

ANAL CANCER: AN OVERVIEW

Gökçe Nur DEVRİM¹, Azra YILDIRIM¹, Selina TÜRKMEN¹, Yeşim ATEŞ*², Sude YAMAÇ³, Murat IHLAMUR^{4,5}

¹Biruni University, Vocational School, Department of Medical Services and Techniques, Istanbul, Turkey

²Biruni University, Vocational School, Property Protection and Security Department, Istanbul, Turkey

³Biruni University, Faculty of Engineering and Natural Sciences, Department of Molecular Biology and Genetics, Istanbul, Turkey

⁴Biruni University, Vocational School, Department of Electronics and Automation, Istanbul, Turkey

⁵Yildiz Technical University, Faculty of Chemical and Metallurgical Engineering, Department of Bioengineering, Istanbul, Turkey

ABSTRACT

The anal region, which marks the end of the digestive system, possesses a complex anatomical arrangement. Surgeons dealing with this region must have thorough knowledge of its anatomy and the various forms of anal cancer that occur. Although anal cancers are rare, they are particularly prevalent among young males. The increasing incidence of anal cancer is attributed to the rise in HPV infections and the high survival rates among individuals with HIV infection. This study discusses the causes of anal cancer, how it is detected, the different types of anal cancer, the stages it is classified into, macroscopic diagnoses of these stages, as well as the features associated with tumors and the treatment processes for cancer.

Keywords: *Anal Cancer, HPV, HIV, Diagnosis, Treatment,*

INTRODUCTION

Cancer is a disease characterized by the uncontrolled growth of abnormal cells, which can originate in almost any organ or tissue of the body and spread to other organs. The next stage is called metastasis, which is the most important cause of death from cancer. In benign tumors, on the other hand, the cells do not spread to other tissues and don't pose a threat. There are 200 different types of cancer, and the incidence of these cancers

varies from person to person. The most common types of cancer in men are lung, prostate, colorectal, stomach and liver cancer, while in women, the most common types are breast, colorectal, lung, cervical and thyroid cancer. Some cancers are quite rare, such as anal cancers. Approximately 22,000 men and 29,000 women are diagnosed with anal cancer each year (Siegel et al., 2023).

Cells in the anal canal lose their ability to control growth due to genetic mutations, leading to accumulation of abnormal cells and the eventual formation of tumors. Anal cancer originates from cells located at the outer edge and within 2-3 cm inside the anal region. Approximately 20% of anal cancers settle near the anus and are classified as skin tumors. They are commonly found in the upper part of the anus and in the mucous-producing glands called the anal verge. Although anal cancers represent only 4% of lower gastrointestinal system cancers, there has been an increase in cancer rates over the past 30 years. The most common type of anal cancer is anal squamous cell carcinoma. According to the World Health Organization (WHO) 2010 data, tumors of the anal canal, anal margin and perianal region are simplified and classified under the title "Anal Canal Tumors" based on both localization and histological types (Gondal et al., 2023).

ANATOMY AND CAUSES OF ANAL CANCER

The anal canal is the terminal part of the gastrointestinal system. Anatomical and surgical definitions of the anal canal may vary. The anal verge (anal margin) is located more distally and is the point where the walls of the anal canal touch each other at rest. The anatomical anal canal is the portion between the dentate line and the anal verge, measuring approximately 2 cm in length. The surgical anal canal averages about 4 cm in length, extending to the length of the internal anal sphincter. In females, it is associated with the posterior wall of the vagina, while in males, it is associated with the urethra. The anal canal is the region where feces exit the body, situated at the end of the rectum, which is the closest part of the large intestine to the external opening called the anus. It has a short tubular structure.

Anal cancer can develop due to genetic factors, as well as certain lifestyle and environmental factors. It is associated with the human papilloma virus (HPV). HPV is a serious issue that increases the risk of anal cancer and cervical cancer. Anal cancer is more common in individuals over the age of 50. Factors such as using immunosuppressive drugs for the treatment of other diseases, engaging in persistent anal intercourse, having multiple sexual partners, smoking, alcohol consumption, and a

history of cancer can increase the risk of developing anal cancer. Symptoms of anal cancer include inflammation and growth of open sores in the anal region, as well as the development of warts. Under conditions where the immune system is compromised, such as HIV infection, chemotherapy, organ transplantation, or receiving pelvic radiation therapy for cancers of the rectum, prostate, bladder, or cervix, the risk of developing anal cancer is also increased (Young et al., 2020).

Human Papilloma Virus (HPV)

HPV is a small, non-enveloped, double-stranded DNA virus. It is known to infect squamous epithelial cells of the anogenital canal, with at least 30 of its 100 different genotypes capable of being transmitted sexually. HPV is highly prevalent in sexually active young populations, and it can be transmitted through skin-to-skin contact, as well as through vaginal, anal and oral sexual activities. Contact with genital areas or sharing objects that have come into contact with genital areas, such as through anal, vaginal or oral sex, can also lead to transmission. HPV infection is detected in approximately 71% of anal cancer, particularly in 78% of squamous cell carcinomas. The majority of HPV-positive patients (85%) are positive for HPV type 16. HPV is responsible for cancers of the oropharynx, anus, penis, vagina and vulva. Globally, approximately 660 million people are infected with HPV each year, equating to around 75,000 individuals per hour (Gami et al., 2014).

Human Immunodeficiency Virus (HIV)

Human immunodeficiency virus is a virus that causes immune system deficiency, leading to disease. When the immune system, which protects the body from microorganisms, fails to function properly, microorganisms can more easily cause disease. HIV can be transmitted from one person to another within very short period of time that the virus will not deteriorate outside the environment. HIV infection is found in 1% of women with anal cancer and 28% of men. Cancer is a factor in one-third of deaths in individuals with HIV infection. HIV can be transmitted through various ways including unprotected sexual intercourse, direct blood contact, organ transplants and from mother to baby. The risk of developing anal cancer in highly active HIV-positive men who have sex with men is found to be 60 times higher than in men without such relationships. It is recommended that individuals aged 35 and above living with HIV and transgender individuals who have sex undergo annual PAP screening. The anal canal and cervix share embryological, histological and pathological characteristics. Both develop from the embryonic cloacal membrane. Both can exhibit abnormal changes

associated with normal metaplastic changes and HPV infection (Dandapani et al., 2010; Khandwala et al., 2021).

TYPES OF ANAL CANCERS

Melanoma

Anal melanomas are a rare disease, constituting 0.1% of anal and perianal lesions. They are a type of skin cancer that begins in the cells that produce melanin pigment in the anal lining or skin. Melanomas can be removed surgically if diagnosed before deep infiltration into the skin or spread to lymph nodes. However, anal melanomas are difficult to detect. Therefore, cancer often manifests itself in the next stage. Symptoms such as anorectal pain, bleeding, changes in bowel habits, and sometimes masses are often vague and can be confused with conditions such as hemorrhoids, leading to delayed diagnosis. Patients often presents with delayed referrals or misdiagnoses. This results in the disease being advanced and frequently causing local lymph node metastasis. Five-year survival depends on the stage of diagnosis. However, the rates for local spread 32%, for regional spread are 17%, and for cases where metastasis occurs, the rates are very low.

Basal cell carcinoma

This type of cancer constitutes a portion of anal cancers and can also manifest in the skin surrounding the anus. While typically 1-2 cm in size, sometimes cases of 10 cm or larger occur. Recurrence rates are low. Lesions are typically seen as hard, ulcerated areas with irregular borders. Basal cell carcinomas rarely metastasize, and mortality rates are quite low. Basal cell carcinoma is a rare disease that develops in areas of the skin not exposed to sunlight. The primary cause of basal cell carcinoma is exposure to ultraviolet and radiation. Perianal basal cell carcinoma arising in the anorectal region accounts for less than 0,2% of all basal cell carcinoma cases. Perianal basal cell carcinoma originates from perianal lesions and tends to be a regional disease. Various treatment methods are used for perianal basal cell carcinoma, including wide local excision, Mohs micrographic surgery, or radiotherapy. Perianal basal cell carcinoma typically progresses slowly and is a regional disease.

Adenocarcinoma

Adenocarcinomas arise from cells that make up the upper portion of the anus or from mucous-producing glands located beneath the anal lining. Adenocarcinomas also originate from apocrine glands, a type of sweat gland in the perianal skin. Anal canal

adenocarcinoma is a rare type of cancer, accounting for only 5-10% of all anal cancers. It is the second most common malignancy of the anal canal after squamous cell carcinoma but tends to be more aggressive. This cancer type originates histologically from glandular cells located proximal to the dentate line. It may arise from anal glands, congenital anorectal duplications, along fistulous tracts, or as vaginal cysts. Treatment involves abdominoperineal resection, chemotherapy and radiation therapy.

Cloacogenic carcinoma

It is a subtype of squamous cell carcinoma that affects the cloacal region located in the anus. It accounts for approximately 25% of anal cancers. Symptoms can range from being asymptomatic to rectal bleeding, constipation, diarrhea, anal swelling or anal itching. During endoscopy, these polyps mimic hemorrhoids, rectal ulcers, villous adenomas, or anorectal carcinoma. Surgical treatment options include endoscopic polypectomy or mucosal resection, while a high-fiber diet is also among the treatments.

Squamous cell carcinoma

Also known as squamous cell carcinoma, it is one of the most common types of anal cancer. It originates in the flat cells covering the lower region of the anus. It constitutes approximately 90% of anal cancers. It starts from squamous cells lining the anal canal and verge. It deeply penetrates the anal canal wall and spreads proximally and distally to involve the submucosa of the distal rectum and proximal anus. It resembles squamous cell carcinomas found in other parts of the body. Symptoms include anal itching, discomfort while sitting, pain, changes in bowel habits, and bleeding. Following chemotherapy and radiotherapy, recurrence rates range from 25% to 40% (Gondal et al., 2023; Grulich et al., 2012; Uronis & Bendell, 2007).

STAGES OF ANAL CANCER

The life expectancy and symptoms of anal cancer vary depending on its stage. Therefore, following the diagnosis of cancer, the first step is to determine the stage of cancer. After determining the cancer stage, cancer treatment begins. When early diagnosis is obtained and treatment is started, the success rate of recovery increases. For this reason, staging is performed for the evaluation of many cancer types. The observed 5-year survival rates for anal canal carcinoma according to stages are as follows: 69,5% for stage 1, 61,8% for stage 2, 45,6% for stage 3A, 39,6% for stage 3B, and 15,3% for stage 4.

Stage-0

This is the initial stage of cancer development. The cancerous cells that are beginning to form are only in the first layer of the anal lining. This stage is also referred to as “carcinoma in situ”. The success rate in treatment is high.

Stage-1

This stage of cancer is also referred to as early stage or initial stage. The cancerous cells are confined to the organ where they originated. Localized growth is observed, an metastasis does not occur. The diameter of anal cancer is maximum 2 cm.

Stage-2

The tumor is larger than 2 cm. They have spread to the organ where they are located, but they have not spread to neighboring organs.

2-A: It is larger than 2 cm but smaller than 5 cm, and it has not spread to nearby lymph nodes.

2-B: It is more than 5 cm, and it has spread to nearby lymph nodes.

Stage-3

It has spread to neighboring organs in addition to the organ where it originated and nearby lymph nodes.

3-A: The tumor is maximum 5 cm. It has spread to the lymph nodes around the rectum but has not spread to distant areas.

3-B: It is larger than 5 cm. It has spread to neighboring organs such as vagina, bladder, urethra and prostate, but has not spread to nearby lymph nodes.

3-C: It can be of any size. It has spread to organs such as the vagina, urethra, prostate gland, bladder and nearby lymph nodes of the bladder.

Stage-4

It is an advanced stage of cancer. It is the final stage of cancer. In this stage, cancer has spread to the organ where it originated and nearby organs, and has started distant metastasis (Maas et al., 2020; Young et al., 2020).

ANAL CANCER SYMPTOMS

Anal cancer symptoms may manifest in some patients as hemorrhoid-like symptoms. Therefore, patients may delay seeking early diagnosis because they do not recognize the symptoms. Symptoms of anal cancer may include fatigue, nausea, vomiting, pain in the anal area, swelling of the glands, bleeding from the anus or rectum, constant itching around the anus, changes in bowel habits, frequent or infrequent bowel movements, constipation, diarrhea, excessive gas, changes in bowel movement and blood in the stool

(Sauter et al., 2016; Young et al., 2020).

ANAL CANCER DIAGNOSIS

In order for the diagnosis of anal cancers to be made, the symptoms need to be first recognized. In such a case, a specialist physician should be consulted, and initially a physical examination should be performed. During the physical examination, palpation of the rectum is performed to determine if there is any swelling, mass or abnormality in the area. In addition to physical examination, various diagnostic studies should also be conducted for the detection of anal tumors.

Complete Blood Count (Hemogram)

Determining whether the red blood cell count is low helps to indicate if the tumor is causing blood loss. A high level of White blood cells indicates an infection that carries the risk of the tumor growing from the wall of the rectum.

PET Scan

This method enables the detection of malignant tumor cells in the body. After injecting a small amount of radioactive glucose into the bloodstream through an intravenous line, a PET scanner shows where glucose is being used in the body. Malignant tumor cells are identified through this method.

Anoscopy

For the examination of the anal canal and rectum, an anoscope (a 10 cm long, rigid and illuminated tube-shaped imaging device) is used. If an abnormality is detected, the doctor or specialist may request an anal canal ultrasound. Anoscopy plays a significant role in diagnosis when suspicious tissue is encountered during a digital rectal examination (DRE) by examining the anal canal or rectum lumen with an anoscope. Endoscopic examination is a device used to take biopsies of suspicious and abnormal lesions.

Ultrasonography

In ultrasound, a probe is inserted into the canal, and images of the area are taken with sound waves.

Rectal touch

It is one of the most important physical examination methods for detecting diseases, especially lesions in the anal canal. DRE is the most common examination method in individuals suspected of having anal cancer.

Biopsy

It is the removal of a specific tissue sample from a living organism for examination under a microscope. Biopsy is required when a diagnosis is not made during examinations or evaluations. This enables a definitive diagnosis to be made. Depending on the size, extent, and type of the disrupted abnormal tissue, there are several methods available, including excisional, incisional or fine needle aspiration biopsy (Aigner & Siegel, 2023; Ciombor et al., 2017; Rüschoff et al., 2011).

PATHOLOGICAL FINDINGS

Squamous cell tumors

Anal region tumors most commonly involve squamous epithelial cells, which have a strong association with HPV infection. In the anal canal, the transition zone between dentate line rectal glandular mucosa and squamous mucosa is known as the colorectal mucosa where squamous metaplasia occurs, termed as the anal transformation zone. Cellular immunity also plays a significant role in HPV-associated carcinogenesis. Squamous carcinoma development in the anal canal progresses from low-grade dysplasia to invasive carcinoma. Although the frequency of dysplasia converting to invasive carcinoma is not well known, it is estimated to be around 5% over approximately a 20-year follow-up period. Recognizing lesions accurately, reporting them correctly, and understanding their management during the pathology of anal canal and tumors are crucial in preventing invasive malignancies. However, if left untreated, the progression rate from high-grade anal intraepithelial neoplasia to squamous cell carcinoma is reported to be 11%. This rate exceeds 50% in individuals with widespread disease and immunosuppression. Conversely, in treated individuals, regardless of disease volume, the malignant progression rate decreases to around 0,4% (Pessia et al., 2020; Pineda & Welton, 2009).

Condylomata acuminatum (Anal Wart)

Condylomata acuminatum is associated with low-risk HPV types. Macroscopically, large exophytic masses should be flat and slightly elevated. While dysplasia in condylomata acuminatum is generally low-grade, high-grade dysplasia is very rare. Condylomata acuminatum is indicated as anogenital warts caused by HPV. It arises from HPV infection. Condylomata acuminatum is a clinical diagnosis, and histopathological examination of lesions is usually not required. Microscopic evaluation of tissue will show acanthosis with hyperkeratosis. Differentiated cells called koilocytes are also identified. Koilocytes are large keratinocytes with abundant cytoplasm and

small shrunken nuclei. These characteristic cells are found in the upper layers of the epidermis, often increasing in frequency. In addition, condylomata acuminatum is distinguished from verruca vulgaris based on the type of hyperplasia present. Condyloma acuminatum appears as elevated, flesh-colored lesions ranging in size from 1 to 5 mm. They can be broad and flat or sometimes have a cauliflower-like appearance. Condylomata acuminatum is generally asymptomatic, but symptoms such as bleeding, itching and pain can occur. If a large tumor mass covers the entire anogenital region, Buschke-Lowenstein, also known as giant condylomata acuminatum, should be considered. These tumors are a malignant complication of condyloma acuminatum. Giant condyloma acuminatum exhibits aggressive, destructive local behavior with a tendency for infection and fistulation. High-grade dysplasia is more common in HIV-positive patients. Cryotherapy, trichloroacetic acid solution, and various surgical methods are available treatments for condyloma acuminatum. There is a chance of recurrence after topical treatments. Surgical excision is the only treatment method with near 100% clearance rates (Shenoy et al., 2019).

Anal Squamous Intraepithelial Neoplasia (Dysplasia)

The morphological findings observed in H&E sections are the main ones used in the diagnosis of intraepithelial neoplasia. In squamous intraepithelial neoplasms, the main features include epithelial stratification and loss of nuclear polarity, nuclear pleomorphism and hyperchromasia, along with an increase in mitotic activity accompanied by mitoses reaching the epithelial surface. Low-grade anal intraepithelial neoplasia typically presents with superficial koilocytosis. Maturation is regular. The cytoplasm/nucleus ratio is less than 1:1, In the absence of inflammation, mitotic figures are limited to the basal layer. Abnormal mitoses are not seen. High-grade anal intraepithelial neoplasia exhibits abnormal full-thickness maturation within the squamous epithelium. Maturation is disrupted. The nucleus/cytoplasm ratio is greater than 1:1. Mitotic figures reach higher levels of the epithelial tissue. Abnormal mitoses are observed. In reactive atypia of squamous epithelium, a patchy staining with p16 is seen weakly, whereas in intraepithelial neoplasms, a band-like and strong staining is observed. In high-grade intraepithelial neoplasia, a diffuse staining of dysplastic cells with p16 is observed (Roberts et al., 2017; Siddharthan et al., 2019).

Perianal Squamous Intraepithelial Neoplasia – PSIN (Bowen’s Disease)

It is the in-situ squamous cell carcinoma of the skin. Microscopically reflects the general characteristics of in-situ squamous cell carcinoma. Bowen’s disease is a rare,

slow-growing, intraepithelial squamous cell carcinoma seen in the anal region. It is a precursor to anal squamous carcinoma. Bowen's disease is common in light-exposed areas of the skin. However, it also affects other areas. Lesions are usually solitary. However, multiple lesions can occur in a few individuals. The morphology of Bowen's disease varies depending on the age of the lesion, the region of origin, and the degree of keratinization. Histopathology is the most important and standard diagnostic method to confirm the diagnosis. Immunohistochemistry, dermoscopy, and reflectance confocal microscopy are supportive methods used in the diagnosis of Bowen's disease. Treatment depends on various factors such as the location, size, immune status, age of patient, and aesthetic outcome. Among the available methods are topical chemotherapy, surgical methods, light-based methods, and destructive therapies. Bowen's disease is generally seen in individuals over 60 years of age. It is very rare in individuals under 30 years of age. Individuals with suppressed immune systems are at risk of developing Bowen's disease at a younger age. Lesions are usually seen in a hyperkeratotic or fissured state. In addition to these images, there are full thickness epidermal atypia with irregular architecture, abnormal mitoses, small Brown globules with irregular distribution, and an intact basal membrane. Even if a small part of the basal layer is disrupted, this leads to the invasive growth of squamous carcinoma. Surgery is used in its treatment. In cases where it is not possible, topical chemotherapy, immune modulation, phototherapy and radiation therapy are used (Cleary et al., 1999; Hoedema, 2018; Palaniappan & Karthikeyan, 2022).

Invasive Squamous Cell Carcinoma

It consists of relatively uniform, narrow cytoplasmic cells that exhibit peripheral palisading similar to basal cell carcinoma of the skin, with keratinization being mostly absent. Verrucous carcinoma (giant malignant condyloma or Buschke-Löwenstein tumor) morphologically resembles classical condyloma, exhibiting both exophytic and endophytic growth patterns. It demonstrates a locally destructive behavior without metastasis (Morton et al., 2018).

Paget's Disease

The anogenital region, one of the areas with dense apocrine glands, is where extramammary Paget's disease occurs. Histopathologically, it is similar to intraepithelial Paget cells. Paget cells are large cytoplasmic cells with large nuclei and they can be seen at the base of the squamous epithelium or obliterating the entire epithelial height. In some cases, Paget cells may have a typical "halo" appearance.

Perianal Paget's disease is a rare malignancy, seldom isolated and often associated with underlying intraepithelial adenocarcinoma. It most commonly occurs between the ages of 50-70. It typically presents with anal itching and discomfort, often confused with other anal conditions. The definitive diagnosis is made by biopsy taken from the anoderm and histological examination. Perianal Paget's disease is the second most common site of extramammary Paget's disease. Perianal Paget's disease is often reported as involvement of perianal skin. However, involvement of anal mucosa is quite rare. Perianal Paget's disease is divided into two types: Primary and Secondary. The treatment approach and prognosis of Paget's disease are different. Therefore, making this distinction is crucial. Primary Paget's disease is not associated with underlying invasive malignancy, while secondary Paget's disease is associated with intraepithelial spread of invasive malignancy. Surgical excision is the preferred treatment for Perianal Paget's disease, followed by reconstructive surgery after excision. In cases with extensive metastasis, sphincter involvement and large lesions, abdominoperineal resection is the best option. Other treatment methods such as radiotherapy, laser therapy and systemic chemotherapy are also being explored within the field (Al Hallak & Zouain, 2009; Chumbalkar et al., 2016).

Malignant Melanoma

Anal margin malignant melanoma is quite rare and accounts for 2-4% of all malignant anorectal neoplasms. It originates from melanocytes, which are located in the basal layer of the skin and give color to the skin. The anal region is the third most common site after the skin and eyes, representing 0,6-1,6% of all melanomas. Symptoms are not different; bleeding, pain and mass are commonly reported. When a lesion is pigmented, melanoma is often suspected, but it is often confused with thrombosed hemorrhoids. Amelanotic lesions constitute 30% of lesions and are very difficult to recognize. Diagnosis is based on demonstrating melanin pigment with immunohistochemistry. Macroscopically, it forms polypoid, ulcerous or infiltrative lesions. Microscopic and immunohistochemical features are similar to malignant melanomas in other regions (Malaguarnera et al., 2018; Row & Weiser, 2009).

Tumor-Like Lesions of The Anal Canal

Macroscopically, lesions presenting as sessile or pedunculated polyps, single or multiple ulcers or broad-based polypoid growths spread over a wide area can be encountered in the anorectal mucosa. Microscopically, the differential diagnosis includes colorectal adenoma, adenocarcinoma (especially mucinous adenocarcinoma) and dysplasia. In

cases where histopathological diagnosis is challenging, involving consultation systems, establishing clinicopathological correlation, gaining full control over the lesion with repeat biopsies when necessary, sometimes rescuing the patient from very severe harm such as abdominoperineal resection, proves crucial. The most commonly encountered tumor-like lesion in the anal region in pathology practice is anal tag. Also referred to as skin tag, anal papilla or anal hypertrophic papilla, this excision material is often sent as polypectomy or sometimes as hemorrhoidectomy. It manifests as a fibroepithelial non-neoplastic benign development covered with squamous mucosa (Leonard et al., 2011; Surabhi et al., 2016).

ANAL CANCER TREATMENT PROCESSES

Treatment processes typically involve three main methods. Treatment methods that are administered along with radiation therapy are often necessary for most anal cancers. Sometimes, very small and early-detected tumors can be surgically removed without the need for any other treatment. The treatment processes are as follows:

Chemotherapy

Chemotherapy is a treatment method using chemotherapeutic drugs. Chemotherapy drugs are administered directly into the bloodstream or orally in pill form. These drugs work to kill rapidly dividing cells. Side effects of this cancer treatment include hair loss, nausea, vomiting, among others. There are three types of chemotherapy, each with different objectives.

Neoadjuvant Chemotherapy: It is applied with the aim of reducing the spread and size of the tumor. It also ensures the differentiation between cancerous tissue and healthy tissue.

Adjuvant Chemotherapy: It is generally known as adjuvant therapy. It is applied to completely eliminate any remaining cancer cells from the body after the tumor has been surgically removed. The aim is to reduce the likelihood of cancer recurrence.

Palliative Chemotherapy: It is a supportive treatment method. It is used to help patients with advanced-stage cancer types manage their symptoms so they can carry out daily activities and alleviate their complaints (Cacheux et al., 2012; Tchelebi et al., 2022).

Radiotherapy

Radiation therapy involves the use of high-powered rays such as X-rays. Chemotherapy is used in conjunction with radiation therapy. The death of cancer cells is expected with radiation rays. Since it is a potent treatment, in some cases, surrounding tissues of the

cancerous area may also be damaged. Types of radiation include:

External Radiotherapy: The radiation device does not come into contact with the body; during the procedure, radiation beams are emitted to the patient from a distance.

Internal Radiotherapy: Radioactive substances are placed near the tumor tissue inside the body.

Whole Body (Systematic) Radiotherapy: It is administered as radiation therapy. In this treatment, the radioactive substance spreads throughout the body. The radioactive medication is administered to the body via injection into a vein, orally as a liquid or in pill form (Dee et al., 2021; Pawlowski & Jones, 2024).

Immunotherapy

It is an innovative treatment method used in addition to radiation therapy and chemotherapy for cancer treatment. The application of advanced technology devices and treatment methods plays a significant role in cancer treatment. It works by activating and strengthening the immune system to enable the body to fight cancer on its own. Smart drugs are used to create cancer memory on cells. Monoclonal antibodies that specifically target cancer cells help the immune system recognize and destroy these cells. It helps prolong the lives of many cancer patients and has fewer side effects compared to chemotherapy and radiation therapy. It can even be used in patients who cannot undergo chemotherapy (Jácome et al., 2022; Phuong & Rajdev, 2020).

Monoclonal Antibody

It is aimed at preventing the proliferation of developing cancer cells and supporting the body's own immune system. Antibodies produced in the laboratory bind to the surface of cancer cells, allowing the immune system to recognize cancer cells, thereby destroying them (Phuong & Rajdev, 2020).

T Cell Therapy

T cells are immune cells of the body. In this method, the patient's own T cells are modified in the laboratory to recognize cancer cells, multiplied and then reintroduced into the patient's body. They are specifically prepared against cancer and administered to the patient at intervals of 2 to 3 weeks (Jácome et al., 2022).

Operation

Decisions are made based on the location, shape and structure of the tumor. Tumors can be removed surgically and the procedure can be completed without damaging the anal sphincter muscles that control bowel movements. Following surgery, chemotherapy and radiation therapy are initiated. For patients who do not respond to chemotherapy, a more

extensive procedure called abdominoperineal resection may be performed. In this surgery, a portion of the anal canal, rectum and colon are removed by cutting (Gilshtein & Khoury, 2015).

CONCLUSION

Cancer is a disease characterized by the uncontrolled growth and spread of any cell or group of cells in the body, potentially leading to death. It is often associated with viruses and infections. Not all tumors are cancerous; benign tumors rarely pose a threat to life. Anal canal cancer is a rare form of cancer. Tumors in the anal canal have a complex structure, making diagnosis challenging due to their rarity. When looking at the rates of anal cancer types, approximately 85% of anal canal cancer are squamous cell carcinomas, 10% are adenocarcinomas and 5% are more rarely encountered melanomas, small cell carcinomas and metastatic tumors. Constipation is a condition that often leads to anal area diseases. Anal fistula occurs after hard stooling and this condition can lead to hemorrhoids, rectal prolapse and anal canal cancer as a result of straining and prolonged sitting in the toilet. If constipation is not addressed in anal area diseases, the success rate of the treatment process decreases. To reduce the risk of anal area diseases, it is important to consume a diet rich in fiber, practice safe sex, get vaccinated against HPV, pay attention to calcium and vitamin D intake, avoid excessive alcohol and smoking, engage in physical exercise and lose excess weight. Most importantly, if blood is seen in the stool, one should not strain in the bathroom and should immediately consult a specialist physician.

REFERENCES

- Aigner, F., & Siegel, R. (2023). [Diagnostics, treatment and aftercare of anal cancer]. *Chirurgie (Heidelb)*, 94(10), 890-898. doi:10.1007/s00104-023-01849-2
- Al Hallak, M. N., & Zouain, N. (2009). Extramammary Perianal Paget's Disease. *Case Rep Gastroenterol*, 3(3), 332-337. doi:10.1159/000256382
- Cacheux, W., Lievre, A., De La Rochefordiere, A., Dieumegard, B., Cvitkovic, F., Labib, A., & Buecher, B. (2012). Chemotherapy in the treatment of anal canal carcinoma. *Dig Liver Dis*, 44(10), 803-811. doi:10.1016/j.dld.2012.04.013
- Chumbalkar, V., Jennings, T. A., Ainechi, S., Lee, E. C., & Lee, H. (2016). Extramammary Paget's Disease of Anal Canal Associated With Rectal Adenoma Without Invasive Carcinoma. *Gastroenterology Res*, 9(6), 99-102. doi:10.14740/gr727e
- Ciombor, K. K., Ernst, R. D., & Brown, G. (2017). Diagnosis and Diagnostic Imaging of Anal Canal Cancer. *Surg Oncol Clin N Am*, 26(1), 45-55. doi:10.1016/j.soc.2016.07.002
- Cleary, R. K., Schaldenbrand, J. D., Fowler, J. J., Schuler, J. M., & Lampman, R. M. (1999). Perianal Bowen's disease and anal intraepithelial neoplasia: review of the literature. *Dis Colon Rectum*, 42(7), 945-951. doi:10.1007/bf02237107

- Dandapani, S. V., Eaton, M., Thomas, C. R., Jr., & Pagnini, P. G. (2010). HIV- positive anal cancer: an update for the clinician. *J Gastrointest Oncol*, 1(1), 34-44. doi:10.3978/j.issn.2078-6891.2010.005
- Dee, E. C., Byrne, J. D., & Wo, J. Y. (2021). Evolution of the Role of Radiotherapy for Anal Cancer. *Cancers (Basel)*, 13(6). doi:10.3390/cancers13061208
- Gami, B., Kubba, F., & Ziprin, P. (2014). Human papilloma virus and squamous cell carcinoma of the anus. *Clin Med Insights Oncol*, 8, 113-119. doi:10.4137/cmo.S13241
- Gilshstein, H., & Khoury, W. (2015). Surgical management of anal cancer. *Minerva Chir*, 70(2), 141-145.
- Gondal, T. A., Chaudhary, N., Bajwa, H., Rauf, A., Le, D., & Ahmed, S. (2023). Anal Cancer: The Past, Present and Future. *Curr Oncol*, 30(3), 3232-3250. doi:10.3390/curroncol30030246
- Grulich, A. E., Poynten, I. M., Machalek, D. A., Jin, F., Templeton, D. J., & Hillman, R. J. (2012). The epidemiology of anal cancer. *Sex Health*, 9(6), 504-508. doi:10.1071/sh12070
- Hoedema, R. E. (2018). Anal Intraepithelial Neoplasia and Squamous Cell Cancer of the Anus. *Clin Colon Rectal Surg*, 31(6), 347-352. doi:10.1055/s-0038-1668104
- Jácome, A. A., Morris, V. K., & Eng, C. (2022). The Role of Immunotherapy in the Treatment of Anal Cancer and Future Strategies. *Curr Treat Options Oncol*, 23(8), 1073-1085. doi:10.1007/s11864-022-00939-3
- Khandwala, P., Singhal, S., Desai, D., Parsi, M., & Potdar, R. (2021). HIV-Associated Anal Cancer. *Cureus*, 13(5), e14834. doi:10.7759/cureus.14834
- Leonard, D., Beddy, D., & Dozois, E. J. (2011). Neoplasms of anal canal and perianal skin. *Clin Colon Rectal Surg*, 24(1), 54-63. doi:10.1055/s-0031-1272824
- Maas, M., Tielbeek, J. A. W., & Stoker, J. (2020). Staging of Anal Cancer: Role of MR Imaging. *Magn Reson Imaging Clin N Am*, 28(1), 127-140. doi:10.1016/j.mric.2019.09.005
- Malaguarnera, G., Madeddu, R., Catania, V. E., Bertino, G., Morelli, L., Perrotta, R. E., & Latteri, S. (2018). Anorectal mucosal melanoma. *Oncotarget*, 9(9), 8785-8800. doi:10.18632/oncotarget.23835
- Morton, M., Melnitchouk, N., & Bleday, R. (2018). Squamous cell carcinoma of the anal canal. *Curr Probl Cancer*, 42(5), 486-492. doi:10.1016/j.currproblcancer.2018.11.001
- Palaniappan, V., & Karthikeyan, K. (2022). Bowen's Disease. *Indian Dermatol Online J*, 13(2), 177-189. doi:10.4103/idoj.idoj_257_21
- Pawlowski, J., & Jones, I. W. (2024). Radiation Therapy for Anal Cancer. In StatPearls. Treasure Island (FL) ineligible companies. Disclosure: William Jones III declares no relevant financial relationships with ineligible companies.: StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.
- Pessia, B., Romano, L., Giuliani, A., Lazzarin, G., Carlei, F., & Schietroma, M. (2020). Squamous cell anal cancer: Management and therapeutic options. *Ann Med Surg (Lond)*, 55, 36-46. doi:10.1016/j.amsu.2020.04.016
- Phuong, L., & Rajdev, L. (2020). Immunotherapy in Anal Cancer. *Curr Oncol Rep*, 22(9), 94. doi:10.1007/s11912-020-00946-3
- Pineda, C. E., & Welton, M. L. (2009). Management of anal squamous intraepithelial lesions. *Clin Colon Rectal Surg*, 22(2), 94-101. doi:10.1055/s-0029-1223840
- Roberts, J. R., Siekas, L. L., & Kaz, A. M. (2017). Anal intraepithelial neoplasia: A review of diagnosis and management. *World J Gastrointest Oncol*, 9(2), 50-61. doi:10.4251/wjgo.v9.i2.50
- Row, D., & Weiser, M. R. (2009). Anorectal melanoma. *Clin Colon Rectal Surg*, 22(2), 120-126. doi:10.1055/s-0029-1223844

- Rüschoff, J., Aust, A., Middel, P., & Heinmöller, E. (2011). [Anal cancer: diagnostic and differential diagnostic issues]. *Pathologe*, 32(4), 336-344. doi:10.1007/s00292-011-1440-4
- Sauter, M., Keilholz, G., Kranzbühler, H., Lombriser, N., Prakash, M., Vavricka, S. R., & Misselwitz, B. (2016). Presenting symptoms predict local staging of anal cancer: a retrospective analysis of 86 patients. *BMC Gastroenterol*, 16, 46. doi:10.1186/s12876-016-0461-0
- Shenoy, S., Nittala, M., & Assaf, Y. (2019). Anal carcinoma in giant anal condyloma, multidisciplinary approach necessary for optimal outcome: Two case reports and review of literature. *World J Gastrointest Oncol*, 11(2), 172-180. doi:10.4251/wjgo.v11.i2.172
- Siddharthan, R. V., Lanciault, C., & Tsikitis, V. L. (2019). Anal intraepithelial neoplasia: diagnosis, screening, and treatment. *Ann Gastroenterol*, 32(3), 257-263. doi:10.20524/aog.2019.0364
- Siegel, R. L., Miller, K. D., Wagle, N. S., & Jemal, A. (2023). Cancer statistics, 2023. *CA Cancer J Clin*, 73(1), 17-48. doi:10.3322/caac.21763
- Surabhi, V. R., Menias, C. O., Amer, A. M., Elshikh, M., Katabathina, V. S., Hara, A. K., & Siegel, C. L. (2016). Tumors and Tumorlike Conditions of the Anal Canal and Perianal Region: MR Imaging Findings. *Radiographics*, 36(5), 1339-1353. doi:10.1148/rg.2016150209
- Tchelebi, L. T., Eng, C., Messick, C. A., Hong, T. S., Ludmir, E. B., Kachnic, L. A., & Zaorsky, N. G. (2022). Current treatment and future directions in the management of anal cancer. *CA Cancer J Clin*, 72(2), 183-195. doi:10.3322/caac.21712
- Uronis, H. E., & Bendell, J. C. (2007). Anal cancer: an overview. *Oncologist*, 12(5), 524-534. doi:10.1634/theoncologist.12-5-524
- Young, A. N., Jacob, E., Willauer, P., Smucker, L., Monzon, R., & Ocegüera, L. (2020). Anal Cancer. *Surg Clin North Am*, 100(3), 629-634.