Radiochemotherapy and interstitial brachytherapy as therapeutical approach for cervical carcinoma and its impact on the patients' quality of life

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LIST OF ABBREVIATIONS

5-FU - 5-Fluorouracil

BSA - Body surface area

BT - Brachytherapy

CI - Confidence interval

CIN - Cervical intraepithelial neoplasia

CT - Computed tomography

DM – Distant metastases

EBRT - External beam radiation therapy

EORTC - European Organization for Research and Treatment of Cancer

FDA - Food and Drug Administration

FIGO - International Federation of Gynecology and Obstetrics

Gy - Gray

HDR - High-dose rate

HIV - Human immunodeficiency virus

HPV - Human papilloma virus

HSIL - High-grade intraepithelial lesion

IMRT - Intensity modulated Radiotherapy

IQR - Interquartile range

LD - Low-dose rate

LN - Lymph nodes

LSIL - Low-grade squamous epithelial lesion

LVSI - Lymphovascular space invasion

mg/m^2 - Milligrams per square meter

ml/min - Milliliters per minute

mm^3 - Cubic millimeter

MRI - Magnetic resonance imaging

NED – no evidence of disease

PAP-smear - Cytological smear after Papanicolaou of the cervix

PD-1 - Programmed cell death protein 1

PD-L1 - Programmed cell death 1 – ligand 1

PET-CT - Positron emission tomography-computed tomography

QLQ - Quality of Life questionnaire

QoL - Quality of Life

RCT - Radiochemotherapy

RS - Raw Score

S - Score

SD - Standard deviation

SIP - Sickness Impact Profile

VEGF - Vascular endothelial growth factor and

VEGFR - Vascular endothelial growth factor-receptor

VMAT - -Volumetric modulated arc therapy

WHO - World Health Organization

1 INTRODUCTION

1.1 Cervical cancer

Cervical cancer ranks as the second most prevalent gynecological malignancy and the fourth most common cancer among women (1). Its prevalence is strongly related to the socioeconomic status of the patient. Survival rates hinge on the stage of diagnosis, with early-staged cases boasting survival rates as high as 90%, while more advanced stages exhibit survival rates below 10% (2).

Treatment options vary based on tumor stage and have also changed significantly over the past few years. Current standard treatment for locally advanced cervical cancer involves extensive radiotherapy or radiochemotherapy, encompassing pelvic irradiation and interstitial brachytherapy (3). Surgical approach with and without adjuvant radiochemotherapy are options with early tumor stages. There is an interdisciplinary consultation process to decide which treatment is best for which stage (4). One of the many factors being held into account is the Quality of life (QoL) of the patient during and after the treatment. QoL is a complex and wide-ranging issue that reflects patients' experiences with the disease, its treatment and the long-term consequences associated with it (5).

To properly assess QoL, two official questionnaires can be utilized. The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 is a comprehensive questionnaire applicable to a wide range of cancer types, while the EORTC-QLQ-CX24 was specifically designed to address the QoL of cervical cancer patients (1).

1.1.1 Etiology

Cervical cancer is primarily caused by infection with high-risk human papilloma virus (HPV) types, particularly HPV type 16 and 18. In about 40-60% of squamous cell carcinoma HPV-type 16 can be found, while HPV-type 18 is predominantly found in adenocarcinoma of the cervix (6). HPV is a common sexually transmitted infection. In most cases it will be cleared by the immune system without long term consequences. However, a persistent infection leading to a chronic course increases the risk of developing a HPV-associated cervical carcinoma due to occurrence of precancerous lesions like cervical intraepithelial neoplasia (CIN) (7).

The recognition of persistent HPV infections as the primary etiological factor behind cervical cancer has propelled the advancement of primary and secondary preventive measures. Primary preventions include vaccines as prophylaxis against the high-risk HPV types (8). There are three vaccinations available, namely Gardasil®, Gardasil 9® and Cervarix®. Gardasil 9® is a nonavalent vaccination (including high-risk HPV type 6, 11, 16, 18, 31, 33, 45, 52, and 58),

whereas Gardasil® helps to prevent an infection with four types (including high risk HPV type 6, 11, 16, 18). Cervarix® protects only against the high-risk HPV types 16 and 18. The vaccines are injected in women between the age of nine and twenty-six years, preferably before the first sexual intercourse. They are also available for boys. Another protection against HPV is the use of condoms during sexual intercourse (9). Secondary preventions encompass a range of strategies, including the screening with validates HPV assays, the cytological smear after Papanicolaou of the cervix (PAP-smear) and the treatment of precancerous lesion (6).

Other risk factors that are contributing to the development of cervical cancer include early beginning of sexual activity, having multiple sexual partners, a weakened immune system or infection with the human immunodeficiency virus (HIV), low socioeconomic status, cigarette smoking and the long-term use of oral contraceptives. The first three mentioned heighten the risk of HPV-associated cervical cancer by increasing the risk of an HPV infection (6,9).

1.1.2 Cervical cancer symptoms

There are usually no symptoms found in early cervical cancer or precancerous lesions. Thus, screening for possible malignant changes is very important. In Germany, every woman over the age of 20 years should have an annual checkup for cervical cancer. This includes a targeted medical history, examination of the internal and external genitalia and a PAP-smear. This screening method under consideration demonstrates a notable capability in detecting cervical cancer and precancerous lesions, boosting a sensitivity of 80% and specificity exceeding 99%.

Symptoms often start to show, if there is already an advanced stage of cervical cancer. Typical initial manifestations of invasive cervical cancer include abnormal vaginal bleeding (metrorrhagia), including bleeding after menopause, bleeding and spotting in between periods, bleeding after vaginal sex (postcoital bleeding), or having menstrual periods that are longer or heavier than usual. Other symptoms include persistent, serosanguinous vaginal discharge.

In context of even further advanced disease, patients may experience symptoms like lumbosacral pain or flank pain (caused by hydronephrosis), and less frequently urination or defecation problems, as well as swelling of the legs. Importantly, the initial indication of tumor spread are deep leg/ pelvic vein thrombosis or lymphedema (10).

1.1.3 Classification

For the classification of cervical carcinoma, a distinction is made between premalignant and invasive changes.

There are two different approaches for the histological classification of premalignant changes in the cervix. One is the cervical biopsy report, or the CIN grading. This is the most widely used classification in Germany. The main factors taken into account are the degree of ablation of the layers, the presence of atypical cells and the number of mitoses. The gold standard for the diagnosis of CIN is histological examination following conspicuous cytology after a PAP-smear test. For precise localization and to determine the severity of a CIN, a colposcopy is performed with sample collection from the ectocervix. In CIN I, there is mild dysplasia involving approximately one third of the basal epithelium, thus the epithelial architecture is mostly intact. The next stage is CIN II, where there is moderate dysplasia with one to two thirds of the basal epithelium being involved. If there is severe, irreversible dysplasia, it is staged CIN III or carcinoma in situ. More than two thirds of the basal epithelium are involved and there is a complete loss of the organized epithelial architecture. In CIN I-III koilocytes may be present, which is pathognomonic for an HPV-infection (11). The other classification is the Bethesda system for reporting cervical cytology report, which is widely used in the USA. This covers “low grade squamous epithelial lesions” (LSIL) and “high-grade intraepithelial lesions” (HSIL). The LSIL correlates with CIN I or HPV negative CIN II, while the HSIL is comparable to HPV-positive CIN II or CIN III and may progress to a squamous cell carcinoma. Importantly, in all premalignant stages the basement membrane is still intact (10).

Invasive cervical cancer is characterized by a disruption of the basement membrane and most commonly arises from metaplastic squamous cell epithelium in the transformation zone, which depicts the area between the endocervix and the ectocervix. In invasive cervical carcinoma, a distinction is mainly made between squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma is histologically detected in approximately 80% of cases, exhibiting considerable diversity in its subtypes, namely large cell keratinizing, large cell nonkeratinizing, and papillary squamous cell carcinoma. Adenocarcinoma, on the other hand, comprises about 11% of cases and also manifests further histological subtypes, including mucinous, endometrioid, clear-cell, and serous adenocarcinoma. Among these, the endocervical mucinous subtype is the most prevalent. While less frequently encountered, other histologically identified invasive carcinomas of the cervix are the adeno-squamous carcinoma, small cell carcinomas, sarcomas and lymphomas (12).

1.1.4 Staging and Diagnostics

The staging of cervical cancer primarily aims to categorize patients into different prognostic groups to allow tailored treatment accordingly. Pretreatment staging is the most accurate way of determining the extent of the disease. A widely accepted framework for staging cervical cancer, is the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging classification (12). Compared to its previous edition of 2009, the 2018 FIGO classification added importance to magnetic resonance imaging (MRI) as a better method for more accurately measuring of tumor size and parametrial involvement and integrated the importance of lymph node involvement into the staging progress (13).

The 2018 FIGO staging Classification is delineated into four distinct stages with each one of them being further subdivided. Stage I is strictly confined to the cervix. In stage II the tumor is invading beyond the uterus but not involving the lower one-third of the vagina nor the parametrium. The third stage includes involvement of the lower one-third of the vagina, or the parametrium, ureters and lymph nodes. And ultimately, if there are adjacent or distant metastasis present, it is classified as stage IV (14).

Further division und subdivisions can be seen in Table 1 below.

Table 1: 2018 FIGO stages for carcinoma of the *cervix uteri* (14)

Stage			2018 FIGO Definition
I			Confined to cervix
	IA		≤5mm depth
		IA1	≤3mm depth
		IA2	>3mm and ≤5mm depth
	IB		> 5mm depth
		IB1	≤2cm maximum diameter
		IB2	>2cm and ≤4cm maximum diameter
		IB3	>4cm maximum diameter
II			Beyond uterus bit not involving the lower one-third of the vagina or the pelvic sidewall
	IIA		Upper two-thirds of the vagina
		IIA1	Upper two-thirds of the vagina and ≤ 4cm
		IIA2	Upper two-thirds of the vagina and > 4cm
	IIB		Parametrial invasion
III			Lower vagina, pelvic sidewall, ureters, and lymph nodes
	IIIA		Lower one-third of the vagina
	IIIB		Pelvic sidewall
	IIIC		Pelvic and para-aortal lymph node involvement
		IIIC1	Pelvic lymph node involvement
		IIIC2	Para-aortic lymph node involvement
IV			Adjacent and distant organs
	IVA		Rectal or bladder involvement
	IVB		Distant organs outside the pelvis

Key components in staging and confirming the diagnosis entail a detailed medical history, a thorough clinical examination, and a gynecologic inspection and palpation examination. In instances where examination conditions prove challenging, it is advisable to conduct an examination under anesthesia with inspection, colposcopy, tissue collection by biopsy or curettage, and rectovaginal palpation to determine the extent of the tumor. Mandatory laboratory diagnostics include a complete blood count, electrolyte and coagulation status, renal and liver function parameters, and tumor markers: SCC in squamous cell carcinoma or CEA and CA 125 in suspected adenocarcinoma (10). Histological confirmation of invasive cervical carcinoma is achieved through biopsy, which may be performed by curettage or similar means, or during surgical staging. The latter additionally serves to clarify the lymph node status and to assess the intra- and retroperitoneal spread (15).

The staging procedure follows a structured approach, where after taking a history, performing clinical examinations, and obtaining a laboratory diagnosis, the first step should be to perform a transvaginal and transrectal ultrasound examination. This is used to determine tumor size and to delineate the tumor from adjacent organs. If involvement or infiltration of neighboring organs is suspected based on the findings in the aforementioned examinations, MRI of the pelvic organs is requested. Cervical carcinomas typically show intermediate signal intensity on T2-weighted MRI images, which optimally distinguishes the normal cervical stroma from the tumor. Tumor size can be graded on MRI with an accuracy of up to 0.5 cm (10,13). However, detection of tumor-involved pelvic lymph nodes presents challenging on ultrasound and on MRI. Computed tomography (CT) can serve as an alternative to MRI but is inferior in terms of specificity and sensitivity for determining tumor size. However, CT scans aid in fine-needle aspiration of enlarged lymph nodes in the retroperitoneum. For identification of pelvic, para-aortic or distant metastases, positron emission tomography (PET)-CT is performed. Final certainty is provided only by invasive surgical, mostly laparoscopic staging with biopsy, as histologic examination is the only valid method for assessing lymph node status (10).

1.2 Therapy of cervical cancer

To ensure the most effective treatment plan for each patient, a multidisciplinary tumor-board consultation involving pathology, gynecology, radiology, and radiation oncology is necessary (10). The FIGO stage established in the staging process, as well as a variety of patient factors, are decisive for the choice of therapy. A decision is made between surgical and a non-surgical approach (13).

According to the FIGO guidelines, surgical treatment is confined to early-stage disease, including FIGO IA and selected cases of FIGO IB and IIA. For locally advanced cervical cancer, namely FIGO stage IIB to IVA, a definite treatment with external beam radiation therapy (EBRT) and brachytherapy in combination with chemotherapy is the standard therapy (16). Another new approach of therapy of cervical cancer includes immunotherapy and is currently under investigation (10).

1.2.1 Surgery

Surgical treatment for cervical cancer is accessible for FIGO stages IA to IIA. It includes several types of procedures and can also be divided into fertility spearing and non-fertility sparing (13).

For individuals diagnosed with stage IA cervical cancer, without lymphovascular space invasion (LVSI) and with negative tumor margins, a conization, electrosurgical loop excision or trachelectomy can be taken into consideration. Trachelectomy, a fertility-sparing technique, involves surgical removal of the cervix, the upper part of the vagina and the parametrium, potentially accompanied by the removal of the pelvic lymph nodes. Importantly, the uterus remains intact, making it a viable option for patients presenting with FIGO IB who wish to conceive (17).

The standard treatment for patients with FIGO stage IA2 to IIA, who do not wish to persevere fertility, includes a radical hysterectomy with bilateral lymph node dissection. Hysterectomy includes the surgical removal of the uterus and can be either subtotal with supracervical excision, total (or simple) with excision of the uterus and the cervix, or radical which comprises the “en-bloc” excision with parametrium and the upper vagina. The surgical approach to this can be either by laparotomy or laparoscopy. Due to the advanced possibilities nowadays, the laparoscopic approach can be robotically-assisted. Performing a radical hysterectomy should only be considered when complementary radiochemotherapy is unlikely to avoid additional morbidity (10,17).

Lymphadenectomy is often performed in combination with other surgical as well as non-surgical procedures to determine the extent of the disease and to prevent further spread. It involves the removal of the lymph nodes in the pelvis and sometimes in the paraaortic region located near the major blood vessels in the retroperitoneum (10,17).

In the rare case of an unexpected histological diagnosis of cervical carcinoma after a simple hysterectomy, an individual decision is required, whether a radical parametrectomy

should be performed or not. In this procedure, the diseased tissue adjacent to the uterus is removed. As an alternative, it is possible to perform postoperative radiochemotherapy (10).

1.2.2 Radiation Therapy

Combined radiochemotherapy followed by brachytherapy is considered standard therapy for locally advanced cervical carcinoma with a FIGO stage IIB or higher (10). The target volume and therapy concept depend on the tumor stage and the status of the paraaortic and the pelvic lymph nodes. Prior to initiation of therapy, FIGO stage, pelvic MRI assessing local spread, and abdominal CT to evaluate possible involvement of the lymph nodes, liver, and kidneys involvement are required. In addition, cystoscopy, sigmoidoscopy, laboratory tests, and a sound audiogram should be performed.

1.2.2.1 External beam radiation

A linear accelerator is used for external beam radiation therapy (EBRT) of cervical cancer (18). Typically, single doses of 1.8-2 Gray (Gy) are administered until a total dose of 45-50.4 Gy is achieved. In cases of extensive lymph node and parametrial involvement, an additional dose in form of a boost of up to 59.4 Gy may be required. Conventional fractionation is given five times a week. Radiation is delivered as intensity-modulated radiotherapy (IMRT) or as rotational irradiation, depending on the hospital standard. The latter is also referred to as volumetric modulated arc therapy (VMAT) or rapid ARC (19). IMRT enables targeted treatment of the tumor, while sparing the organs at risk, especially the small intestine. However, this results in a larger volume being occupied by lower radiation doses (10). In IMRT, better modulation of the irradiation fields and more precise dose distribution are achieved (20). In rotational irradiation, the tumor region is irradiated continuously from different directions. This attains a homogeneous dose distribution in the target volume and a lower burden on the surrounding tissue (21). The standard target volume includes the uterus with primary tumor region and the pelvic lymph node stations (22). When advanced tumors extend dorsolateral, the anterior rectal wall may be included. The lateral delineation of the target volume is depicted by the bony pelvis, ventrally by the posterior third of the bladder and dorsally by the sacral cavity. The cranial field boundary is given by the intervertebral disc between lumbar vertebral bodies 4 and 5. If the paraaortic lymph nodes are affected, the cranial field boundary is set up to the 12th thoracic vertebra. Caudally, depending on the involvement of the vagina, the field is extended either to the inferior border of the *obturator foramina* or to the *introitus vaginae*. The

intestine, rectum, bladder, both femoral heads and the kidneys are considered the most important organs at risk in the radiation of cervical carcinoma (23).

1.2.2.2 Brachytherapy

Brachytherapy is the application of a radioactive source in close proximity to the tumor and is a fundamental component of cervical cancer therapy allowing a precise application of high-dose radiation to the tumor target volume due to its close treatment distance, while sparing the surrounding organs at risk (16,18). For small superficial tumors (FIGO stage IA) with extremely low lymphogenic metastatic risk, brachytherapy alone can be a viable option, and for smaller stage IB1 and IIA tumors, combined tele-brachytherapy can be used alternatively to surgery (18,24). In locally advanced stages brachytherapy is applied after the radiochemotherapy to achieve maximal local control of the tumor.

For planning of the brachytherapy, MRI and CT are the standard imaging modalities (25). The target volume includes the macroscopic tumor, the cervix as well the adjacent part of the parametria and the upper part of the vagina (10). Intracavitary irradiation can be used either as low-dose-rate (LDR) brachytherapy or high-dose-rate (HDR) brachytherapy. In LDR, radiation source delivers a radiation dose of 0.4-2 Gray (Gy)/hour. Radiation sources are loaded into an intrauterine tandem and vaginal ovoid system placed in the operating room during anesthesia. After surgical insertion of the applicator, inpatient hospitalization of approximately 24-72 hours is necessary to perform adequate LDR treatment. HDR brachytherapy is performed at a dose rate of 12 Gy/h, using mainly the isotope iridium-192 (16). The small iridium source is attached to the end of a cable and is moved through multiple channels robotically. It is then stopped at predetermined points, so called dwell positions, for variable lengths of time. After insertion of the Wiener-Applicator in the operating room, subsequent treatments may not require hospitalization in HDR brachytherapy. Instead they are performed on an outpatient basis, thus offering greater patient comfort (10,26). This approach of HDR brachytherapy allows for a pear-shaped dose distribution encompassing the uterus and the cranial portions of the vagina. A steep dose fall-off allows high dose concentration at the tumor while optimally sparing surrounding organs at risk, such as the rectum, the sigmoid colon (coecum), the small intestine, the urinary bladder, the ureter, and the urethra (10,27). Depending on the institution, 4 fractions of 7 Gy each are usually prescribed for cervical cancer. The target volume for the high-risk area, which is irradiated in to a cumulative total dose of 85-90 Gy, does not include safety margins and the main radiation effect here develops at a tissue depth of 0.5 to 1 cm (28). To spare normal tissue long-term toxicity, specific attention is necessary to avoid exposure of

normal tissue including rectal mucosa, bladder, and urethra. For this purpose, constraints have been established (24).

1.2.2.3 Toxicity of Radiation Therapy

A distinction is made between therapy-related acute and late toxicity. Both show a dependence on the applied single and total dose. The former includes all side effects within the first 90 days after the start of therapy. These occur relatively frequently, but in the vast majority of cases they are reversible and can be managed without specific therapy or only with symptomatic measures. Late toxicity includes all therapy-related side effects that occur later than 90 days after the start of treatment (29). They are usually chronic and can hardly be influenced by therapy. The acute and chronic side effects primarily affect the organs at risk. These include the bladder, ureter, urethra, rectosigmoid, small intestine, vagina, kidneys, and lymphatic system (10,25). All side effects show a dependence on the single and total dose applied. In this context, the dose contribution of both external radiotherapy and brachytherapy must be considered, especially to avoid rectal complications.

Up to 84% of the patients exhibit some form of acute toxicity during EBRT (29). This may include loose stools, diarrhea, pollakisuria, urinary tract infections, burning sensation and pain during urination. Irradiation of the paraaortic lymphatics involves larger portions of the small bowel, which may result in additional nausea, vomiting, and diarrhea. Under brachytherapy, mucositis of the vagina may occurs, and there is also an increased tendency to infection (10). For stage IVA and above, radiotherapy is associated with a high risk of fistula (30). These usually force discontinuation of radiochemotherapy. During brachytherapy, mucositis of the vagina may occur; here again, an increased tendency to infection develops (10). Simultaneous chemotherapy can have additional hematotoxic, nephrotoxic and ototoxic effects. Weekly measuring of bloodwork is key for patients undergoing concurrent chemotherapy, because in setting of hematologic toxicities, the radiation should be delayed until it is resolved or has at least improved (16).

Possible therapy-induced late damages are mainly chronic proctitis with recurrent blood and mucus discharges, chronic cystitis and possibly a reduced bladder volume. In addition, after intracavitary brachytherapy there is a risk of stenosis of the rectosigmoid, urethra or ureters and vagina, as well as chronical dryness of the mucous membranes with resulting dyspareunia (10). Other known late complications are pelvic insufficiency fractures and osteoradionecrosis, which are less prevalent but still documented as late toxicities (31). When brachytherapy is performed, a full bladder is recommended because an increased bladder volume mitigates rectal

exposure to radiation (32). The chronic toxicities of the bowel generally develop within the first two years after the end of therapy, while the late damage to the genitourinary system can manifest much later. Simultaneous chemotherapy may additionally result in hearing or renal function impairment (10).

To record the toxicities of cancer treatment, the Common Toxicity Criteria (CTC) are used as a scoring system. According to these criteria, side effects are graded into five severity levels. Mild side effects that do not require special therapy receive grade 1. Grade 2 includes moderate side effects that require outpatient medication, while grade 3 includes more severe side effects that require hospitalization. Grade 4 are life-threatening side effects and Grade 5 is defined as side effects that lead to the patients' death (33). Adverse reactions are further categorized in terms of organ systems affected, namely hematologic, gastrointestinal, pulmonary, hepatic, renal/urogenital, dermatologic, cardiac, neurologic musculoskeletal and other toxicities. Others include constitutional symptoms, pain, fever, alopecia and maybe syndromes that are appearing as adverse reaction to therapy (33,34).

1.2.3 Chemotherapy

In locally advanced or nodal positive cervical carcinoma, combined radiochemotherapy is the therapy of choice given, with cisplatin-based chemotherapy being administered (10). Simultaneous chemotherapy results in significant improvement of overall survival, disease-free, and local recurrence-free survival (16,18). Cisplatin is considered standard therapy being given concurrently with radiotherapy. The improvement in treatment outcome by the addition of cisplatin is explained by mechanisms that inhibit the repair of sublethal damage from radiation, synchronize cells to a particularly radiosensitive phase of the cell cycle, and by their in vitro cytotoxicity (35).

A typical regimen is the intravenous administration of cisplatin at a dose of 40 milligrams per square meter (mg/m^2) of body surface area (BSA). In this case, administration is once weekly, during the external radiation period. A total dose of 200 mg/m^2 should be aimed for (16,21). Another regimen is the administration of 20 mg/m^2 BSA on 5 days in the first and the last week of treatment. Chemotherapy should be given only if blood counts are in a normal range. Leukocytes should be above 3,000/cubic millimeter (mm^3) and platelets above 100,000/mm^3. Normal liver function and creatinine clearance above 60 milliliters per minute (ml/min) are important prerequisites to proceed with therapy (36). The patient's blood count must be monitored regularly during therapy. In case of contraindications of cisplatin, the

administration of carboplatin or 5-fluorouracil (5-FU) and mitomycin C may be contemplated (37).

Besides the combination of chemotherapy with EBRT and brachytherapy, there are other applications. As adjuvant therapy, chemotherapy can again be used postoperatively after R1-resections in combination with EBRT but without the brachytherapy. This could be an option in patients with increased risk for local recurrence or distant metastases after R0-resection. Since there is no clear evidence-based data, neoadjuvant chemotherapy may be offered to patients only within prospective controlled trials. Here, total doses between 100-300 mg/m^2 BSA are applied over a period of 10-21 days. Chemotherapy with cisplatin alone plays an important role in the treatment of both distant metastases and patients who have relapsed after surgery and/or radiochemotherapy. However, the response to chemotherapy after prior therapy is worse than in chemotherapy-naive patients. In addition to cisplatin, other chemotherapeutic agents may be considered in the therapy of metastatic or recurrent cervical carcinoma, depending on the response rate. Multiple agents may also be combined, but the resulting increase in toxicity must be taken into account (10).

1.2.4 Immunotherapy

In Immunotherapy the person's own immune system is harnessed to recognize and kill cancer cells. Right now, there are three Food and Drug Administration (FDA)-approved immunotherapy options available for the treatment of cervical cancer. These include two targeted antibodies. Bevacizumab is a monoclonal antibody, which inhibits the tumor blood vessel growth by targeting the vascular endothelial growth factor (VEGF) and VEGF-receptor (VEGFR) pathway. Tistozumab vedotin targets the tissue factor, thus inhibiting tumor growth. But the antibody-drug conjugate is only approved for a subset of patients with advanced cervical cancer. The third options in an immunomodulator, called Pembrolizumab. It is a checkpoint inhibitor targeting the programmed cell death protein 1 and the programmed cell death ligand 1 (PD-1/PD-L1) pathway, but is again only approved for a small subset of patients with advanced cervical cancer (38).

In non-pretreated patients, a combination treatment with retinoids and interferon can also be taken into consideration and in studies showed a high response rate, but no effect in patients, who were already pretreated with radiotherapy and chemotherapy. A combination of interferon and doxorubicin may also be considered as immunotherapy. Studies have tested neoadjuvant use of topically applied natural interferon in FIGO stages IA-IIB preoperatively, which showed a large increase in 10-year survival compared with surgery alone (10).

1.3 Quality of life

As defined by the World Health Organization (WHO), the concept of QoL encompasses a person's subjective perception of his or her position in life in relation to the culture and value systems in which he or she lives, and in relation to his or her goals, expectations, standards, and concerns (39). This concept is a multifaceted and complex paradigm reflecting the physical, psychological, and social well-being of patients (1). Cancer and its treatment have a significant impact on patients, as well as on their families. In addition to coping with the immediate side effects of cancer therapy, physical, social, and psychological/emotional functioning should evenly affected and should also be taken into account (5). Some of the psychological factors that act on the patient include low self-esteem, changes in self-image, marital tensions, beliefs about the origin of cancer, fears and worries. Altogether, there is a need to measure health outcomes for cancer patients beyond the traditional indicators such as mortality and morbidity (40). Hence the QoL data regarding patients' overall well-being and functioning should be routinely included as a complementary monitoring tool during follow-up. Moreover, QoL should also be included in treatment planning and monitoring. Understanding the QoL in women during radiochemotherapy of cervical carcinoma will help with introduction of intervention resulting in better outcomes and better care for these patients (1,40).

1.3.1 Measuring the Quality of life

In medicine, there is no standard way for measuring QoL. Different methods and techniques are used by physicians, psychologists, psycho-oncologists and specialized personnel. In oncology, it is common to use the Sickness Impact Profile (SIP), the Karnofsky-Index, or by measuring the QoL with the EORTC questionnaire (41).

The SIP has been widely used in the past and assesses patient condition based on performance of activities of daily living. It is a measure of disease-related behavioral disturbances. The patient can answer the questions, which are divided into 12 categories, independently or with the help of an interviewer (42).

The Karnofsky-Index is determined by physicians and nurses. It measures the general well-being, performance and physical condition of tumor patients. A scale from 0 to 100 is used for orientation and the degree of functional limitation is determined. If a patient has no complaints or signs of disease, he or she receives a score of 100 points, graded in 10-point increments. The Karnofsky-Index is used to give a prognosis. Depending on the stage and course of the disease, the objective of the therapy can vary (43).

The EORTC-QLQ-C30 is a widely used tool to assess the QoL of cancer patients. This general questionnaire compromises 30 questions and is divided into several domain (44).

For cervical cancer patients, the EORTC-QLQ-CX24 questionnaire was developed for assessment of disease- and treatment-specific of cervical cancer. It was established to supplement the EORTC-QLQ-C30 core questionnaire (4).

1.3.2 EORTC-questionnaires

The domains of the EORTC-QLQ-C30 questionnaire include 30 questions and those are divided into five function domains (physical, emotional, social, role, cognitive), eight symptoms (fatigue, pain, nausea and vomiting, constipation, diarrhea, insomnia, dyspnea, appetite loss), as well as global health/quality-of-life and financial impact (44,45). The domains of the EORTC-QLQ-C30 questionnaire (Table 2) are:

Table 2: Domains of the EORTC-QLQ-C30 questionnaire (44) .

Physical functioning	Question 1-5
Role functioning	Question 6-7
Emotional functioning	Question 21-24
Cognitive Functioning	Question 20 and 25
Social functioning	Question 26-27
Fatigue	Question 10,12, and 18
Nausea and vomiting	Question 14-15
Pain	Question 9 and 19
Dyspnea	Question 8
Insomnia	Question 11
Appetite loss	Question 13
Constipation	Question 16
Diarrhea	Question 17
Financial difficulties	Question 28
Global health status/ QoL	Question 29-30

Each domain consists of a set of questions that are scored and analyzed separately. The results of the questionnaire can help healthcare providers to identify areas where a patient may be struggling and to develop interventions to improve their QoL. The first 28 questions had the following four answer options (Table 3):

Table 3: Answer options of questions 1-28 of the EORTC-QLQ-C30 questionnaire.

1	2	3	4
Not at all	A little	Quite a bit	Very much

The last two questions Nr. 29 and Nr. 30 had a scale from one to seven where the patients were advised to circle the accurate number, with one being very poor and seven being excellent.

Table 4: Answer options of question 29-30 of the EORTC-QLQ-C30 questionnaire.

1	2	3	4	5	6	7
Very poor						excellent

The composition of the scores of the QLQ-C30 questionnaire is summarized in Table 5 below:

Table 5: Composition of the scores of the EORTC-QLQ-C30 questionnaire (44).

	Scale	Number of items	Item range*	Version 3.0 Item number	Function scales
Global Health status/QoL[a]					
Global health status/ QoL[a]	QL2	2	6	29, 30	
Functional scales					
Physical functioning	RF2	5	3	1-5	F
Role functioning	RF2	2	3	6-7	F
Emotional functioning	EF	4	3	21-24	F
Cognitive functioning	CF	2	3	20 and 25	F
Social functioning	SF	2	3	26-27	F
Symptom scales/items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14-15	
Pain	PA	2	3	9, 19	
Dyspnea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

*_Item range_ is the difference between the maximum possible value of _RS_ and the minimum possible.
[a]Quality of life

The EORTC-QLQ-CX24 questionnaire compromises 24 questions and is like the EORTC-QLQ-C30 divided into several domains, including three multi-item scales and several single item scales. The multi-item scales are symptom experience (11 items), body image (3 items), and sexual/vaginal functioning (4 items) (46). The other dimensions of the questionnaire are covered by single-item scales including lymphedema, peripheral neuropathy, menopausal symptoms, sexual worry, sexual activity and sexual enjoyment (4) The composition of the score of the EORTC-QLQ-CX24 questionnaires are shown in Table 7 below. In general, the questions can be divided in these four top points:

Symptom experience	Question 31-44
Body image	Question 45-47
Sexual function	Questions 48-49
Vaginal function	Question 50-54

For the QLQ-CX24-questionnaire there were the following four answer options:

Table 6: Answer options of the EORTC-QLQ-CX24 questionnaire (47).

1	2	3	4
Not at all	A little	Quite a bit	Very much

The composition of the scores of the QLQ-CX24 questionnaire is summarized in Table 7 below:

Table 7: Composition of the scores of EORTC-QLQ-CX24 (47)

	Scale	Number of items	Item range*	QLQ-CX24 item numbers
Symptom scales/items				
Symptom Experience	SE	11	3	31-37, 39, 41-43
Body Image	BI	3	3	45-47
Sexual/Vaginal Functioning	SV	4	3	50-53
Lymphedema	LY	1	3	38
Peripheral Neuropathy	PN	1	3	40
Menopausal Symptoms	MS	1	3	44
Sexual Worry	SXW	1	3	48
Functional Items				
Sexual Activity	SXA	1	3	49
Sexual Enjoyment	SXE	1	3	54

**Item range* is the difference between the maximum possible value of *RS* and the minimum possible.

2 OBJECTIVES AND HYPOTHESIS

2.1 Aim of the study

This study aims to evaluate the QoL and survival data of cervical cancer patients after undergoing radiochemotherapy and brachytherapy as treatment in the Cancer Center Coburg, Germany. The patients live in Coburg and the surrounding neighboring towns in Bavaria and Thuringia with a catchment area of 50 kilometers. The goal is to identify prognostic factors for overall survival, no evidence of disease (NED)-survival, recurrence pattern and to work out whether there are significant associations between these and QoL.

2.2 Hypothesis

Following radiochemotherapy and brachytherapy the QoL and the sexual functioning in patients with cervical cancer is not decreased.

3 MATERIALS AND METHODS

3.1 Design and description of the study

This retrospective and prospective study is investigating the QoL and the sexual functioning of patients being treated for cervical cancer at the Cancer Center in Coburg, Germany. The patients received radiochemotherapy and brachytherapy as their definite treatment. The patients' history was collected for data regarding their disease and its course via patients' records of the practice over the course of 20 years and evaluated for this study for the Thesis for the University of Split, School of Medicine. In addition, a questionnaire regarding QoL was sent to the patients for them to complete themselves, namely the Questionnaires EORTC QLQ-C30 (Version 3) and EORTC QLQ-CX24 for assessing QoL.

3.2 Subjects and Methods

The sample will consist of all patients with cervical cancer who received a combination of radiochemotherapy and brachytherapy as their definite treatment between 2003 and 2023.

Patients that received post-operative radiochemotherapy, radiotherapy without brachytherapy, neoadjuvant radiochemotherapy, palliative radiochemotherapy or treatment for cancer recurrence were excluded. Furthermore, patients with synchronous other types of cancer were excluded as well.

Written and oral informed consent were obtained from all patients or their legal representatives for the QoL questionnaires.

To properly describe the process of inclusion and exclusion of patients in this study, a flow diagram according to the CONSORT-criteria was created (Figure 1).

Between 2003-2023, total of 132 patients with cervical cancer were evaluated for treatment at the Department of Radiation Oncology of the Coburg Cancer Center. A subgroup of 51 patients received radiochemotherapy and brachytherapy as their definitive treatment, the other 81 were excluded from this study. From the remaining 51 eligible patients, 30 did not participate in the evaluation of the EORTC-QLQ-C30 and EORTC-QLQ-CX24 questionnaires due to death, missing consent or no response after receiving the questionnaires by mail. Thus, altogether 21 patients answered the questionnaire and are being taken into account regarding the evaluation of the QoL.

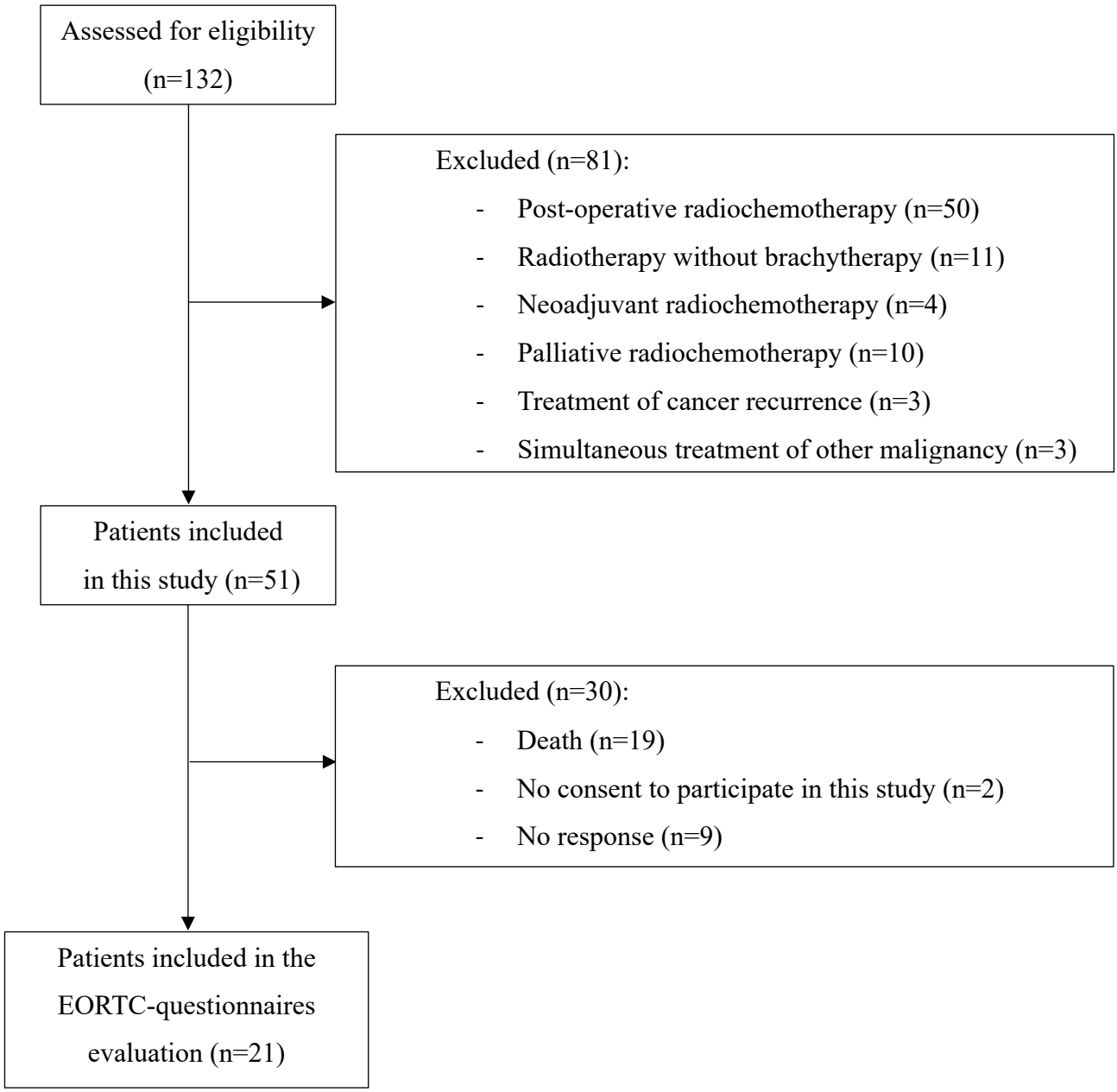

Figure 1: CONSORT Flow Diagram

3.3 Independent variables

Independent variables being collected include name, age, phone number, marital status, educational status, age at diagnosis, tobacco smoking, menstrual status, parity, number in Isynet data base, number in this study, and abbreviation in this study.

3.4 Outcome measures

These included the evaluation of survival data using the Kaplan-Meier method. Survival curves for different subgroups of patients were compared by the log-rank test.

The most important outcome is the QoL measuring by evaluation of the EORTC-QLQ-C30 (Version 3) and EORTC-QLQ-CX24 questionnaires of the patients after receiving radiochemotherapy and brachytherapy.

The structure of the questionnaires has already been explained in detail in the Introduction section (see Table 2-7). The EORTC-QLQ-C30 contains five functional scales, three symptomatic scales, one measure of global health status/QoL, and six additional single items. The EORTC-QLQ-CX24 consists of three symptomatic scales, four single items, and one functional scale. Therefore, these questionnaires are a combination of multi-item scales and single-item scales. A single test question is referred to as an item. This test question can either stand alone or be one of several characteristics of an examination unit (score). Each score and single-item measurement can be assigned a value between 0 and 100. A high value in a functional scale represents a high level of functionality. A high value for global health represents a high QoL. Therefore, high values in these areas are to be considered positive. If, on the other hand, a high value is achieved in the symptomatic scales, this represents a high degree of symptomatology and should therefore be assessed negatively.

The values of all scales are calculated according to a general scheme. First, the Raw Score (RS) is determined, which is the average value of all items that belong to the unit of investigation. Thus, if the items I_1-I_n form a scale, this results in a raw score of $(I_1+I_2+...+I_n)/n$. In order to later achieve results between 0 and 100 for all single-item measurements, a linear transformation of the raw score must be performed. The resultant value is then called Score (S). For this transformation, another variable, the range, is necessary. This describes the difference between the maximum and minimum possible Raw Score, i.e., the difference between the highest answer possibility and the lowest (42).

For the functional scales, the score is obtained by substituting the variables into the following formula:

$$S = \left(1 - \frac{(RS - 1)}{range}\right) \times 100$$

For the symptomatic scales and items, and for global health status/QoL, respectively, the formula is:

$$S = \left(\frac{(RS - 1)}{range}\right) \times 100$$

The summary of items to study units, as well as the number of items and the range, can be found in Table 5 and 7 above.

Another outcome measure that is analyzed is the overall survival and its prognostic factors.

3.5 Calculation of minimal sample size

The sample size becomes irrelevant in the absence of a direct comparison between two hypotheses.

3.6 Statistical tests

IBM SPSS Statistics 29 for macOS (IBM Corp, 2022) was used to analyze the results. The Kolmogorov-Smirnov test is used to analyze the normality of the data distribution. Furthermore, survival rates are calculated by the Kaplan-Meier method, and the log-rank test is used to compare survival rates between different groups of patients. Qualitative data are expressed as whole numbers and percentages, while quantitative data are expressed as mean ± standard deviation (SD) or mean and interquartile range (IQR). Results are presented as tables and figures with a 95% confidence interval (CI).

For analysis of the EORTC questionnaires, all data are summarized in descriptive statistics. To compare differences between two groups, the t-test is performed. The chi-square test is applied to compare two categorical variables, and regression analysis is used to examine the influence of certain variables on QoL. Frequencies are reported for categorical variables. The significance of all tests was set at 0.05.

3.7 Possible biases and confounding variables

The patients' health plays a significant role on their willingness to participate in the study and to complete the questionnaire. Generally, better health increases the likelihood of patients answering the questionnaire as well. Furthermore, younger patients tend to be more inclined to participate compared to older patients. Additionally, there is a follow-up bias: patients might have moved or switched doctors, or stopped coming for follow-up visits.

3.8 Ethical approval

Ethical approval was obtained from the Ethics-Committee of the University Hospital of Erlangen (Report No 23-5-B) on March 21, 2023.

4 RESULTS

4.1 Descriptive statistics of the sample (n=51)

Patient-related data were extracted from the respective files and analyzed. A summary was then prepared, presented in Table 8 and Figure 2-5.

Table 8: Patient and treatment characteristics.

Variables		
Total number of patients		51 (100%)
FIGO stage	IIA- IIIA	27 (53%)
	IIIB-IVA	24 (47%)
Tobacco smoking	Yes	31 (61%)
	No	20 (40%)
Histology	Squamous cell carcinoma	42 (82%)
	Adenocarcinoma	9 (18%)
Menstrual status	Premenopausal	14 (27%)
	Perimenpausal	8 (16%)
	Postmenopausal	29 (57%)
Age at diagnosis	Mean	58 years
	Minimum	27 years
	Maximum	86 years
Total dose of EBRT[a]	Mean	48.4 Gy
	IQR	48.6 – 50.4 Gy
Total dose of BT[b]	Mean	23.2 Gy
	IQR	22-28 Gy
Dose paraaortic LN[c‡]	Mean	14.3 Gy
	IQR	0-45.5 Gy
Dose pelvic LN[c]	Mean	48.3 Gy
	IQR	46.8-50.4 Gy
Dose primary tumor	Mean	53.2 Gy
	IQR	50.4-56 Gy
Duration of EBRT[a] and BT[b]	Mean	62.5 days
	IQR	53-59 days
Total dose of Cisplatin[‖]	Mean	158.8 mg/m^2 BSA
	IQR	90-200 mg/m^2 BSA

[*] One patient did not show up to follow-ups regularly, so they could not be determined.
[a] External beam radiation therapy (EBRT).
[b] Brachytherapy (BT).
[c] lymph nodes (LN).
[‡] Out of the 51 patients, only 15 received paraaortic radiation.
[‖] Eight Patients did not receive Cisplatin but Carboplatin or 5-FU due to hematotoxic or nephrotoxic complications.

A total of 51 female patients were selected for this study, and can be classified based on several variables. The median age at initial diagnosis was 58 years (IQR: 49-72 years). However, the overall age distribution ranged from 27 to 86 years. The 51 patients could additionally be divided based on their menstrual status. More than half (57%) were already postmenopausal, 14 (27%) were still premenopausal and 8 (16%) of the patients were perimenopausal. Twenty-four (47%) patients achieved complete remission, while of the remainder, pelvic recurrence was noted in 6 (12%) patients and distant metastases were found

in 17 (33%) patients. Overall, there were 19 deaths (37%) among the 51 participants in the study. FIGO stage IIA-IIIA was assigned to 27 (53%) patients, while 24 patients were classified as FIGO stage IIIB-IVA. Squamous cell carcinoma was much more common than adenocarcinoma (18%, 9 patients) with an incidence of 82% (42 patients).

The median dose administered as external radiotherapy was 50.4 Gy (IQR: 48,6-50,4 Gy), with a maximum total of 58.0 Gy (compare Figure 2). The median dose delivered to the primary tumor volume was 55.8 Gy (IQR: 50.4-56 Gy), for the pelvic lymph nodes it was 50.4 Gy (IQR 46.8-50.4 Gy), and for the paraaortic lymph nodes it was 0 Gy (IQR: 0-45.5 Gy) since only 15 out of the 51 patients received radiation of this area. For brachytherapy, the standard 28 Gy was also administered in most cases (IQR: 22-28 Gy), with a few exceptions, compare Figure 2. The EBRT together with BT lasted a median time of 60 days (IQR: 53-69 days). For simultaneous cisplatin administration, a median of 200 mg/m^2 BSA was applied (IQR: 90-200 mg/m^2 BSA), which corresponds to the standard regimen (Figure 5). However, it should be noted that a total of 8 patients had another chemotherapeutic agent such as carboplatin or Mitomycin C together with 5-fluoruracil (5-FU) used instead of cisplatin due to hematological or nephrological complications. Overall, 29 of them (56.9%) complained of acute toxicities after therapy and 13 (25.5%) of the patients complained of late toxicities.

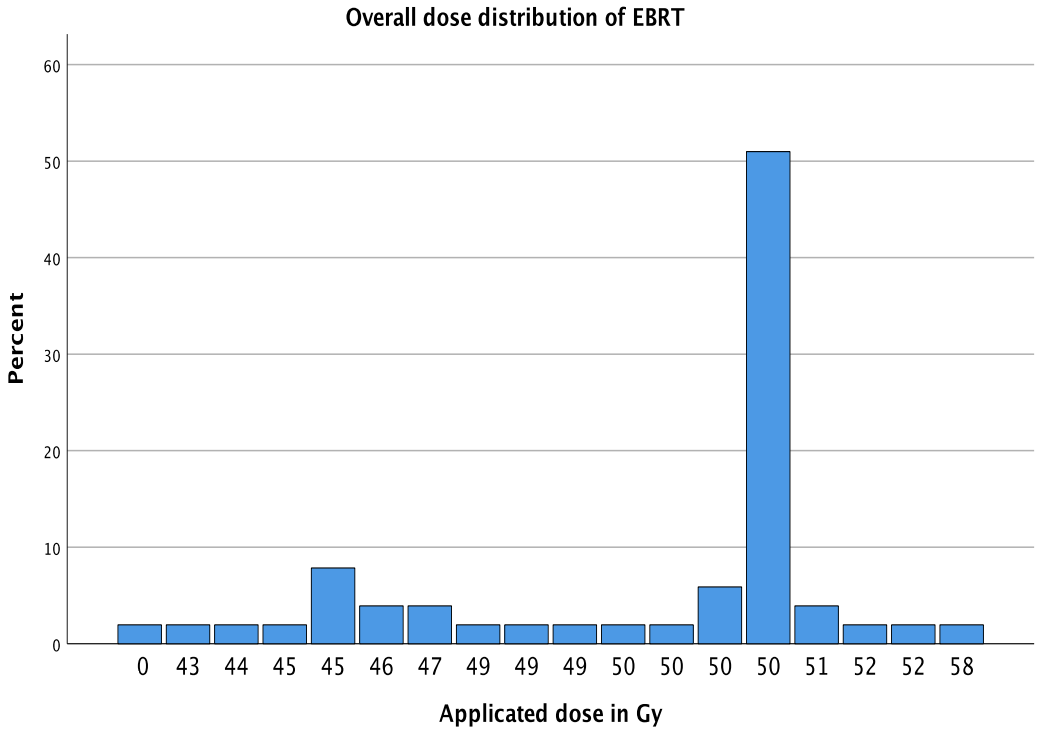

Figure 2: Overall dose distribution of EBRT

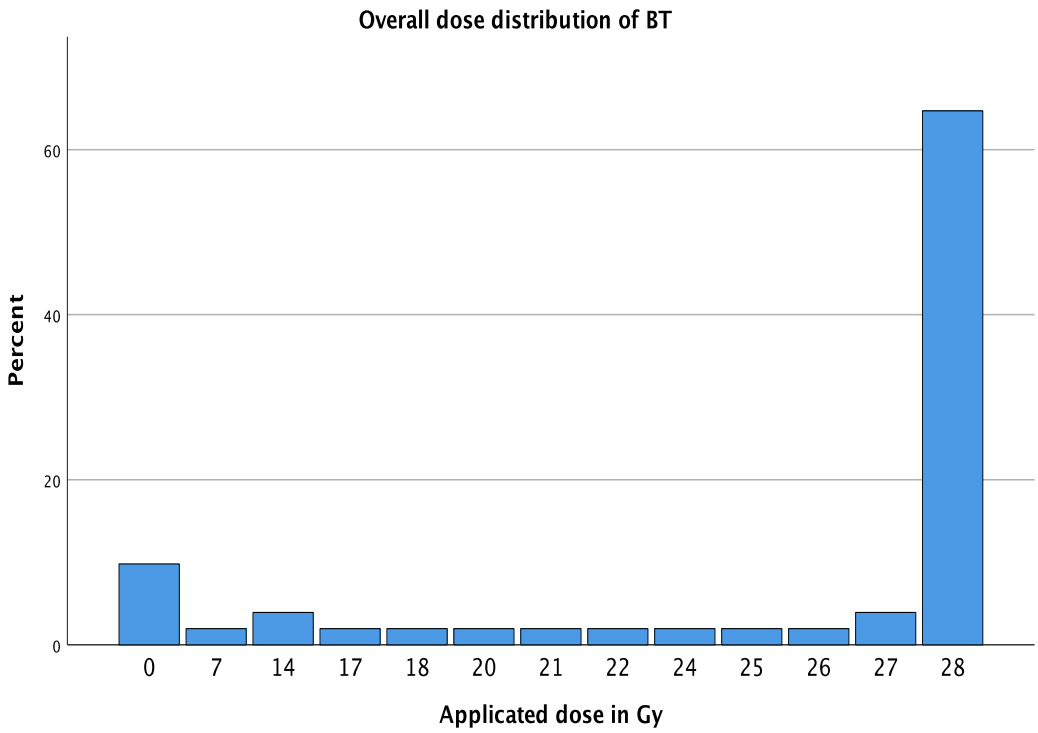

Figure 3: Overall dose distribution of BT

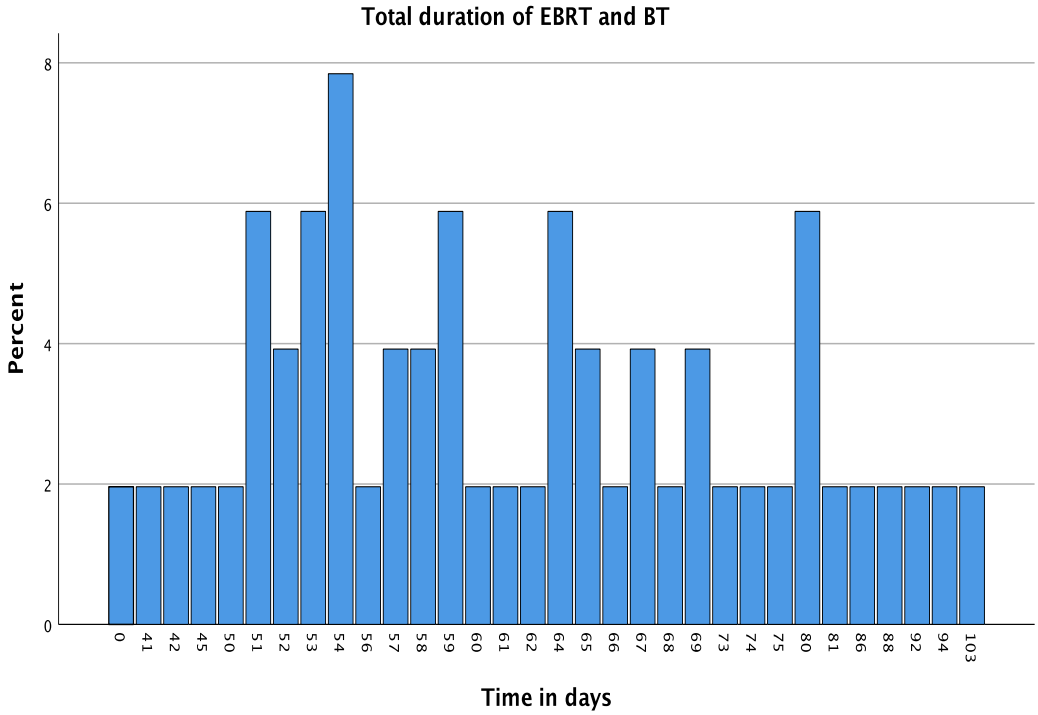

Figure 4: Total duration of EBRT and RT in days

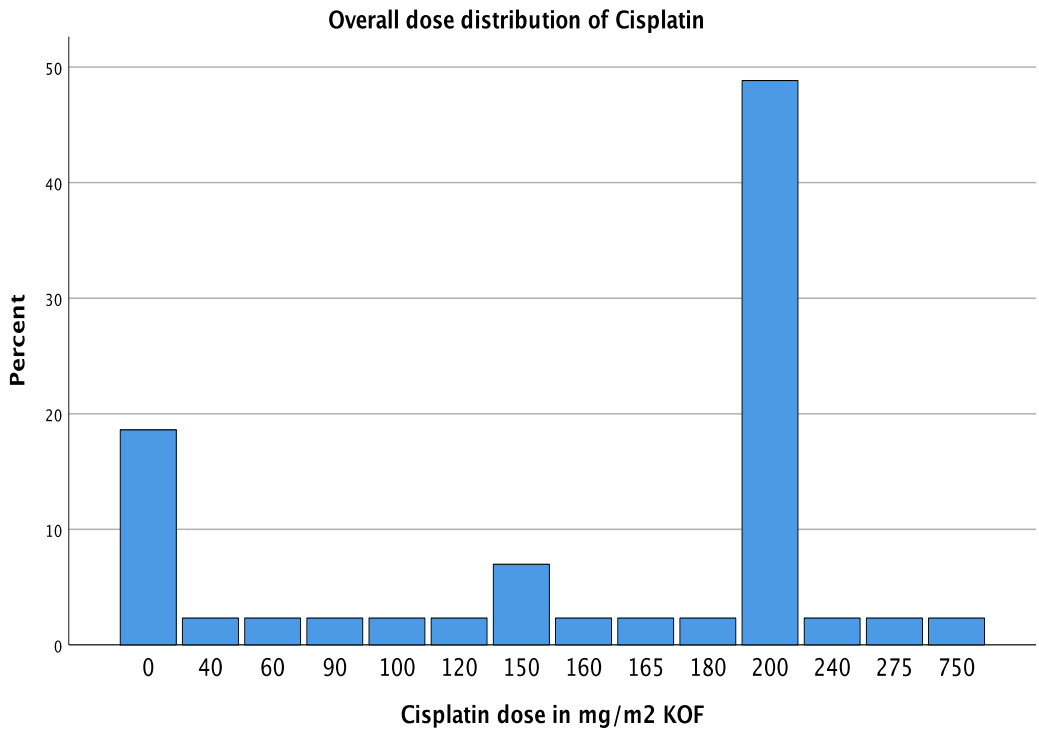

Figure 5: Overall dose distribution of Cisplatin

Furthermore, toxicities were evaluated and summarized according to the patients' CTC grading system. A total of 39 acute toxicities were recorded, distributed among 29 patients (51%), of whom seven suffered more than one toxicity. For late toxicities, a total of 14 events were recorded in ten patients (20%). Three of them had to deal with more than one late toxicity. The following Table 9 summarizes the distribution of toxicities among organ systems and their severity.

Table 9: Distribution of acute and late toxicities among organ systems and their severity.

Affected organ system	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total occurrence
Acute Toxicity						39 (100%)
Gastrointestinal	2 (25%)	6 (75%)	0	0	0	8 (20%)
Hematologic	0	9 (64%)	5 (36%)	0	0	14 (36%)
Musculoskeltal	2 (100%)	0	0	0	0	2 (5%)
Renal/urogenital	3 (37%)	5 (63%)	0	0	0	8 (21%)
Pulmonary	0	0	2 (100%)	0	0	2 (5%)
Cutaneous	1 (50%)	1 (50%)	0	0	0	2 (5%)
Pain	0	1 (100%)	0	0	0	1 (3%)
Constitutional	0	2 (100%)	0	0	0	2 (5%)
Late Toxicity						14 (100%)
Gastrointestinal	3 (75%)	1 (25%)	0	0	0	4 (29%)
Musculoskeletal	0	2 (100%)	0	0	0	2 (15%)
Urogenital	5 (83%)	1 (17%)	0	0	0	6 (42%)
Constitutional	0	1 (100%)	0	0	0	1 (7%)
Lymphatic	0	1 (100%)	0	0	0	1 (7%)

Hematologic complications were most frequently noted as acute toxicities. This was followed by gastrointestinal and urogenital acute toxicities. Less represented were musculoskeletal, pulmonary, cutaneous, constitutional symptoms, and pain. In general, most symptoms could be treated in an outpatient setting, and were thus staged grade 2. Pulmonary acute toxicity included a pulmonary embolism in two patients requiring hospitalization. This was assessed grade 3.

The late toxicities were less frequent than the acute toxicities. The patients complained most about urogenital side effects, followed by gastrointestinal and musculoskeletal complaints. In contrast to the acute toxicities, late effects included complaints in the lymphatic system. However, these were, just like the constitutional symptoms, rather less represented. Again, most of the late toxicities could be treated with a level 2 outpatient treatment.

Figure 6 and 7 below again graphically illustrate the distribution of acute and late toxicities.

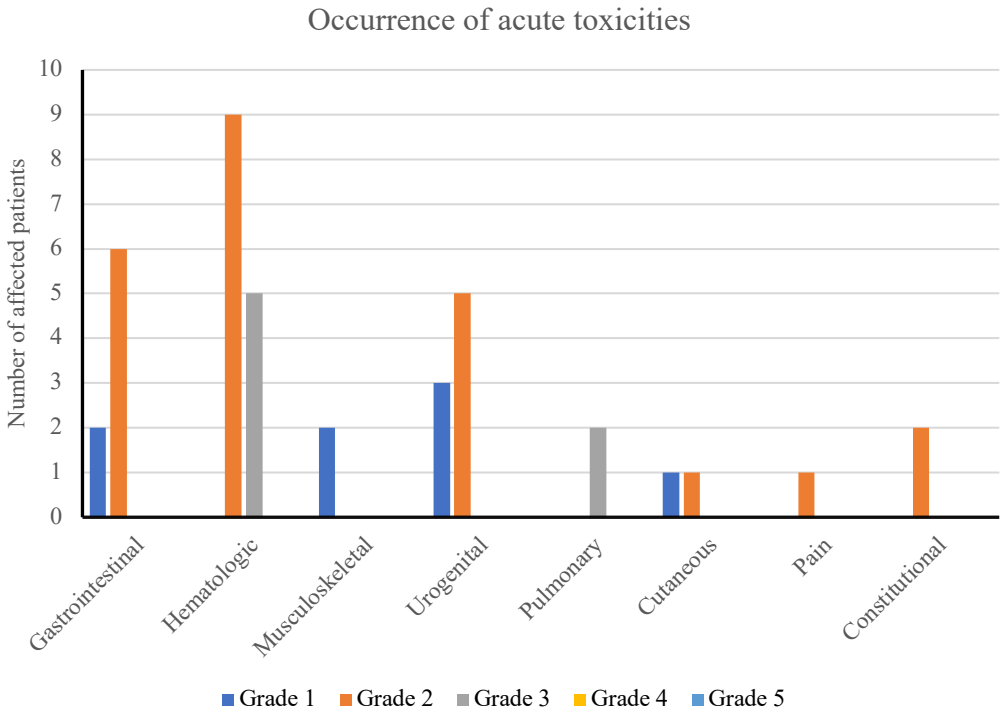

Figure 6: Occurrence of acute toxicities.

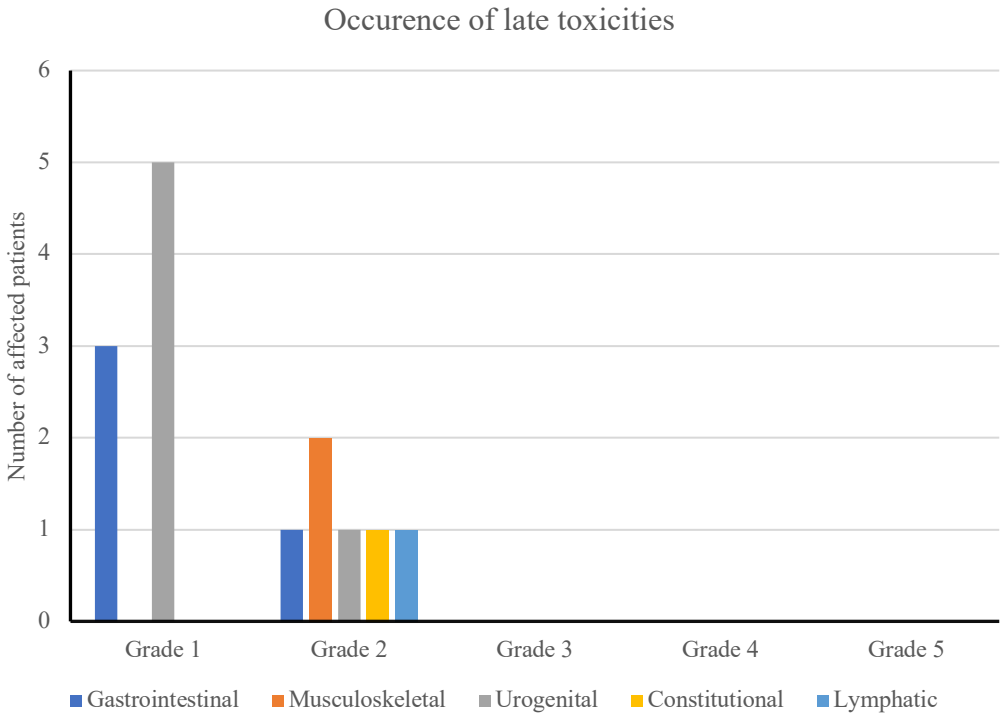

Figure 7: Occurrence of late toxicities.

The patterns of recurrence, which include complete remission, pelvic recurrence, the development of distant metastases, and the death of the patient, are shown in Table 10.

Table 10: Patterns of recurrence.

Patterns of recurrence		
Complete remission	Yes	24 (47%)
	No	27 (53%)
Pelvic recurrence	Yes	6 (12%)
	No	45 (88%)
Distant metastases	Yes	17 (33%)
	No	34 (67%)
Exitus letalis	Yes	19 (37%)

Twenty-four (47%) patients achieved complete remission, while of the remainder, pelvic recurrence was noted in 6 (12%) patients and distant metastases were found in 17 (33%) patients. Overall, there were 19 deaths (37%) among the 51 participants in the study.

4.2 Survival date and prognostic factors

An analysis of overall patient survival was performed using the Kaplan-Meier method. The results are summarized in Figure 8-12.

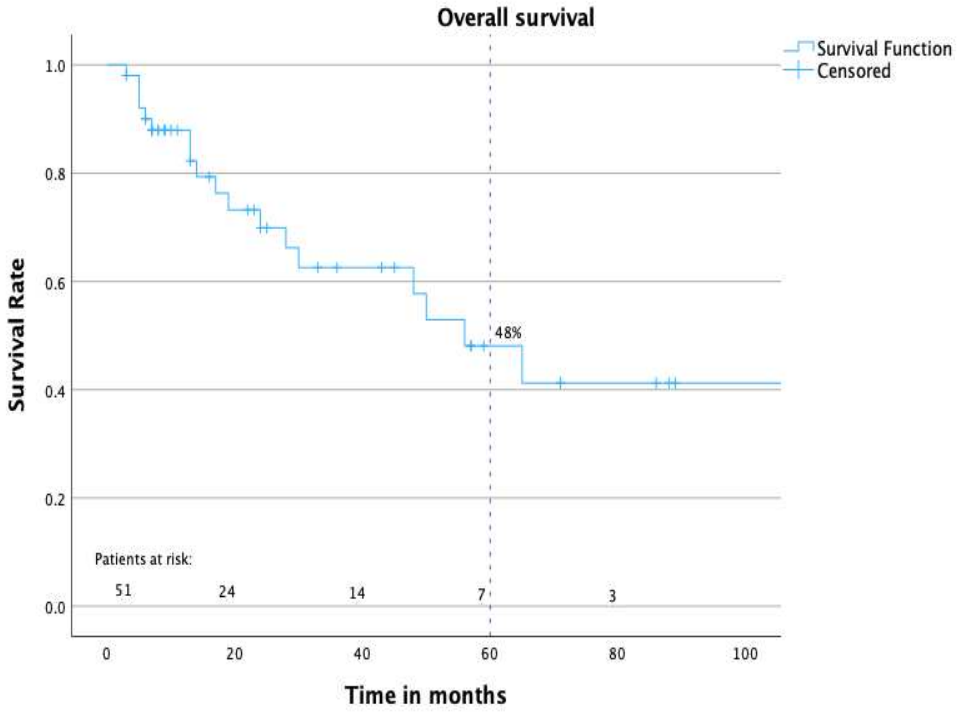

Figure 8: Overall survival.

The overall survival rate for all 51 patients is given in Figure 8. Nineteen out of all 51 patients died. The median survival time was 56 months (CI: 36-75 months; SD ± 10). Survival ranged from a minimum of three months to a maximum of 232 months since the time of diagnosis. The five-year survival rate was 48% (±9%).

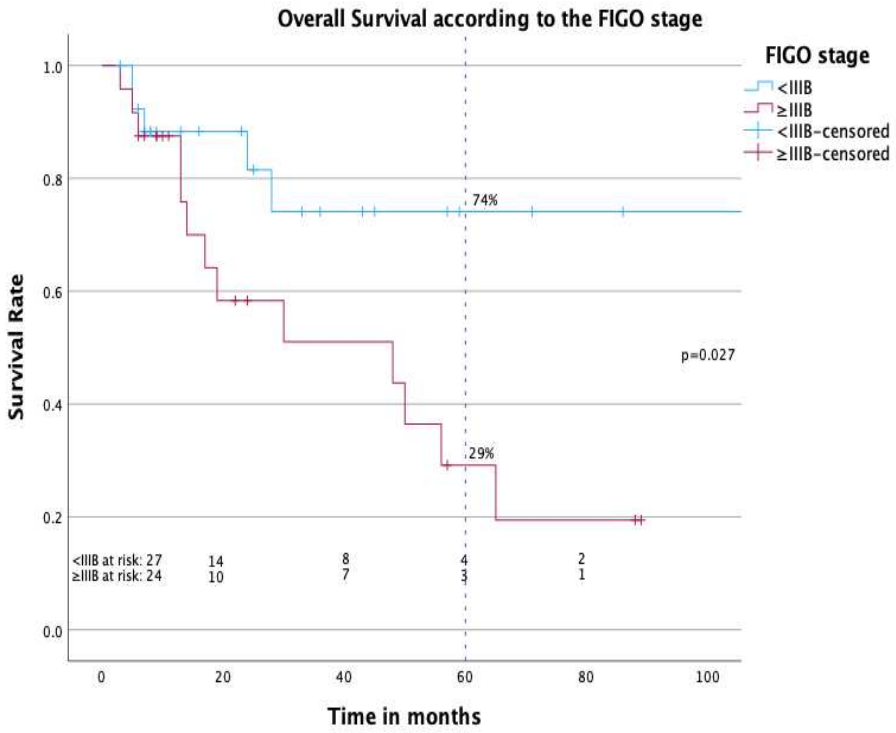

Figure 9: Overall Survival according to the FIGO stage.

Figure 9 gives Kaplan-Meier curves for overall survival according to FIGO stage. There is a significant difference between survival rates in patients with FIGO stage less than IIIB and greater than or equal to IIIB (p=0.027). A total of 27 patients were diagnosed with cervical carcinoma with FIGO stage <IIIB. Overall, 5-year-survival rate for patients with stage IIA-IIIA was 74% (±13%). Within the 232 months, a total of 6 patients died. FIGO stage ≥IIIB was diagnosed in a total of 24 patients; in this group 13 patients died. Therefore, the overall 5-year-survival rate was 29% (±12%).

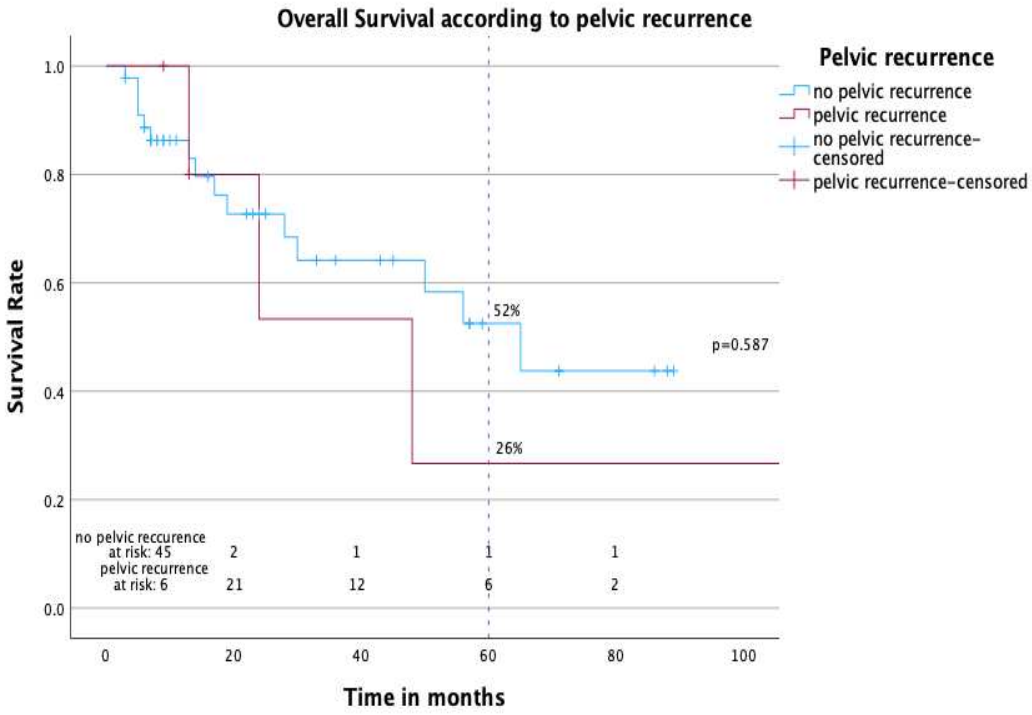

Figure 10: Overall Survival according to pelvic recurrence.

Figure 10 depicts Kaplan-Meier curves for overall survival in patients with and without pelvic recurrence. There is no significant difference in overall survival with respect to the occurrence of pelvic recurrence (p=0.587). 45 out of the 51 patients did not have pelvic recurrence. Of these 45, 15 died. Thus, the overall survival was 66.7% and the median survival amounts 65 months (CI: 41-89, SD 12). Pelvic recurrence was diagnosed in 6 patients. There was, after 4 died, an overall survival of 33.3%. The median survival was 48 months (CI: 19-77; SD±15). The 5-year survival rates were 52% (±10%) in patients without a pelvic recurrence and 26% (±22%) with pelvic recurrence.

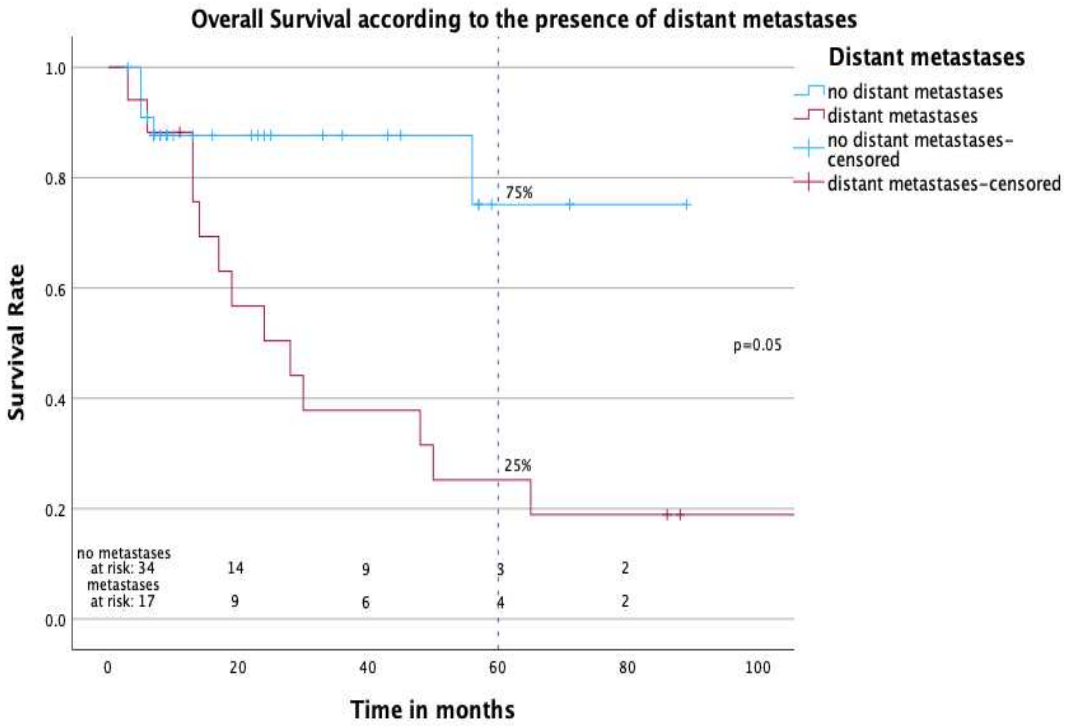

Figure 11: Overall Survival according to the development of distant metastases.

Looking at the overall survival in relation to distant metastases (Figure 11), there is a significant difference between survival with and without presence of distant metastases (p=0.05). 34 patients had no distant metastases, from which 5 had died. Here, the overall survival was 85.3%. In 17 patient's distant metastases were found. 14 of them died, thus the overall survival amounts 17.6%.

The median survival totals 28 months (CI: 11-45; SD±9). 5-year survival rates had been 75% (±12%) in patients without distant metastasis and 25% (±11%) associated with the presence of distant metastases.

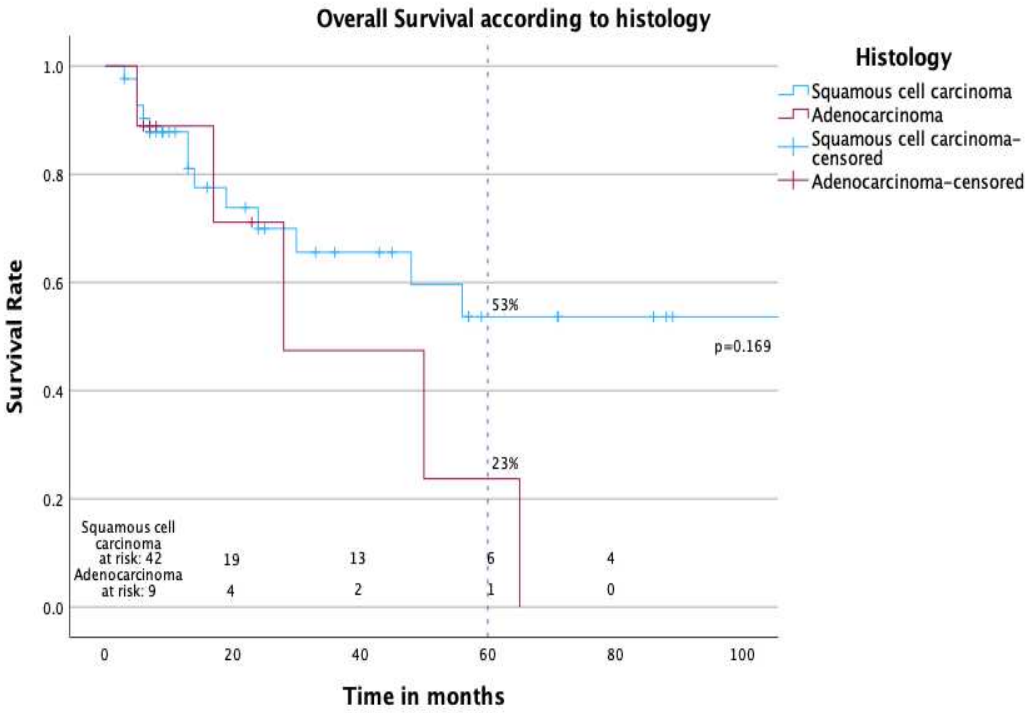

Figure 12: Overall Survival according to the histology.

The survival rates between the histological types of cervical carcinoma, squamous cell and adenocarcinoma, do not differ significantly (p=0.169). 42 patients received a diagnosis of squamous cell carcinoma, while 9 patients were confirmed to have adenocarcinoma. Of the patients with squamous cell carcinoma 14 died and overall was 66.7%. In patients with adenocarcinoma, 5 died and overall survival accounts 44.4%. The median survival is 28 months (CI: 0-60; SD ± 16). For patients diagnosed with adenocarcinoma, the 5-years-survival rate was 23% (±20%), while for the patients with diagnosis of a squamous cell carcinoma it was 53% (±10%).

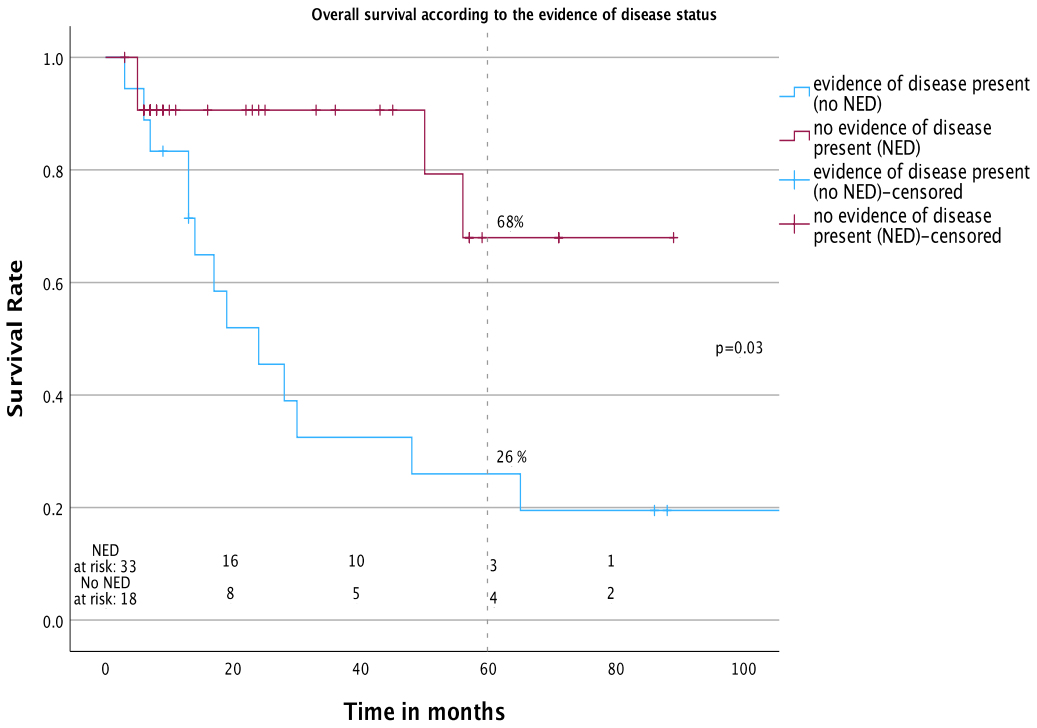

Figure 13: Overall survival according to the evidence of disease status.

Stated in Figure 13 is the overall survival of patients with NED or no NED. A significant difference was found between those two groups in terms of overall survival (p=0.03). 33 of the 51 patients showed no evidence of disease (NED), in the remaining 18 residual disease was found after completion of therapy. The 5-year-survival-rate in patients with NED was 68±14%, while for the patients with residual disease (no NED) it ranged 26±11%.

Stated in Table 11 is a summary of the prognostic factor for the survival of patients.

Table 11: Prognostic factors for overall survival.

Variable	n	5-year survival rate	P-value
All patients	51	48% (±9%)	
FIGO stage			
< IIIB	27	66% (±13%)	0.02
≥ IIIB	24	34% (±12%)	
Pelvic recurrence			
Yes	6	26% (±22%)	0.58
No	45	52% (±10%)	
Distant metastases			
Yes	17	25% (±11%)	0.05
No	34	75% (±12%)	
Histology			
Adenocarcinoma	9	23% (±20%)	0.17
Squamous cell carcinoma	42	53% (±10%)	
NED[a] status			
NED[a]	33	68% (±14%)	0.03
No NED[a]	18	26% (±11%)	

[a] No evidence of disease (NED).

4.3 Evaluation of the EORTC-QLQ-C30 and EORTC-QLQ-CX24 questionnaires

For the evaluation of the questionnaires (n=21), the global health score (overall health), the general QoL score and the cervical cancer specific QoL score after receiving RCT and interstitial BT as treatment were assessed. The results are given on a scale from 0 to 100, where 100 is considered full functionality for the functional scales, and considered with the worst outcome in symptom scales, whereas 0 is the worst possible outcome for functional scales, and the best for the symptom scales. The outcomes are seen in Table 12 and 13.

Table 12: General QoL scores according to EORTC-QLQ-C30 questionnaire

Scales for QLQ-C30	Mean	IQR	CI for 95%	Standard Deviation
Global health				
Global health/QoL[a]	63	50.0 - 66.6	56.9 - 70	±14.3
Functional scale				
Physical functioning	73	66.6 – 86.3	65.4 – 79.9	±15.8
Role functioning	67	58.3 – 100	55.1 – 79.8	±27.1
Emotional functioning	74	58.3 - 91.6	65.7 – 82.7	±18.6
Cognitive functioning	84	66.6 – 100	75.6 – 92.6	±18.6
Social functioning	73	50.0 – 100	60.2 – 85.8	±28.1
Symptom scale				
Fatigue	41	20.0 – 66.6	29.5 – 53.6	±26.5
Nausea and Vomiting	6	0 – 16.6	1.3 – 11.4	±11.1
Pain	29	16.6 – 33.3	20.9 – 38.1	±18.8
Dyspnea	32	0.0 – 66.6	17.7 – 45.7	±30.7
Insomnia	46	0 – 66.6	29.0 – 62.9	±37.2
Appetite loss	10	0 – 16.5	1.0 – 18.0	±18.7
Constipation	13	0 – 33.3	2.5 – 22.8	±22.3
Diarrhea	21	0 – 33.3	6.6 – 34.6	±30.7
Financial difficulties	25	0 – 33.3	10.3 – 40.5	±33.2

[a] Quality of life (QoL).

Table 13: Cervical cancer specific parameters according to EORTC-QLQ-CX24 questionnaire.

Scales for QLQ-CX24	Mean	IQR	CI for 95%	Standard Deviation
Symptom scale				
Symptom experience	14	6.0 – 16.5	0.8 – 35.3	±11.9
Body image	22	0 – 38.3	-21.7 – 60.5	±29.8
Sexual/Vaginal functioning	32	8.3 – 54.1	-2.9 – 66.3	±27.9
Lymphedema	32	0 – 66.6	-25.2 – 91.8	±32.4
Peripheral Neuropathy	36	0 – 66.6	-18.7 – 71.9	±34.8
Menopausal Symptoms	21	0 – 33.3	-13.9 – 93.9	±28.8
Sexual worry	22	0 – 33.3	5.4 – 74.5	±30.2
Functional scale				
Sexual activity	11	0 – 16.5	9.6- 83.7	±24.3
Sexual enjoyment	27	0 – 49.9	-7.9 – 61.2	±27.9

According to the evaluation of the EORTC-QLQ-C30 questionnaire general health scored an average of 63 out of 100. (IQR: 50.0-66.6; SD±14.3). The least impaired was cognitive function, with a score of 84 (IQR: 66.6-100%; SD±18.6). Emotional functions had a mean score of 74 (IQR: 58.3-91; SD±18.6).

For the symptom scale, 0 is considered optimal because the lower the score, the less frequently the symptom occurred in the patients. The symptom limiting the patients most was insomnia scoring 46/100 (IQR: 0-66.6%; SD±37.2). Thereafter, the most incisive symptoms perceived were fatigue with a mean score of 41 (IQR: 20-66.6; SD±26.5), dyspnea with a mean of 32 (IQR: 0-66.6; SD±30.7), and pain with an average score of 29 (IQR: 16.6-33.3; SD±18.8). Patients complained less frequently about diarrhea, constipation, and loss of appetite.

The additional evaluation of the EORTC-QLQ-CX24 questionnaire allows deeper insight into the occurrence of side effects specifically related to cervical cancer radiation and also on sexual functioning. Patients perceived symptoms that they experienced related to bowel movements, urination, continence, and vaginal discharge or bleeding as less bothersome and gave them a total score of 12 out of 100 (IQR: 6-16.5; SD±11.9). Menopausal symptoms or sexual concern was rated moderately distressing with a mean scoring of 21-22. Furthermore, body image of patients was also moderately affected in a negative way with a mean of 22 (IQR: 0-38.3.; SD±29.8). Most observed by patients and influencing QoL was the presence of lymphedema (mean score of 32; IQR: 0-66.6; SD: ±32.4), the limitations of sexual/vaginal functioning (mean score of 32; IQR: 8.3-554.1; SD±27.9), and the peripheral neuropathy (mean score of 36; IQR: 0-66.6; SD±34.8). The last part of the questionnaire could be answered, if one was sexually active in the last four weeks. This was true for 5 female patients and showed the result that less than one third of these 5 had enjoyed sex.

The following figures 14-16 again provide a better overview of the influences of the different aspects of QoL discussed in the questionnaires and aforementioned tables 9 and 10.

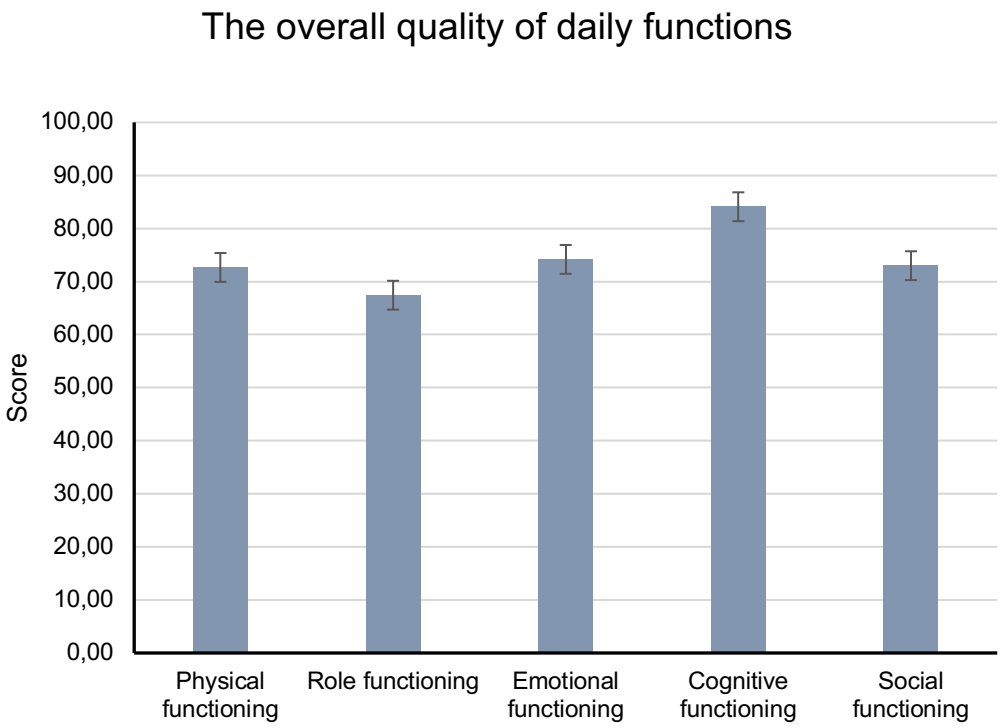

Figure 14: Overall quality of daily functions according to the EORTC-QLQ-C30. Data are presented as mean ± standard deviation

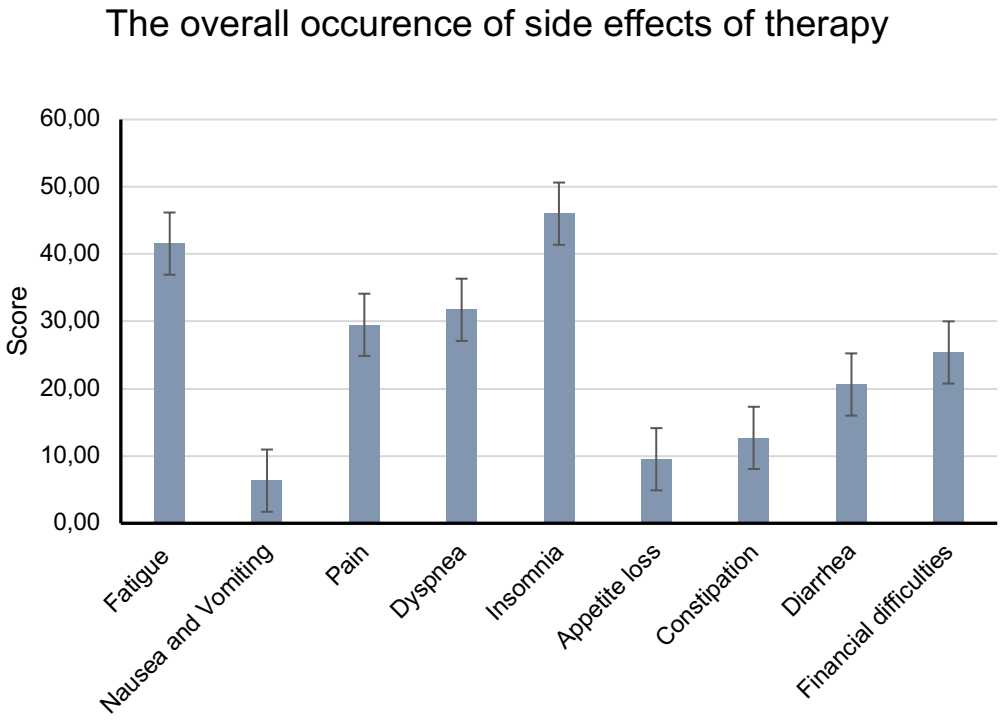

Figure 15: Overall occurrence of side effects of therapy according to the EORTC-QLQ-C30. Data are presented as mean ± standard deviation

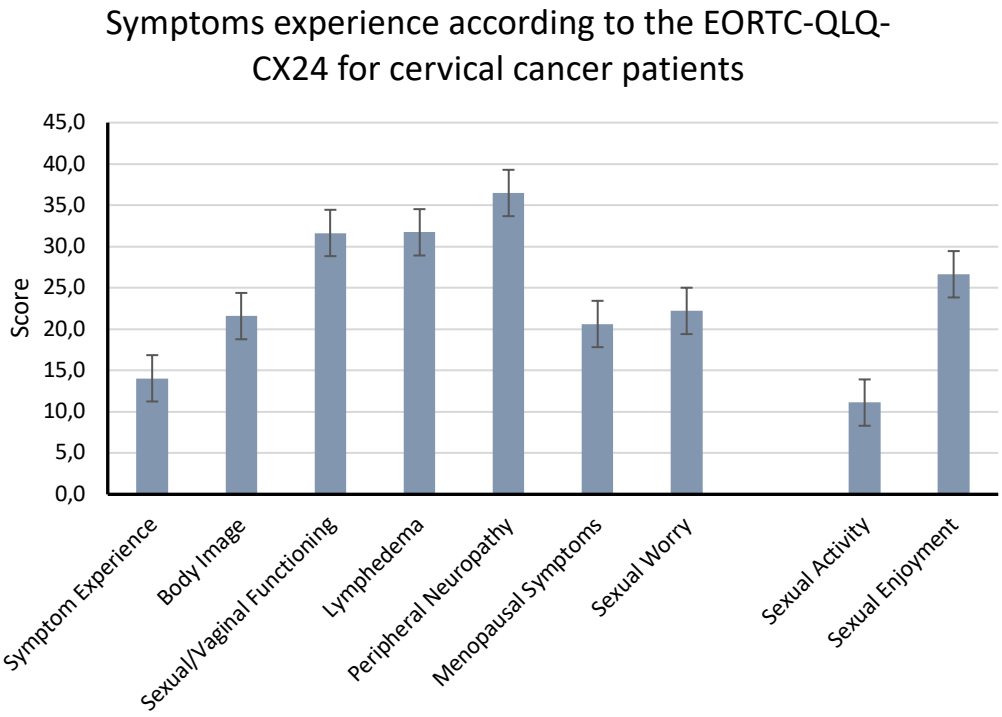

Figure 16: Functional scale and symptom scale of the EORTC-QLQ-CX24.

Data are presented as mean ± standard deviation

4.4 Correlation between results of the EORTC-questionnaires and the patient characteristics

The results of the EORTC-QLQ-C30 and EORTC-QLQ-CX24 questionnaires were compared with the patients' characteristics, namely age at initial diagnosis and FIGO stage. The QoL parameters being compared include general QoL, the functionals scale of the EORTC-QLQ-C30 questionnaire, and the symptom scale of each, the EORTC-QLQ-C30 and CX-24 questionnaires. Age was divided into ≥58 years and <58 years according to the mean age at initial diagnosis. For FIGO stage, a distinction was made between stages <IIIB and ≥IIIB.

In Table 14 below, an overview of the results of the correlation can be seen.

Table 14: Correlation of age at diagnosis and FIGO to the QoL parameters according to the EORTC-QLQ-C30 and EORTC-QLQ-CX24.

QoL[a] parameters	Age at diagnosis	Mean	Standard Deviation	P-value
Functional scale C30	≥58 years (n=10)	79,5	±15.5	0.145
	<58 years (n=11)	69,9	±18.9	
Overall QoL[a]	≥58 years	63.3	±13.7	0.783
	<58 years	61.6	±14.8	
Symptom scale of C30	≥58 years	21.3	±11.7	0.426
	<58 years	26.6	±13.9	
Symptom scale of CX24	≥58 years	15.8	±12.5	0.179
	<58 years	27.6	±17.9	
QoL[a] parameters	**FIGO stage**	**Mean**	**Standard Deviation**	**P-value**
Functional scale C30	≥IIIB (n=4)	68.7	±22.3	0.092
	<IIIB (n=17)	82.7	±17.6	
Overall QoL[a]	≥IIIB	52.1	±4.1	0.306
	<IIIB	77.1	±18.5	
Symptom scale C30	≥IIIB	23.9	±9.2	0.346
	<IIIB	15.5	±12.6	
Symptom scale CX24	≥IIIB	28.4	±18.5	0.618
	<IIIB	20.3	±18.5	

[a] Quality of life (QoL).

Comparison of QoL parameters with age at initial diagnosis did not reveal any significant differences between patients who were over 58 years old or younger than 58 years old at diagnosis. There is a tendency for the overall QoL and daily functions scores to be slightly higher in the older patients. In addition, the trend for symptoms is also that they were less burdensome for patients with initial diagnosis age over 58 years.

FIGO stages above IIIB and less than IIIB did also not differ significantly. However, there is a trend for QoL and daily functions to be less impaired in FIGO stage <IIIB, and symptom distress is also less in this patient group.

This is again illustrated in Figure 17 and 18 below.

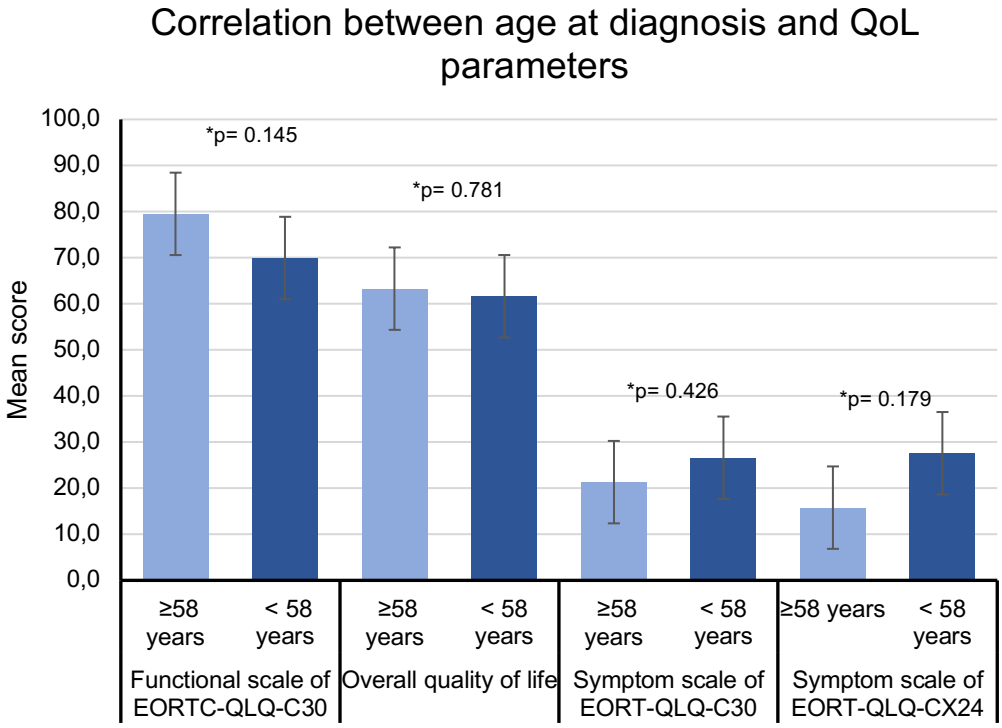

Figure 17: Correlation between age at diagnosis and QoL parameters.

Data are presented as mean ± standard deviation

* t-test for dependent samples

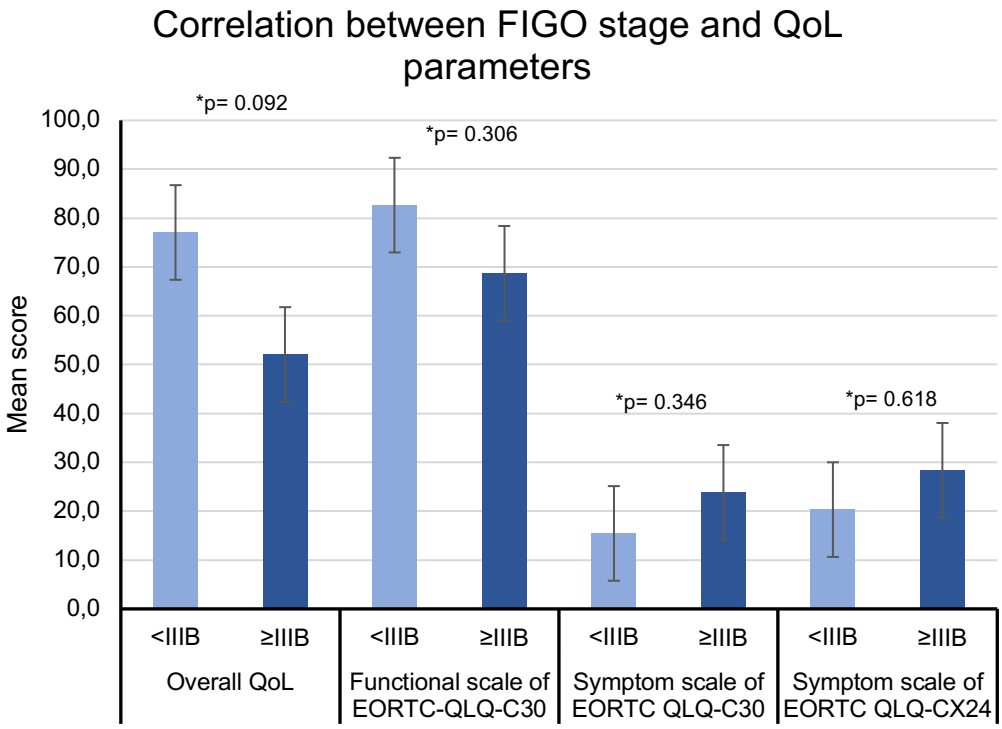

Figure 18: Correlation between FIGO stage and QoL parameters.

Data are presented as mean ± standard deviation

* t-test for dependent samples

5 DISCUSSION

Radiochemotherapy followed by brachytherapy is considered the standard of practice for the treatment of locally advanced cervical cancer. Brachytherapy allows escalation of the dose reaching the primary tumor and the parametria, resulting in better local control of the cancer while protecting the surrounding organs at risk (48). In addition to treatment complications, the QoL of patients after and during therapy is becoming increasingly important. Evaluation of this should become a standard of follow-up in order to continue to improve treatment modalities (1).

In this study, overall survival was first determined in general and in relation to prognostic factors such as the assigned FIGO stage, the presence of distant metastases, the diagnosis of pelvic recurrence, and different histology types of cervical carcinoma, namely adenocarcinoma and squamous cell carcinoma. Then, using the EORTC-QLQ-C30 and CX24 questionnaires, the QoL of patients after therapy was evaluated to discuss the impact of radiochemotherapy and brachytherapy on it.

The average age at initial diagnosis was 58 years, which was also the case in some studies regarding cervical carcinoma (49,50). At 53%, FIGO stages IB2 to IIIA were represented slightly more frequently than patients with FIGO stages IIIB and larger (47%), which is confirmed by at least one other study (50). Squamous cell carcinoma was far more common at 82%, consistent with the standard distribution of cervical carcinoma histology types (18). The median duration of radiation therapy was 62.5 days and the median external radiation dose was 50.4 Gy with a possible boost of up to 62.6 Gy of primary tumor. This dosing also corresponds nicely to the standard doses applied in similar studies. Also standard was the brachytherapy dose with a mean of 23.2 Gy and fractionation of four times 7 Gy, as well as simultaneous cisplatin administration averaging 158.8 mg/m2 BSA, with 8 patients receiving carboplatin or 5-FU (48,49).

The most common acute complications were hematologic (36%), renal/urogenital (21%) and gastrointestinal (20%). The hematologic toxicities included mostly anemia, thrombocytopenia and leukopenia with a CTC-grading of grade 2 and 3, as also shown in a retrospective study from 2023 (18). This complication is due to simultaneous cisplatin administration. In all patients, the blood count recovered after transfusions or pausing chemotherapy. The most affected organs at risk of radiation therapy are the gastrointestinal tract and the urogenital tract. The toxicities recorded here ranged between severity 1 and 2 according to the CTC classification and could thus be treated in an outpatient setting. The distribution of the occurrence of the most frequent acute complications reflects the normal distribution in patients with EBRT and brachytherapy for cervical carcinoma (50).

In contrast to the acute toxicities, the incidence of late complications was only 20% overall and of these, only patients with severity grade 1 and 2 were recorded. In the setting of other studies, the rate of severity of late complications was 10% for grade 1-2 and only 5% for grade 3 or higher. This decrease in late complications is thought to be related to the benefit of IMRT together with an individualized approach for MRI-based brachytherapy (51,52). The most commonly affected organ systems here were renal/urogenital, gastrointestinal, and musculoskeletal. While the first two late toxicities were also reported in other analyses and overlapped in distribution and incidence with these others (51,52). Musculoskeletal complaints were less reported and these were not mentioned as a typical late toxicity.

The 5-year overall survival rate observed among these 51 patients was 48±9% with a median survival of 56 months (CI 95%: 36-75 months). In another study, which also included women being treated with radiochemotherapy and brachytherapy, a median survival time of only 39.8 months was observed (18). The 5-year survival rate in yet other studies with the same spectrum of therapy of the patients is comparable with 53-55% (51).

Survival is different in studies that do not include only patients with locally advanced cervical cancer. Here survival rates of 75% (48) are listed or even a 5-year survival rate of 76% (50). However, it can be said that overall survival and 5-year survival rates have increased significantly in locally advanced cervical cancer since the 1990s. This is due to the simultaneous administration of chemotherapy and the additional interstitial brachytherapy as compared to EBRT alone (51,53).

Significant prognostic factors were the presence of distant metastases and a FIGO stage of IIIB and more advanced. In patients with distant metastases, the median survival was 28 months and a 5-year survival rate of 25%, while in metastasis-free patients the 5-year survival achieved 75%. Similar results regarding the occurrence of distant metastases and the significant difference between patients with and without distant metastases, were also found in a 2022 study from China (54). In this study, histology is also mentioned as a significant prognostic factor with the result that adenocarcinoma has worse overall survival (54). However, no significant difference was found between histological types of adenocarcinoma and squamous cell carcinoma of the *cervix uteri* in the 51 patients evaluated in this follow-up. In another study from India, there was no difference in the two histologic types found either (51). But the lack of significance may also be due to the lower number of participants with adenocarcinoma for this particular study.

There was also no significant difference in the survival of patients with pelvic recurrence, which had a median survival of 48 months (±15). In contrast, the median survival

of patients without pelvic recurrence was 65 months (±12). Since there were only 6 (12%) patients diagnosed with pelvic recurrence, this result can be skewed due to the small sample size. In other studies, the rate of pelvic recurrence was around 30% and was found to be a significant prognostic factor (49,52).

In addition to pelvic recurrence, FIGO stage was also discussed as a significant prognostic factor for survival in these aforementioned studies. Their results are consistent with that from the present study, in which overall survival for FIGO stage <IIIB was 77.8% with a 5-year survival rate of 74%. In contrast, overall survival in FIGO stage ≥IIIB was 45.8% with a 5-year survival rate of 29%. A similar 5-year survival rate was mentioned in a report from Thailand in 2022 (51). A study from India in 2018 and from China in 2022 also confirmed a significant difference depending on the progression of the FIGO stage (54,55).

As survival of cancer patients increases, QoL after treatment becomes increasingly important (56). Analysis of EORTC questionnaires from 21 female patients showed moderately good overall QoL with only slightly reduced functional activities, where all still had a function of at least 67 out of 100. Similar results for overall QoL after radiochemotherapy were reported from a BMC Women's health study (57). The functional scale gave the best results for cognitive abilities in our study. Physical, social and emotional functioning did about equally well, while role functioning did the worst. In other studies, emotional functioning showed the greatest cut, while they reported good physical functioning (58). The latter is also true for the study presented here. Emotional function is expected to be low, due to the fear of patients of recurrence of cancer (57). In this study of 21 patients that were able to complete the QLQ, only one suffered a recurrence of the disease, which might explain the good overall emotional functioning observed in this patient group. Psychosocial factors could be partly responsible for the low score of role functioning. It has been described that after treatment women feel less able to continue their role in society, for example as a housewife or a mother (58).

After evaluating the symptom scale of the EORTC-QLQ-C30, it was found that the most distressing symptom after cancer treatment was insomnia and fatigue, followed by dyspnea, pain and diarrhea. The results are consistent with the most common symptoms reported in the study from India (57). But while in the aforementioned study, constipation was a less frequently reported problem among the patients of this study. Financial difficulties were in the upper middle range of distressing symptoms. According to literature, financial difficulties are most stressful immediately after radiotherapy (56). This is also reflected in this study, as financial difficulties were rated with the highest score by patients who received radiotherapy up to 8 months ago.

Evaluation of the EORTC-QLQ-CX24 revealed that patients most frequently experienced peripheral neuropathy, lymphedema, and sexual/vaginal dysfunctioning. Due to radiation induced late effects to the vaginal mucosa, vaginal functions are more frequently impaired (40), as also observed in other studies (57). Furthermore, the occurrence of peripheral neuropathy after treatment was also described in other study (57), but the prevalence of lymphedema was lower. Overall, only 5 of the 21 patients were sexually active within the last four weeks, and one third of them were able to enjoy it. The rare participation in this question, thus the low sexual activity among the patients, can be partly attributed to the negatively affected body image and the resulting low self-esteem, and partly due to the side effects of the therapy like vaginal dryness, pain, constitutional symptoms and more. On the other hand, the decrease in sexual activity can be related to decreased sexual activity with increasing age and the increased likelihood of being a widow, thus not having a sexual partner. Similar rates related to sexual enjoyment were also reflected in the study from India (57).

Last, the EORTC-QLQ results of different groups of patients were compared. First, the QoL of patients younger than 58 at initial diagnosis was compared with those older than 58 at that time. There was no significant difference in overall QoL, daily functions and symptoms, both general and cervical cancer specific. However, a tendency could be seen that patients who were ≥58 years old at initial diagnosis did slightly better. This was refuted in a study in which a significant difference was found between the two age groups in that younger patients achieved better scores (57). The result from this study may be biased by the small sample of patients who completed the questionnaire and therefore needs to be discussed again using a larger group of subjects. As a second group, different FIGO stages were compared again with respect to QoL. Here, there was again no significant difference between patients with FIGO stage <IIIB and ≥IIIB. However, the trend was in the direction that the more advanced the cervical cancer, i.e., the higher the FIGO stage, the more limited the QoL. This conclusion was also reached by other studies that looked at QoL after cancer therapy (1,57,59).

This study is limited by its small sample size. There were in total 51 eligible patients, which received radiochemotherapy and brachytherapy. Of those, 21 answered the EORTC-QLQ-C30 and CX24 questionnaires. In addition, all patients were recruited from one single Cancer Center. Therefore, the results can only be applied to a larger population to a limited extent. In addition, the QoL was only assessed after the therapy, and also at irregular intervals, so that for each patient a different amount of time elapsed between the end of the therapy and the completion of the questionnaires. In addition, it can be assumed that the more severe the

complications of the therapy, the lower the willingness to participate in a study. The willingness to participate in a study is also greater in younger patients.

6 CONCLUSION

1. Among a total of 51 patients with advanced cervical carcinoma that were uniformly treated by a combined radiochemotherapy and brachytherapy, 5-year overall-, NED-survival and pelvic-recurrence free survival rates of 48%, 68% and 52% were found.

2. There was a significant difference in 5-year overall survival rates between patients diagnosed with distant metastases and patients without distant metastases (26% vs 75%, p=0.05).

3. There was also a significant difference in 5-year overall survival rates between patients with FIGO stages IIA-IIIA and IIIB-IVA (66% vs 34%, p=0.02).

4. Furthermore, there was a significant difference in 5-year survival rates between patients with NED and patients with evidence of residual disease (68% vs. 26%, p=0.03).

5. Radiochemotherapy and brachytherapy for locally advanced cervical cancer resulted in a moderately good overall QoL according to EORTC-QLQ-C30, scoring 63/100.

6. Evaluation of cervical cancer specific quality of life parameters according to EORTC-QLQ-CX24 questionnaire revealed high symptom scores for lymphedema, and peripheral neuropathy as well as low functional scores for sexual functioning and sexual enjoyment.

7 REFERENCES

1. Rahman Z, Singh U, Qureshi S, Nisha, Srivastav K, Nishchal A. Assessment of quality of life in treated patients of cancer cervix. J -Life Health. 2017;8(4):183.
2. Li H, Wu X, Cheng X. Advances in diagnosis and treatment of metastatic cervical cancer. J Gynecol Oncol. 2016;27(4):e43.
3. Keys H, Gibbons SK. Optimal management of locally advanced cervical carcinoma. J Natl Cancer Inst Monogr. 1996 January 1;(21):89–92.
4. Greimel ER, Kuljanic Vlasic K, Waldenstrom AC, Duric VM, Jensen PT, Singer S, u. a. The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life questionnaire cervical cancer module: EORTC QLQ-CX24. Cancer. 2006 October 15;107(8):1812–22.
5. Tax C, Steenbergen ME, Zusterzeel PLM, Bekkers RLM, Rovers MM. Measuring health-related quality of life in cervical cancer patients: a systematic review of the most used questionnaires and their validity. BMC Med Res Methodol. December 2017;17(1):15.
6. Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, u. a. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Health. 2020 February 1;8(2):e191–203.
7. Vu M, Yu J, Awolude OA, Chuang L. Cervical cancer worldwide. Curr Probl Cancer. 2018 September 1;42(5):457–65.
8. Moreno V, Bosch FX, Muñoz N, Meijer CJ, Shah KV, Walboomers JM, u. a. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. The Lancet. March 2002;359(9312):1085–92.
9. Tsikouras P, Zervoudis S, Manav B, Tomara E, Romanidis C, Bothou A, u. a. Cervical cancer: screening, diagnosis and staging.
10. Schneider A, Kaufmann AM, Köhler C, Marnitz S. Zervixkarzinom. In: Hiddemann W, Bartram CR, Herausgeber. Die Onkologie [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010 [cited 2023 May 23]. S. 1038–68. Available from: http://link.springer.com/10.1007/978-3-540-79725-8_52
11. Balasubramaniam SD, Balakrishnan V, Oon CE, Kaur G. Key Molecular Events in Cervical Cancer Development. Med Kaunas Lith. 2019 July 17;55(7):384.
12. Kaur H, Silverman PM, Iyer RB, Verschraegen CF, Eifel PJ, Charnsangavej C. Diagnosis, Staging, and Surveillance of Cervical Carcinoma. Am J Roentgenol. June 2003;180(6):1621–31.
13. Salib MY, Russell JHB, Stewart VR, Sudderuddin SA, Barwick TD, Rockall AG, u. a. 2018 FIGO Staging Classification for Cervical Cancer: Added Benefits of Imaging.

RadioGraphics. October 2020;40(6):1807–22.

14. Bhatla N, Berek JS, Cuello Fredes M, Denny LA, Grenman S, Karunaratne K, u. a. Revised FIGO staging for carcinoma of the cervix uteri. Int J Gynecol Obstet. 2019;145(1):129–35.

15. Díaz-Feijoó B, Acosta Ú, Torné A, Gil-Ibáñez B, Hernández A, Domingo S, u. a. Surgical Outcomes of Laparoscopic Pelvic Lymph Node Debulking during Staging Aortic Lymphadenectomy in Locally Advanced Cervical Cancer: A Multicenter Study. Cancers. 2022 April 13;14(8):1974.

16. Kamrava M, Banerjee R. Brachytherapy in the treatment of cervical cancer: a review. Int J Womens Health. May 2014;555.

17. Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A, Colombo N. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. July 2017;28:iv72–83.

18. Aghili M, Andalib B, Karimi Moghaddam Z, Maddah Safaei A, Amoozgar Hashemi F, Mousavi Darzikolaei N. Concurrent Chemo- Radiobrachytherapy with Cisplatin and Medium Dose Rate Intra- Cavitary Brachytherapy for Locally Advanced Uterine Cervical Cancer. Asian Pac J Cancer Prev [Internet]. October 2018 [cited 2023 May 23];19(10). Available from: https://doi.org/10.22034/APJCP.2018.19.10.2745

19. Hartmann T, Kahl-Scholz M, Vockelmann C. Fachwissen MTRA: Für Ausbildung, Studium und Beruf. Springer-Verlag; 2018. 717 S.

20. Krukemeyer MG, Wagner W. Strahlenmedizin: Ein Leitfaden für den Praktiker. Walter de Gruyter; 2009. 372 S.

21. Stöver I, Feyer P. Praxismanual Strahlentherapie [Internet]. Berlin, Heidelberg: Springer; 2018 [cited 2023 June 6]. Available from: http://link.springer.com/10.1007/978-3-662-56577-3

22. Sauer R. Strahlentherapie und Onkologie [Internet]. 5. Bd. 1. München: Urban & Fischer in Elsevier; 2009 [cited 2023 June 6]. 538 S. Available from: https://shop.elsevier.de/strahlentherapie-und-onkologie-9783437475016.html

23. Goyal MK, Rai DV, Kehwar TS, Manjhi J, Heintz BH, Shide KL, u. a. Anatomy-based definition of point A utilizing three-dimensional volumetric imaging approach for high-dose-rate (HDR) intracavitary brachytherapy dose prescription when treating cervical cancer using limited resources. J Appl Clin Med Phys. 2016 July 16;17(6):69–77.

24. Strnad V, Herausgeber. Praktisches Handbuch der Brachytherapie. 2., [überarb.] Aufl. Bremen: UNI-MED-Verl; 2010. 271 S. (UNI-MED SCIENCE).

25. Chino J, Annunziata CM, Beriwal S, Bradfield L, Erickson BA, Fields EC, u. a. Radiation Therapy for Cervical Cancer: Executive Summary of an ASTRO Clinical Practice Guideline. Pract Radiat Oncol. July 2020;10(4):220–34.
26. Patankar SS, Tergas AI, Deutsch I, Burke WM, Hou JY, Ananth CV, u. a. High versus Low-Dose Rate Brachytherapy for Cervical Cancer. Gynecol Oncol. March 2015;136(3):534–41.
27. Alternative operative Therapien in der Uroonkologie: Operationen, Interventionelle Techniken, Radiochemotherapie | SpringerLink [Internet]. [cited 2023 June 6]. Available from: https://link.springer.com/book/10.1007/978-3-662-44420-7
28. Lang S, Kirisits C, Dimopoulos J, Georg D, Pötter R. Treatment planning for MRI assisted brachytherapy of gynecologic malignancies based on total dose constraints. Int J Radiat Oncol Biol Phys. 2007 October 1;69(2):619–27.
29. Radojevic MZ, Tomasevic A, Karapandzic VP, Milosavljevic N, Jankovic S, Folic M. Acute chemoradiotherapy toxicity in cervical cancer patients. Open Med. 2020 September 1;15(1):822–32.
30. Moore KN, Gold MA, McMeekin DS, Zorn KK. Vesicovaginal fistula formation in patients with Stage IVA cervical carcinoma. Gynecol Oncol. September 2007;106(3):498–501.
31. Danko CM, Hong LJ, Slater JD. Multiple severe late adverse effects after definitive chemoradiation for locally advanced cervical cancer. Precis Radiat Oncol. 2021;5(3):202–4.
32. Sharma AD, Poddar J, K US, Shah SP, Parikh A, Mehta V, u. a. Dosimetric analysis of the effects of the bladder volume on organs at risk (OAR) in high-dose-rate intracavitary brachytherapy in carcinoma cervix – an institutional study. J Contemp Brachytherapy. 2018;10(1):26–31.
33. Müller RP, Segenschmiedt MH, Höffken K, Junginger T, Sauer H. Common Toxicity Criteria (CTC): Dokumentation von Nebenwirkungen in der Onkologie. Dtsch Ärztebl. 1999;96(A-489-495).
34. Franklin HR, Simonetti GPC, Dubbelman AC, Ten Bokkel Huinink WW, Taal BG, Wigbout G, u. a. Toxicity grading systems. Ann Oncol. February 1994;5(2):113–7.
35. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, u. a. Concurrent Cisplatin-Based Radiotherapy and Chemotherapy for Locally Advanced Cervical Cancer. N Engl J Med. 15. April 1999;340(15):1144–53.
36. Wannenmacher M, Wenz F, Debus J, Herausgeber. Strahlentherapie [Internet]. Berlin, Heidelberg: Springer; 2013 [cited 2023 June 6]. Available from: https://link.springer.com/10.1007/978-3-540-88305-0

37. Dimopoulos JCA, Petrow P, Tanderup K, Petric P, Berger D, Kirisits C, u. a. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): Basic principles and parameters for MR imaging within the frame of image based adaptive cervix cancer brachytherapy. Radiother Oncol. April 2012;103(1):113–22.
38. Cancer Research Institute [Internet]. [cited 2023 June 9]. Immunotherapy for Cervical Cancer. Available from: https://www.cancerresearch.org/cancer-types/cervical-cancer
39. Thapa-Görder N. Prävention und Gesundheitsförderung - Aufgaben der Ergotherapie: 10 Tabellen. Georg Thieme Verlag; 2010. 240 S.
40. Dahiya N, Acharya AS, Bachani D, Sharma DN, Gupta S, Haresh KP, u. a. Quality of Life of Patients with Advanced Cervical Cancer before and after Chemoradiotherapy. Asian Pac J Cancer Prev. 2016 July 1;17(7):3095–9.
41. Kovács L, Kipke R, Lutz R, Herausgeber. Lebensqualität in der Medizin [Internet]. Wiesbaden: Springer Fachmedien; 2016 [cited 2023 June 9]. Available from: http://link.springer.com/10.1007/978-3-658-10679-9
42. Carter WB, Bobbitt RA, Bergner M, Gilson BS. Validation of an interval scaling: the sickness impact profile. Health Serv Res. 1976;11(4):516–28.
43. Dörfler H, Eisenmenger W, Lippert HD, Wandl U, Herausgeber. Medizinische Gutachten [Internet]. Berlin, Heidelberg: Springer; 2015 [cited 2023 June 9]. Available from: https://link.springer.com/10.1007/978-3-662-43425-3
44. Fayers PM, Aaronson N, Bjordal K, Groenvold M, Curran D, Bottomley A. EORTC QLQ-C30 scoring manual: this manual is intended to assist users with scoring procedures for the QLQ-C30 version 3 and earlier, and the QLQ supplementary modules. 3rd ed. Brussels: EORTC; 2001.
45. Snyder CF, Blackford AL, Okuyama T, Akechi T, Yamashita H, Toyama T, u. a. Using the EORTC QLQ-C30 in Clinical Practice for Patient Management: Identifying Scores Requiring a Clinician's Attention. Qual Life Res Int J Qual Life Asp Treat Care Rehabil. December 2013;22(10):10.1007/s11136-013-0387–8.
46. Hua CH, Guo HM, Guan XL, Kong FJ, Hou RJ, Zhang XY, u. a. Validation of the European Organization for Research and Treatment of Cancer cervical cancer module for Chinese patients with cervical cancer. Patient Prefer Adherence. 2013 October 17;7:1061–6.
47. Araya LT, Gebretekle GB, Gebremariam GT, Fenta TG. Reliability and validity of the Amharic version of European Organization for Research and Treatment of cervical Cancer module for the assessment of health related quality of life in women with cervical cancer in Addis Ababa, Ethiopia. Health Qual Life Outcomes. 2019 January 14;17:13.

48. le Guyader M, Lam Cham Kee D, Thamphya B, Schiappa R, Gautier M, Chand-Fouche ME, u. a. High-dose-rate brachytherapy boost for locally advanced cervical cancer: Oncological outcome and toxicity analysis of 4 fractionation schemes. Clin Transl Radiat Oncol. 2021 November 6;32:15–23.
49. Wang Y, Lo TT, Wang L, Hsu ST, Hwang SF, Lu CH, u. a. Long-Term Efficacy and Toxicity of Intensity-Modulated Radiotherapy in Bulky Cervical Cancer. Int J Environ Res Public Health. 2023 January 9;20(2):1161.
50. DE SANCTIS V, FACONDO G, VULLO G, ANZELLINI D, SANGUINETI G, NARDANGELI A, u. a. Clinical Outcomes and Toxicity of CT-guided High Dose-rate Brachytherapy in Women With Locally-advanced Cervical Cancer. Cancer Diagn Progn. 3. March 2023;3(2):194–200.
51. Chopra S, Gupta M, Mathew A, Mahantshetty U, Engineer R, Lavanya G, u. a. Locally advanced cervical cancer: A study of 5-year outcomes. Indian J Cancer. 2018;55(1):45–9.
52. Dang YZ, Li P, Li JP, Bai F, Zhang Y, Mu YF, u. a. The Efficacy and Late Toxicities of Computed Tomography-based Brachytherapy with Intracavitary and Interstitial Technique in Advanced Cervical Cancer. J Cancer. 2018;9(9):1635–41.
53. Vittrup AS, Tanderup K, Bentzen SM, Jensen NBK, Spampinato S, Fokdal LU, u. a. Persistence of Late Substantial Patient-Reported Symptoms (LAPERS) After Radiochemotherapy Including Image Guided Adaptive Brachytherapy for Locally Advanced Cervical Cancer: A Report From the EMBRACE Study. Int J Radiat Oncol. January 2021;109(1):161–73.
54. Xiu YT, Meng FX, Wang Z, Zhao KK, Wang YL, Chen ZS, u. a. Prognostic factors for IB2-IIIB cervical cancer patients treated by radiation therapy with high-dose-rate brachytherapy in a single-institution study. J Contemp Brachytherapy. August 2022;14(4):332–40.
55. Tharavichitkul E, Jia-Mahasap B, Muangwong P, Chakrabandhu S, Klunklin P, Onchan W, u. a. Survival outcome of cervical cancer patients treated by image-guided brachytherapy: a 'real world' single center experience in Thailand from 2008 to 2018. J Radiat Res (Tokyo). 2022 June 19;63(4):657–65.
56. Seol KH, Bong SH, Kang DH, Kim JW. Factors Associated with the Quality of Life of Patients with Cancer Undergoing Radiotherapy. Psychiatry Investig. January 2021;18(1):80–7.
57. Mvunta DH, August F, Dharsee N, Mvunta MH, Wangwe P, Ngarina M, u. a. Quality of life among cervical cancer patients following completion of chemoradiotherapy at Ocean Road Cancer Institute (ORCI) in Tanzania. BMC Womens Health. 2022 October 27;22:426.

58. Dos Santos LN, Castaneda L, De Aguiar SS, Thuler LCS, Koifman RJ, Bergmann A. Health-related Quality of Life in Women with Cervical Cancer. Rev Bras Ginecol E Obstetrícia RBGO Gynecol Obstet. April 2019;41(04):242–8.
59. Park J, Kim Y, Kim J, Kang S, Kim K, Kim JH, u. a. Health-Related Quality of Life of Patients with Cervical Cancer According to the Duration of Treatment and Cancer Progression. Asian Pac J Cancer Prev APJCP. June 2022;23(6):1945–50.

8 SUMMARY

Objectives: This study aimed to evaluate survival and recurrence data as well as the QoL data in cervical cancer patients following radiochemotherapy (RCT) and brachytherapy as definitive treatment. The goal was to identify factors that can be modified to enhance overall survival and QoL for these patients.

Materials and methods: Between 2003 and 2023, a total of 132 patients with advanced cervical cancer were evaluated for possible treatment at the Coburg Cancer Center. For this retrospective analysis, 81 patients were excluded due to various reasons (post-operative RCT, radiotherapy without brachytherapy, neoadjuvant RCT, palliative RCT, treatment of cancer recurrence, simultaneous treatment of other malignancy). Thus, 51 patients were included in this study. Analysis of patient data was primarily focused on age at initial diagnosis, menstrual status, FIGO stage, histology, overall survival, remission, occurrence of distant metastases or pelvic recurrence, total dose of radiation, brachytherapy, and concurrent chemotherapy, and occurrence of acute or late toxicities. Additionally, QoL was assessed prospectively by patient self-completion of the EORTC-QLQ-C30 and EORTC-QLQ-CX24.
For the analysis of the statistical data IMB SPSS Statistics 29 for macOS (IBM Corp, 2022) was used. Survival rates were calculated by the Kaplan-Meier method, and the log-rank test was used to compare survival rates between different groups of patients. Qualitative data were expressed as whole numbers and percentages, while quantitative data were expressed as mean ± standard deviation or mean and interquartile range. For analysis of the EORTC questionnaires, all data were summarized in descriptive statistics. To compare differences between two groups, the t-test was performed. The chi-square test was applied to compare two categorical variables, and regression analysis was used to examine the influence of certain variables on QoL.

Results: 5-year overall survival, NED-survival, and pelvic-recurrence-free survival rates were 48±9%, 68±14% and 52±10%, respectively. A significant impact on 5-year overall survival rates was seen for FIGO-stage (IIA-IIIA: 74±13% vs IIIB-IVA: 29±12%, p=0.027) for distant metastases (W/o DM: 75±12% vs with DM: 25±11%, p=0.05). Neither development of pelvic recurrence nor histology had significant impact survival rates.
QoL-questionnaire evaluation resulted in a score of 63/100 for the overall QoL of patients. Cognitive function was the least impaired with a score of 84, while role functioning was the worst with a score of 67. On the symptom scale, Insomnia (46/100), Fatigue (41/100), Dyspnea (32/100), and Pain (26/100) scored the worst. Financial difficulties also burdened some patients

and achieved a score of 25/100. Diarrhea, constipation, appetite loss, and nausea/vomiting were rated as less distressing by patients. The cervical cancer-specific questions of the EORTC-QLQ-CX24 questionnaire revealed that peripheral neuropathy, score of 36/100, and lymphedema, score of 32/100, occurred most frequently. Patients also reported that their sexual/vaginal functioning was impaired (32/100) and that their own body image (22/100) was also affected. The functional sexual activity scale could only be completed by 5 patients who had been sexually active in the last four weeks. This showed that only one third of them could enjoy sex. Comparing the result of evaluation of the EORTC-questionnaires showed no significant differences in the QoL of patients above and under the age of 58 years, and there was also no difference seen in patients diagnosed with FIGO stage <IIIB and ≥IIIB. However, there was a tendency for QoL to be less limited at an earlier stage of diagnosis.

Conclusion:

In patients with advanced inoperable cervical carcinoma a combination of radiochemotherapy and brachytherapy is able to cure around 50% of the patients. Advanced stages IIIB and IVA according to FIGO and the development of distant metastases have a significantly negative impact on outcome. In terms of patient reported long-term quality of life specific support is needed to alleviate symptoms including lymphedema, peripheral neuropathy, and impaired sexual activity.

9 CROATIAN SUMMARY

Naslov: Radiokemoterapija i intersticijska brahiterapija kao terapijski pristup karcinomu vrata maternice i njezin utjecaj na kvalitetu života bolesnica.

Ciljevi: Ova studija imala je za cilj procijeniti podatke o preživljenju i recidivu, kao i podatke o kvaliteti života kod pacijenata s rakom vrata maternice nakon radiokemoterapije (RCT) i brahiterapije kao konačnog liječenja. Cilj je bio identificirati čimbenike koji se mogu modificirati kako bi se poboljšalo ukupno preživljenje i QoL za ove pacijente.

Materijali i metode: Između 2003. i 2023. ukupno 132 pacijentice s uznapredovalim rakom vrata maternice procijenjene su za moguće liječenje u Centru za rak u Coburgu. Za ovu retrospektivnu analizu isključen je 81 pacijent zbog različitih razloga (postoperativni RCT, radioterapija bez brahiterapije, neoadjuvantni RCT, palijativni RCT, liječenje recidiva raka, istovremeno liječenje drugih malignih bolesti). Tako je u ovo istraživanje bio uključen 51 pacijent. Analiza podataka pacijenata prvenstveno je bila usmjerena na dob pri početnoj dijagnozi, menstrualni status, stadij FIGO, histologiju, ukupno preživljenje, remisiju, pojavu udaljenih metastaza ili recidiva u zdjelici, ukupnu dozu zračenja, brahiterapiju i istodobnu kemoterapiju te pojavu akutne ili kasne toksičnosti. Dodatno, QoL je procijenjen prospektivno samoispunjavanjem EORTC-QLQ-C30 i EORTC-QLQ-CX24 pacijenta.
Za analizu statističkih podataka korišten je IMB SPSS Statistics 29 za macOS (IBM Corp, 2022.). Stope preživljenja izračunate su Kaplan-Meier metodom, a log-rank test korišten je za usporedbu stopa preživljenja između različitih skupina bolesnika. Kvalitativni podaci izraženi su kao cijeli brojevi i postoci, dok su kvantitativni podaci izraženi kao srednja vrijednost ± standardna devijacija ili srednja vrijednost i interkvartilni raspon. Za analizu EORTC upitnika svi podaci su sažeti u deskriptivnu statistiku. Za usporedbu razlika između dviju skupina proveden je t-test. Hi-kvadrat test primijenjen je za usporedbu dviju kategoričkih varijabli, a regresijskom analizom ispitan je utjecaj pojedinih varijabli na QoL.

Rezultati: Stope 5-godišnjeg ukupnog preživljenja, NED-preživljenja i stope preživljenja bez recidiva u zdjelici bile su 48±9%, 68±14% odnosno 52±10%. Značajan utjecaj na petogodišnje ukupne stope preživljenja primijećen je za stadij FIGO (IIA-IIIA: 74±13% u odnosu na IIIB-IVA: 29±12%, p=0,027) za udaljene metastaze (bez DM: 75± 12% u odnosu na DM: 25±11%, p=0,05). Niti razvoj recidiva u zdjelici niti histologija nisu značajno utjecali na stope preživljavanja.

Procjena QoL-upitnika rezultirala je rezultatom od 63/100 za ukupni QoL pacijenata. Najmanje je oštećena kognitivna funkcija s ocjenom 84, dok je funkcioniranje uloga najlošije s ocjenom 67. Na ljestvici simptoma nesanica (46/100), umor (41/100), dispneja (32/100), i Bol (26/100) je dobio najlošiju ocjenu. Financijske poteškoće također su opteretile neke pacijente te su postigle ocjenu 25/100. Pacijenti su proljev, zatvor, gubitak apetita i mučninu/povraćanje ocijenili kao manje uznemirujuće. Pitanja specifična za rak vrata maternice iz upitnika EORTC-QLQ-CX24 otkrila su da su se najčešće javljali periferna neuropatija, rezultat 36/100, i limfedem, rezultat 32/100. Pacijenti su također izjavili da je njihova spolna/vaginalna funkcija bila oslabljena (32/100) te da je također bila pogođena slika vlastitog tijela (22/100). Ljestvicu funkcionalne seksualne aktivnosti moglo je ispuniti samo 5 pacijenata koji su bili spolno aktivni u posljednja četiri tjedna. To je pokazalo da samo jedna trećina njih može uživati u seksu. Usporedba rezultata evaluacije EORTC-upitnika nije pokazala značajne razlike u QoL bolesnika starijih i mlađih od 58 godina, a također nije bilo razlike uočenih u bolesnika s dijagnosticiranim FIGO stadijem <IIIB i ≥IIIB. Međutim, postojala je tendencija da QoL bude manje ograničen u ranijoj fazi dijagnoze.

Zaključak: U bolesnika s uznapredovalim inoperabilnim karcinomom vrata maternice kombinacija radiokemoterapije i brahiterapije može izliječiti oko 50% bolesnika. Uznapredovali stadiji IIIB i IVA prema FIGO te razvoj udaljenih metastaza imaju značajno negativan utjecaj na ishod. Što se tiče dugotrajne kvalitete života koju su pacijenti prijavili, potrebna je posebna podrška za ublažavanje simptoma uključujući limfedem, perifernu neuropatiju i oslabljenu seksualnu aktivnos.