0.783$), The days between CT and surgery (39±27, 53±68, $p=0.205$) ($p>0.05$). The "Pack Years" variable quantifies the cumulative smoking exposure of patients, determined by multiplying the daily cigarette pack consumption by the total number of years smoked.

Table 3 provides a comparative overview of the classification performance across different models for detecting EGFR and KRAS mutations. Among these, CatBoost emerged as the top-performing algorithm in both categories. Specifically, it achieved an accuracy of 96.7%, sensitivity of 99.1%, F1-score of 97.9%, and ROC-AUC of 98.9% for EGFR, while delivering similarly high metrics for KRAS with 96.5% accuracy and 99.4% sensitivity. Although XGBoost followed closely behind, its sensitivity and F1-score remained marginally lower. Random Forest and SVM, on the other hand, yielded comparatively suboptimal outcomes, especially in balanced accuracy and precision. These results point to CatBoost's strong predictive capacity and its potential utility in accurately distinguishing mutation types in genomic classification tasks.

Table 1. Descriptive Statistics of Categorical Variables Related To EGFR And KRAS Mutation Status

Variables	Categories	EGFR Mutation			KRAS Mutation		
		Yes N(%)	No N(%)	p 0.558*	Yes N(%)	No N(%)	p-value
Recurrence	No	30 (69.80)	127 (75.60)		28 (73.70)	129 (74.60)	0.987*
	Yes	13 (30.20)	41 (24.40)		10 (26.30)	44 (25.40%)	
Patient affiliation	Veterans Affairs System	8 (18.60)	85 (50.60)	**<0.001***	19 (50.00)	74 (42.80%)	0.417*
	Stanford Health System/Hospital	35 (81.40)	83 (49.40)		19 (50.00)	99 (57.20)	
Gender	Male	19 (44.20)	116 (69.00)	**0.002***	27 (71.10)	108 (62.40)	0.414*
	Female	24 (55.80)	52 (31.00)		11 (28.90)	65 (37.60)	
Ethnicity	Caucasian	32 (74.40)	140 (83.30)	0.552**	33 (86.80)	139 (80.30)	0.508**
	Native Hawaiian/Pacific Islander	0 (0.00)	3 (1.80)		0 (0.00)	3 (1.70%)	
	Asia	10 (23.30)	14 (8.30)		2 (5.30)	22 (12.70)	
	Afro-Amerikan	0 (0.00)	6 (3.60)		2 (5.30)	4 (2.30)	
	Hispanik/Latino	1 (2.30)	5 (3.00)		1 (2.60)	5 (2.90)	
Smoking status	Smokers	2 (4.70)	31 (18.50)	**<0.001***	8 (21.10)	25 (14.50)	0.119**
	Previous users	19 (44.20)	111 (66.10)		26 (68.40)	104 (60.10)	
	Non-smokers	22 (51.20)	26 (15.50)		4 (10.50)	44 (25.40)	
Histology	Adenokarsinom	43 (100.00)	129 (76.80)	**0.002****	37 (97.40)	135 (78.00)	**0.010****
	Squamous cell carcinoma	0 (0.00)	35 (20.80)		0 (0.00)	35 (20.20)	
Pathological Tumor stage	T1a	2 (4.70)	38 (22.60)	0.080**	8 (21.10)	32 (18.50)	0.750**
	T1b	8 (18.60)	23 (13.70)		5 (13.20)	26 (15.00)	
	T2a	27 (62.80)	69 (41.10)		16 (42.10)	80 (46.20)	
	T2b	1 (2.30)	9 (5.40)		2 (5.30)	8 (4.60)	
	T3	3 (7.00)	18 (10.70)		6 (15.80)	15 (8.70)	
	T4	1 (2.30)	6 (3.60)		0 (0.00)	7 (4.00)	
	Tis	1 (2.30)	5 (3.00)		1 (2.60)	5 (2.90)	
Pathologic Lymph Node stage	N0	38 (88.40)	140 (83.30)	0.699**	32 (84.20)	146 (84.40)	0.969**
	N1	2 (4.70)	13 (7.70)		3 (7.90)	12 (6.90)	
	N2	3 (7.00)	15 (8.90)		3 (7.90)	15 (8.70)	
Pathologic Metastasis stage	M0	42 (97.70)	164 (97.60)	0.989**	36 (94.70)	170 (98.30)	0.221**
	M1b	1 (2.30)	4 (2.40)		2 (5.30)	3 (1.70)	
Histopathological Grades	G1	7 (16.30)	25 (14.90)	**0.014****	5 (13.20)	27 (15.60)	0.650**
	G2	29 (67.40)	96 (57.10)		21 (55.30)	104 (60.10)	
	G3	0 (0.00)	33 (19.60)		9 (23.70)	24 (13.90)	
	Other, Type I	4 (9.30)	5 (3.00)		1 (2.60)	8 (4.60)	
	Other, Type II	3 (7.00)	9 (5.40)		2 (5.30)	10 (5.80)	
Lymphovascular invasion	Yes	3 (7.00)	18 (10.70)	0.579*	4 (10.50)	17 (9.80)	0.968*
	No	40 (93.00)	150 (89.30)		34 (89.50)	156 (90.20)	
Pleural invasion (elastic, visceral or parietal)	No	34 (79.10)	135 (80.40)	0.998*	30 (78.90)	139 (80.30)	0.978*
	Yes	9 (20.90)	33 (19.60)		8 (21.10)	34 (19.70)	
Adjuvant Treatment	No	37 (86.00)	125 (74.40)	0.158*	28 (73.70)	134 (77.50)	0.774*
	Yes	6 (14.00)	43 (25.60)		10 (26.30)	39 (22.50)	
Kemoterapi	No	37 (86.00)	125 (74.40)	0.158*	28 (73.70)	134 (77.50)	0.774*
	Yes	6 (14.00)	43 (25.60)		10 (26.30)	39 (22.50)	
Radiation	No	41 (95.30)	154 (91.70)	0.535*	35 (92.10)	160 (92.50)	0.980*
	Yes	2 (4.70)	14 (8.30)		3 (7.90)	13 (7.50)	
Survival Status	Dead	7 (16.30)	56 (33.30)	**0.046***	10 (26.30)	53 (30.60)	0.741*
	Live	36 (83.70)	112 (66.70)		28 (73.70)	120 (69.40)	

GFR: Epidermal Growth Factor Receptor; KRAS: Kirsten Rat Sarcoma viral oncogene homolog; G1: Well Differentiated; G2: Moderately Differentiated; G3: Poorly Differentiated; Type I: Good to moderately differentiated; Type II: Moderately to poorly differentiated; * : Pearson Chi-square; **: Fisher's Exact Test

Table 2. Descriptive Statistics For Quantitative Data

Variables			Age at Histologic Diagnosis	Weight (lbs)	Pack Years	The days between CT and surgery
EGFR Mutation Status	Yes	Mean ± SD	68±10	122±18	32±16	39±27
	No	Mean ± SD	68±10	123±22	41±24	53±68
		p*	0.924	0.783	0.004	0.209
KRAS Mutation Status	Yes	Mean ± SD	66±10	128±26	43±28	48±39
	No	Mean ± SD	68±10	121±20	38±21	51±67
		p*	0.165	0.096	0.257	0.789

EGFR: Epidermal Growth Factor Receptor; KRAS: Kirsten Rat Sarcoma viral oncogene homolog; * : Independent Two Sample t-test; SD: Standard Deviation.

Table 3. Metrics on classification performance

Group	Model	Accuracy	Balanced Accuracy	Precision	Sensitivity	F1-Score	ROC-AUC
EGFR	CatBoost	0.967 ± 0.010 (0.966 - 0.967)	0.931 ± 0.022 (0.931 - 0.932)	0.968 ± 0.010 (0.968 - 0.969)	0.991 ± 0.003 (0.990 - 0.991)	0.979 ± 0.006 (0.979 - 0.980)	0.989 ± 0.002 (0.988 - 0.989)
	Random Forest	0.888 ± 0.017 (0.887 - 0.888)	0.786 ± 0.038 (0.785 - 0.788)	0.907 ± 0.017 (0.907 - 0.908)	0.957 ± 0.006 (0.956 - 0.957)	0.931 ± 0.010 (0.931 - 0.932)	0.933 ± 0.021 (0.932 - 0.934)
	SVM	0.730 ± 0.015 (0.730 - 0.731)	0.714 ± 0.015 (0.713 - 0.714)	0.903 ± 0.011 (0.902 - 0.903)	0.742 ± 0.028 (0.741 - 0.743)	0.814 ± 0.014 (0.813 - 0.815)	0.786 ± 0.017 (0.786 - 0.787)
	XGBoost	0.963 ± 0.010 (0.963 - 0.964)	0.931 ± 0.012 (0.930 - 0.931)	0.969 ± 0.004 (0.968 - 0.969)	0.985 ± 0.009 (0.985 - 0.986)	0.977 ± 0.006 (0.976 - 0.977)	0.985 ± 0.007 (0.984 - 0.985)
KRAS	CatBoost	0.965 ± 0.015 (0.964 - 0.966)	0.954 ± 0.021 (0.953 - 0.955)	0.953 ± 0.024 (0.952 - 0.954)	0.994 ± 0.007 (0.994 - 0.995)	0.973 ± 0.011 (0.973 - 0.974)	0.990 ± 0.005 (0.990 - 0.991)
	Random Forest	0.879 ± 0.008 (0.878 - 0.879)	0.839 ± 0.010 (0.839 - 0.840)	0.848 ± 0.012 (0.848 - 0.849)	0.986 ± 0.020 (0.985 - 0.987)	0.912 ± 0.007 (0.911 - 0.912)	0.942 ± 0.008 (0.942 - 0.942)
	SVM	0.813 ± 0.024 (0.812 - 0.814)	0.795 ± 0.018 (0.794 - 0.796)	0.846 ± 0.010 (0.845 - 0.846)	0.863 ± 0.043 (0.861 - 0.864	0.854 ± 0.022 (0.853 - 0.855)	0.847 ± 0.013 (0.847 - 0.848)
	XGBoost	0.951 ± 0.006 (0.950 - 0.951)	0.936 ± 0.007 (0.935 - 0.936)	0.935 ± 0.009 (0.934 - 0.935)	0.991 ± 0.011 (0.991 - 0.992)	0.962 ± 0.005 (0.962 - 0.962)	0.982 ± 0.011 (0.981 - 0.982)

Figure 1 depicts the superpixel segmentation approach applied to lung slices from an NSCLC patient. By isolating the tumor from its surroundings, this technique serves as a critical preprocessing step for visual analysis and ML-based diagnostic systems.

The Otsu thresholding approach, seen in Figure 2, facilitated the delineation of lung structures from the background and effectively highlighted lung areas throughout the segmentation phase.

Figure 3 illustrates (a) Grid: a geometric network framework employed for superpixel segmentation; (b) the original grayscale DICOM image; (c) the binary segmentation mask delineating the tumor region in white; and (d) the analysis of the final reference points, with boundaries defined in red, alongside the evaluation and classification data.

Figure 4 shows that the tumor locations detected from the pictures were colored green. Tumor centers were delineated in blue, and contours were used to identify tumor borders. Contours were delineated using red lines. In the NSCLC image processing phase, (a) Grid: denotes a geometric network framework utilized for superpixel segmentation; (b) the original grayscale DICOM image; (c) the binary segmentation mask illustrating the tumor region in white; and (d) signifies the final analytical outcome, encompassing a color image alongside the evaluation and classification data.

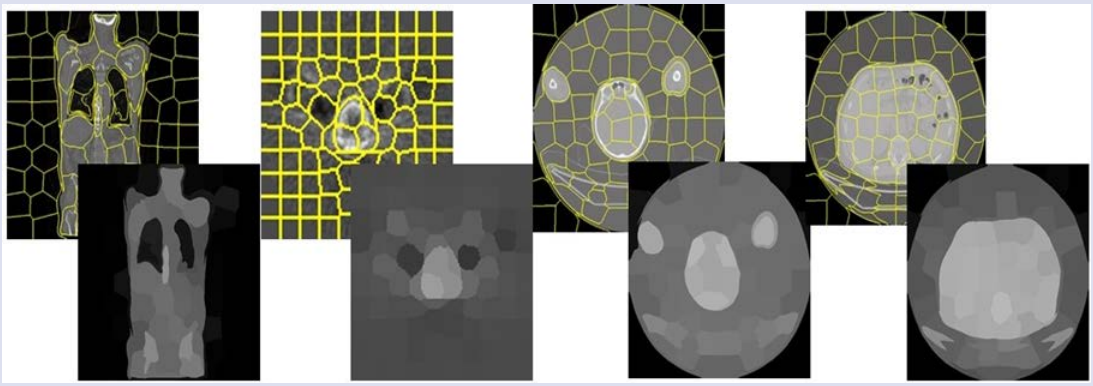

Figure 1. Superpixel Segmentation İn CT İmages And İts Results

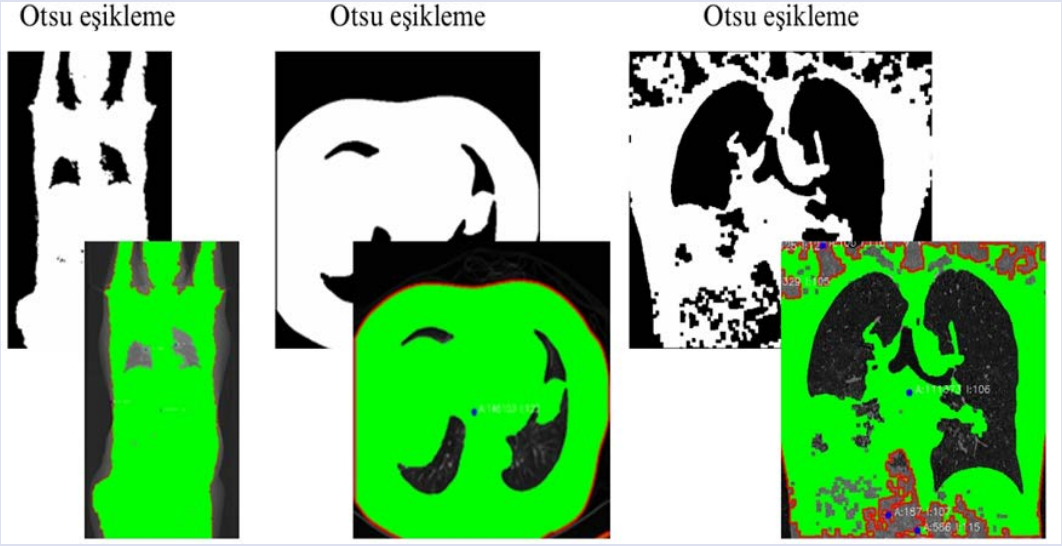

Figure 2. Masking The İmage After Herbaceous Thresholding And Determination Of Reference Points

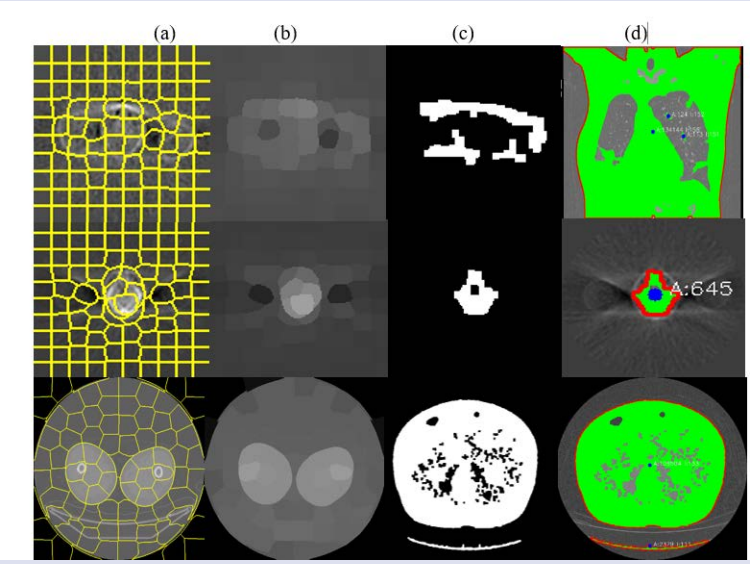

Figure 3. Segmentation, Masking And Contour Analysis Of DICOM İmages Of NSCLC Patients

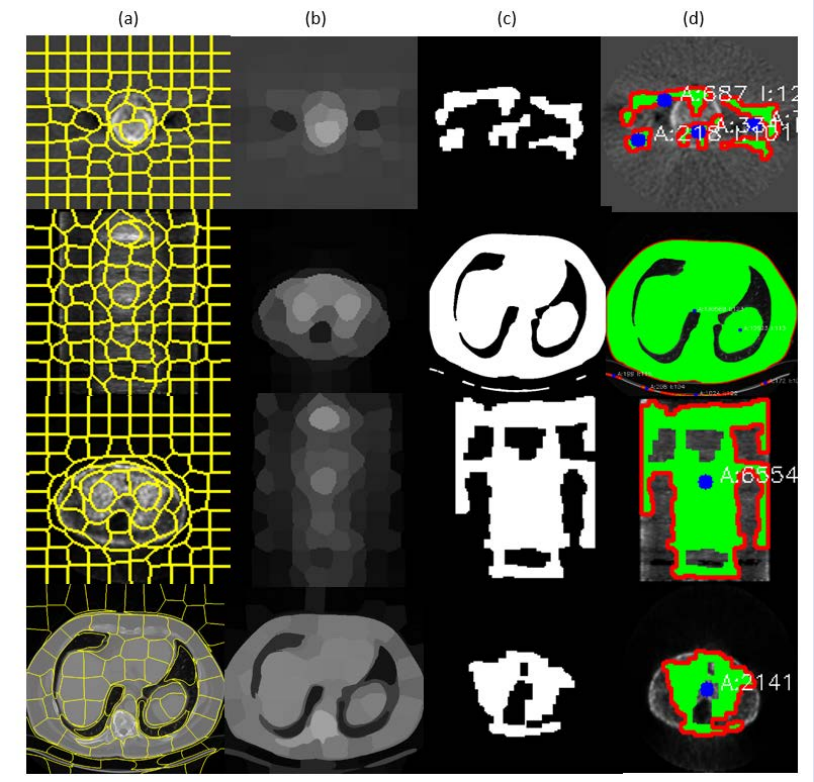

Figure 4. Segmentation, Masking And Contour Analysis İn Lung İmages.

Discussion

The structural characteristics of NSCLC have lately provided professionals with an edge in patient therapy and decision-making. Mutations in EGFR and KRAS enable healthcare providers to enhance therapeutic targets and implement tailored therapy. The invasiveness of repeated biologics and tumor heterogeneity provide significant clinical problems in genomic profiling. Radiomics utilizes several features to extract picture characteristics from high-throughput radiographic images, facilitating biomarker prediction and non-invasive estimation of lesion phenotypes. Extensive research has been conducted on the use of radiomic characteristics in lung cancer prevention, including the selection of tumor phenotypes and the prediction of biomarkers. Non-invasive imaging modalities, like ultrasound and MRI, are used to diagnose conditions such as cancer [36].

Imaging methods are used by healthcare practitioners to identify disease types and forecast illness progression, facilitating early diagnosis and treatment. Non-invasive imaging technologies (CT, MRI, PET) are used to ascertain tumor size, quantity, and density within an image. Imaging techniques not only identify the existence of pulmonary illness but also provide critical information on biological or clinical biomarkers, including prognostic indicators such as disease progression, treatment efficacy, and life expectancy [37].

This aim of the study was to assess the prevalence of EGFR and KRAS mutations in NSCLC patients in relation to clinical data and to analyze the effectiveness of different machine learning methodologies for early detection of these mutations in DICOM images. It may facilitate the implementation of customized medicine and targeted therapeutic choices. The research on The Cancer Imaging Archive (TCIA) comprises a comprehensive clinical dataset of 211 individuals with non-small cell lung cancer (NSCLC) and biomedical imaging datasets [38,39]. A study utilizing the same dataset, augmented by 161 cohort patients from a total of 211 NSCLC patients, revealed that the XGBoost model achieved EGFR and KRAS scores of 0.83 and 0.86, respectively, through 10-fold cross-validation for predicting EGFR and KRAS mutations. The AUC-ROC values for these mutations were recorded at 0.89 and 0.812, respectively. Our study demonstrated significant performance in predicting EGFR and KRAS mutations in NSCLC patients by integrating clinical data with radiomic variables derived from 2,231 medical images, in comparison to the AUC values of the ML-based study and the reference study. Our methodology using CatBoost (AUC = 0.99 ± 0.00) and XGBoost (AUC = 0.99 ± 0.01) for the EGFR mutation scenario, as well as CatBoost (AUC = 0.99 ± 0.00) and XGBoost (AUC = 0.98 ± 0.01) for the KRAS mutations scenario, demonstrates a significant increase in predictive accuracy. In contrast to the 10-fold cross-validation method used in the reference research, we utilized 5-fold cross-validation for a precise evaluation of model performances. The models demonstrated consistency and reliability with a minimum standard deviation. The exceptional performance attained is founded on a cohesive data approach that amalgamates clinical characteristics with extensive radiomic variables,

alongside the utilization of sophisticated gradient boosting methods. Upon evaluating the model's performance for EGFR mutation status, four machine learning models were compared, with the CatBoost model demonstrating superior efficacy in predicting the mutation status. The CatBoost model exhibited superior performance with an accuracy of 0.967 ± 0.010, balanced accuracy of 0.931 ± 0.022, precision of 0.968 ± 0.010, sensitivity of 0.991 ± 0.003, F1-Score of 0.979 ± 0.006, and ROC-AUC of 0.989 ± 0.002, compared to the accuracy of 0.888 ± 0.017, balanced accuracy of 0.786 ± 0.038, precision of 0.907 ± 0.017, sensitivity of 0.957 ± 0.006, F1-Score of 0.931 ± 0.010, and ROC-AUC of 0.933 ± 0.021 of another model, as well as the SVM model's accuracy of 0.730 ± 0.015, balanced accuracy of 0.714 ± 0.015, precision of 0.903 ± 0.011, sensitivity of 0.742 ± 0.028, F1-Score of 0.814 ± 0.014, and ROC-AUC of 0.786 ± 0.017. The CatBoost model was succeeded by the XGBoost model, which exhibited comparable performance metrics, demonstrating commendable classification efficacy with an accuracy of 0.963 ± 0.010, precision of 0.969 ± 0.004, and ROC-AUC of 0.985 ± 0.007. The CatBoost and XGBoost models had excellent precision scores of 0.991 and 0.985, respectively. In this instance, false negatives are reduced, and all performance indicators exhibit low standard deviation values, indicating that the models are dependable and consistent. Upon analyzing the model's performance for KRAS mutation status it is evident that the CatBoost model exhibits superior performance across the machine learning measures. The CatBoost model exhibited the following metrics: accuracy (0.965 ± 0.015), balanced accuracy (0.954 ± 0.021), precision (0.953 ± 0.024), sensitivity (0.994 ± 0.007), F1-score (0.973 ± 0.011), and ROC-AUC (0.990 ± 0.005). The accuracy of the Random Forest model was 0.879 ± 0.008 (0.878 - 0.879), balanced accuracy was 0.839 ± 0.010 (0.839 - 0.840), precision was 0.848 ± 0.012 (0.848 - 0.849), precision was 0.986 ± 0.020 (0.985 - 0.987), F1-score was 0.912 ± 0.007 (0.911 - 0.912), and ROC-AUC was 0.942 ± 0.008 (0.942 - 0.942). The performance metrics of the SVM model are as follows: accuracy is 0.813 ± 0.024 (0.812 - 0.814), balanced accuracy is 0.795 ± 0.018 (0.794 - 0.796), precision is 0.846 ± 0.010 (0.845 - 0.846), sensitivity is 0.863 ± 0.043 (0.861 - 0.864), F1-score is 0.854 ± 0.022 (0.853 - 0.855), and ROC-AUC is 0.847 ± 0.013 (0.847 - 0.848). The XGBoost model exhibits an accuracy of 0.951 ± 0.006 (0.950 - 0.951), a precision of 0.935 ± 0.009 (0.934 - 0.935), and a ROC-AUC of 0.982 ± 0.011 (0.981 - 0.982), which closely approximates the performance of the CatBoost method. Integrating biomedical data with data from images has not only improved the prediction accuracy of ML models, but also demonstrated strong generalization capabilities across different data splits.

Conclusion

The performance metrics of the models were evaluated using diverse machine learning methods on biomedical pictures of NSCLC patients and associated clinical data. Model performance indicators are evaluated against the outcomes derived from the integration of biological data and image-related factors. The CatBoost algorithm demonstrated superior classification performance in predicting both EGFR and KRAS mutation statuses.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: E.G., A.P.; Control/Supervision: A.K.A., E.G., A.P.; Analysis and/or Interpretation: E.G., A.K.A., A.P.; Literature Review: A.P., A.K.A., EG; Writing the Article: A.P., E.G; Critical Review: A.P., E.G.; References and Fundings: A.P.; Materials: A.P., E.G Data Avability Statement

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False Positive Hepatitis A IgM in Membranous Nephropathy: A Treatment Dilemma

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ABSTRACT

Membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults, and is frequently associated with autoantibodies against M-type phospholipase A2 receptor (PLA2R). Immunosuppressive regimen, such as rituximab and calcineurin inhibitors, are recommended for high-risk patients. This case report discusses a 74-year-old female with anti-PLA2R-positive MN, whose treatment was delayed due to a false-positive hepatitis A virus (HAV)-IgM result. Despite asymptomatic presentation and normal liver function, concerns about potential viral reactivation complicated clinical decisions. After a month of monitoring, immunosuppressive treatment was initiated, and the patient's proteinuria achieved remission. This case underscores the importance of thorough evaluation of serological results, especially in cases where viral markers could influence critical treatment decisions. The risk of delaying MN treatment must be balanced against the potential dangers of initiating therapy under uncertain viral infection status.

Keywords: Membranous nephropathy (MN), Anti-PLA2R, Hepatitis A virus (HAV), Immunosuppressive therapy

Membranöz Nefropatide Yanlış Pozitif Hepatit A IgM: Tedavi Sürecinde Bir Kararsızlık

Olgu Sunumu

Süreç

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ÖZ

Membranöz nefropati (MN), erişkinlerde nefrotik sendromun yaygın bir nedenidir ve çoğunlukla M-tipi fosfolipaz A2 reseptörüne (PLA2R) karşı gelişen antikorlarla ilişkilidir. Yüksek riskli MN vakalarında immünosupresif tedavi önerilmekte olup, tedavi öncesi viral enfeksiyonların değerlendirilmesi önemlidir. Hepatit A virüsü (HAV) enfeksiyonu, genellikle akut ve kendini sınırlayan hepatit ile ilişkilidir ve anti-HAV IgM pozitifliği aktif enfeksiyon göstergesi olarak kabul edilir. Ancak nadiren yanlış pozitif sonuçlar tedavi sürecini karmaşıklaştırabilir. Bu çalışmada, anti-PLA2R pozitif MN tanısı konulan ve yanlış pozitif anti-HAV IgM sonucu nedeniyle tedavi süreci geciken 74 yaşındaki bir kadın hasta sunulmaktadır. Hasta, nefrotik düzeyde proteinüri ile başvurdu ve böbrek biyopsisi ile MN tanısı doğrulandı. Yüksek anti-PLA2R titresi nedeniyle immünosupresif tedavi planlandı ancak hepatit taramasında anti-HAV IgM pozitifliği saptandı. Hastanın karaciğer enzimleri normal ve hepatit semptomları olmamasına rağmen, tedavi ertelendi. Farklı merkezlerde yapılan testler pozitifliği doğruladı ancak bir aylık izlemde hepatit gelişmemesi üzerine yanlış pozitiflik düşünüldü. Rituksimab ve ardından kalsinörin inhibitörü tedavisi başlatıldı. Tedavi süresince hepatit bulgusu gözlenmedi ve hasta remisyona girdi. On sekiz aylık takipte remisyon devam etti ancak anti-HAV IgM pozitifliği sürdü. Bu olgu, MN tedavisinde viral serolojilerin dikkatli değerlendirilmesi gerektiğini ve yanlış pozitif sonuçların tedavi kararlarını etkileyebileceğini göstermektedir.

Anahtar Kelimeler: Membranöz nefropati (MN), Anti-fosfolipaz A2 reseptörü (Anti-PLA2R), Hepatit A virüsü (HAV), İmmünsüpresif tedavi

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Introduction

Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults, characterized by thickening of the glomerular capillary walls due to immune complex deposition. The majority of primary MN cases are associated with antibodies against the M- type phospholipase A2 receptor (PLA2R), which serve as a key diagnostic and prognostic marker.[1-3] Immunosuppressive therapy, including rituximab and calcineurin inhibitors, is often employed in high-risk MN cases to prevent disease progression.[4-5]

Hepatitis A virus (HAV) is a widespread infectious agent known for causing acute, self- limiting hepatitis, with HAV-IgM typically indicating active infection. However, in rare instances, HAV-IgM can yield false positive results, complicating clinical decisions, particularly when immunosuppression is considered.[6-9] The use of immunosuppressive agents in patients with viral infections carries significant risks, including viral reactivation and liver failure, as documented with hepatitis B virus.[9] Risk of fulminant hepatitis is unknown during course of HAV.

This case report presents a unique challenge in the management of a 74-year-old female with anti-PLA2R positive MN who exhibited a false positive HAV-IgM result complicating treatment process.

Case Presentation

A 74-year-old female presented with complaints of leg swelling, leading to the detection of nephrotic-level proteinuria. The albumin was at 2.8 g/dL, the creatinine was 0.83 mg/dL, and the estimated glomerular filtration rate was 63 mL/min/1.73 m². Her 24-hour urine protein excretion was 8.6 g/day. Due to the delay in receiving the anti-PLA2R test results at our center, a renal biopsy was performed to diagnose the cause of her nephrotic-level proteinuria. The biopsy confirmed membranous nephropathy, and the anti-PLA2R test returned a high-titer positive result of 427 RU/mL, which further supported the diagnosis and advocated for a worse prognosis.

Before initiating immunosuppressive therapy for primary membranous nephropathy, routine hepatitis screening revealed a positive HAV ıgG and anti-HAV IgM result. The patient, however, remained asymptomatic with normal liver enzyme levels, including AST at 26 U/L, ALT at 21 U/L, ALP at 96 U/L, GGT at 243 U/L, total bilirubin at 0.35 mg/dL, and direct bilirubin at <0.10 mg/dL. Given the known risks associated with immunosuppression in patients with hepatitis, such as the potential for fulminant hepatitis B reactivation and death [9], the patient was referred to the gastoenterology department for further evaluation.

After assessing the risk, the gastroenterology team recommended delaying immunosuppressive therapy until the anti-HAV IgM result became negative. Subsequent hepatitis tests, conducted at external centers using General Biological's Corporation (company, ELISA) and ClearTest kits (company, ELISA), confirmed the initial positive results.

Immunological tests for autoimmune diseases were reviewed, and no significant pathology was detected. Additionally, serological tests for other viral antigens that could potentially cause heterologous reactions—including Epstein-Barr virus IgM (EBV IgM), cytomegalovirus IgM (CMV IgM), hepatitis C virus IgM (HCV IgM), and parvovirus B19 IgM—were performed, all of which yielded negative results. Monoclonal gammopathy was excluded. Due to the persistent positive anti-HAV IgM results, treatment initiation was delayed. However, after more than one month of follow-up without any signs or symptoms of hepatitis, a false positive result was suspected. In this case, following consultation with the gastroenterology department, liver biopsy was not considered necessary due to the absence of clinical or laboratory signs of hepatitis and the suspicion of a false-positive serological result. Therefore, a non-invasive monitoring approach was preferred. Consequently, the patient was treated with intravenous rituximab at an initial dose of 1 gram and and a further 1gram dose 14 days later. With this treatment, the patient was evaluated as non-responsive due to less than a 50% reduction in proteinuria at the 6-month follow-up, and a calcineurin inhibitor was subsequently added to the treatment regimen. Throughout the treatment, the patient was closely monitored, and no signs of hepatitis were observed. Eventually, her proteinuria achieved remission. After 18 months of follow-up she remains in remission, however she is still Anti-HAV IgM positive.

Discussion

Membranous nephropathy (MN) is a leading cause of idiopathic nephrotic syndrome, particularly in the non-diabetic white population. Approximately 80% of cases are primary, with one-third undergoing spontaneous remission, one-third progressing to end-stage renal disease (ESRD), and the remaining one-third manifesting as chronic kidney disease.[1]

Immunosuppressive therapy is a key component of treatment for high-risk MN patients, and anti-PLA2R titers are used to assess disease activity and predict response to therapy.[3]

Our case had KDIGO high risk MN. Furthermore, the high-titer anti-PLA2R positivity decreased the likelihood of spontaneous remission.[3] However, the unexpected positive HAV-IgM result complicated the treatment approach. HAV is generally associated with acute, self-limiting hepatitis, with HAV-IgM typically persisting for 3 to 6 months.[6-8] While rare, false positive HAV-IgM results have been reported, potentially due to factors such as cross- reactive antibodies, polyclonal B cell activation, or subclinical viral reactivation.[10]

In our patient, the persistently positive HAV-IgM result led to a delay in initiating immunosuppression, despite the absence of clinical symptoms or abnormal liver function

tests. This case underscores the importance of carefully evaluating serological results in the context of the patient's overall clinical picture. The potential risks associated with delaying treatment in MN, such as progression to ESRD, must be weighed against the risks of initiating immunosuppression in the presence of a potential active viral infection.[9]

The literature documents cases of false positive HAV-IgM results in other conditions, such as autoimmune events and diuretic therapy.[11-12] Landry, reported a 78-year-old patient with positive HAV-IgM following diuretic therapy for heart failure, but the patient continued to be monitored without any clinical symptoms.[13] Our patient had received diuretic treatment for hypervolemia at an external facility, and we postulate this treatment might have caused false antibody positivity.

Ultimately, in the absence of clinical and laboratory signs of hepatitis, we carried on with immunosuppressive therapy, leading to remission of proteinuria without any hepatic complications. This case emphasizes the need for a cautious and individualized approach in managing complex cases where viral serologies may confound treatment decisions.

This case study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

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Multidisciplinary Treatment of Oligodontia: Orthodontic, Periodontal, and Restorative Approach: A Case Report

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ABSTRACT

This case report describes a multidisciplinary approach to treating a 12-year-old female with oligodontia, presenting with congenital absence of maxillary lateral incisors, maxillary second premolars, and mandibular premolars. The patient exhibited generalized diastemas, bilateral Angle Class III molar relationships, and a skeletal Class II pattern. Treatment consisted of 36-month orthodontic therapy to position maxillary canines in lateral incisor positions, soft tissue procedures including frenectomy and gingivectomy to improve gingival symmetry, and esthetic rehabilitation with direct composite laminate veneers. Maxillary second primary molars were retained as space maintainers despite radiographic root resorption. Post-treatment results showed successful space closure and improved esthetics with clear removable retainers provided for retention. This case report presents how a multidisciplinary approach integrating orthodontic space management, soft tissue recontouring, and minimally invasive restorations can facilitate functional and esthetic treatment planning in oligodontia cases.

Keywords: Oligodontia, Multidisciplinary treatment, Direct composite veneers

Oligodontinin Multidisipliner Tedavisi: Ortodontik, Periodontal ve Restoratif Yaklaşım: Olgu Sunumu

Olgu Sunumu

Süreç

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Kabul: 14/05/2025

ÖZET

Bu olgu sunumu, bilateral maksiller lateral kesici dişler, maksiller ikinci premolarlar ve mandibular premolarların konjenital olarak eksik olduğu 12 yaşında kadın bir oligodonti hastasının tedavisinde uygulanan multidisipliner yaklaşımı tanımlamaktadır. Hastada yaygın diastemalar, bilateral Angle Sınıf III molar ilişkisi ve iskeletsel Sınıf II patern saptanmıştır. Tedavi kapsamında, maksiller kaninlerin lateral diş pozisyonuna yerleştirilmesini içeren 36 aylık ortodontik tedavi, gingival simetriyi sağlamak amacıyla yapılan frenektomi ve gingivektomi işlemleri, ve direkt kompozit lamina restorasyonları ile estetik rehabilitasyon gerçekleştirilmiştir. Maksiller ikinci süt azı dişlerinde radyografik olarak kök rezorpsiyonu gözlenmesine rağmen, mobilite bulunmadığı için bu dişler yer tutucu olarak ağızda tutulmuştur. Tedavi sonunda boşluklar başarıyla kapatılmış, estetik açıdan tatmin edici sonuçlar elde edilmiş ve retansiyon amacıyla şeffaf hareketli plaklar verilmiştir. Bu olgu, ortodontik boşluk yönetimi, yumuşak doku şekillendirme ve minimal invaziv restorasyonları içeren multidisipliner yaklaşımın, oligodonti olgularında fonksiyonel ve estetik açıdan etkin bir tedavi planlamasını mümkün kıldığını göstermektedir.

Anahtar Kelimeler: Oligodonti, Multidisipliner tedavi, Direkt kompozit veneer

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Introduction

Dental anomalies are generally classified into four main categories: anomalies of number, shape, size, and tissue structure.[1] Among numerical anomalies, hypodontia, oligodontia, and anodontia are the most frequently observed types. Hypodontia refers to the congenital absence of one or more teeth, oligodontia is defined as the absence of six or more teeth, and anodontia indicates the complete absence of all teeth.[2,3] The most commonly missing teeth are the maxillary and mandibular third molars, maxillary lateral incisors, and mandibular second premolars.[4] Oligodontia is seen in approximately 0.3% of the general population in the permanent dentition, 5 with a similar prevalence reported in the Turkish population.[3]

Congenital multiple tooth agenesis can reduce masticatory efficiency and, particularly when it affects the anterior region, may lead to speech impairments and reduced self-confidence. Addressing these challenges often requires a multidisciplinary treatment approach. During orthodontic treatment, existing spaces can be closed, or spaces can be opened to accommodate future restorative or prosthetic procedures. In addition to orthodontic alignment, reshaping the soft tissue contours prior to the final restorative stage significantly contributes to achieving optimal esthetic results. [5]

Case Presentation

A 12-year-old female patient with no systemic disease presented to our clinic with the chief complaint of spacing between her teeth. Clinical examination revealed that these spaces were due to congenital tooth agenesis. Oral examination showed generalized diastemas and a prominent labial frenum attachment. Intraoral assessment revealed bilateral Angle Class III molar relationships and a 1 mm midline shift to the right. No mobility was observed in the maxillary second primary molars. Extraoral examination revealed a convex facial profile (Figure 1).

Panoramic radiographic evaluation revealed congenital absence of the maxillary second premolars and lateral incisors, as well as the mandibular second premolars and the left mandibular first premolar. Except for the left third molar, no other third molar germs were detected. Cephalometric analysis showed bimaxillary retrognathia, a skeletal Class II relationship, and a normodivergent facial pattern (Figure 2). Model analysis revealed an overjet of 4 mm and an overbite of 3 mm. Space analysis indicated 5 mm of excess space in the maxilla and 17 mm in the mandible.

The patient and her legal guardian were fully informed about the procedures and provided written informed consent for the publication of this case report and related clinical images.

Figure 1. *A, B, C; pre-treatment extraoral photographs. D, E, F, G, H; pre-treatment intraoral photographs.*

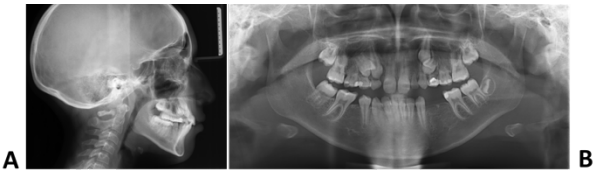

Figure 2. *A, pre-treatment cephalometric radiograph. B, pre-treatment panoramic radiograph*

Table 1. *Mutations and enzyme defects in Disorders of Sexual Development.*

Measurements	Pre-treatment (T0)	Post-treatment (T1)
SNA	81.34°	81,90°
SNB	75.80°	76,58°
ANB	5.54°	5,32°
1-NA	3.07 mm / 21°	2.04 mm / 17°
1-NB	7,58 mm / 28°	3,88 mm / 20°
Overjet	3,93 mm	4,26 mm
Overbite	3,06 mm	3,11 mm

WNT4, In the treatment plan, since the maxillary second primary molars showed no signs of mobility, they were retained as space maintainers. In the mandible, the plan was to close the existing spaces to achieve an ideal molar relationship. Considering the absence of maxillary lateral incisors, the permanent canines were planned to be moved into the lateral incisor positions. To support soft tissue esthetics, frenectomy and gingivectomy procedures were planned after orthodontic treatment.

During orthodontic treatment, 0.018-inch slot Roth brackets were used. Leveling and alignment were performed using 0.014 and 0.016-inch nickel-titanium archwires, followed by 0.016 × 0.016 and 0.016 × 0.022-inch stainless steel archwires (Figure 3). The impacted maxillary left canine was surgically exposed and brought into alignment using a closed-flap technique.

Figure 3. *A, B, C: intra-treatment intraoral photographs.*

The total duration of orthodontic treatment was 36 months. At the end of treatment, the maxillary spaces were completely closed. In the mandibular arch, a single implant site was preserved due to the bilateral premolar agenesis on the left side (Figure 4). Post-treatment panoramic radiography revealed root resorption in the maxillary second primary molars; however, since no clinical mobility was observed, these teeth were retained as functional space maintainers. No resorption was detected in the other permanent teeth. Since no orthopedic treatment was applied, the skeletal Class II relationship persisted at the end of treatment (Figure 5). Final model analysis showed an overjet of 3.5 mm and an overbite of 4 mm. The cephalometric and clinical changes observed before and after treatment are summarized in Table 1.

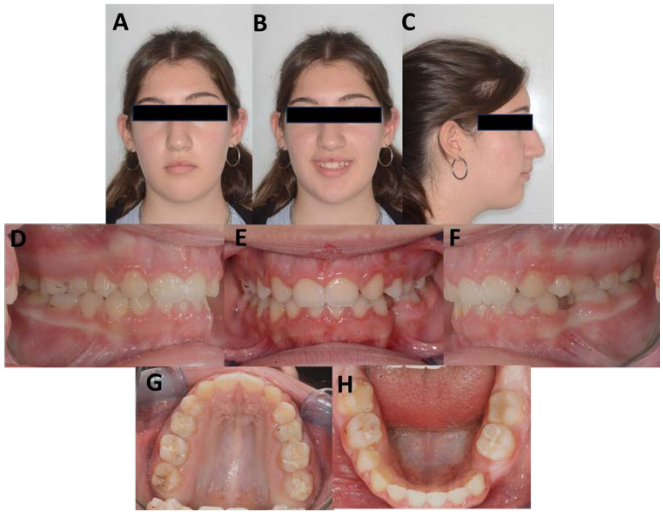

Figure 4. *A, B, C: post-treatment extraoral photographs. D, E, F, G, H: post-treatment intraoral photographs.*

Figure 5. *A, post-treatment cephalometric radiograph; B, post-treatment panoramic radiograph.*

After orthodontic treatment, a frenectomy was performed due to a thick labial frenum attachment at the maxillary midline. This was followed by localized gingivectomy procedures to improve gingival symmetry in the esthetic zone. All periodontal procedures were performed under local anesthesia (0.5 ml). The frenectomy site was sutured with non-resorbable silk sutures, which were removed after one week. After complete healing of the soft tissues, restorative procedures were initiated.

Direct composite laminate veneers were completed in a single session. For the restorations, Tokuyama Estelite Asteria A2B (body) for dentin shade and NE (enamel) for enamel shade were used. In areas requiring increased opacity, Tokuyama Omnichroma Blocker was applied for substructure masking. The palatal shell was created using the NE shade due to its translucent nature. GC G-Premio Bond Universal adhesive system was used for bonding, and polishing was performed with EVE composite polishing spirals (Figure 6). At the end of treatment, clear removable retainers were delivered for both arches to ensure long-term retention. Follow-up examinations revealed that the patient was satisfied with the outcome, and both functional and esthetic results were successfully achieved.

Figure 6. *A, intraoral photograph following frenectomy and gingivectomy procedures. B, intraoral photograph following completion of restorative treatment.*

Discussion

Congenital tooth agenesis is one of the most frequently encountered developmental anomalies in dentistry. While genetic factors are considered the primary cause, environmental influences may also play a role in its etiology. In patients with oligodontia, esthetic, functional, and phonetic concerns often coexist, necessitating a multidisciplinary treatment approach.[6]

In this case, due to the absence of the maxillary lateral incisors in the anterior region, the permanent canines

were orthodontically positioned in the lateral incisor space. This was considered in the restorative planning, and esthetic harmony was achieved with direct composite laminates. Rosa and Zachrisson emphasized that in young patients with missing lateral incisors, orthodontic space closure with canine substitution can provide satisfactory esthetic and functional outcomes.[7] However, for optimal results, such approaches must be supported with proper soft tissue recontouring.

Kokich stated that symmetrical and healthy gingival tissues are essential for achieving an ideal smile esthetic, especially in the anterior region. In this case, frenectomy and localized gingivectomy procedures performed after orthodontic treatment improved the gingival profile and contributed significantly to the esthetic outcome of the composite laminates.[8]

Direct composite laminates are a conservative and widely preferred option, especially in young patients. Their minimally invasive nature, single-session applicability, and reversibility make them advantageous for both clinicians and patients. Tekçe et al. reported high success rates and patient satisfaction after a 4-year follow-up of anterior direct composite restorations.[9] The esthetic success of such restorations is closely linked to the material's opacity, translucency, and color stability. In the present case, Tokuyama Estelite Asteria composite, with its high light transmittance and nano-hybrid structure, provided an optical effect closely resembling natural dental tissues. Additionally, Tokuyama Omnichroma Blocker was used to mask underlying structures in opaque areas, enhancing the restoration's depth and uniformity. The long-term success of composite restorations is influenced by factors such as occlusal forces, oral hygiene, operator technique, and the quality of finishing and polishing. Well-performed polishing not only preserves esthetic appearance but also reduces plaque accumulation.[10] In this case, the EVE spiral polishing system was used, contributing to a smooth surface and long-term color stability.

Post-treatment panoramic radiographs showed root resorption in the maxillary second primary molars. However, since no clinical mobility was observed, these teeth were retained as temporary space maintainers. Aktan et al. reported that under certain conditions, retained primary molars can serve as interim solutions until implant placement.[11] Similarly, Robertsson and Mohlin emphasized that in growing patients, implant placement should be postponed and orthodontic space closure may provide long-term advantages.[12]

Removable clear retainers were used for post-treatment retention due to their esthetic acceptability in young patients. However, it is well established that fixed retainers may contribute to greater long-term stability, especially in cases involving anterior restorations.[13] Therefore, future follow-ups may consider the option of fixed retention.

In this case, no functional orthopedic treatment was applied due to the axial positions of the incisors. Consequently, the skeletal Class II relationship persisted following treatment. This limitation should be acknowledged in the interpretation of the treatment outcome.

Conclusion

Congenital tooth agenesis, particularly when multiple teeth are involved, presents both functional and esthetic challenges that require comprehensive and well-coordinated treatment planning. This case highlights the importance of a multidisciplinary approach integrating orthodontic treatment, soft tissue management, and direct composite restorations to achieve satisfactory outcomes. The successful resolution of esthetic concerns, maintenance of occlusal balance, and the patient's satisfaction underscore the effectiveness of conservative and individualized strategies in the management of oligodontia cases.

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None

Authors' Contributions

NT, NG, AMC and OO carried out the study design, data collection, and statistical analysis and drafted the manuscript. NG and AMC treated the patients and acquired the data. NT and OO conceived the study and participated in its design, coordination, and manuscript writing. The authors read and approved the final manuscript.

Conflict of Interest Statement

The authors deny any conflicts of interest related to this study.

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