Chemoradiation in anal carcinoma: results and prognostic factors

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CHEMORADIATION IN ANAL CARCINOMA: RESULTS AND PROGNOSTIC FACTORS

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LIST OF ABBREVIATIONS

3D CRT = three dimentional conformal radiation therpy

5FU = 5-fluorouracil

AIDS = acquired Immunodeficiency Syndrome

AJCC = american Joint committe on Cancer

APR = abdominal perineal resection

BMI = body mass index

CRC = colorectal cancer

CT = computer tomography

DNA = deoxyribonucleic acid

DVT = deep vein thrombosis

ERBT = external radiation beam therapy

EUS = endoscopic ultrasound

Gy = gray

HPV= human papilloma virus

IMRT = intensity modulated radiation therapy

IQR = interquartile range

MRI = magnet resonanz tomography

MSI = microsatellite instability

NED = no evidence of disease

OS = overall survival

PET= position emissons tomography

RT = radiotherapy

SBRT = sterotaktik body radiation therapy

SCCA = squamous cell carcinoma of the anus

TNM= tissue node metastasic

UICC = Union for international cancer control

1. INTRODUCTION

1.1. Epidemiological data

In 2023, estimates from the American Cancer Society project that over 9,000 individuals in the United States will receive a diagnosis of anal cancer, marking a substantial concern within the landscape of cancer incidence (1). The incidence of new cases of anal cancer has been steadily increasing over several years. Anal cancer is infrequent among individuals under the age of 35 and is predominantly identified in older adults, typically with an average age in the early 60s (2). The incidents of anal cancer are rising in the younger population.

Anorectal cancer exhibits variations in its global distribution, with regional disparities in incidence rates. According to the World Cancer Research Fund, the highest incidence rates are reported in developed regions such as North America, Europe, and Australia, while lower rates are observed in less economically developed regions like Africa and parts of Asia (3).

A conspicuous association exists between infection with the human papillomavirus (HPV), particularly the high-risk subtype HPV 16, and the development of anal cancer. Consequently, specific demographic groups, such as young men harboring genital viral infections, demonstrate an elevated incidence of anal cancer. Robust epidemiological investigations have underscored a correlation between both the frequency of sexual activity and the prevalence of venereal infections with the occurrence of anal cancer.

Earlier, albeit less statistically robust studies indicated a potential link between engaging in anal-receptive intercourse and an escalated risk of anal cancer. However, this association awaits confirmation through larger-scale clinical trials. In addition to HPV, infections with condylomas have been implicated in the pathogenesis of anal cancer, affecting both the general population and homosexual men.

A comprehensive study illuminated the correlation between anal cancer, Human Papillomavirus, and *Chlamydia trachomatis* in women with genital warts. Conversely, in men devoid of a history of genital warts, an association was identified between anal cancer and *Neisseria gonorrhoeae* infection. Beyond the aforementioned etiological factors, a notable connection exists between acquired immunodeficiency syndrome (AIDS) and anal cancer. In individuals infected with the human immunodeficiency virus (HIV), the risk of developing anal cancer is amplified approximately 40 times in comparison to the general population (4–6).

Significant risk factors for colorectal cancer (CRC) were identified through a comprehensive risk modeling strategy. Inflammatory bowel disease and a family history of CRC in first-degree relatives emerged as particularly influential, indicating a substantially higher risk of CRC in individuals with these conditions. Moreover, analysis revealed that an

elevated body mass index (BMI) contributes to an increased risk of CRC within the overall population. Lifestyle factors also played a role, with lower levels of physical activity associated with an elevated. Cigarette smoking and the consumption of red meat were positively correlated with increased CRC risk In contrast, certain dietary habits were associated with a moderately decreased risk of CRC. Specifically, higher fruit consumption and vegetable consumption demonstrated a protective effect against CRC (7).

1.2. Definition and classification of anorectal carcinomas

Anorectal carcinomas, a subset of gastrointestinal malignancies, encompass tumors that arise in the anal canal or rectum. Understanding their definition and classification is essential for accurate diagnosis, prognosis, and treatment planning. These malignant tumors are characterized by their uncontrolled growth of cells within the tissues of the anal canal or rectum. These cancers typically originate from the mucosal lining and can manifest as squamous cell carcinomas or adenocarcinomas, representing the two primary histological types (8). A classification of anorectal carcinomas involved categorizing them based on various criteria, including histology, anatomical location, and staging.

1.2.1. Anatomical classification

The anorectal region, encompassing the anus and rectum, constitutes a vital component of the human digestive and excretory systems. A nuanced comprehension of its anatomy is indispensable for unraveling the intricacies associated with the development and progression of anorectal carcinomas.

The anorectal region is marked by a sophisticated anatomy, necessitating an in-depth exploration. The anal canal, situated at the terminal end of the large intestine, terminates at the anus. Notable anatomical features within this region include the anal columns, anal valves, and the pectinate line, demarcating the transition from the upper two-thirds to the lower one-third of the anal canal. Furthermore, the anal sphincters, comprising the inner involuntary sphincter and the outer voluntary sphincter, play a pivotal role in regulating bowel movements (9).

Tissues and Structures Involved in Carcinogenesis:

The genesis and progression of anorectal carcinomas involve a multitude of tissues and structures within the anorectal milieu.

Anal Mucosa: The mucosal lining of the anal canal emerges as a primary site susceptible to carcinogenesis. Squamous cell carcinomas predominantly originate in the squamous

epithelium of the anal canal, while adenocarcinomas may find their inception in the glandular tissue.

Anal Glands: Positioned within the anal canal, anal glands represent potential sites for the initiation of certain types of tumors.

Lymph Nodes: Understanding the drainage pathways of lymph nodes in the anorectal region is paramount in elucidating the potential metastatic spread of carcinomas. Key lymph nodes implicated in metastasis include the inguinal, internal iliac, and external iliac nodes (10).

The anatomical classification considers whether the tumor is situated in the anal canal or the rectum. The rectum, situated in the midline of the pelvis and measuring approximately 15 cm in length, presents variability in defining the rectosigmoid junction, ranging from anatomical landmarks like the confluence of the taeniae coli to the shape of the colon. Distally, the rectum extends to the proximal anorectal sphincter, demarcated by the palpable upper border of the puborectalis muscle. Covered anteriorly and laterally by peritoneum in the proximal rectum, and partially covered in the mid rectum, the distal rectum is extraperitoneal, surrounded by perirectal fat, mesorectal lymph nodes, and vessels encased within the mesorectal fascia. The anal sphincter comprises an internal and external component, composed of smooth and skeletal muscle, respectively. Extending from the anorectal sphincter to the anal verge is the anal canal which typically measures 3–6 cm in length. The anal margin radiating in a 5–6 cm radius across the external skin-covered region as shown in Figure 1. Lymphatic drainage pathways from the rectum and anus encompass both inguinal and mesenteric components. Proximal rectal cancers often lead to mesenteric adenopathy, while distal rectal cancers may result in internal iliac adenopathy. In contrast, anal cancers are more prone to producing inguinal adenopathy, occasionally accompanied by internal iliac adenopathy.

Histologically, most anal cancers are squamous cell carcinomas, presenting distinctive features based on the tumor's location relative to the dentate line. Tumors originating near the transitional zone are often basaloid squamous cell carcinomas, while those distal to the dentate line are typically well-differentiated keratinizing squamous cell carcinomas. Despite histologic variations, there is no significant difference in behavior or prognosis between these subtypes (11).

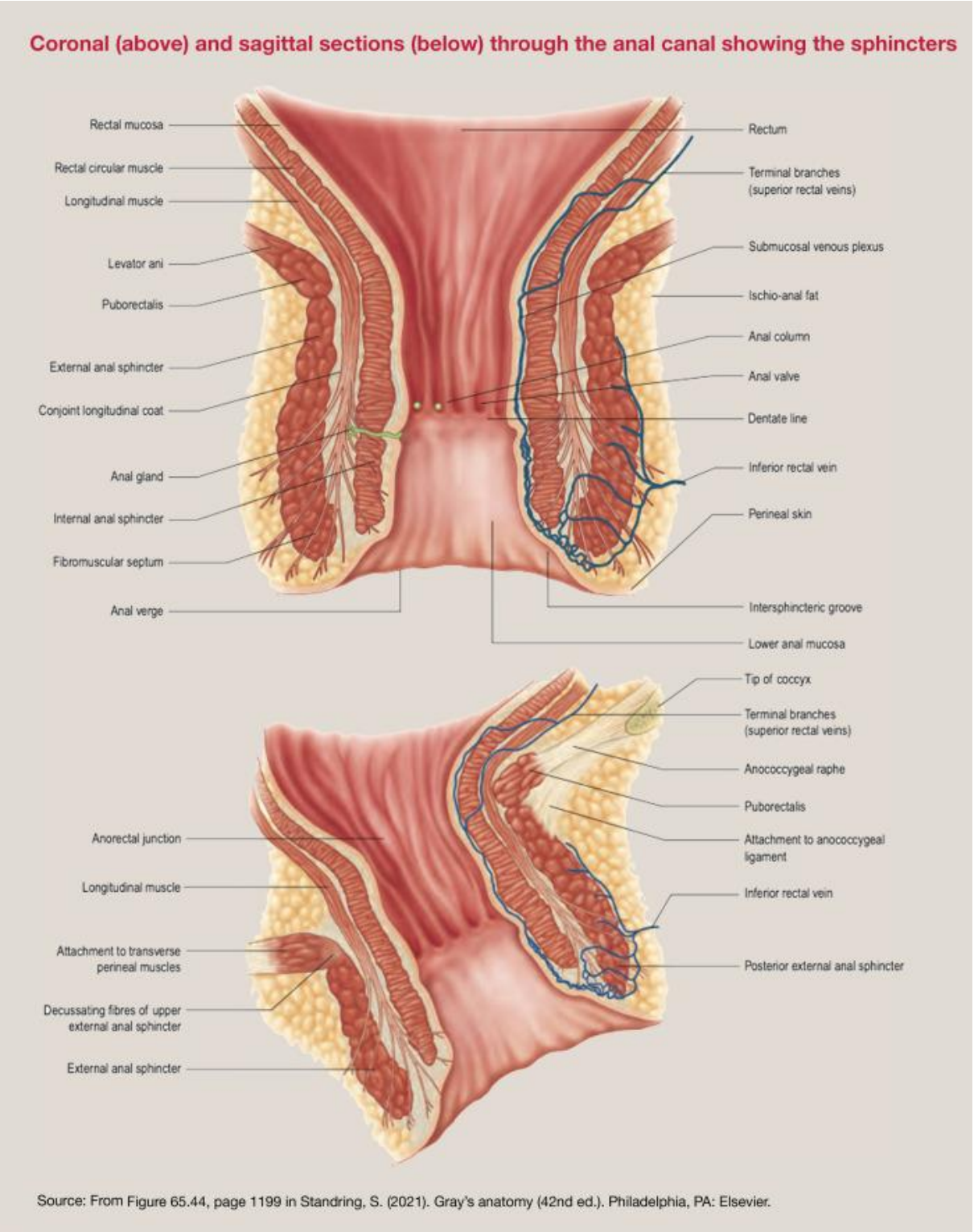

Figure 1. Anatomy of the rectum and anal canal

Source: Figure 65.44, page 1199 in Standring, S. (2021). Gray*s anatomy (42nd ed.)Philadelphia, PA: Elsevier.

1.2.2. Histological classification

Histologically these cancers can be classified into squamous cell carcinomas and adenocarcinomas. Squamous Cell Carcinomas predominantly originate in the squamous epithelium of the anal canal and are associated with risk factors such as human papillomavirus (HPV) infection (12). A second type of anorectal carcinomas arise from the glandular tissue. Adenocarcinomas are often located in the rectum and are linked to conditions like inflammatory bowel disease .

1.2.3. Staging of anal carcinoma

As in other tumor types in anorectal carcinomas the TNM (Tumor, Node, Metastasis) staging system is widely employed, incorporating factors such as tumor size, lymph node involvement, and distant metastasis (15). The staging system for anal carcinoma, based on the UICC 7th edition, provides a comprehensive classification to assess the extent and spread of the disease. The staging involves the primary tumor (T), regional lymph nodes (N), and potential infiltration into adjacent organs. This classification aids in determining prognosis and guiding appropriate treatment strategies. The primary tumor (T) staging provides a detailed assessment of the size and local invasion of anal carcinomas. It is divided as followed into multiple stages depending on the tissues dimension and distribution:

T1: Primary tumor 2 cm or less in its greatest dimension.

T2: Primary tumor more than 2 cm but not more than 5 cm in its greatest dimension.

T3: Primary tumor more than 5 cm in its greatest dimension.

T4: Invasion into adjacent organs, such as the vagina, urethra, or bladder. One important note on this is that the infiltration of the Sphincter ani (anal sphincter) is NOT categorized as T4.

A second important role plays the invasion of regional or distant lymph nodes denoted with the capital letter N. It categorizes the extent of lymph node involvement, indicating the potential spread of anal carcinoma beyond the primary site and is as followed:

N0: No regional lymph node metastasis.

N1: Metastasis in perirectal lymph nodes.

N2: Metastasis in pelvic lymph nodes and/or inguinal lymph nodes on one side.

N3: Metastasis perirectally and inguinally (groin) and/or metastasis in pelvic lymph nodes on both sides and/or inguinal lymph nodes on both sides.

The final component of the TNM classification, represented by the letter "M," assesses

the presence or absence of distant metastasis. This is critical in determining the spread of cancer to parts of the body remote from the original tumor site. The metastasis classification is simplified into two categories:

M0: Indicates no signs of distant metastasis. This suggests that the cancer has not spread to distant organs or tissues beyond the regional lymph nodes.

M1: Indicates that distant metastasis is present. This confirms that cancer cells have spread to distant parts of the body, which can include organs such as the lungs, liver, bones, or other locations beyond the direct regional environment of the primary tumor.

The presence of metastasis (M1) generally corresponds to a more advanced disease stage and typically necessitates more aggressive and systemic treatment approaches compared to M0, where cancer is localized. The determination of metastatic status is crucial for developing a comprehensive treatment plan and for prognosticating outcomes for patients with anal carcinoma. Understanding the metastatic spread is vital for assessing the overall severity of the cancer and guiding decisions regarding chemotherapy, radiation therapy, and potential surgical interventions.

Understanding the stage of anal carcinoma is crucial for treatment planning and prognostic evaluation. Additionally, advances in imaging techniques, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), play a significant role in refining the accuracy of staging. Molecular markers and genetic profiling are emerging areas that may further enhance our ability to stratify patients based on their tumor biology and guide tailored treatment approaches.

It is important in healthcare to consider a multidimensional aspects of staging and employ a holistic approach that integrates clinical, radiological, and molecular information for optimal patient care. Regular updates to staging classifications underscore the dynamic nature of oncology, reflecting ongoing research and advancements in understanding the complexities of anal carcinoma (15).

1.2.4. Grading of anorectal cancer

A second essential classification of anorectal cancers involves grading. Thereby the evaluation of cellular differentiation and architectural patterns is taken into consideration. The grade assigned to anorectal cancer aids in prediction of behavior, guiding treatment decisions, and estimating overall prognosis. The cornerstone in the process of grading remains the histological examination. In the examination the degree of glandular differentiation is

considered. In detail it distinguishes between well-differentiated tumors resembling normal tissue and poorly differentiated tumors displaying chaotic cellular arrangements (16).

In well-differentiated or G1 types glandular formation closely resembles normal tissue and G1 tumors typically exhibit a favorable prognosis with a more indolent course. Moderately differentiated tumors demonstrate intermediate glandular architecture and are summarized as G2. They reflect a moderate level of cellular abnormality. Prognosis and treatment considerations often fall between well-differentiated and poorly differentiated cases. Furthermore, poorly differentiated G3 tumors completely lack regular and common glandular structures. In these types a higher degree of cellular disarray can be seen. These tumors often exhibit aggressive behavior and are associated with a less favorable prognosis (15).

Another mode of categorization is done by methods of molecular grading. Technical advancements have introduced a complementary layer to traditional histological grading. This profiling based on molecular structures enables a refined and nuanced understanding of anorectal cancer biology, offering insights into genetic mutations, chromosomal aberrations, and signaling pathway dysregulations (17).

Next to molecular structural analysis, microsatellite instability (MSI) detection lead to a deeper understanding of distinct pathological features and altered responses to treatment. Reason for this is that cancers with a high MSI are indicative of DNA mismatch repair deficiencies (18). Moreover, the presence of KRAS mutations, commonly evaluated in anorectal cancer, can influence tumor aggressiveness and impact response to targeted therapies (19).

To summarize the above findings, grading plays a pivotal role in treatment stratification. Well-differentiated tumors may respond favorably to less aggressive interventions, while poorly differentiated tumors may necessitate more comprehensive therapeutic approaches. Additionally, grading informs prognosis, aiding in discussions about disease progression and potential outcomes. It integrates histological and molecular insights, offering a comprehensive understanding of the disease's biological spectrum. Embracing both traditional and contemporary grading modalities is paramount for personalized treatment strategies and improved patient outcomes.

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ (i.e., Bowen disease, high-grade squamous intraepithelial lesion, and anal intraepithelial neoplasia II–III)
T1	Tumour ⩽2 cm in greatest dimension
T2	Tumour >2 cm but ⩽5 cm in greatest dimension
T3	Tumour >5 cm in greatest dimension
T4	Tumour of any size invades adjacent organ(s), e.g., vagina, urethra, and bladder.

Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in perirectal lymph node(s)
N2	Metastases in unilateral internal iliac and/or inguinal lymph node(s)
N3	Metastases in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes

Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Anatomic stage/prognostic groups

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
	T3	N0	M0
IIIA	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4	N0	M0
IIIB	T4	N1	M0
	Any T	N2	M0
	Any T	N3	M0
IV	Any T	Any N	M1

Figure 2. TNM staging. American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) Source: Anal_cancer_ESMO-ESSO-STRO_clinical_practice_guidelines_for_diagnosis_treatment_and_follow-up [accessed Feb 29 2024].|Available from: https://www.researchgate.net/publication/263296322

1.2.5. Challenges and bridging research gaps

Anorectal carcinomas pose a complex medical challenge due to their intricate nature and the critical role the anorectal region plays in gastrointestinal function. The anus and rectum, both vital components of the digestive system, are responsible for maintaining fecal continence and facilitation bowel movements. The unique physiological characteristics of this region, combined with the complexity of anorectal carcinoma pathogenesis, poses the importance for a deeper exploration of these malignancies.

Current research in oncology has made significant strides in understanding the molecular and genetic underpinnings of various cancers (20,21). However, there remains an evident gap in our comprehension of anorectal carcinomas. Limited attention has been devoted to decipher specific mechanisms driving the initiation, progression, and metastasis of these tumors. To address this disparity, it is crucial to research the intricate interplay of genetic mutations, environmental factors, and molecular pathways involved in anorectal carcinoma

development.

A comprehensive review of the existing literature reveals a dearth of studies focusing specifically on anorectal carcinomas. While research on cancers has provided valuable insights, anorectal malignancies necessitate a distinct and specialized investigation. This underscores the need for dedicated research to unravel the complexities of anorectal carcinogenesis (22).

The clinical implications of advancing our understanding of anorectal carcinomas are profound. Improved knowledge can contribute to the development of targeted therapies tailored to the unique characteristics of anorectal tumors. Early detection methods, currently less refined compared to other gastrointestinal cancers, could benefit significantly from a more nuanced understanding of the disease. This thesis, building on the foundation laid by landmark studies such as Lee *et al.* (23), aims to fill the existing research gaps and shed light on the significance of anal carcinomas as a distinct and pressing medical concern.

1.3. Symptoms and clinical manifestations

1.3.1. Early and late symptoms of anorectal carcinomas

Anorectal carcinomas exhibit a spectrum of symptoms, encompassing both early indicators and manifestations that emerge at later stages. Early symptoms often include subtle changes, such as alterations in bowel habits, rectal bleeding, or discomfort during bowel movements. As the disease progresses, late symptoms become more apparent and may involve persistent pain, unintended weight loss, and changes in bowel consistency (24). Understanding these nuances is crucial for timely diagnosis and intervention. In the early stages, symptoms might be subtle and easily overlooked, underscoring the importance of heightened clinical awareness. Comprehensive clinical assessments can aid in identifying and interpreting these early symptoms.

1.3.2. Differences in presentation based on localization

The localization of anorectal carcinomas plays a significant role in shaping their clinical presentation. Tumors arising in the rectum may present distinctively compared to those originating in the anal canal or other anorectal regions. For instance, rectal carcinomas might be associated with changes in bowel habits, tenesmus, or a feeling of incomplete evacuation. In contrast, anal canal carcinomas could manifest with bleeding, pain, or palpable masses (25) .

Recognizing these nuances requires a nuanced understanding of anorectal anatomy and pathology. Authoritative works such as "Anorectal Disease: Contemporary Management" by Beck et al. provide comprehensive insights into the clinical presentation of anorectal malignancies based on their specific anatomical localization (26).

1.4. Diagnostic Procedures

1.4.1. Imaging modalities in anorectal carcinomas

Diagnostic imaging plays a pivotal role in characterizing anorectal carcinomas, offering insights into their extent, localization, and involvement of adjacent structures. Among the advanced imaging techniques, Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) stand out as cornerstones in the diagnostic armamentarium.

1.4.2. Magnetic resonance imaging (MRI)

MRI excels in providing detailed soft tissue contrast, making it particularly valuable in evaluating the anorectal region. High-resolution MRI aids in assessing tumor size, invasion into surrounding structures, and potential involvement of regional lymph nodes (34). Studies, such as those by Brown et al., underscore the efficacy of MRI in accurately staging anorectal cancers (27).

1.4.3. Computed tomography (CT)

CT scans are instrumental in assessing the extent of local invasion and detecting distant metastases. They offer a comprehensive view of the pelvic region, aiding in the determination of tumor size and potential involvement of adjacent organs (28).

1.4.4. Positron emission tomography-computed tomography (PET-CT)

PET-CT provides functional information by highlighting areas of increased metabolic activity, aiding in the detection of distant metastases and lymph node involvement. This modality is particularly valuable in cases where conventional imaging might fall short (29).

1.5. Role of endoscopy and biopsy

1.5.1. Colonoscopy

Colonoscopy is a crucial diagnostic tool for evaluating anorectal carcinomas, allowing direct visualization of the tumor and surrounding mucosa. Additionally, it facilitates biopsy collection for histopathological analysis, aiding in definitive diagnosis (30).

1.5.2. Endoscopic ultrasound (EUS)

EUS seamlessly integrates endoscopy with ultrasound, offering intricate insights into the layers of the anorectal wall and neighboring structures. This sophisticated technique proves instrumental in precisely evaluating tumor depth and the potential involvement of adjacent lymph nodes.

A staging system grounded in tumor invasion holds promise for enhancing the prognostic significance of anal cancer, aligning it more closely with the staging methodologies applied to various intestinal cancers. The incorporation of US staging, when coupled with other prognostic variables, facilitates the identification of distinct patient groups with varying prognoses. In the prospective landscape, US staging emerges as a plausible candidate for inclusion among predictive clinical parameters for anal cancer. Its integration could not only elevate prognostic accuracy but also pave the way for a tailored therapeutic approach.

Research outcomes indicate the superiority of US staging over conventional clinical staging methodologies. Notably, US staging exhibits a significant correlation with Disease-Free Survival in anal cancer patients. This underlines the potential of EUS in refining prognostic assessments and underscores its candidacy for becoming a pivotal element in the comprehensive management of anal cancer (31).

1.5.3. Biopsy

Histopathological examination of biopsy specimens remains the gold standard for confirming the diagnosis of anorectal carcinomas. Biopsy findings not only confirm malignancy but also provide essential information on tumor type, grade, and molecular characteristics (32). The work by Goldstein *et al.* emphasizes the significance of accurate biopsy for optimal patient management (33).

In conclusion, a multimodal diagnostic approach, incorporating advanced imaging techniques, endoscopy, and precise histopathological analysis, forms the cornerstone for the accurate diagnosis and staging of anorectal carcinomas.

1.6. Pharmacological approaches and the role of radiation therapy

1.6.1. Chemotherapy

A crucial arm in the therapeutic arsenal against anorectal cancer is represented by chemotherapy agents, exerting an influence at various stages of the disease. The pharmacological agents employed aim to eradicate cancer cells, impede their proliferation, and prevent metastatic spread. One of them being Fluoropyrimidines. It is integral to many chemotherapeutic regimens and includes fluoropyrimidines such as 5-fluorouracil (5-FU) and capecitabine. They play a central role in disrupting DNA synthesis and thereby curbing the uncontrolled growth of cancer cells (34). Another possibility in treatment include platinum compounds. Drugs like oxaliplatin, with their ability to induce DNA cross-linking, bring forth additional efficacy in combination therapies, especially in advanced or metastatic settings (35). Moreover, a synergy achieved by combining different classes of chemotherapeutic agents, also reffered to as combination therapy, aims to enhance treatment efficacy while managing potential side effects (36).

1.6.2. Radiationtherapy

Beyond surgery and chemotherapy, radiation therapy assumes a vital adjuvant role in the comprehensive management of anorectal cancer. By employing high-energy radiation beams, this therapeutic modality seeks to eradicate residual cancer cells and minimize the risk of local recurrence. Various types of radiation are utilized in the management of anal cancer. A tailored therapeutic approach is essential and among the forefront modalities diverse forms of radiation therapy employed. Two primary categories distinguish these modalities. One of them being external beam radiation therapy (EBRT). It directs radiation externally onto the cancerous

site, a method frequently employed in addressing anal cancer and its metastases. The procedure resembles an extended X-ray session and involves a painless process with each session lasting briefly. Standard protocols often entail daily treatments over 5 to 7 weeks, although variations exist based on the specific EBRT variant and its clinical rationale. More innovative techniques are also being applied and consist of a three-dimensional conformal radiation therapy (3D-CRT). Here, advanced computer technology for meticulous cancer localization is employed. Radiation beams are shaped and directed in order to reduce damage to surrounding healthy tissues. Customized body molds are often utilized to ensure precise patient positioning. A third possibility is the intensity-modulated radiation therapy (IMRT). In this method IMRT utilizes computer-controlled machinery for radiation delivery. This method allows for dynamic adjustment of beam intensity, minimizing impact on normal tissues and ameliorating side effects. IMRT enables the administration of higher radiation doses to the cancerous site compared to conventional techniques. Next, stereotactic body radiation therapy (SBRT) can be applicable in recurrent anal cancers or limited metastases. SBRT diverges from the conventional protracted approach. It employs highly focused, high-dose radiation beams delivered in fewer sessions (typically 1 to 5). Precision is ensured by a specialized body frame securing the patient's immobility during treatment.

1.6.3. Brachytherapy in anal cancer management

In the context of anal cancer treatment, Brachytherapy, an internal radiation modality, assumes a niche role, often employed as a supplementary measure when a tumor exhibits resistance to conventional chemoradiation—chemotherapy in conjunction with external radiation. This approach is considered when a tumor fails to respond adequately to prior conducted standard chemoradiation protocols. It involves the strategic placement of small radioactive sources within or in proximity to the tumor. By doing so, the radiation is concentrated within the cancerous region, mitigating the impact on adjacent normal tissues. Two variations, namely interstitial radiation and intracavitary radiation, delineate the nuances of Brachytherapy. Brachytherapy is often integrated as a radiation boost, supplementing external radiation in cases of tumor resistance to conventional treatment (37). One type of protocol is the neoadjuvant radiation. It is administered prior to surgery, which aids in shrinking the tumors, facilitating a more conservative surgical approach while enhancing the chances of achieving a complete resection (38). Secondly, adjuvant radiation is applied following surgical resection. It is indicated in cases to target potential residual cancer cells, reducing the likelihood

of local recurrence (39). Lastly, another form of radiation approach is in palliative situations. When curative measures may not be feasible, palliative radiation therapy aims to alleviate symptoms, improve quality of life, and manage complications associated with advanced disease (40) (53).

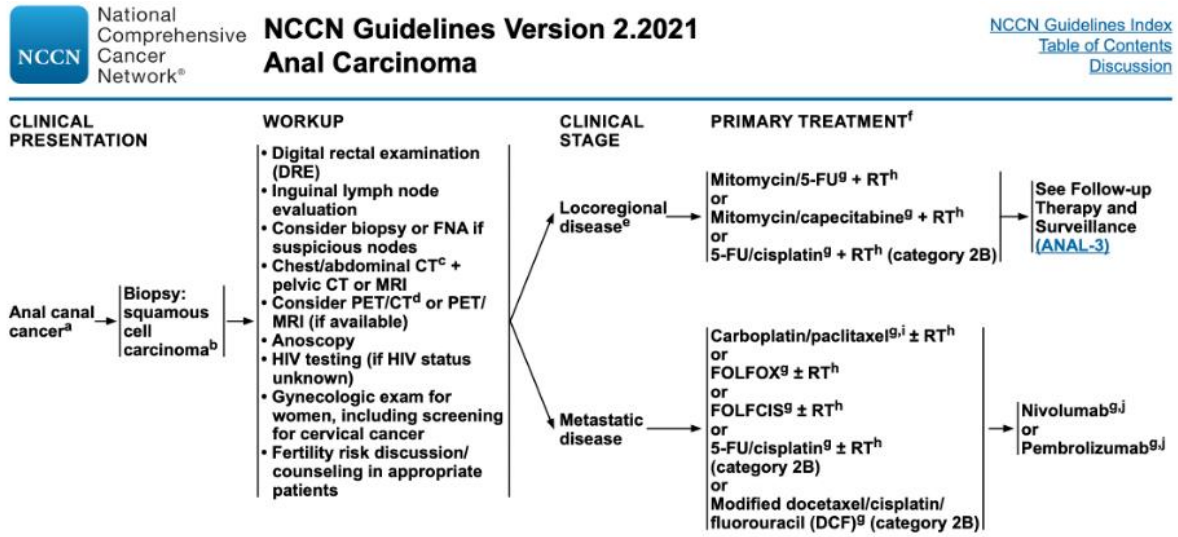

Figure 3. Anal Cancer Foundation. (2024, 22. February). Anal cancer Treatment Options & Stages | The Anal Cancer Foundation. The Anal Cancer Foundation | [accessed Feb 27 2024] Available from: https://www.analcancerfoundation.org/treatment/

1.7. Surgical options for anorectal cancer: resection techniques and reconstruction possibilities

Anorectal cancer, a formidable challenge in oncology, necessitates a nuanced approach to surgical interventions. The selection of optimal resection procedures and subsequent reconstruction methodologies plays a pivotal role in achieving favorable outcomes.

1.7.1. Resection procedures

Resection, the cornerstone of anorectal cancer treatment, involves the surgical removal of the tumor along with a margin of healthy tissue to ensure complete eradication. Several techniques are employed based on the tumor's location, size, and the extent of its invasion.

One of the common techniques includes local excision. It is mainly reserved for early-stage tumors confined to the mucosa or submucosa, local excision entails the removal of the tumor without the need for major abdominal surgery. This approach is often considered for small, superficial lesions, allowing for a quicker recovery and preservation of anal function.

Secondly, abdominoperineal resection (APR) which is indicated for more advanced

tumors or those situated close to the anus. APR involves the removal of the entire rectum and anal canal, followed by the creation of a permanent colostomy. While effective in achieving oncological clearance, APR has implications for patients' quality of life due to the permanent stoma (41).

1.7.2. Reconstruction possibilities

Post-resection, restoration of normal anorectal function is a critical consideration. Reconstruction methods aim to achieve optimal functional outcomes while addressing the potential impact on patients' quality of life.

Coloanal Anastomosis poses one of the techniques which involves reconnecting the remaining portion of the rectum to the anus. Thereby, the technique facilitates of restoration of a more natural bowel function. Coloanal anastomosis is often employed after LAR, offering an alternative to a permanent colostomy (42).

In situations where a permanent diversion is deemed necessary, a colostomy may be created. This involves bringing a segment of the colon to the abdominal wall, allowing for the elimination of stool through a stoma. While effective in diverting fecal flow, it poses challenges in terms of body image and daily living (43).

It is essential to emphasize that the selection of appropriate resection techniques and reconstruction methods in anorectal cancer surgery is a dynamic process, tailored to the individual patient's disease characteristics and overall well-being.

1.8. Challenges and Future Perspectives in Anorectal Cancer

Despite ongoing efforts, anorectal cancer often eludes early detection due to the subtlety of symptoms and the lack of routine screening programs. The consequence is a significant proportion of patients presenting with advanced disease (44). Limited treatment options pose another challenge for patients and clinicians. Current therapeutic modalities, including surgery, chemotherapy, and radiation, face limitations, especially in cases refractory to standard treatments. There is a pressing need for novel and targeted therapies to address this clinical gap (45). Functional implications of surgery are often the result of surgical interventions. Even though they are essential for tumor removal they are impacting the patient's quality of life (46). Striking a balance between oncological efficacy and functional outcomes poses an ongoing challenge. Moreover, the complex nature of anorectal cancer demands coordinated efforts from diverse medical specialties and therefore a multidisciplinary approach. Challenges arise in

achieving seamless collaboration, particularly in healthcare systems with fragmented care structures.

Anorectal cancer lacks well-defined prevention strategies and systematic screening programs, contributing to delayed diagnoses. Overcoming these gaps requires a comprehensive public health approach (47).

1.8.1. Future perspectives

Advancements in early detection are made by applying molecular diagnostics, circulating tumor markers, and advanced imaging techniques, including PET and MRI (48). Additionally, immunotherapeutic approaches, particularly immune checkpoint inhibitors, are gaining attention in anorectal cancer research. Preliminary studies suggest potential efficacy in advanced cases (49). Based on the innovative findings in research an integration of genomic profiling and precision medicine principles is emerging as a transformative approach. Thereby, tailored treatment built on individual tumor genetics and molecular characteristics holds potential for optimizing therapeutic outcomes. Furthermore, evolving towards a patient-centered care model addresses not only the disease but also the psychosocial and functional aspects of patient well-being. Survivorship programs and holistic support contribute to an improved patient experience (50). In times of digitalization, integrated healthcare platforms are leveraging technology for integrated healthcare platforms, such as electronic health records and telemedicine. This can enhance communication and streamline multidisciplinary collaboration (51).

1.9. Challenges in the treatment of anorectal cancer

1.9.1. Therapeutic resistance

An enduring challenge in anorectal cancer treatment is the emergence of therapeutic resistance, limiting the effectiveness of standard interventions. Despite advancements in chemotherapy and targeted therapies, a subset of patients develops resistance, leading to disease progression (52). Understanding the molecular mechanisms driving resistance and developing strategies to overcome it stand as pivotal areas of ongoing research (53,54).

1.9.2. Adverse effects and long-term consequences

While treatment modalities such as surgery, chemotherapy, and radiation aim to

eradicate cancer cells, they often bring about significant adverse effects and potential long-term consequences. Surgical interventions, essential for tumor removal, may result in functional impairments and altered quality of life. Chemotherapy, while targeting rapidly dividing cells, can lead to systemic toxicity and adverse effects on normal tissues. Additionally, radiation therapy, while effective in tumor control, may cause damage to surrounding healthy structure.

Understanding and mitigating treatment-related adverse side effects represent crucial aspects of improving patient outcomes. Management strategies include personalized treatment plans, supportive care interventions, and the development of targeted therapies with reduced systemic toxicity (55).

1.9.3. Adverse effects of external radiation therapy in anal cancer patients

The repercussions of external radiation therapy in anal cancer management are contingent upon the specific anatomical region targeted and the administered radiation dosage. Short-term effects are more immediately apparent and include diarrhea or similar forms of acute gastrointestinal responses. A second fairly common side effect are cutaneous alterations of areas subjected to radiation and exhibit skin changes akin to a sunburn. Anal irritation and pain, collectively termed radiation proctitis, might follow as well. Furthermore, bowel discomfort, alongside with fatigue and nausea are present. Fluctuations in blood cell counts, particularly reductions, have to be considered. A special group of gynecological side effects are present in women, who also experience and suffer from vaginal irritation, discomfort, and discharge. These are also categorized potential long-term outcomes.

Long-term adverse effects take some time to occur and can include anal tissue damage due to the chronic exposure to radiation. Thereby, is induces scar tissue formation in anal tissue, potentially compromising anal sphincter muscle functionality and leading to bowel movement issues. Further side effects of the radiation in the pelvic region include the risk of weakening bones, predisposing individuals to pelvic or hip fractures. One has to keep in mind that the radiation induced impairment of blood vessels supplying the rectal lining leads to vascular damage. This can result in chronic radiation proctitis, characterized by rectal bleeding and pain. As in all cases of applying radiation to the human organism it may adversely affect fertility in men and women, necessitating discussions about options such as sperm banking or egg freezing. Also, lymph nodes or lymph drainage might be affected by radiation causing specific complications in form of local lymphedema. Patients might experience genital and leg swelling leading to specific and individual problems in their daily lives.

It is imperative for healthcare providers to apprise anal cancer patients of these potential side effects, both immediate and delayed, fostering informed decision-making and comprehensive patient care (37) (56).

1.9.4. Adverse events following anal cancer surgery

Anal cancer surgery, while a crucial intervention, carries inherent risks and potential complications, ranging from minor issues to more severe, life-threatening problems. The risk for postoperative infections encompassing the wound, chest, or urinary tract, has to be kept in mind. In order to prevent such outcomes the management includes prophylactic antibiotics administration to reduce infection risks. Vigilance for symptoms like fever, shivering, and wound abnormalities is vital. Immediate medical attention is essential to avert complications, with the rare possibility of requiring additional surgical intervention for a wound infection. A second threatening adverse event of surgery are blood clots forming in the deep veins of the legs. The higher occurrence of deep vein thrombosis (DVT) is due to reduced mobility post-surgery heightens the likelihood of DVT. As a measure of prevention patients are advised to start as early as possible with leg exercises and mobilization. Furthermore, anticoagulant injections during hospitalization aim to prevent clot formation. Continued injections and compression stockings post-discharge may be prescribed based on the surgical procedure. Pelvic or abdominal bleeding can on one hand be expected in form of blood loss during surgery. On the other hand, a rare complication such as an internal bleeding, demands a secondary surgical intervention. Respiratory complications raise concerns for potential chest infections, including pneumonia. With the aim of reducing the risk, patients are advised to a preoperative smoking cessation, early postoperative ambulation, and respiratory exercises recommended by physiotherapists. Especially in case of anorectal cancers, sexual and urinary function implications are a topic a clinician has to be open to discussing it with the patients undergoing surgical treatment. The risk of nerve damage which can impact sexual and urinary function, particularly in abdominoperineal resection (APR), has to be considered. Other potential complications involve abscess formation, slowed bowel movement leading up to an ileus and a partial or complete bowel obstruction. More special adverse events include stoma issues, delayed wound healing and wound dehiscence. It is crucial to identify and manage these issues timely which requires close postoperative monitoring and prompt medical intervention. Patients are encouraged to communicate openly with healthcare professionals to address concerns and facilitate optimal recovery (57) 74.

1.10. Future directions

Addressing these challenges necessitates a multidisciplinary approach, integrating insights from molecular biology, immunology, and translational research. Advances in precision medicine, immunotherapies, and supportive care interventions offer promising avenues for enhancing treatment efficacy while minimizing adverse effects. Ongoing research endeavors, coupled with a patient-centered care model, are instrumental in navigating the complexities posed by therapeutic resistance and treatment-related side effects in the landscape of anorectal cancer.

2. OBJECTIVES

2.1. Aim of the study

This study aims to evaluate the survival data of anal cancer patients after undergoing treatment in the Cancer Center Coburg, Germany. The patients live in Coburg and the surrounding neighboring towns in Bavaria and Thuringia. The goal is to identify clinical prognostic factors for overall survival, no evidence of disease (NED)-survival, recurrence pattern and to work out whether there are significant associations between any of these.

2.2. Hypothesis

1. T status is associated with five-year overall survival in patients.
2. N status influences five-year survival rates.
3. The use of chemotherapy during treatment impacts five-year survival outcomes.

3. Subjects and Methods

3.1. Study design

For this retrospective cohort study 63 subjects, who were the initial diagnosis of anal cancer (ICD 10: C21) and undergoing treatment between 2010 and 2020 at the Coburg Cancer Center were analyzed and compared according to the outcomes and prognostic factors. Three patients were excluded from the study because of change of citizenship or incomplete data. The history of the remaining 60 patients was collected for data regarding their disease and its course via patients' records of the practice over the course of the treatment and evaluated for this study.

The study utilized anonymous, saved data from the ORBIS (DEADALUS Healthcare group, Bonn, Germany) system, a hospital information system used by hospitals of REGIOMED. Additional data was sourced from the programs Isynet –(Medatixx GmbH & Co. KG, Eltville/Rhein, Germany) and Aria (Varian Medical Systems, Darmstadt, Germany)

3.2. Variables

A multitude of variables pertinent to this study were extracted from the relevant datasets. Demographic information of the participants at baseline included gender and age. Additional variables encompassed the duration of radiotherapy along with the corresponding doses administered. The utilization of chemotherapy during the treatment period, age at diagnosis, and unique patient identifiers within the Isynet database were also documented. Furthermore, the TNM classification for each patient at the time of diagnosis was included. The study also incorporated several key outcome variables to assess patient prognoses and treatment efficacy. These variables included overall survival, which measures the time from diagnosis until death from any cause, providing a comprehensive indicator of patient longevity. The no evidence of disease (NED) status identifies patients, who showed no signs of cancer following treatment. The local recurrence-free survival, which tracked the time during which patients remained free from local recurrence of the disease. Additionally, incidences of local recurrence and distant recurrence were documented.

3.3. Statistical analyses

The results of the study were meticulously analyzed using IBM SPSS Statistics 29.0.2.0 (IBM Deutschland GmbH, Böblingen, Germany), a robust and widely recognized software for statistical analysis. To determine the normality of the data distribution was visualized via a histogram, QQ plots and the Shapiro-Wilk test was used. The Mann-Whitney U test was used to determine if there are significant differences between the medians of independent samples.

Survival rates were calculated using the Kaplan-Meier method, which is a non-parametric statistic used to estimate the survival function from lifetime data. This method is particularly useful for measuring the fraction of patients living for a certain amount of time after treatment. In addition to this, the log-rank test was applied to compare survival rates between different patient groups, allowing for a rigorous statistical comparison of survival distributions.

Quantitative data in the study are expressed as mean ± standard deviation (SD) to represent the average values and their variability. Additionally, for data that do not follow a normal distribution, the median is reported, providing a measure of central tendency and dispersion that is less affected by outliers and skewed data. On the other hand, qualitative data are presented as whole numbers and percentages, which facilitate a straightforward understanding of the frequency and proportion of categorical variables within the dataset.

3.4. Ethical approval

The research project received approval from the Institutional Review Board (IRB) of the Medical School REGIOMED Coburg on February 19th, 2024, in accordance with §2 of its Statutes. Given the retrospective nature of this project, additional study registration was not deemed necessary.

4. RESULTS

Patient-related data were extracted from the respective files and analyzed. A summary was then prepared, presented in Table 1.

Table 1. Patients and Treatment Characteristics

Variable		n (%)
All patients		60 (100)
Gender	Male	15 (25)
	Female	45 (75)
Age	Median	66 years
	Range	29-90 years
T-Category	T1-2	36 (60)
	T3-4	24 (40
N-Category	N0	44 (73)
	N1-2	16 (27
Total dose radiotherapy	Median	50.4 Gy
	Range	45-59.4 Gy
Chemotherapy	No chemotherapy	14 (23)
	FU/Mitomycin	46 (77)

Data are presented as absolute number of cases (%)

A total of 60 patients were selected for this study and classified based on several variables. The median age at initial diagnosis was 66 years, with an overall age distribution ranging from 29 to 90 years. Gender distribution revealed 15 males (25%) and 45 females (75%).

The cohort was stratified according to the TNM classification: 36 patients (60%) presented with T1 or T2 diagnoses at the beginning, while 24 patients (40%) had T3 or T4 diagnoses. Additionally, 44 patients (73%) were classified as N0 at the start of treatment, and 16 patients (27%) as N1-2.

In our study six patients (10%) experienced locoregional failure, with cancer reappearing at the original site following the completion of the initial treatment cycle. Ten patients (17%) exhibited treatment failure, defined as recurrence of cancer at any anatomical site after the conclusion of therapy. Fourteen patients (23%) succumbed to various causes during the study period.

To visualize the distribution of our data set, we used quantile-quantile plots (Q-Q plots) and histograms for each group. Figures 4-8 show non-normal distributions, as evidenced by points that clearly deviate from the reference line and the Gaussian distribution curve.

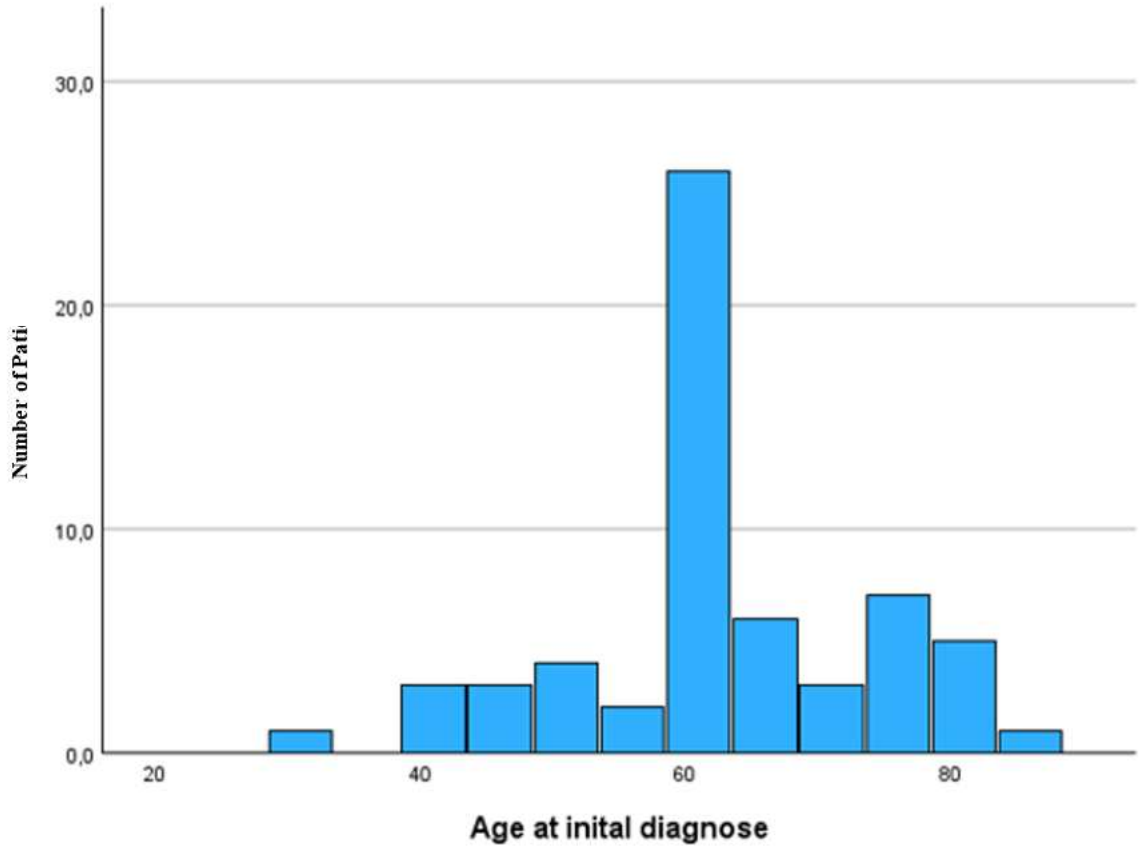

Figure 4. Histogram “Age at initial diagnose”

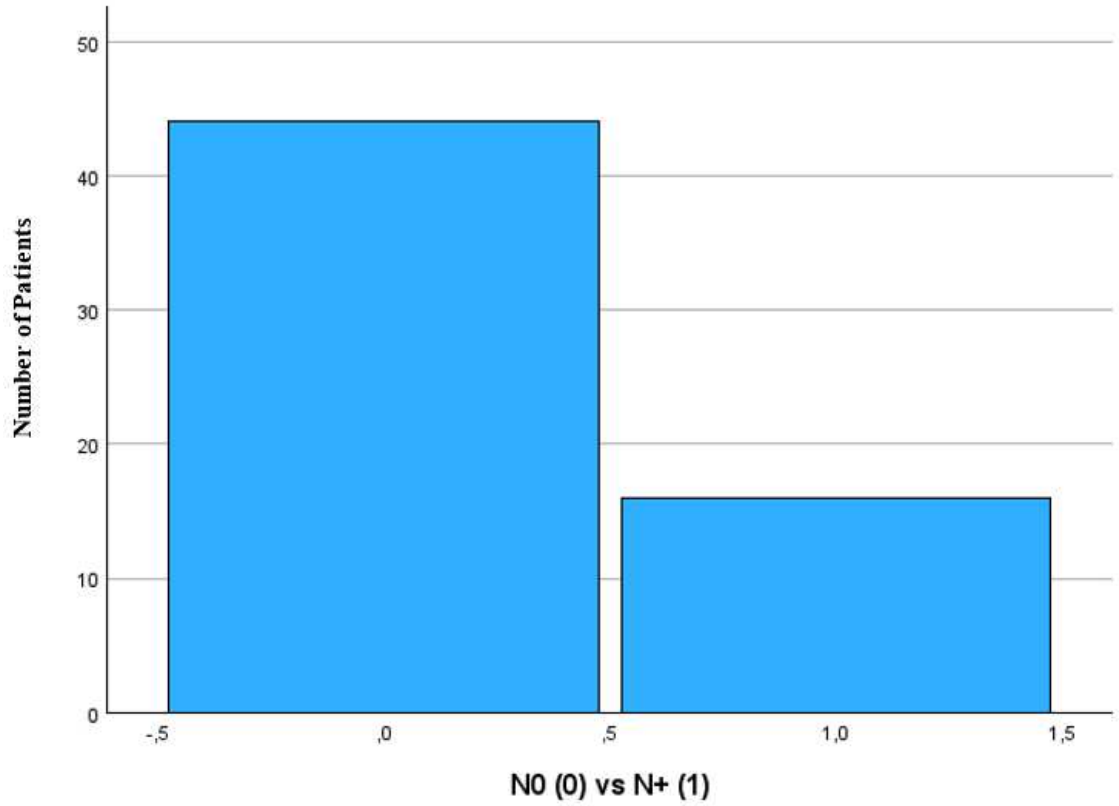

Figure 5. Histogramm “N0 vs N+”

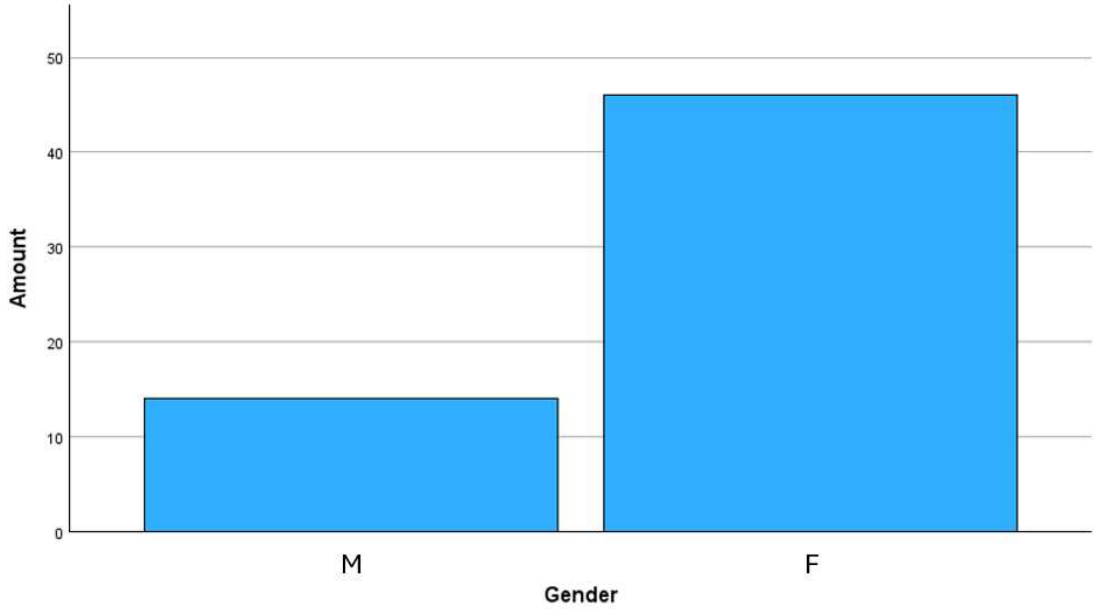

Figure 6. Histogramm “Gender”
M: male
F: female

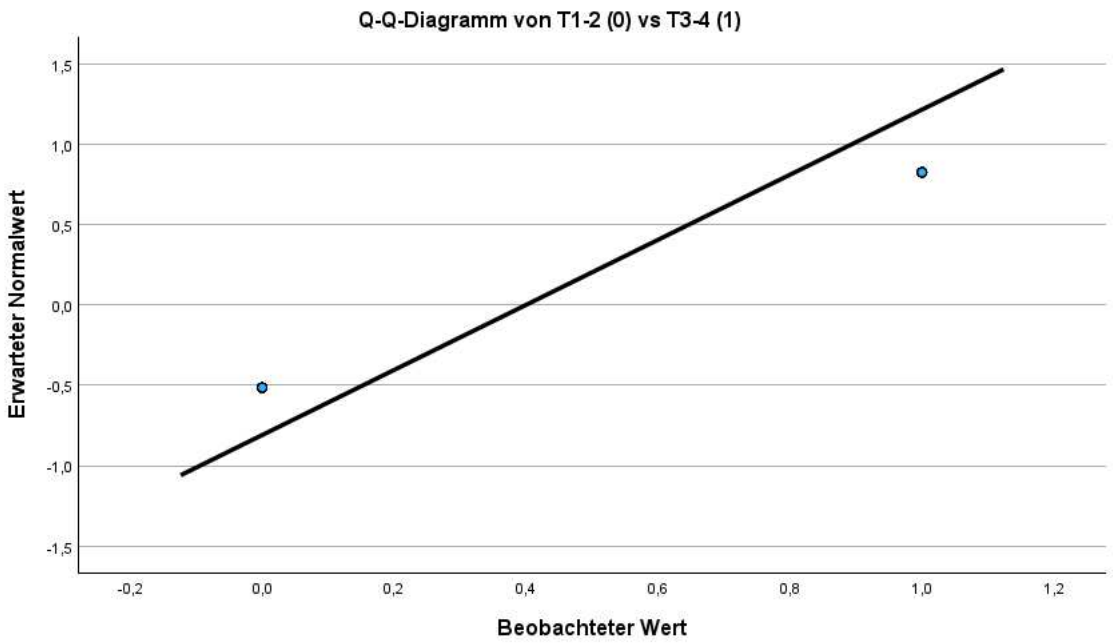

Figure 7. Q-Q-Plot "T1-2 vs T3-4" in our patient pool

Figure 8 shows that patients were further categorized based on their treatment regimen: 46 patients (77%) received radiochemotherapy with 5-Fluorouracil (5-FU) and Mitomycin C, while 14 patients (23%) received radiotherapy alone.

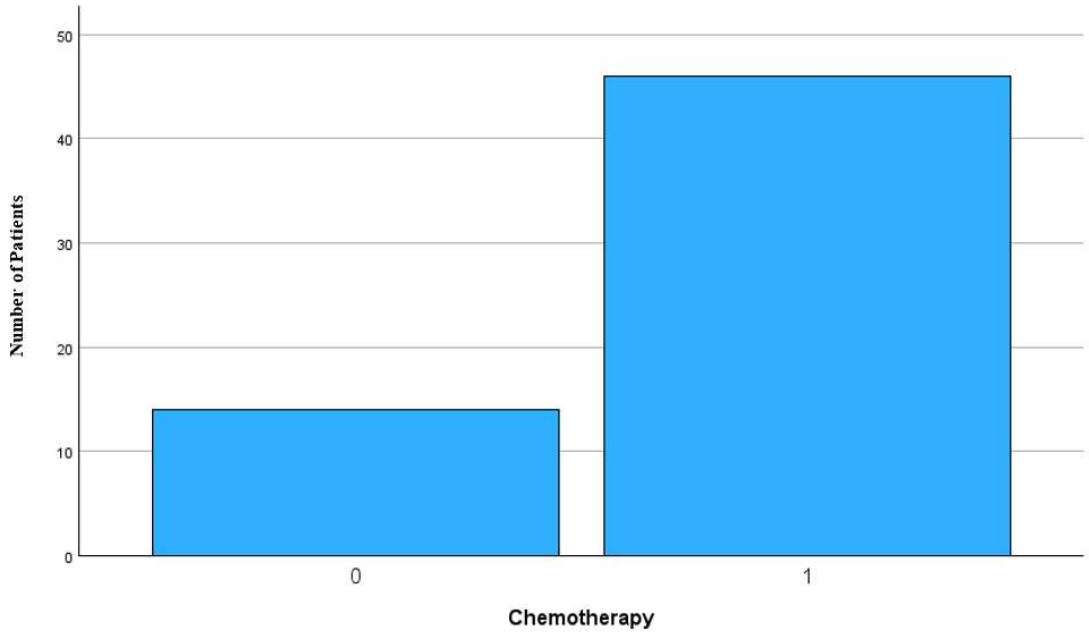

Figure 8. Histogramm in the "Chemotherapy"

This histogram (Figure 9) shows the distribution of the duration of radiotherapy for the sample size of 60 observations. The x-axis represents the duration, while the y-axis represents the frequency of occurrences for each duration interval. The histogram reveals a right-skewed distribution of the duration variable, with a concentration of values around the mean (41.92). The standard deviation of 9.149 suggests moderate variability in the data, indicating that while most durations are close to the mean, there are some longer durations present in the dataset. The total dose of radiotherapy administered had a median of 50.4 Gy, with doses ranging from 45 Gy to 59.4 Gy.

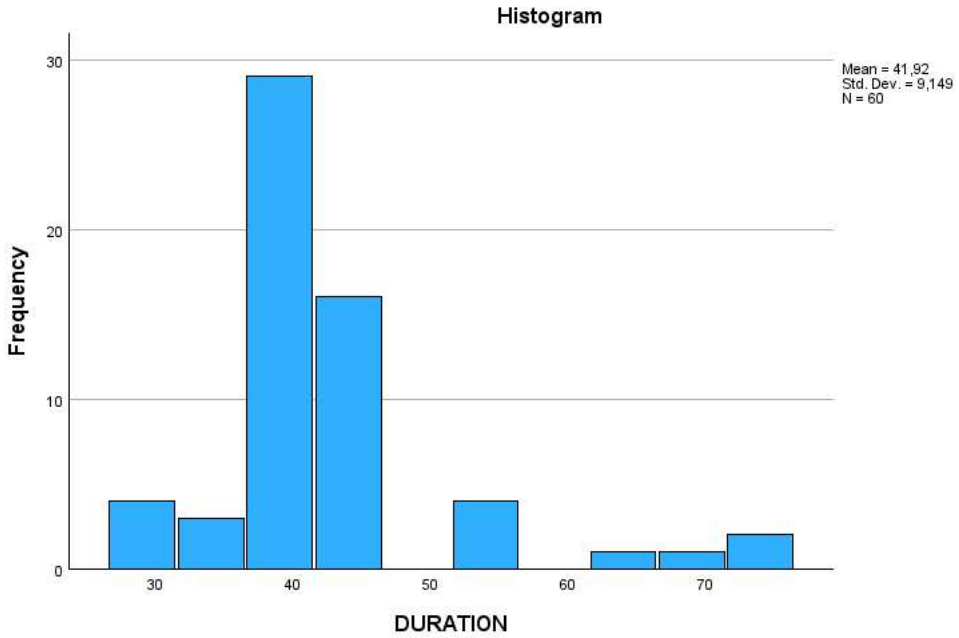

Figure 9. Histogramm in the "Duration of radiotherapy"

The examination of the Q-Q plots and histograms present a non-normal distribution. Since the variables are in absolute numbers the visualization is easy comprehensive. The skewness strongly suggests a non-normal distribution. Unlike a normal distribution where the bars are typically of similar height and distribution, here the data significantly deviates from this pattern. Additionally, the positioning of the bars, is not symmetrical around the median, further confirming the asymmetrical nature of the distribution. This observation was verified using the Shapiro-Wilk Test of normality for each metric and group, as detailed in Table 2. The results of these tests revealed a significant departure from normal distribution for each group, as evidenced by p-values less than 0.05. Given the breach of the normality prerequisite needed for parametric testing, we opted for non-parametric methods for our further analyses.

Table 2. Shapiro-Wilk Test

Group	Variable	*W*†	*P**
Patients	Chemotherapy	0.524	<0.001
Patients	T1-2 vs T3-4	0.522	<0.001
Patients	N0 vs N+	0.552	<0.001
Patients	OS	0.524	<0.001

Data are presented as numbers
* Shapiro-Wilk test for normality
† Test statistic for Shapiro Wilk Test

Five year overall patient survival was analyzed using the Kaplan-Meier method, with the results summarized in Figure 10.

The graph in figure 10 depicts a Kaplan-Meier survival analysis, illustrating the five-year overall survival rate over time, measured in months. Fourteen out of all 60 patients died (23.3%). Five year overall survival was 68% (±7.8%). The y-axis represents the cumulative survival probability, ranging from 0 to 1, while the x-axis represents time in months. The survival curve starts at 1 (100% survival) and decreases over time. The graph specifically highlights the five-year survival rate, which is 68%. This indicates that 68% of patients are alive five years after the start of the observation period. The curve shows a steady decline in survival probability within the first 100 months. Beyond 100 months, the survival curve stabilizes. The initial decline in the survival curve suggests that the first few years are critical for patient outcomes, with more substantial decreases in survival probability. However, the stabilization of the curve beyond 100 months indicates that those who survive the initial period tend to have a relatively stable long-term prognosis.

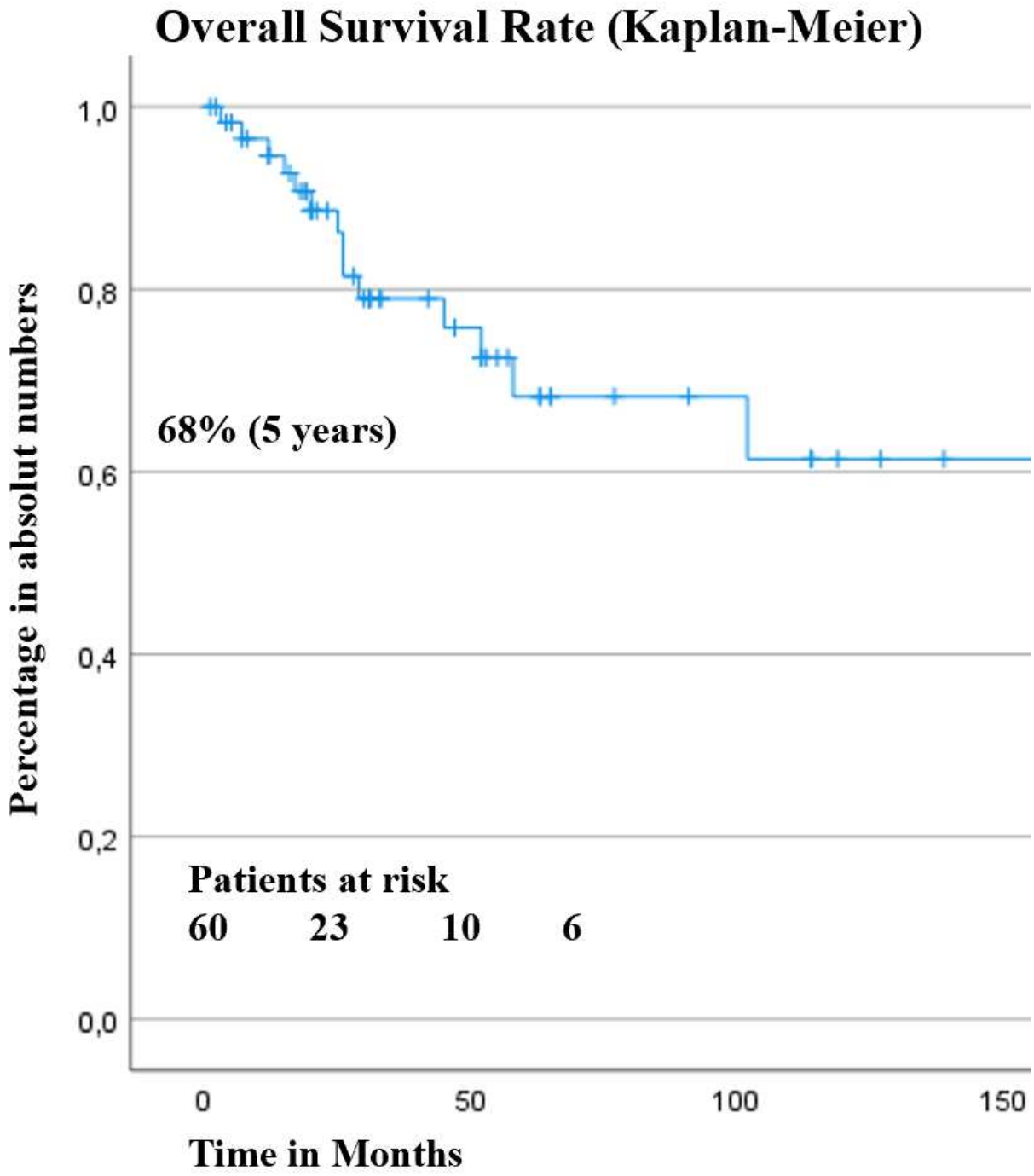

Figure 10. Overall Survival Rate based on Kaplan Meier Test

Figure 11 presents a Kaplan-Meier survival analysis comparing the cumulative survival rates of patients with different tumor stages at the time of diagnosis. The y-axis represents cumulative survival probability, ranging from 0 to 1, while the x-axis represents time in days. T1-2 (0)**:** Patients with early-stage tumors (indicated by the blue line). T3-4 (1): Patients with advanced-stage tumors (indicated by the green line).

The early decline in survival probability is observed in both groups, but the T3-4 group shows a more pronounced drop initially. Around 100 months, the survival curves show a noticeable separation, with the T1-2 group stabilizing at a higher survival rate than the T3-4 group.

This Kaplan-Meier survival curve clearly demonstrates the impact of tumor stage at diagnosis on patient survival. Patients with early-stage tumors (T1-2) have a higher cumulative survival probability compared to those with advanced-stage tumors (T3-4). Still the Logrank test demonstrated no significant difference in overall survival between the two groups, with survival rates of 69% for T1-2 and 67% for T3-4 (P=0.83).

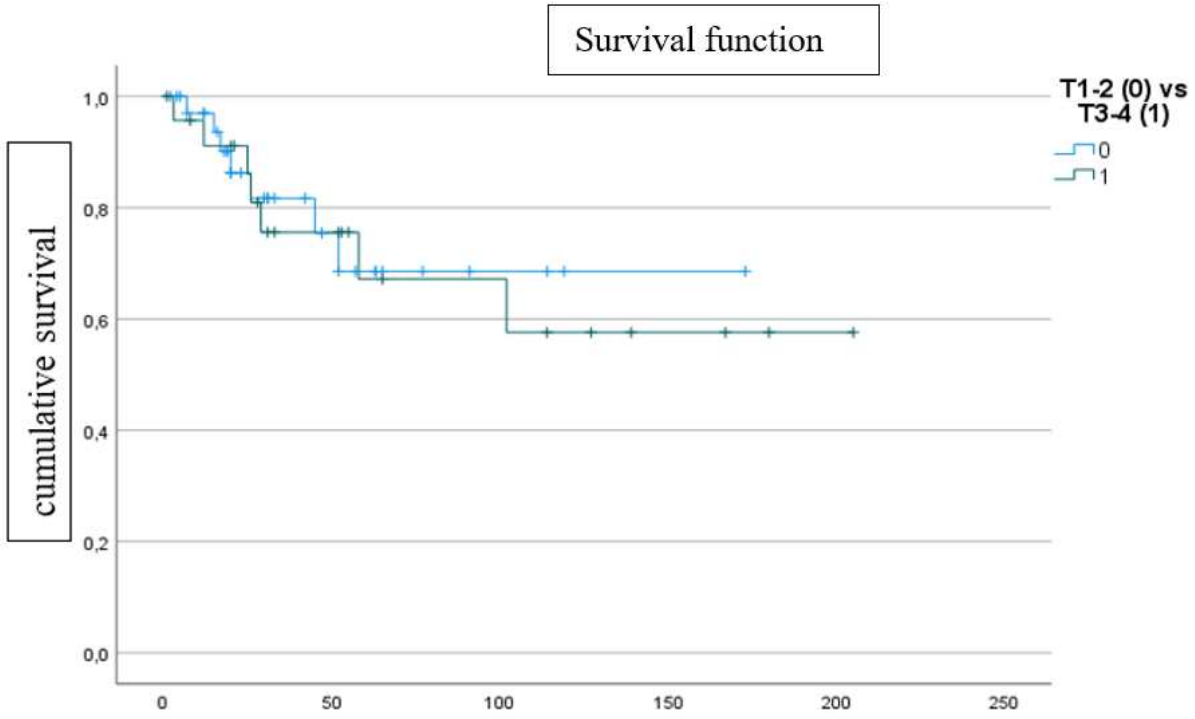

Figure 11. Five year OS comparison between T1-2 vs T3-4

This graph in Figure 12 presents a Kaplan-Meier survival analysis comparing the cumulative survival rates of patients with and without lymph node involvement at the time of diagnosis. The y-axis represents cumulative survival probability, ranging from 0 to 1, while the x-axis represents time in months. Patients without lymph node involvement (N0), including 44 (73%), at the time of diagnosis (indicated by the blue line). Patients with lymph node involvement (N+), consisting of 16 (27%), at the time of diagnosis (indicated by the green line). The survival rates for these groups were 72% and 59%, respectively. The graph demonstrate the five-year survival according to the groups. The p-value for the Logrank rest showed no

significant difference (p=0.74). Early in the observation period, the N+ group demonstrates a steeper decline in cumulative survival, indicating a higher mortality rate among patients with lymph node involvement at the time of diagnosis.

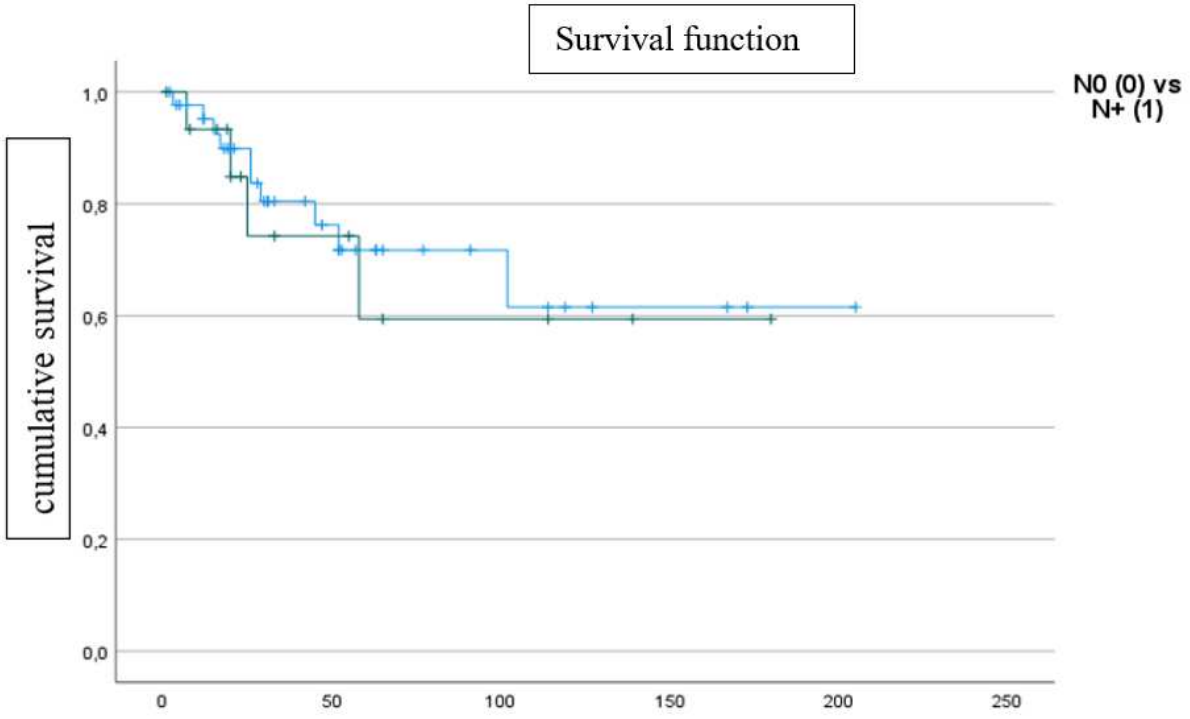

Figure 12. Five year OS comparison between N0 vs N+

The Figure 13 includes two survival curves labeled "Chemo" with two groups: "0" and "1." These represent patients who did not receive chemotherapy (0) and those who did (1).The graph shows that patients who received chemotherapy (Chemo 1) tend to have better survival outcomes compared to those who did not receive chemotherapy (Chemo 0) over the observed period. The blue curve (Chemo 0) appears to decline more steeply and has a lower survival probability compared to the green curve (Chemo 1). Additionally, the evaluation of the impact of concurrent chemotherapy and radiotherapy versus radiotherapy alone revealed survival rates of 62% for patients receiving combined treatment and 81% for those receiving only radiotherapy. The p-value for this comparison was 0.65, suggesting no significant difference between the two treatment modalities in this study.

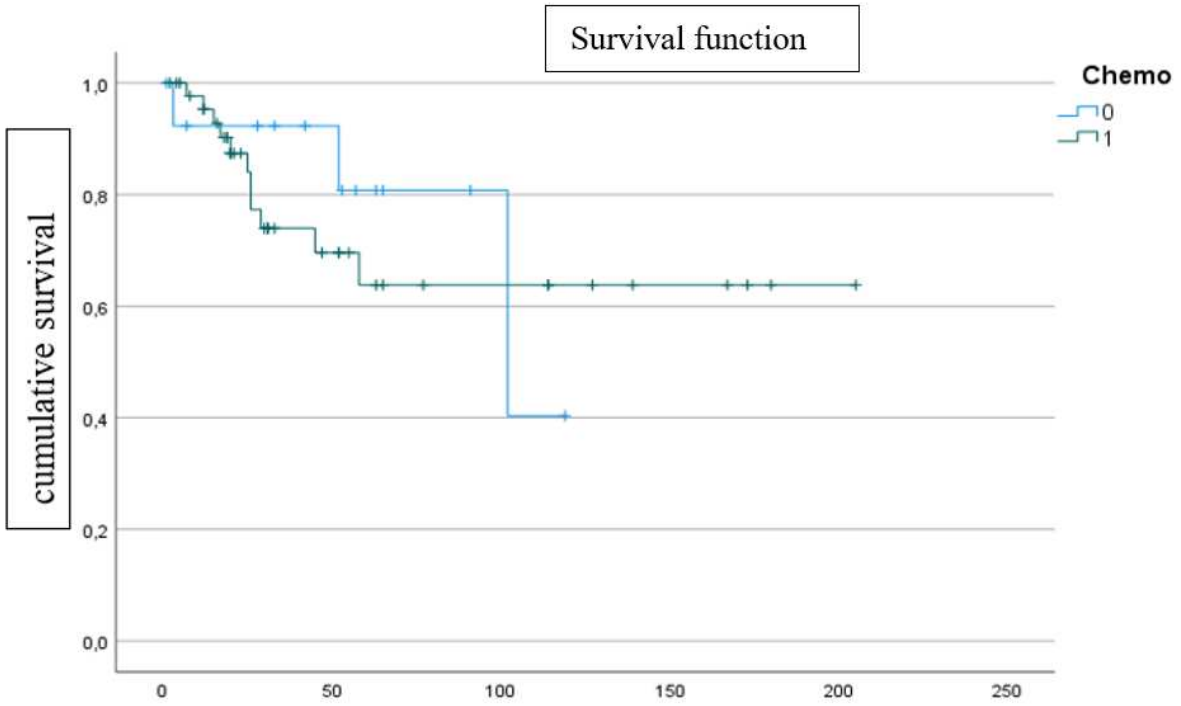

Figure 13. Five year OS comparison between receiving chemotherapy and only radiation therapy

Radiochemotherapy = 1

Only radiotherapy = 0

Stated in Figure 14 is the five-year no evidence of disease (NED) survival rate. The analysis revealed an mean five-year NED survival of 82 month (±5.5%). the Kaplan-Meier survival curve demonstrates that the majority of patients (82%) remain disease-free five years after the initial observation period, with the survival rate stabilizing beyond this point. This information is crucial for understanding the long-term efficacy of the treatment or intervention being studied. The survival curve shows an initial decline in the NED survival rate, with several drops indicating disease recurrence or deaths. After approximately 50 months, the curve stabilizes, suggesting a plateau in the survival rate.

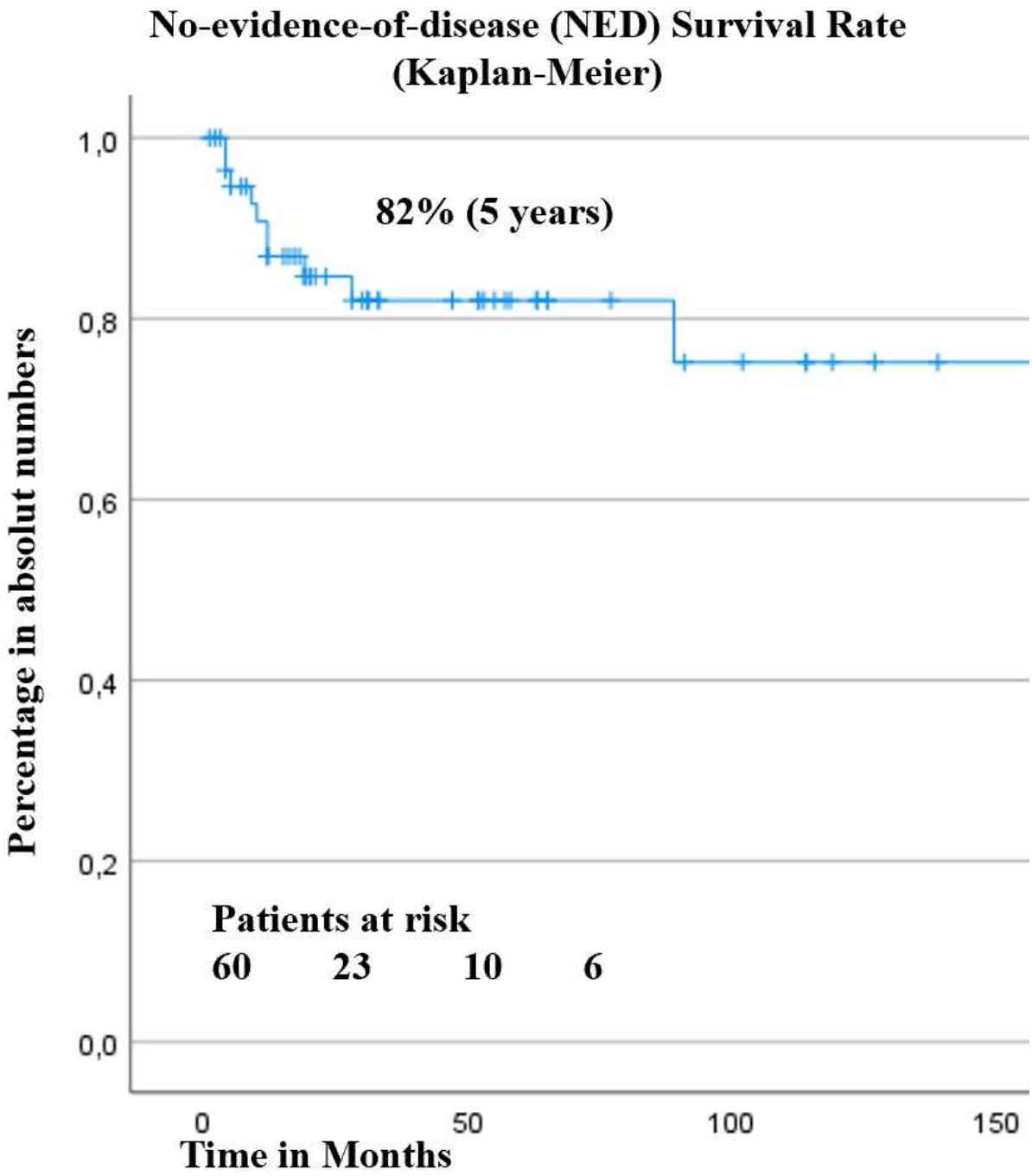

Figure 14. Five year survival rate for NED time

Stated in Figure 15 is the five-year locoregional failure-free survival rate. The analysis revealed a mean five-year locoregional failure-free survival of 87% (±4.9%). The Kaplan-Meier survival curve demonstrates that the majority of patients (87%) remain free from locoregional failure five years after the initial observation period, with the survival rate showing only minor declines. Notably, locoregional failure occurred in 6 out of 60 patients (10%), highlighting specific instances where the treatment did not prevent disease progression.

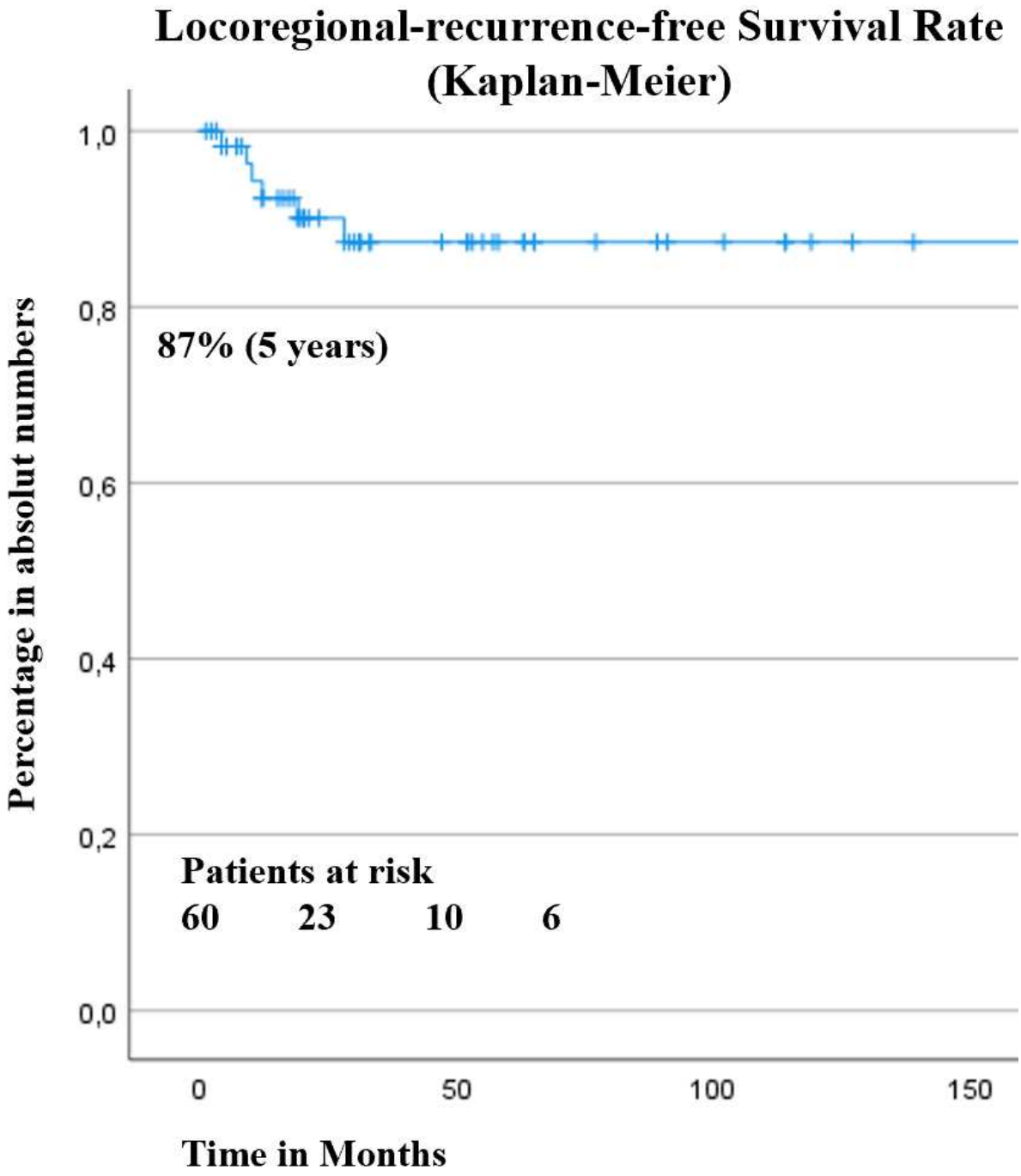

Figure 15. Five year OS for locoregional-recurrence free survival rate

To test the statistically significants in the differences between Chemotherapy use, T1-2 vs T3-4, N0 vs N+ and the overall survival rate, we used the Wilcoxon Rank Sum Test (Table 3). The findings indicate that there was no significant influence on the overall survival for Chemotherapy (W = 419, P = 0.849), T1-2 vs T3-4 (W = 1056, P = 0.387) and N0 vs N+ (W = 1334, P = 0.855).

Table 3. Wilcoxon Rank Sum Test

Group	W†	*P**
Chemotherapy	419.00	0.849
T1-2 vs T3-4	1056.00	0.387
N0 vs N+	1334.	0.855

Data are presented as numbers
* Wilcoxon Rank Sum Test
† Test statistic for Wilicoxon Rank Sum test
‡ Effect Size

Table 4 summarizes the outcomes for the Logrank test used for the Kaplan-Meier curves for the prognostic factors with the associated p values.

Table 4. Prognostic factors for overall survival (Logrank-Test)

Factor	Five year overall survival	P value
T1-2 vs T3-4	69% vs 67%	0.83
N0 vs N+	72% vs 59%	0.74
Chemotherapy vs no Chemotherapy	64% vs 81%	0.65

This graphical representation in Figure 15 uses a color scale where shades of blue indicate positive correlations and shades approaching red suggest negative correlations. The strength of each correlation is numerically depicted, with values close to 1 or -1 representing strong positive or negative correlations, respectively, and values near 0 indicating negligible correlation.

Overall Survival Time shows a strong positive correlation (0.97) with both NED Time (No Evidence of Disease) and Locoregional Recurrence-Free Time, suggesting that longer overall survival is closely associated with extended periods without disease and without locoregional recurrence. This implies that factors enhancing overall survival are likely beneficial for prolonging disease-free intervals and preventing regional recurrence.

Colostomy-Free Survival Time also exhibits a strong positive correlation with Overall Survival Time (0.71), NED Time (0.72), and Locoregional Recurrence-Free Time (0.72). This relationship indicates that longer durations without the need for a colostomy are associated with better overall survival and longer disease-free periods, highlighting the importance of maintaining intestinal integrity as part of the treatment efficacy.

The duration of radiotherapy shows only weak correlations with the other metrics (ranging from -0.04 to 0.23). This suggests that the length of treatment does not significantly impact the survival outcomes in our dataset.

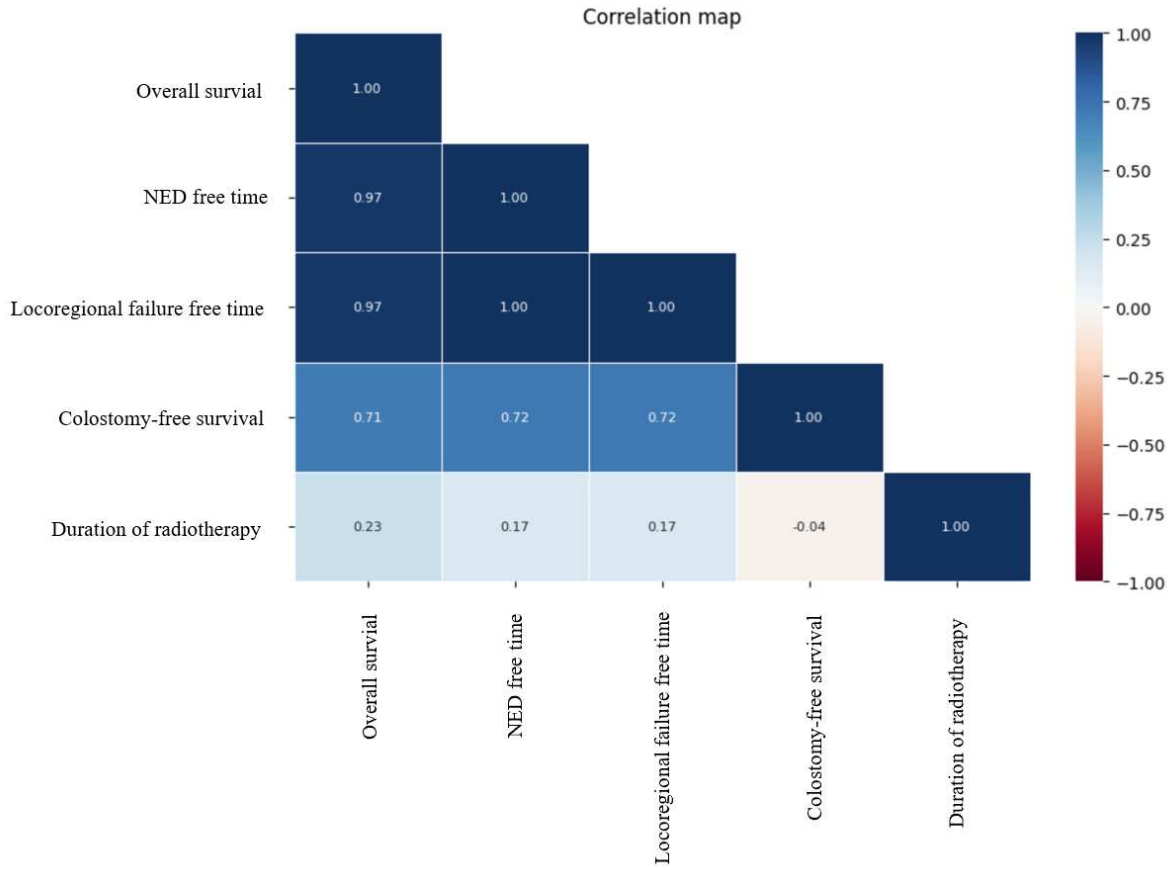

Figure 15. Correlation map

5. DISCUSSION

The incidence of new cases of anal cancer has been steadily increasing over several years. To address this problem, many studies have been conducted on identification, treatment, and outcome. In this study we wanted to evaluate the prognostic parameters in patients in this with ICD 10: C21 diagnosed anal cancer, who have received treatment in the Coburg cancer center, in the outcome. Radiotherapy with or without chemotherapy is considered the standard of practice for the treatment (58) of anal cancer. Radiotherapy allows us to treat the cancer locally. Chemotherapy works systemically and reduces the risk of the cancer spreading to adjacent or distant other tissues.

In this study, overall survival was first determined in general and in relation to prognostic factors such as the TMN classification, the presence of recurrence, the type of treatment the patients received and the gender.

The average age of patients at their initial diagnose was 66 years, which is slightly higher than the worldwide average of 64 years (59,60).

The mean duration of the radio therapy was 41.92 days (range: 29-73 days). The usual time span for treatment is five days per week over five weeks (61). This leads to 33 days minimum, not accounting for sickness of the patient, the missing of appointments or closure of the medical practice. For this dataset the correlation between the duration and patient outcome were unsignificant.

Another study found out that a reduction in the number of fractions delivered per week was independently associated with decreased overall survival (OS). Specifically, a threshold of 4.72 fractions per week (equivalent to approximately 2 missed fractions over a 30-fraction treatment) marked the most significant differences in OS. Efforts should be made to prevent any interruptions in radiotherapy (RT) for patients with anal cancer (SCCA) and to adequately compensate for any unavoidable treatment breaks to minimize the overall duration of RT (62).

The total dose of radiotherapy administered had a median of 50.4 Gy which corresponds to the standard doses applied in similar studies (63,64).

The 5-year overall survival rate observed among these 60 patients was 68±7.8% months. Fourteen out of the 60 patients died, which leads to a survival rate of 76.7%. This is comparable and even better than other research papers suggest (65,66). The 5-year-NED survival was 82±5.5%. Eight out of 60 patients had a recurrence. Also, the 5 year locoregional failure-free survival 87±4.9%. These timespans are in accordance to similar studies in that field (67). As demonstrated in figure 15 these aspects have an high impact on the overall survival in our study.

In our study the patients diagnosed with T1-2 had a slightly better overall survival (69%) than patients diagnosed with T3-4 (67%). The logrank test and the Wilcoxon Rank test did not

demonstrate a significant difference (p = 0.83 and p = 0.387, respectively) in these prognostic factors. The same is true for the stating of N0 versus N+ at the initial diagnosis (p= 0.74). The OS was 72% and 59% respectively. This is opposite to the importance of T and N stages according to the literature (68).

The comparison between patients treated with Chemotherapy additionally to the radiation therapy against no Chemotherapy had the greatest effect. The survival was 64% vs 81% OS, but still had no significant impact according to the Logrank and Wilcoxon Rank test (p=0.65 and p=0.849). These findings are not according to the latest literature since chemotherapy remains the gold standard (69).

The significance of enhancing our knowledge of anorectal carcinomas cannot be overstated. Enhanced insights could lead to the creation of targeted treatments that are specifically designed for the distinct properties of anorectal tumors. Furthermore, early detection techniques, which are currently less advanced than those for other gastrointestinal cancers, stand to gain considerably from a deeper and more detailed comprehension of this disease (70).

The table displayed summarizes various randomized trials focusing on radiotherapy and chemoradiotherapy for anal carcinoma, providing insights into treatment regimens and their outcomes in terms of survival rates, disease-specific survival, and colostomy rates. Each trial explores different aspects of treatment efficacy, such as the impact of intensified radiotherapy doses or the addition of chemotherapy agents like Mitomycin C and cisplatin. These studies contribute valuable data regarding the comparative effectiveness of various treatment protocols over periods extending up to 12 years.

Despite the substantial body of research represented in these trials, the complexity of anal carcinoma and the variability in patient responses underscore the need for continued research in this field. There is a particular necessity to develop more refined therapeutic approaches that can be tailored to individual patient profiles, enhancing both the effectiveness and tolerability of treatments. Furthermore, advancements in molecular biology and genetics offer promising avenues for identifying biomarkers that could predict treatment responses and potentially guide personalized therapy strategies.

Moreover, the ongoing need for better understanding of the long-term impacts of these treatments on patient quality of life and functional outcomes remains critical. As such, future studies should not only strive to improve survival metrics but also focus on minimizing the adverse effects associated with treatment, thereby enhancing overall patient well-being. The goal of such research would be to achieve a balance between therapeutic efficacy and quality

of life, ensuring that survivors of anal carcinoma can lead full and active lives post-treatment.

Available randomized trials on radiotherapy/chemoradiotherapy for anal carcinoma

Trial	Cases (*n*)	Treatment regimen	FU (y)	LRR	DSS (%)	CR (%)	OAS (%)
EORTC 22861 (27)	110	A: RT 45 Gy + 15 to 20 Gy boost B: CRT 45 Gy + 15 to 20 Gy boost; 5-FU (750 mg/m^2, d1 to 5 and d29 to 33); MMC (15 mg/m^2, d1)	3.5	A: 48% (25/52) B: 29% (15/51) At 5 years: 18% improvement in arm B (p = 0.02)	N/A	At 5 years: 32% improvement in arm B (p = 0.02)	At 5 years: 56% for all patients (p = ins.)
UKCCCR/ACT I (28. 29)	577	A: RT 45 Gy, possibly 15 to 25 Gy boost B: CRT 45 Gy, possibly 15 to 25 Gy boost; 5-FU (750 mg/m^2, d1 to 5 and d29 to 33 or 1000 mg/m^2, d1 to 4 and d29 to 32); MMC (12 mg/m^2, d1)	13.1	A: 54% (153/285) B: 29% (86/292) (p <0.001)	At 12 years: 12.5% improvement in arm B (p = 0.004)	At 12 years: approx. 10% improvement in arm B (p = 0.004)	At 12 years: 5.1% better in arm B (p = ins.)
RTOG 87-04 (30)	291	A: RT 45 to 50.4 Gy; 5-FU (1000 mg/m^2, d1 to 4 and d28 to 31) B: CRT: 45 to 50.4 Gy; 5-FU (1000 mg/m^2, d1 to 4 and d28 to 31); MMC (10 mg/m^2, d1 + 28) N.B.: Salvage CRT (9 Gy; cisplatin) if positive biopsy following induction in both arms	3	N/A	N/A	A: 22% (32/145) B: 9% (13/146) (p = 0.002)	A: 71% (103/145) B: 78% (114/146) (p = ins.)
RTOG 98-11 (31. 32)	649	A: CRT 45 to 59 Gy; 5-FU (1000 mg/m^2, d1 to 4 and d29 to 32); MMC (10 mg/m^2, d1 + 29) B: CRT 45 to 59 Gy; 5-FU (1000 mg/m^2, d1 to 4, d29 to 32, d57 to 60 and d85 to 88); cisplatin (75 mg/m^2, d1, 29, 57, 85)	5	A: 21% (67/325) B: 27% (86/324) (p = ins.)	N/A	A: 33% (106/325) B: 41% (132/324) (p = 0.05)	A: 78% (238/325) B: 71% (209/324) (p = 0.026)
ACT II (33)	940	A: CRT 50.4 Gy; 5-FU (1000 mg/m^2, d1 to 4 and d29 to 32); MMC (12 mg/m^2, d1) B: CRT 50.4 Gy; 5-FU (1000 mg/m^2, d1 to 4 and d29 to 32); cisplatin (60 mg/m^2, d1, 29) N.B.: Second randomization to 5-FU and cisplatin maintenance chemotherapy in both groups	5.1	N/A	N/A.	A: 11% (52/472) B: 13% (60/468) (p = ins.)	A: 22% (103/472) B: 23% (108/468) (p = ins.)
UNICANCER ACCORD 03 (34)	307	A: CRT 45 Gy + 15 Gy boost; 5-FU (800 mg/m^2, d1 to 4 and d29 to 32); cisplatin (80 mg/m^2, d1 + 29) B: CRT 45 Gy + 20 to 25 Gy boost; 5-FU (800 mg/m^2, d1 to 4 and d29 to 32); cisplatin (80 mg/m^2, d1 + 29) N.B.: Second randomization to 5-FU and cisplatin induction chemotherapy in both groups	4.2	At 5 years: 4.9% better in arm B (p = ins.) No difference in terms of induction	At 5 years: 4.1% better in arm B (p = ins.) No difference in terms of induction	At 5 years: 4.1% better in arm B (p = ins.) No difference in terms of induction	N/A

Figure 16. Overview of available cancer research studies

Source: Table 1. Available randomized trials on radiotherapy/chemoradiation for anal carcinoma | [accessed July 25 2024]

Abbreviations: FU, Follow-up time; years; LRR, Locoregional relapse rate; DSS, Disease-specific survival; CR, Colostomy rate; OAS, Overall survival; A, Standard treatment arm; B, Experimental arm; RT, Radiotherapy; CRT, Chemoradiotherapy; MMC, Mitomycin C. | https://www.aerzteblatt.de/int/archive/article/169021/The-differential-diagnosis-and-interdisciplinary-treatment-of-anal-carcinoma

It is essential to acknowledge the inherent limitations of this study, including the study design, sample size, and other factors that may bias the interpretation and generalizability of the findings. The retrospective design of the study poses limitations due to the reliance on existing documentation. Data for this study was acquired through ORBIS, a well-structured electronic database integral to healthcare documentation. However, the potential for bias exists if the documentation is incomplete, inaccurate, or flawed.

We were unable to analyze all possible confounding factors. Specific variables such as exact body measurements, regular alcohol consumption, smoking patterns, sleeping patterns, patterns of daily physical behavior, and detailed nutritional habits, including supplement intake, could not be integrated into the analysis.

This study is limited by its small sample size. There were in total 60 eligible patients, which received treatment. In addition, all patients were recruited from one single Cancer Center. The reginal influences of the environment and others were not investigated in this study.

Therefore, the results can only be applied to a larger population to a limited extent. Furthermore, other comorbidities have not been taken into account. This makes a definitive statement about the influence of different prognostic factors difficult. There should be further investigation into those elements to find a definitive answer to the question.

6. CONCLUSION

1. Among our patient group of 60 people with anal cancer, who were treated in the Coburg Cancer center, the patterns of recurrence for locoregional failure and any failure were 10% and 17%.
2. In our study the five year overall survival was 68%, NED survival was 82% and locoregional failure free survival was 87%
3. There was no significant difference in five-year overall survival between T status groups (69% vs 67%, p=0.83).
4. N status did not significantly affect five-year survival (72% vs 59%, p=0.74).
5. The use of chemotherapy during treatment did not significantly impact five-year survival (64% vs 81%, p=0.65).

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8. SUMMARY

Objectives: This study aimed to evaluate survival data in anal cancer patients following treatment in the Coburg cancer center. The objective was to identify prognostic factors that modify the outcome for these patients.

Material and methods: Patients treated between 2011 and 2022 for anal cancer were selected from the Coburg Cancer center. For this retrospective study 60 patients were used after excluding 3 patients due to various reasons (change of citizenship und inclomplete treatment) Analysis of the data was focused age at initial diagnosis, gender, duration of radiotherapy, single and total dosages of radiation, TMN classification, overall survival, NED survival, reoccurrences and treatment differences like the concurrent usage of chemotherapy. For the analysis of statistical data IMB SPSS Statistic version 19 was used. To determine the distribution of data the Shapiro-Wilk Test was employed. Survival rated were calculated by Kaplan Meier method. The log rank and Wilcoxon Rank test were used to calculate differences in survival rated between groups of patients. Qualitative data were expressed as whole numbers and percentages, while quantitative data were expressed as mean ± standard deviation or median and iqr.

Results: In this study the gender distribution was 15 male and 45 female patients. From these 60 people 36 were in the T1-2 stadium at initial diagnose and 24 were in T3-4. 73% (44 patients) had no lymph node involvement. The median radiation dose received was 50.4 Gy with a range from 45 to 59.4 Gy. During the treatment 14 people received a combination of chemotherapy and radiotherapy, while the other 46 received only radiotherapy. The five-year overall survival, 5-year-NED survival, 5- locoregional failure-free survival rates were 68%, 82%, 87%, respectively. Correlations between OS and NED free time, locoregional failure free time and colostomy free time have been established. No significant impact on the five year survival was found for TMN classification or differences in treatment with or without chemotherapy in this study. Slight differences were seen using the Kaplan Meier curves but not to a great extent.

Conclusion: No significant prognostic factor for the outcomes for anal cancer patients has been found in this study. Relationships between OS and NED survival time, locoregional failure-free time, and colostomy-free time have been established. Interpreting these findings should be done with caution due to the consideration of confounding factors. More research is required to comprehend the factors that influence outcomes in patients with anal cancer.