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СТЕПЕН НА КОМПЛИКАЦИЈА НА УРИНАРНА ФУНКЦИЈА КАКО РЕЗУЛТАТ НА ЗРАЧНАТА ТЕРАПИЈА ПРИ ЛЕКУВАЊЕ НА КАРЛИЧЕН МАЛИГНИТЕТ

Апстракт

Вовед: Малигните заболувања во карлицата (цервикален, ректален и ендометријален карцином) се многу честа и смртоносна болест. Адјувантната терапија се состои од режими кои вклучуваат истовремено хемотерапија / радиотерапија (RT) и адјувантна хемотерапија. Целта на истражувањето беше да се оцени и да се анализира бубрежната функција преку промените во GFR (Glomerular Filtration Rate/ стапка на гломеруларна филтрација) при користење на техники на 3D конформална радиотерапија (3DCRT) во третманот на пациентите со карличен малигнитет и да се оцени акутна и доцна токсичност на ГУ (генито-уринарниот тракт), во тек и после третманот според системот на бодување на RTOG (Radiotherapy Oncology Group /радиотераписка онколошка група). Анализата на пациентите со несакани ефекти на ГУ тракт на 9 и 12-ти месец од третманот, биле исто така оценети и со цистоскопија.

Методи: Оваа студија беше спроведена во Клиничкиот центар на Косово, Одделение за онкологија. Неколку варијабли беа проценети кај 75 пациенти: пол, возраст, тип на примарен малигнитет, евиденција на средна доза на тумор (TD) под 50 и над 50 Gray (Gy). Времето на појава на токсичност беше проследено со оценка на промени на GFR во период од 3 и 6 месеци. На почетокот, во 3-тиот и 6-тиот месец од третманот, пациентот беше следен со пополнување на прашалникот според системот за бодување RTOG. Хемотерапијата беше применета врз основа на примарната туморска локација и истовремено со радиотерапија. Средната вредност на следење (FU= Median follow up) траеше 12 месеци. Кај пациентите со евидентирани Г2 и Г3 несакани генито-уринарни ефекти во однос на RTOG од месец 9 до 12, беше изведена цистоскопија. Пациентите претходно третирани поради генитоуринарен морбидитет (PGUM- pretreatment genitourinary morbidity) и пациентите кои веќе имале заболување на генито-уринарниот тракт на почетокот на третманот, биле исклучени од студијата.

Резултати: Нашата група се состоеше од 75 пациенти со карличен малигнитет, од кои 53 (70,7%) се жени и 22 (29,3%) машки. Просечната возраст на пациентите вклучени во студијата била $57,5 \pm 11,2$ години. Триесет (40,0%) од 75 пациенти имале карцином на ректален карцином, 28 (37,3%) рак на грлото на матката и 17 (22,7%) ендометријален карцином. Просечната вредност на GFR во почетокот беше $71,7 \pm 23,1$ ml / min, тоа беше $75,6 \pm 25,6$ ml / min три месеци по почетокот на терапијата и $79,1 \pm 25,9$ ml / min шест месеци по терапијата. Тестот за споредба покажа дека постои статистички значајна разлика помеѓу вредностите на GFR на почетокот на третманот во однос на три месеци по терапијата ($P < 0.05$), почетокот на третман во однос на шест месеци по терапија ($p < 0.001$), додека немало статистички значајна разлика помеѓу вредностите на GFR по три месеци и по шест месеци по терапијата. Во следењето по 3 месеци, 11 пациенти (14,7%) имале Г1 ГУ токсичност, за која не бил потребен било каков третман. 5 пациенти (6,7%) имале Г2 токсичност на ГУ. Додека во следењето по 6 месеци, 15 пациенти (20%) имале токсичност од Г1 степен, 7 пациенти (9,3%) Г2 ГУ токсичност и 4 пациенти (5,3%) имале токсичност степен Г3.

Споредувајќи го степенот на токсичност помеѓу 3 и 6 месеци, не се појавија статистички значајни разлики според RT третманот. При следење од 9-12 месеци кај 26.66% од пациентите се застапени степен 1 и степен 2 на уринарни AEs (adverse effects/ несакани дејства).

Заклучок: Свкупно, функцијата на бубрезите се подобрува на 3 и 6 месеци од почетокот на третманот кај повеќето пациенти. Не се забележани значајни разлики во несаканите ефекти помеѓу групите третирани со радиотерапијата и групите за хеморадијација. Степенот 3 AEs најчесто се јавува кај пациенти со веќе локално напредната малигна болест и прогредија по третманот. На пациентите кај кои била применета цистоскопија биле евидентирани мали или спорадични оштетувања на сидот на мочниот меур и без потреба од било каков третман. Овие пациенти биле со симптоми на циститис, со честа потреба за уринирање, напрегање и печење при уринирање.

Клучни зборови: бубрежна функција, стапка на гломеруларна филтрација, карличен малигнитет, радиотерапија, уринарна токсичност, несакани ефекти RTOG, карлична радиотерапија.

COMPLICATION GRADE OF URINARY FUNCTION FOLLOWING RADIATION THERAPY TREATING PELVIC MALIGNANCY

Abstract

Introduction: Pelvic malignancy (cervical, rectal and endometrial carcinoma) are a very common and deadly disease. Adjuvant therapy consists of regimens that include both concurrent chemotherapy/radiotherapy (RT) and adjuvant chemotherapy. The aim of the study was to evaluate and analyze renal function through the changes in GFR (Glomerular Filtration Rate), using 3D conformal radiotherapy (3DCRT) techniques in the treatment of patients with pelvic malignancy, and to evaluate acute and late toxicity of GU genito-urinary tract, during and after treatment according RTOG (Radiotherapy Oncology Group) scoring system. Analyzing patients adverse GU effects at the 9 and 12th month of treatment have been also helped by using cystoscopy.

Methods: This study was conducted at the Clinical Center of Kosovo, Oncology Department. Several variables were evaluated in 75 patients: sex, age, type of primary malignancy, median tumor dose (TD) evidence over 50 and under 50 Gray (Gy). Time of the appearance of toxicity was followed by GFR changes during 3- and 6-month follow-up period. At the beginning, at 3rd and 6th months of the treatment patient have been followed by fulfilling in the questioner according RTOG scoring system. Chemotherapy have been employed based on primary tumor site concurrently with radiotherapy. Median follow up (FU) have taken 12 months. To the patient that had G2 and G3 adverse genito-urinary effects regarding RTOG at month 9 up to 12, was performed cystoscopy. Patients with pretreatment genitourinary morbidity (PGUM) were excluded from the study and patients who had genito-urinary problems such as obstruction in the beginning of treatment with the urinary tract ultrasonography examination have been excluded.

Results: Our cohort consisted of 75 patients with pelvic malignancy, of whom 53 (70.7%) were female and 22 (29.3%) male. The average age of the patients included in the study was 57.5 ± 11.2 years. Thirty (40.0%) of the 75 patients had rectal carcinoma, 28 (37.3%) cervical cancer and 17 (22.7%) endometrial carcinoma. The average value of GFR in the beginning was 71.7 ± 23.1 ml/min, it was 75.6 ± 25.6 ml/min three months after beginning of therapy and 79.1 ± 25.9 ml/min six months after therapy. The test of comparison showed a significant statistical difference between the values of GFR at the baseline of treatment vs three months after therapy ($P < 0.05$), baseline of therapy vs six months after therapy ($P < 0.001$), while there was no difference between GFR values three months and six months after therapy. In the follow up after 3 months, 11 patients (14.7 %) had G1 GU toxicity that did not need any kind of treatment. 5 patients (6.7%) had G2 GU toxicity. Whereas in the follow up after 6 months 15 patients (20%) had G1 GU toxicity, 7 patients (9.3%) G2 GU toxicity and 4 patients (5.3%) had G3 GU toxicity.

Compering grade of toxicity between follow up 3 and 6 months no significant differences have been appeared according RT treatment. At the 9-12 months follow up we reached incidence of grade 1 and grade 2 urinary AEs (adverse effects) is 26.66%.

Conclusion: Overall, the kidney function improved at 3 and 6 months in majority of patients. No significant differences in treatment related site effects between radiotherapy and chemo-radiation groups were found. Grade 3 AEs mostly have been appeared according to locally advanced cancer and progression after treatment. Patients that have performed cystoscopy have had slight or occasional damage to the walls of the bladder and they have not need any treatment. Same patients had like cystitis feeling symptoms with often wanting urination, straining to pass urine and burning urination.

Keywords: renal function, glomerular filtration rate, pelvic malignancy, radiation therapy, Urinary toxicity, adverse effects RTOG, pelvic radiotherapy.

INTRODUCTION

Radiation is an integral part of the treatment of many pelvic tumors. The cellular death induced by radiotherapy (RT) benefits cancer control but can also result in adverse effects (AEs) on the organ being treated or those adjacent to it. RT for cancers of the pelvis (rectum, uterus or cervix) can result in AEs in the urinary tract. While the acute urinary AEs of pelvic RT are well described, late AEs are less well characterized. The burden of treatment for late AEs may be large given because the prevalence of tumors in the pelvis and the high utilization of RT to treat them.

Cervical cancer and endometrial cancer are two localization of gynecological malignant diseases which make over 80% of gynecological malignant diseases. Cervical and colorectal cancer are 2 place localization that according to UICC are obliged to massive screening for many reasons. Basic reasons for that are as below:

- Cervical cancer is the most frequent localization in gynecology; Cervical cancer can be easily diagnosed by methods available (gynecological examination, colposcopy, pap test). With the use of massive screening for cervical cancer, although morbidity is increasing, mortality is declining due to early diagnosis.
- Endometrial cancer is not part of the group that is obliged to screening based on recommendations of UICC (Union for International Cancer Control), luckily, this localization is more rare than cervical cancer, but in terms of treatment is identic to cervical cancer, therefore the favors and the consequences of two localizations are approximate.
- Rectal cancer is one of the most frequent malignant pathologies, after lung and breast cancer. In terms of diagnostics is made a lot of work from the inclusion of this localization in programs of early detection of the disease by UICC recommendations. Potential of Conformal radiotherapy (CFRT) is a technique that aims to exploit the potential biological improvements consequent on better spatial localization of the high dose irradiation volume. Benefits of whole pelvic radiation treatments are:
 - Reduction in acute small bowel morbidity.
 - Reduction in acute hematological toxicity with bone marrow sparing.
 - Prevention of late term anorectal/ GI and GU dysfunction.
 - Escalation of dose to the pelvic lymph nodes.
 - Better matching of dose profiles in simultaneous treatments.
 - For simultaneous extended field irradiation.
 - Better target coverage with modern day improvements in conjunction with image based brachytherapy
 - As an alternative to brachytherapy:
 - In distorted anatomy to circumvent limitations of brachytherapy.
 - To give higher dose to pelvic nodes present at time of brachytherapy.

Significantly increased expenditure:

- Machine with treatment capability
- Imaging equipment: Planning and Verification
- Software and Computer hardware
- Extensive physics manpower and time required.
- Conformal nature – highly susceptible to motion and setup related errors.¹

1. Cervical cancer

Cervical cancer is considered one of the most frequent malignant diseases that occurs in females. According to statistical data, cervical cancer occurs in 8-30 new cases in 100,000 females within a year, depending on the region and state. In Albania, this incidence is approximately 8 new cases in 100,000 females, within a year. These tumors most commonly occur in the adult years (50 to 60-years).² Cervical cancer can rarely occur at females aged under 20. Persistent human papillomavirus (HPV) infection is the most important factor in the development of cervical cancer.^{3,4} The incidence of cervical cancer appears to be related to the prevalence of HPV in the population. In countries with a high incidence of cervical cancer, the prevalence of chronic HPV is approximately 10% to 20%, whereas the prevalence in low-incidence countries is 5% to 10%. Squamous cell carcinomas account for approximately 80% of all cervical cancers and adenocarcinoma accounts for approximately 20%.

In developed countries, the substantial decline in incidence and mortality of squamous cell carcinoma of the cervix is presumed to better result of effective screening, although racial, ethnic, and geographic disparities exist.⁵ However, adenocarcinoma of the cervix has increased over the past 3 decades, probably because cervical cytologic screening methods are less effective for adenocarcinoma.

1.1 Treatment

The primary treatment of early-stage cervical cancer is either surgery or RT. Surgery is typically reserved for early-stage disease, fertility preservation, and smaller lesions, such as stage IA, IB1, and selected IIA1.⁶ The panel agrees that concurrent chemo-radiation is generally the primary treatment of choice for stages IB2 to IVA disease based on the results of 5 randomized clinical trials.^{7,8}

Chemo-radiation can also be used for patients who are not candidates for hysterectomy. Although few studies have assessed treatment specifically for adenocarcinomas, they are typically treated in a similar manner to squamous cell carcinomas.⁹⁻¹¹

Pelvic RT or chemo-radiation will invariably lead to ovarian failure in premenopausal women.¹² To preserve intrinsic hormonal function, ovarian transposition may be considered before pelvic RT for select women younger than 45 years of age with squamous cell cancers.^{13,14}

The role of radiation therapy in the treatment of cervical cancer has been long established through clinical trial, providing strong evidence of support as an effective cervical cancer treatment. The traditional approach utilizes external beam irradiation therapy to the pelvis \pm periaortic lymph nodes, as well as some form of brachytherapy boost, based on clinical and pathologic factors. There have been improvements in radiation therapy technology, reducing dose to normal surrounding tissue (bladder, rectum, and small bowel).

Although there have been significant advances in imaging, planning and treatment delivery, this must be tailored to a thorough understanding to the stage of disease, pathways for dissemination and recurrence risk. Most external beam treatments are delivered using a high-energy linear accelerator.

Treatment of cervical cancer is stratified by stage as delineated in the Guideline External Beam Radiation Therapy (EBRT) is done by use of CT-based treatment planning and conformal blocking is considered the standard of care for EBRT. MRI is the best imaging modality for determining soft tissue and parametrial involvement in patients with advanced tumors. In patients who are not surgically staged, PET imaging is useful to help define the nodal volume of coverage. The volume of EBRT should cover the gross disease (if present), parametrial, uterosacral ligaments, sufficient vaginal margin from the gross disease (at least 3 cm), presacral nodes, and other nodal volumes at risk. For patients with negative nodes on surgical or radiologic imaging, the radiation volume should include the entirety of the external iliac, internal iliac, and obturator nodal basins. For patients deemed at higher risk of lymph node involvement (eg, bulkier tumors; suspected or confirmed nodes confined to the low true pelvis), the radiation volume should be increased to cover the common iliacs as well. In patients with documented common iliac and/or para-aortic nodal involvement, extended-field pelvic and para-aortic radiotherapy is recommended, up to the level of the renal vessels. Coverage of microscopic nodal disease requires an EBRT dose of approximately 45 Gy (in conventional fractionation of 1.8–2.0 Gy daily), and highly conformal boosts of an additional 10–15 Gy may be considered for limited volumes of gross unresected adenopathy. For the majority of patients who receive EBRT for cervical cancer, concurrent Cisplatin-based chemotherapy (either Cisplatin alone, or Cisplatin + 5-fluorouracil) is given during the time of EBRT.⁵

Intensity-modulated radiation therapy (IMRT) and similar highly conformal methods of dose delivery may be helpful in minimizing the dose to the bowel and other critical structures in the post-hysterectomy setting and in treating the para-aortic nodes when necessary. These techniques can also be useful when high doses are required to treat gross disease in regional lymph nodes. RT is often used in the management of patients with cervical cancer either 1) as definitive therapy for those with locally advanced disease or for those who are poor surgical candidates; or 2) as adjuvant therapy following radical hysterectomy for those who have one or more pathologic risk factors (eg, positive lymph nodes, parametrial infiltration, positive surgical margins, large tumor size, deep stromal invasion).

1.2 Protocol of Radiotherapy for Cervical Cancer

Indication of radiotherapy

The cervical cancer has two components

a) **Central component:**

- disease confined to cervix , vagina and medial parametria
- best treated by brachytherapy

b) **Peripheral component:**

- disease involving lateral parametria and regional lymph nodes
- best treated by EBRT and brachytherapy as boost

Indications of EBRT is:

- As definitive RT
- As adjuvant RT in post operative settings
- As palliative

Indication of definitive RT:

- may be considered in stages IA and CIS :
- if patients deemed inoperable or avoids surgery or RT preferred
- IA1: Brachytherapy alone
- IA2 or IA1 with LVSI:ICBT plus external beam radiotherapy
- Stages IB-IIA
- if patients deemed inoperable or avoids surgery or RT preferred
- EBRT and brachytherapy ¹⁵

Stages IIB to IVA:

- EBRT + BT + concurrent chemo radiotherapy

Indications of Post-op EBRT:

> 1/3rd Stromal Invasion

LV space Invasion

Large (>4 cm) tumor

Positive Pelvic Nodes

Microscopic positive/close (<3 mm) margins

Microscopic involvement of Parametrium

Brachytherapy is generally delivered as either low dose permanent implant or high dose rate implant. Principles of radiation therapy for these guidelines closely follow what is recommended both by the American Brachytherapy Society (Cervical Cancer Brachytherapy Task Group), as well as in National Comprehensive Cancer Network Practice Guidelines for Cervical Cancer.¹⁶

Planning for RT in cervical cancer must take into account the potential impact on surrounding critical structures, such as rectum, bladder, sigmoid, small bowel, and bone. Acute effects (eg, diarrhea, bladder irritation, fatigue) occur to some degree in most patients undergoing radiation and are typically magnified by concurrent chemotherapy.

However, acute effects can often be managed with medications and supportive care, and they generally resolve soon after completion of radiation. To avoid treatment-related menopause, ovarian transposition can be considered before pelvic RT in select young patients (<45 years with early-stage disease).¹²⁻¹⁴

After therapy for cervical cancer, late side effects may include potential injury to bladder, rectum, bowel, and pelvic skeletal structures.¹⁷ The risk of major complications (eg, obstruction, fibrosis/necrosis, and fistula) is related to the volume, total dose, dose per fraction, and specific intrinsic radio sensitivity of the normal tissue that is irradiated.

2. Endometrial cancer

It is among the most common forms of cancer for women, depending on certain countries, in Albania, for many reasons is somewhat rare. The age group most affected is 60-69 years. The risk of suffering from the disease increases with age, about 2/3 of the disease is notified after menopause time, about 1/3 before menopause.^{2,18}

Adenocarcinoma of the endometrium (also known as endometrial cancer, or more broadly as uterine cancer or carcinoma of the uterine corpus) is the most common malignancy of the female genital tract in the United States. It is estimated that 61,380 new uterine cancer cases will occur in 2017, with 10,920 deaths resulting from the disease.¹⁹

Risk factors for uterine neoplasms include increased levels of estrogen (caused by obesity, diabetes, and high-fat diet), early age at menarche, null parity, late age at menopause, Lynch syndrome, older age (≥ 55 years), and tamoxifen use.²⁰⁻²³ Thus, the incidence of endometrial cancer is increasing because of increased life expectancy and obesity.

In 2017, 67% of patients with adenocarcinoma of the endometrium were diagnosed with disease confined to the uterus at diagnosis.¹ Regional and distant disease comprised 21% and 8% of cases, respectively. Many physicians believe that adenocarcinoma of the endometrium is a more treatable malignancy because the early symptoms of irregular vaginal bleeding (in this predominantly

postmenopausal patient population) often trigger patients to seek care when the disease is at an early and treatable stage. However, data show that the mortality rate for uterine cancer has increased more rapidly than the incidence rate.²⁴

This increased mortality may be related to an increased rate of advanced-stage cancers, high-risk histologies (eg, serous carcinomas), and patients being diagnosed at an older age. In addition to grade and depth of myometrial invasion, other risk factors associated with poor prognosis include age, lymph node status, tumor size, lymph vascular space invasion (LVSI), and tumor involvement of the lower uterine segment.^{25,26}

2.1 Treatment

Treatment of endometrial carcinoma depends by stage, operating radical treatment or definitive pelvic radiotherapy.¹⁸ Initiate RT as soon as the vaginal cuff is healed, preferably 6-8 weeks after surgery but in general initiation of brachytherapy should not exceed 12 weeks. To help select a patient population who may benefit from adjuvant RT, the GOG 99 (Gynecology Oncology Group) and PORTEC (Post-Operative Radiation Therapy in Endometrial Carcinoma) trials defined risk factors for women at high-intermediate risk (HIR) for recurrence.^{27,28}

These risk factors include: age, in addition to deep myometrial invasion, grade, and LVSI. In GOG 99, women younger than 50 years had to have all 3 histologic risk factors to be considered HIR.²⁸

If they were 50 to 70 years, they were considered HIR if they had 2 histologic risk factors.

Women 70 years or older were defined as HIR if they also had one risk factor. In PORTEC-1, women had to have 2 of 3 risk factors (eg, age >60 years, deep myometrial invasion, grade 3 histology) to be considered at HIR for recurrence.^{27,29}

RT is directed at sites of known or suspected tumor involvement and may include external beam RT (EBRT) and/or brachytherapy. RT has been a widely used modality in the treatment of patients with endometrial cancer; it clearly improves loco regional control.

Imaging is required to assess loco regional extent and to rule out distant metastases before administration of RT. In general, EBRT is directed to the pelvis with or without the para-aortic region. Brachytherapy can be delivered: 1) to an intact uterus, either preoperatively or definitively; or 2) more commonly, to the vagina after hysterectomy. Pelvic radiotherapy should target the gross disease (if present), the lower common iliacs, external iliacs, internal iliacs, parametria, upper vagina/para-vaginal tissue, and presacral lymph nodes (in patients with cervical involvement). Extended-field radiotherapy should include the pelvic volume and also target the entire common iliac chain and para-aortic lymph node region. The upper border of the extended field depends on the clinical situation but should at least be 1-2 cm above the level of the renal vessels. External-beam doses for microscopic disease should be 45 to 50 Gy.

2.2 Indications for radiation therapy

Post-operative

Brachytherapy Only (HDR or LDR, 5 fx maximum)

- Stage IA – with adverse risk factors
- Stage IA – without risk factors (Grades G2, 3)
- Stage IB
- Stage II – (Grade G1)

External Beam Radiation Therapy Only (3D-CRT, 45-50.4 Gy, 28 fx maximum)

- Stage IA – with adverse risk factors (Grades G2, 3)
- Stage IB – without adverse risk factors (Grade G3)
- Stage IB – with risk factors
- Stage II – (Grade G1)
- Stage III
- Stage IV

External Beam (3D-CRT, 45-50 Gy, 28 fx maximum) and Brachytherapy (HDR or LDR, 5 fx maximum)

- Stage IA – with adverse risk factors (Grades G2, 3)
- Stage IB – without risk factors (Grade G3)
- Stage IB – with risk factors
- Stage II – (Grades G1, 2, 3)
- Stage IIIA and IIIB and IIIC (Grades G1, 2, 3)

Medically Inoperable/ Pre-Operative

Brachytherapy Only (HDR or LDR, 7 fx maximum)

- Stage I and II

External Beam Radiation Therapy Only (2D, 3D-CRT, 45-50 Gy, 28fx maximum)

- All Stages

External Beam (2D, 3D-CRT, 45-50.4 Gy) and Brachytherapy (HDR or LDR, 4 fx maximum)

- All Stages³⁰

3. Rectal cancer

Rectal cancer is a very common and deadly disease. It is the third cause of cancer death in men and the second cause cancer death in women. It is difficult to separate epidemiological considerations of rectal cancer from those of colon cancer because epidemiological studies often consider colon and rectal cancer (i.e., colorectal cancer) together.

Worldwide, colorectal cancer is the third most common form of cancer. In 2012, there were an estimated 1.36 million new cases of colorectal cancer and 694,000 deaths.³¹

Estimated new cases and deaths from rectal cancer in the United States in 2018:³²

New cases of rectal cancer: 43,030.

New cases of colon cancer: 97,220.

Deaths: 50,630 (colon and rectal cancers combined).

Colorectal cancer affects men and women almost equally. Among all racial groups in the United States, African Americans have the highest sporadic colorectal cancer incidence and mortality rates.³³

It is thought that the factors predispose to this geographic reach are the way of feeding, food including red meat, animal fats and meals without enough fibers. Rectal cancer, the most commonly occurs after age 50 years, 90 % of patients are this age, while the average age is 72 years old.²

The rectum is located within the pelvis, extending from the transitional mucosa of the anal dentate line to the sigmoid colon at the peritoneal reflection; by rigid sigmoidoscopy, the rectum measures between 10 cm and 15 cm from the anal verge.³⁴ The location of a rectal tumor is usually indicated by the distance between the anal verge, dentate line, or anorectal ring and the lower edge of the tumor, with measurements differing depending on the use of a rigid or flexible endoscope or digital examination.³⁵

The distance of the tumor from the anal sphincter musculature has implications for the ability to perform sphincter-sparing surgery. The bony constraints of the pelvis limit surgical access to the rectum, which results in a lesser likelihood of attaining widely negative margins and a higher risk of local recurrence.³⁴

Risk Factors

Increasing age is the most important risk factor for most cancers. Other risk factors for colorectal cancer include the following:

Family history of colorectal cancer in a first-degree relative.

Personal history of colorectal adenomas, colorectal cancer, or ovarian cancer.

Hereditary conditions, including familial adenomatous polyposis (FAP) and Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC])

Personal history of long-standing chronic ulcerative colitis or Crohn colitis.

Excessive alcohol use.

Cigarette smoking.

Race/ethnicity: African American.

Obesity.^{36, 37}

3.1 Treatment of rectal cancer

The approach to the management of rectal cancer is multimodal and involves a multidisciplinary team of cancer specialists with expertise in gastroenterology, medical oncology, surgical oncology, radiation oncology, and radiology. The management of rectal cancer varies somewhat from that of colon cancer because of the increased risk of local recurrence and a poorer overall prognosis. Differences include surgical technique, the use of radiation therapy, and the method of chemotherapy administration. In addition to determining the intent of rectal cancer surgery (i.e., curative or palliative), it is important to consider therapeutic issues related to the maintenance or restoration of normal anal sphincter, genitourinary function, and sexual function.

Primary Surgical Therapy

The primary treatment for patients with rectal cancer is surgical resection of the primary tumor. The surgical approach to treatment varies according to the following:

Tumor location.

Stage of disease.

Presence or absence of high-risk features (i.e., positive margins, lymphovascular invasion, perineural invasion, and poorly differentiated histology).

Chemo-radiation Therapy

Preoperative chemo-radiation therapy

Neoadjuvant therapy for rectal cancer, using preoperative chemo-radiation therapy, is the preferred treatment option for patients with stages II and III clinical disease. However, postoperative chemo-radiation therapy for patients with stage II or III rectal cancer remains an acceptable option.

Preoperative chemo-radiation therapy has become the standard of care for patients with clinically staged T3–T4 or node-positive disease (stages II/III), based on the results of several studies:

German Rectal Cancer Study Group trial.

Multiple phase II and III studies examined the benefits of preoperative chemo-radiation therapy, which include the following:

Tumor regression and down staging of the tumor.

Improved tumor resectability.

Higher rate of local control.

Improved toxicity profile of chemo-radiation therapy.

Higher rate of sphincter preservation.

Complete pathologic response rates of 10% to 25% may be achieved with preoperative chemo-radiation therapy. However, preoperative radiation therapy is associated with increased complications compared with surgery alone; some patients with cancers at a lower risk of local recurrence might be adequately treated with surgery and adjuvant chemotherapy.

Postoperative chemo-radiation therapy

Is the current standard of care for stages II and III rectal cancer. However, before 1990, the following studies noted an increase in both disease-free survival (DFS) and overall survival (OS) with the use of postoperative combined-modality therapy:

The Gastrointestinal Tumor Study Group trial (GITSG-7175).

The Mayo/North Central Cancer Treatment Group trial (NCCTG-794751).

The National Surgical Adjuvant Breast and Bowel Project trial (NSABP-R-01).

Treatment is done depending on the stage of rectal cancer. Adjuvant therapy for rectal cancer consists of regimens that include both concurrent chemotherapy/RT and adjuvant chemotherapy. A total of approximately 6 months of perioperative treatment is preferred.

3.2 Principles of radiation therapy

Indication of neoadjuvant CCRT:

(1) cStage II, III

(2) Lower rectum cStage I disease for organ preservation (RT +/- C/T) (optional)

Indication of adjuvant CCRT:

(1) pStage II, III

(2) After local excision, pT1Nx with high risk factors (close/positive margin, LVI, PNI, and poorly differentiated, or sm3 invasion), pT2Nx Radiation therapy fields should include the tumor or tumor bed, with a 2–5 cm margin, the presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures. Multiple radiation therapy fields should be used (generally a 3- or 4-field technique). Positioning and other techniques to minimize the volume of small bowel in the fields should be encouraged. For postoperative patients treated by abdominoperineal resection, the perineal wound should be included within the fields.

Intensity-modulated radiation therapy (IMRT) should only be used in the setting of a clinical trial or in unique clinical situations including re-irradiation of recurrent disease after previous radiotherapy.

Radiation doses: 45–50 Gy in 25–28 fractions to the pelvis. For resectable cancers, after 45 Gy a tumor bed boost with a 2-cm margin of 5.4 Gy in 3 fractions could be considered for preoperative radiation and 5.4–9.0 Gy in 3–5 fractions for postoperative radiation. Small bowel dose should be limited to 45 Gy. A number of randomized trials have evaluated the effectiveness of the addition of chemotherapy to radiation administered either preoperatively following clinical evaluation/staging (eg, T3–4 by endoscopic ultrasound) or postoperatively following pathologic staging of rectal cancer as pT3 and/or N1–2.³⁸ Putative benefits of the addition of chemotherapy concurrent with either pre- or postoperative RT include local RT sensitization and systemic control of disease (eg, eradication of micro metastases). Preoperative chemo-RT also has the potential to increase rates of pathologic complete response and sphincter preservation. An estimated 40,340 rectal cancers occurred in 2013, and 90% of cases are diagnosed in people over the age of 50.³⁹ Total mesorectal excision (TME), which consists of the removal of all mesorectal fat and lymph nodes, is the surgical standard of care in rectal cancer; still, 52% of patients undergo RT within six months of diagnosis.^{40,41} At more advanced stages of disease, many studies have demonstrated decreased local recurrence with adjuvant chemo-RT when compared with surgery alone. Postoperative complications like anastomotic leakage, delayed wound healing, bleeding, and ileus were not significantly different between the two groups. Therefore, a preoperative course of neoadjuvant RT is recommended for rectal cancers that are T3 or have regional lymph node

involvement (stage II or III).^{42,43,44} RT is typically administered as CRT in 2 Gy fractions up to a total dose of 46-50 Gy over 20+ weeks, or in 5 Gy fractions up to 25 Gy over five days.^{40,42}

Only disease stage (designated by tumor [T], nodal status [N], and distant metastasis [M]) has been validated as a prognostic factor in multi-institutional prospective studies.⁴⁵ A major pooled analysis evaluating the impact of T and N stage and treatment on survival and relapse in patients with rectal cancer who are treated with adjuvant therapy has been published and confirms these findings.⁴⁶

A large number of studies have evaluated other clinical, pathologic, and molecular parameters.⁴⁷ As yet, none has been validated in multi-institutional prospective trials. For example, microsatellite instability–high, also associated with Lynch syndrome–related rectal cancer, was shown to be associated with improved survival independent of tumor stage in a population-based series of 607 patients with colorectal cancer who were 50 years old or younger at the time of diagnosis.⁴⁸ In addition, gene expression profiling has been reported to be useful in predicting the response of rectal adenocarcinomas to preoperative chemo-radiation therapy and in determining the prognosis of stages II and III rectal cancer after neoadjuvant 5-fluorouracil-based chemo-radiation therapy.

Racial and ethnic differences in overall survival (OS) after adjuvant therapy for rectal cancer have been observed, with shorter OS for blacks than for whites. Factors contributing to this disparity may include tumor position, type of surgical procedure, and presence of comorbid conditions.

4. Pathophysiology of radiation-induced urinary tract injury

Radiation is an effective cancer treatment due to its direct and indirect interaction with living cells. The direct interaction induces immediate cell death by damaging DNA and/or tissue protein. The indirect interaction occurs by the formation of free radicals by ionizing radiation that interacts with enzymes leading to cell death and/or future mutation.⁴⁹ These direct and indirect interactions lead to cellular injury by affecting division delay, reproductive failure and interphase arrest. All these consequences are more frequently encountered in rapidly dividing cells.⁵⁰

The radiation-induced damage to tissue architecture develops in a linear threshold model. Damage to the basement membranes of blood vessels can lead to occlusion, thrombosis and neovascularization. The atrophy and contraction of tissue results from increased proliferation of fibroblasts.⁵¹ All these changes have the potential to cause significant urinary tract injury. Bladder damage and loss of capacity can cause significant urinary symptoms. Neovascularization is an important factor for radiation cystitis and subsequent hemorrhagic cystitis. Replacement of the corpus spongiosum with fibrosis and subsequent occlusion of the urethral lumen is an important factor for the increased incidence of urethral strictures after RT.⁵²

5. Cisplatin's nephrotoxicity

The kidneys help the body pass waste as urine. They also help filter blood before sending it back to the heart. The kidneys perform many crucial functions, and affects the maintenance of homeostasis including:

- maintaining overall fluid balance
- regulating and filtering minerals from blood
- filtering waste materials from food, medications, and toxic substances
- creating hormones that help produce red blood cells, promote bone health, and regulate blood pressure.⁵³

Therefore in these serious diseases, maintenance of stable renal function is of great importance, both for the success of the therapy and for the outcome of the disease.

Cisplatin's nephrotoxicity is attributed to two main factors:

1. High concentrations of Cisplatin in the kidneys and
2. Adverse impacts on the renal transport system.

Cisplatin is predominantly excreted by the kidneys, biliary and intestinal excretion is minimal. However, in renal excretion the drug accumulates in the kidneys and even non-toxic blood levels may reach toxic levels in the kidneys. Cisplatin concentrations in tubular epithelial cells are five times greater than in blood. Cisplatin-induced renal toxicity is dose-dependent, and thus limits the possibility of increasing dosages, consequently, treatment effectiveness may be impaired. Toxic effects occur primarily in the proximal tubule, particularly in S3 segment of the tubular epithelial cells, glomeruli and distal tubules are affected subsequently. Renal function deterioration is seen in 25% to 35% of the patients treated with a single dose of Cisplatin. Decreases of 20% to 40% in glomerular filtration can be observed 10 days after drug intravenous administration, and are followed by increased levels of creatinine, reduced glomerular filtration rates (GFR), hypomagnesaemia, and hypokalemia.^{54,55}

6. Clinical Manifestation of Radiation Injury

The clinical manifestation of radiation to the lower urinary tract can be categorized into acute and late reactions. Acute reactions occur during and up to 3 months after radiation exposure. Most acute symptoms subside within several weeks of standard radiation therapy. Late reactions occur at least 3 months after radiation exposure.⁵⁶

6.1 Acute Toxicity

Acute radiation-induced symptoms, can be irritative or obstructive, and depend on gender, region of exposure, and dose. Radiation-induced inflammation, edema, and loss of urothelial integrity are thought to be the underlying events that contribute to acute symptoms. Irritative symptoms include increased urinary frequency, dysuria, urgency, and nocturia. Obstructive symptoms include weak stream, incomplete voiding, hesitancy, and in rare cases, complete obstruction with overflow incontinence. It is difficult to distinguish between the side effects of radiation to the prostate and radiation to the bladder, as both can manifest similarly. The reported incidence of acute toxicity varies from 23% to 80% in patients treated with radiation to the pelvis for various malignancies.⁵⁷⁻⁶⁵ Such wide range in incidence rates reflects the heterogeneity in treatment techniques, dose, and treatment fields for different malignancies and also reflects the inherent difficulty in collecting such subjective data.

The Radiation Therapy Oncology Group (RTOG) has published scoring criteria for a qualitative assessment of the degree of acute radiation morbidity.⁶⁶

6.2 Late Toxicity

Late effects of radiation arise from epithelial and micro vascular alterations, nerve damage, fibrosis, and changes in bladder physiology. Clinical manifestation ranges from decreased bladder capacity, to ureteral strictures, to secondary malignancies. In contrast to acute toxicity, late toxicity tends to be chronic and irreversible. Those changes can be seen and analyze by cystoscopy.

Radiotherapy to pelvic area can make the blood vessels in the bladder more fragile. This may cause bleeding sometime after the radiotherapy treatment ends. Patients can see small amounts of blood or tiny blood clots in urine.⁶⁷

Irritated bladder can cause increased feeling wanting to pass urine, straining to pass urine or burning feeling during urination. This symptoms usually progress through the course the radiotherapy. In rare cases the bladder may shrink after radiotherapy.⁶⁸

Depending on site and dose of radiation, late toxicity can involve the entire bladder, a portion of bladder mucosa, or the urethra. Fibrotic constriction of the bladder occurs months to years after radiation, with collagen deposition and replacement of smooth muscle tissue with fibroblasts. If bladder contracture is severe, there will be incontinence, pronounced frequency, and sensation of incomplete emptying. Chronic urethritis and urethral strictures are additional complications that can occur. Hematuria can occur as a result of chronic cystitis and/or telangiectasia. Hemorrhagic cystitis, is a rare and potentially severe long-term side effect of radiation, is very uncommon with recent technologic advances in radiation therapy, that allow safe delivery of high doses of radiation to tumor while sparing adjacent bladder tissue.

The RTOG has published criteria to grade late effects of radiation to the bladder, noting that late effects of radiation on normal tissues increase with time, and long periods of observation are necessary to accurately assess effects of radiation

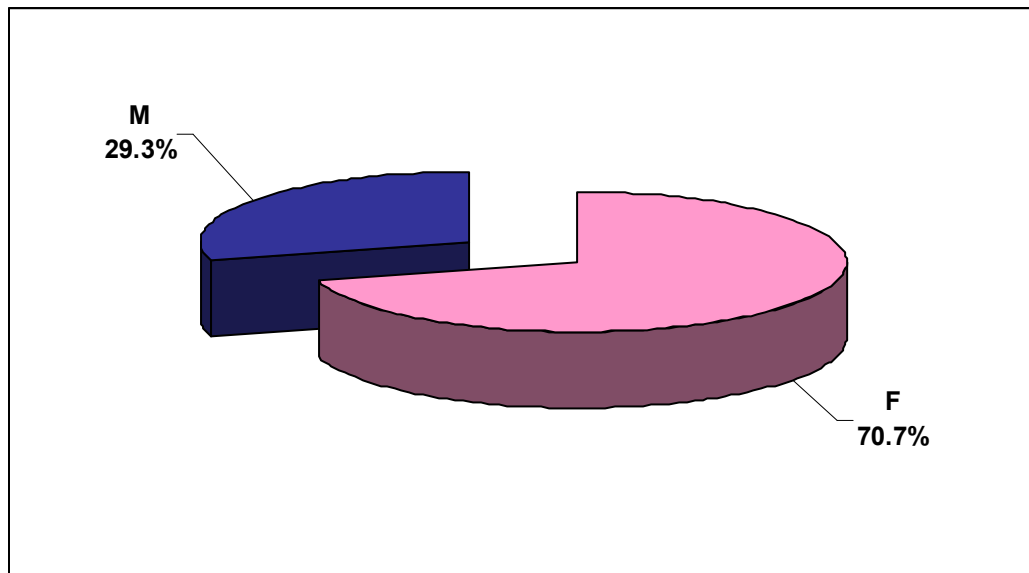
MATERIAL AND METHODS

This was a prospective follow-up study conducted at the Clinic of Oncology in Prishtina, Kosovo.

- Inclusion criteria: pelvic malignancy (cervical, endometrial and rectal).
- Exclusion criteria: patients with PGUM (pretreatment genitourinary morbidity), without any obstruction in the beginning of treatment confirmed with urological ultrasonography.

Patient were followed up for one year. pTNM system was used for histopathology classification of cervical, endometrial and rectal cancer.

Graphic 1. Patients involved in research by gender in %



The research included 75 patients with pelvic tumors of which 53 or 70.7% were female and 22 or 29.3% of male

Table 1. Patients involved in research by age and gender

Age (years)		Sex				Total	
		F		M			
		N	%	N	%	N	%
30-39		5	9.4	2	9.1	7	9.3
40-49		9	17.0	1	4.5	10	13.3
50-59		17	32.1	5	22.7	22	29.3
60-69		15	28.3	10	45.5	25	33.3
70+		7	13.2	4	18.2	11	14.7
In total	N	53	100.0	22	100.0	75	100.0
	%	70.7	-	29.3	-	100.0	-

Table 2. The average age of the researched patients by gender

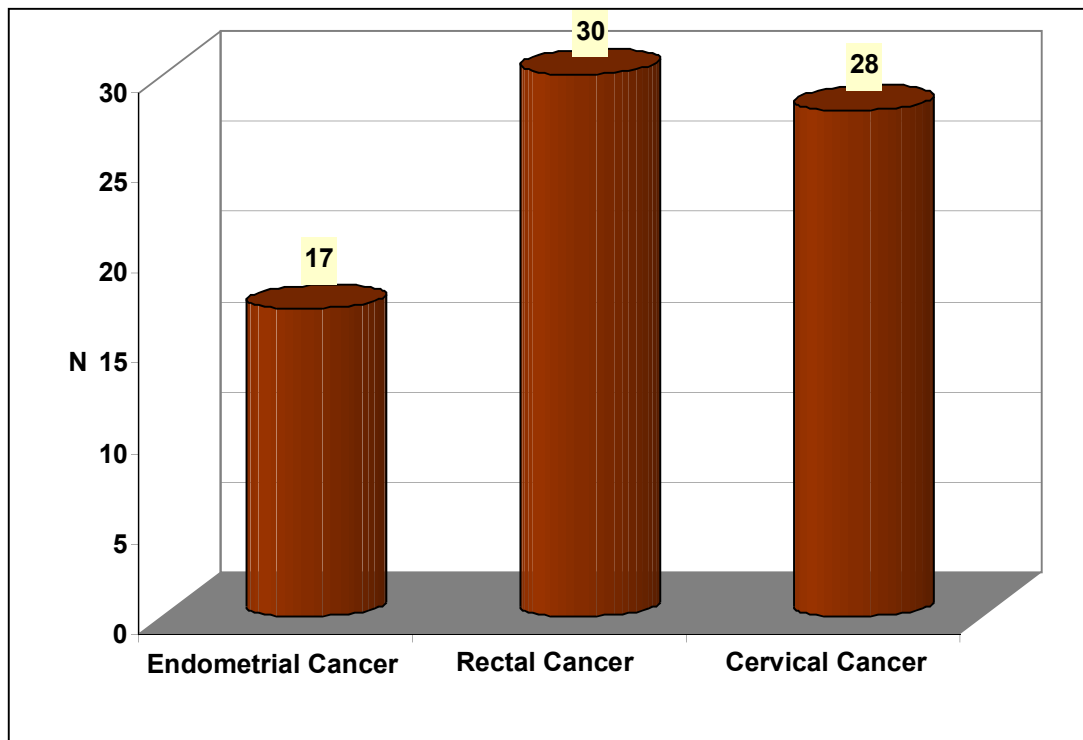
	Sex		Total
	F	M	
N	53	22	75
Mean \pm SD	56.1 \pm 11.1	60.8 \pm 11.1	57.5 \pm 11.2
Rank	33 – 77	37 – 74	33 - 77

The average age of the patients involved in the research was 57.5 years (SD \pm 11.2 years) range 33-77 years. The average age of the female patients involved in the research was 56.1 years (DS \pm 11.1 years), range 33 – 77 years. The average age of the male patients involved in the research was 60.8 years (DS \pm 11.1 years), range 37 – 74 years (Table 2).

Table 3. Patients involved in the research based on the diagnosis and gender

Diagnosis	Sex				Total	
	F		M			
	N	%	N	%	N	%
Endometrial Cancer	17	32.1	-	-	17	22.7
Rectal Cancer	8	15.1	22	100.0	30	40.0
Cervical Cancer	28	52.8	-	-	28	37.3
Total	53	100.0	22	100.0	75	100.0

Graphic 2. Patients involved in the research based on the diagnosis



From 75 patients involved in the research 30 or 40.0% were rectal cancer, 28 or 37.3% were cervical cancer and 17 or 22.7% were endometrial cancer. All male patients involved had rectal cancer (Table 3 and Graphic 2).

From 28 patients diagnosed with cervical cancer, 8 were inoperable and 20 were operated, regarding to the staging they are treating with chemo-radiotherapy or radiotherapy alone. Dosing Schedules for Concurrent Chemotherapy/RT: Cisplatin 40 mg/m² have been applied once weekly during radiation, after which continued next fraction of radiation 1h up to 3 hours after it.

All endometrial diagnosed cancer patients were operated and continued with adjuvant radiotherapy treatment in our clinic.

Patient diagnosed with rectal cancer were treated postoperative with chemo-radiotherapy. Dosing Schedules for Concurrent Chemotherapy/RT: ChemoRT + Capecitabine 825 mg/m² twice daily 5 d/wk + ChemoRT x 5 weeks.

Table 4. Patients classified by method of treatment

RT, RT+Ch	Cisplatin/Ca pecitabine	Dose	category of treatment dose group	No of pat	%
RT+Ch	Cisplatin	over 50 Gy	1	22	29.3
RT+Ch	Capecitabine	under 50 Gy	2	21	28.0
RT+Ch	Cisplatin	under 50 Gy	3	7	9.3
RT	0	under 50 Gy	4	12	16.0
RT	0	over 50 Gy	5	13	17.3
Total				75	100.0

RT-Radiotherapy; Ch-Chemotherapy

Table 5. Patients involved in the research based on the diagnosis and associated disease.

Associated disease	Diagnosis						In total	
	Endometrial Cancer		Rectal Cancer		Cervical Cancer			
	N	%	N	%	N	%	N	%
Diabetes	1	5.9	3	10.0	-	-	4	5.3
Diabetes + Hypertension	1	5.9	3	10.0	1	3.6	5	6.7
Hypertension	1	5.9	5	16.7	1	3.6	7	9.3
Without associated disease	14	82.4	19	63.3	26	92.9	59	78.7
In total	17	100.0	30	100.0	28	100.0	75	100.0

As we can see in table 5, 21.3% of patients involved on research had associated disease, 5.3% Diabetes Mellitus, 6.7% Diabetes Mellitus and Hypertension, and 9.3% of them Hypertension.

For clinical manifestation of acute and late GU (genito-urinary) adverse effect we use RTOG acute/late morbidity scoring criteria determined the grade of toxicity as below.

Acute toxicity is scored from days 1 through 90. Symptoms related to radiation exposure must be distinguished from underlying disease. Grade I criteria are defined as frequency of urination or nocturia that is twice pretreatment habit, or dysuria, or urgency, not requiring medication. Grade II criteria include urinary frequency or nocturia that is less frequent than every hour, or dysuria, urgency, bladder spasms requiring pharmacologic intervention. Grade III criteria are defined as frequency and nocturia that is hourly or greater, or gross hematuria, or dysuria, pelvic pain, or bladder spasm requiring regular, frequent doses of narcotics. Grade IV criteria include hematuria that requires transfusion or acute bladder obstruction that is not secondary to clots, ulceration, or necrosis.

Table 6. RTOG Acute Radiation Morbidity Scoring Criteria

0	1	2	3	4
No Change	Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication	Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic	Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/ gross hematuria with/without clot passage	Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration or necrosis

Table 7. RTOG/EORTC Late Radiation Morbidity Scoring Scheme

0	1	2	3	4
Non	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)	Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria	Severe frequency and dysuria; severe telangiectasia; frequent hematuria; reduction in bladder capacity (<150 cc)	Necrosis/contracted bladder (capacity <100 cc)

Cystoscopy as a monitoring and diagnostic examination were used to determine grade of affecting bladder after radiotherapy, however cystoscopy generally is used as diagnostic examination, investigating, cause of blood in the urine incontinence over active bladder and painful urination.⁶⁹

Slight epithelial atrophy and minor telangiectasia manifesting as microscopic hematuria are considered grade I toxicity. Moderate frequency, generalized telangiectasia, and intermittent macroscopic hematuria are criteria for grade II late toxicity. Severe frequency and dysuria,

frequent hematuria, severe telangiectasia, and reduction in bladder capacity to <150 mL are criteria for grade III late toxicity. Necrosis, bladder contraction to 100 mL capacity, and severe hemorrhagic cystitis are criteria for grade IV toxicity.

The radiation therapy technique and doses were strictly defined for all regimens. Patients were treated by whole pelvic RT with different site of pelvic malignancy following the International Commission on Radiation Units and Measurements (ICRU) No. 50 /62 recommendations.

CT simulation is performed at all patients at same CT-simulator Siemens Somatom emotion, with scanning Field of View (SFOV) 50 cm –70 cm – Allows wider separation to be imaged. Multi slice capacity, speed up acquisition times, reduce motion and breathing artifacts, allow thinner slices to be taken – better.

DRR (Digital Reconstruction Radiograph) and CT resolution, allows gating capabilities, flat couch top – simulate treatment table.

Planning technique for cervical cancer treatment

Positioning and Immobilization

Initial step was giving a drinking water to the patient.

Patients have been positioned in supine position, preferred because of most comfortable reproducible position and stabilizes pelvis.

- This position can be combined with immobilization devices in our case knee rest to relax lower back, making patient more comfortable and minimizing rotation of pelvis. Several types of immobilization options are available in radiotherapy that needs to be comfortable, reproducible, minimal beam attenuating and affordable.

Patient was directed with had to gentry with arms overhead. The positioning is performed according to the lasers as follow: the laser on axis X is positioned centrally on the body and pass through symphysis, umbilicus and the processus xyphoideus. The laser on the Y axis is 9-10 cm below the umbilical cord, and laser on the Z axis is at 11 cm from high of the couch. These positions are marked on the skin of the patient with the marker and small metal markers, supine positioning with skin marking gave as cheap, reproducible and comfortable feeling for patient. Those parameters are written in the radiation file.

We didn't use any thermoplastic type for mobilization.

We didn't use any kind of contrast during simulation, usually not needed in gynecological CT simulation because structures can be contoured even without contrast. CT scanning is recommended for data acquisition. CT scan is obtained from T10-T11 interspace to upper third of femur, slice thickness 5 mm. These images are transferred to treatment planning system (TPS). At the end the centers are tattooed on the skin and repainted with color. Planning technic of radiation is isocentric. Once the isocenter is positioned accurately within the patient, the remaining fields are arranged simply by gantry rotation or couch movement, not by displacing the patient relative

to the couch and patient is not moved between fields. Target volume delineation was done on planning CT scans using RTOG contouring guidelines.

Field borders: AP-PA fields

Superior border

- at the L4-5 space to include external & internal iliac L.N.
- extended to the L3-4 space if common iliac nodal coverage is indicated.
- extended to the T11-12 space if paraaortic coverage is indicated.

Inferior border

- at inferior border of the obturator foramen.
- for vaginal involvement: 3cm below the lower most extent of disease.

Lateral borders

- 1.5 - 2cm margin on the widest portion of pelvic brim.
- tumours that involve lower third of vagina, inguinal nodes have been included in the fields.

Field borders: lateral field

Anterior margin

- vertical line to the anterior edge of pubic symphysis to cover external iliac lymph nodes.

Posterior margin

- at S2 – S3 junction.
- extend to sacral hollow in patients with advanced tumors to cover uterosacral ligaments, cardinal ligaments & presacral lymph nodes.

Superior and inferior margins

- same as that for AP/PA Fields

Target Volume delineation: the most important step in radiotherapy, also called Image segmentation.

The target volume is of following types:

GTV (Gross Tumor Volume)

CTV (Clinical Target Volume)

ITV (Internal Target Volume)

PTV (Planning Target Volume)

Other volumes:

Targeted Volume

Irradiated Volume

Biological Volume

Target Volumes

GTV: Macroscopic extent of the tumor as defined by radiological and clinical investigations.

CTV: The GTV together with the surrounding microscopic extension of the tumor constitutes the CTV.

The CTV also includes the tumor bed of a R0 resection (no residual).

ITV (ICRU 62): The ITV encompasses the GTV/CTV with an additional margin to account for physiological movement of the tumor or organs. It is defined with respect to an internal reference – most commonly rigid bony skeleton.

PTV: A margin given to above to account for uncertainties in patient setup and beam adjustment.

Treated Volume: volume of the tumor and surrounding normal tissue that is included in the isodose surface representing the irradiation dose proposed for the treatment (V95).

Irradiated Volume: volume included in an isodose surface with a possible biological impact on the normal tissue encompassed in this volume. Choice of isodose depends on the biological end point in mind.

CTV Delineation: the CTV to be delineated for cervical cancers consists of three components (if patient is treated with RT/ Chemotherapy alone)

Low Risk CTV: consists volume at risk of potential microscopic disease spread at the time of diagnosis. Typically treated to a dose of 45 -50 Gy.

Intermediate Risk CTV: major risk of local recurrence in areas that correspond to initial macroscopic extent of disease. The intent is to deliver a total radiation dose appropriate to cure significant microscopic disease in cervix cancer, which corresponds to a dose of at least 60 Gy.

High Risk CTV: Major risk of local recurrence because of residual macroscopic disease. The intent is to deliver a total dose as high as possible (85 - 90 Gy) and appropriate to eradicate all residual macroscopic tumor.

PTV Delineation:

The exact PTV depends on setup inaccuracies, organ motion, and the extent of setup inaccuracies will differ from institution to institution we use the following margins:

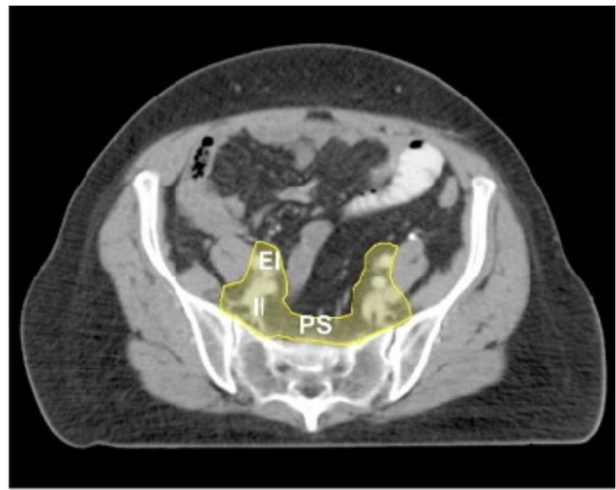
1 cm cranio-caudal direction

0.7 cm lateral

0.7 cm antero posterior

Delineation of Nodal Volume Common Iliac Nodes:

7 mm margin around vessels, extend posterior and lateral borders to psoas and vertebral body.

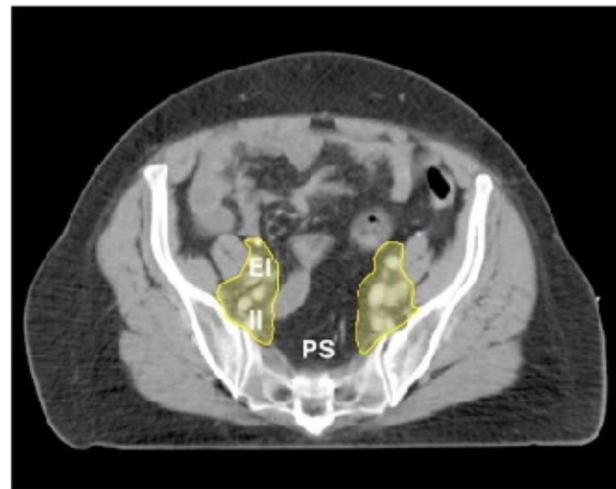
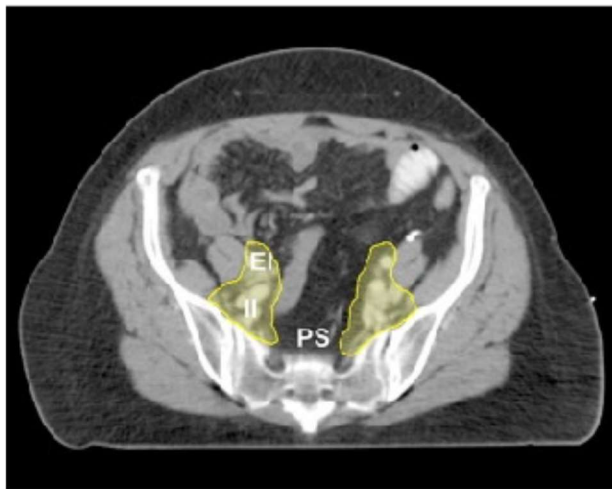


External iliac nodes:

7 mm margin around vessels. Extend anterior border by a further 10 mm anterolateral along the iliopsoas muscle to include the lateral external iliac nodes

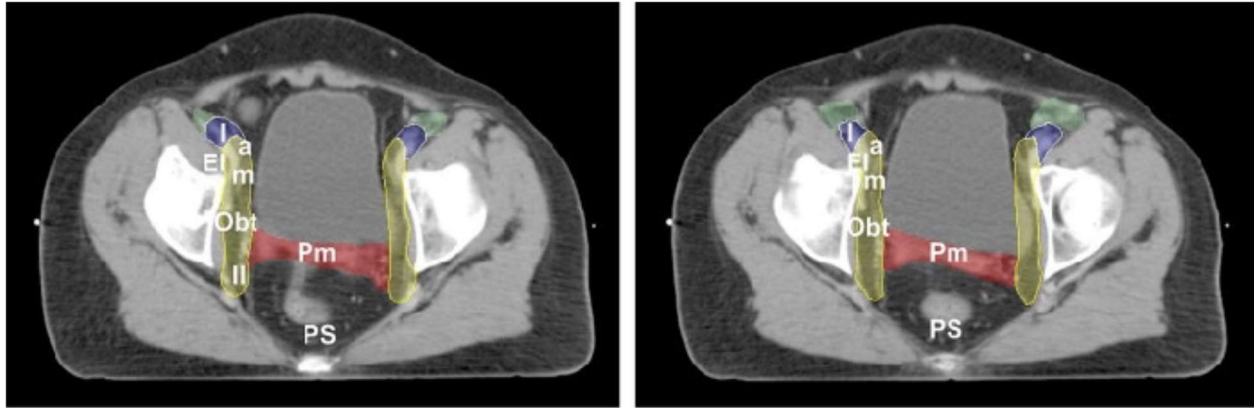
Internal iliac Nodes:

7 mm margin around vessels. Extend lateral borders to pelvic side wall



Presacral Nodes:

Subaortic: 10 mm strip over anterior sacrum; Mesorectal: cover entire mesorectal space.



Consensus guidelines for the delineation of the intensity modulated pelvic radiotherapy ctv in the postoperative treatment of endometrial and cervical cancer. William Small Jr., M.D., Radiation Oncology, Robert H. Lurie Comprehensive Cancer Center of Northwestern University. Arno J. Mundt, MD, Radiation Oncology, University of California San Diego.

Obturator Nodes:

Join external and internal iliac regions with a 17 mm wide strip along the pelvic side wall.

Normal Tissue Delineation (RTOG)

- **Bowel:** The small and large bowel have been contoured together as a Bowel-Bag.
- Inferiorly, the bowel bag begin with the first small or large bowel loop or above the ano-rectum, whichever is most inferior.
- The contours end 1 cm. above the PTV.
- **Ano-Rectum:** Ano-Rectum have been contoured from the level of the anus to the sigmoid flexure. It extend from the anal verge (marked by a radiopaque marker at simulation) to superiorly where it loses its round shape in the axial plane and connects anteriorly with the sigmoid.
- **Bladder:** Contoured inferiorly from its base.
- **Femoral Heads:** the ball of the femur, trochanters, and proximal shaft to the level of the bottom of ischial tuberosities.

BEAM ENERGY

Because of the thickness of the pelvis, high-energy photon beams (15MV) are especially suited for this treatment decrease the dose of radiation delivered to the peripheral normal tissues (particularly bladder and rectum) providing a more homogeneous dose distribution in the central pelvis and avoid subcutaneous fibrosis.

Dose and fractionation

Primary radiotherapy

Stage IB2 and IIA, Stage IIB or above:

- 50.4 Gy in 28 daily fractions of 1.8 Gy given in 5 1/2 weeks followed by Intracavitary brachytherapy.

Persistent /bulky parametrial tumor: boost up to 60 Gy.

Adjuvant radiotherapy

- 50.4 Gy in 28 daily fractions of 1.8 Gy in 5 1/2 weeks.

Planning and dosing it's done with Xio treatment planning system 4.2.

Depending on the relationship between PTV and the organs of risk optimization of the distribution of dose was done by changing the angle of gentry, changing the weight points of the dose by field, using wedge filters, etc. The target volume delineated was then projected into the digitally reconstructed radiograph (DRR) and the distance of the target volume from the edges of the field was measured using the Beam's Eye View.

Verification of the field position it's done in the first section of treatment in MLC PRIMUS 2 Siemens linear accelerator, deviation of treated and planned fields was 0.5 acceptable. If it is no alteration of the position of the portal field no further portals are required, and have not been done. The volume of the target receiving at least 95% of the prescribed dose was calculated (V95).

V95 was subtracted from the total target volume to calculate the volume that would have been missed in conventional planning based on bony landmarks. DVH was used for evaluating treatment plans.

Constraints of OAR for cervical and endometrial cancer have been:

Box field:

-kidney: 20 Gy (max);

<50% of combined both kidneys

<75% of one side of kidney if another kidney is not functional

-spinal cord: 40 Gy (max)

-rectum:

40 Gy (<60%)

45 Gy (<50%)

60 Gy (<40%)

70 Gy (<20%)

75.6 Gy (<15%)

78 Gy (<5%)

-Small bowel: 48 Gy (max)

-Femoral heads: 45 Gy (max)

-Bladder: 70 Gy (<20%)

Simulation and Treatment Planning in Endometrial cancer

- Use of CT simulation and 3D treatment planning is required to ensure adequate target volume coverage and avoid normal tissue irradiation.
- All patients have been simulated and treated in the supine position. Other characteristics for CT-simulation were like in the cervical cancer.

Radiation Treatment Fields

(A.) CTV for lymphatic drainage (CTVn):

- a. Pelvic lymph node (LN) only: the anatomical component of pelvic nodes, including external, internal and lower common iliac nodes. The presacral lymph nodes have been included in patients with cervical involvement.
- b. Extended-field: the anatomical component of lymphatic drainage for pelvic nodes and entire common iliac chain and para-aortic LN (PALN). The upper border of the extended field depends on the clinical situation but at least have been to the level of the renal vessels.

(B.) CTV for vaginal stump (CVTv):

- a. For uterine tumor without invasion to the vagina: CTV includes the upper border of vaginal stump and extends downward for at least 2 cm.
- b. For uterine tumor invasion to vagina: CTV includes the upper border of vaginal stump and extends downward below the lower border of pubic symphysis.

(C.) PTV 0.7 cm around the CTV.

Since the position of vagina stump have been affected by the bladder and rectum, the PTV for vagina was 0.7 cm around the CTV.

(D.) Vaginal brachytherapy

Brachytherapy was performed outside country.

Radiation dose

External beam radiation therapy 50 Gy (25 fractions, 2.0 Gy/fraction, once daily, 5 fractions per week)

Simulation and Treatment Planning in Rectal cancer

Patients have been simulated in supine and prone position. Prone positioning used to minimize the volume of small bowel in the field. Supine position were used to patient with stoma. Other CT simulator procedures were same as in a cervical cancer simulation.

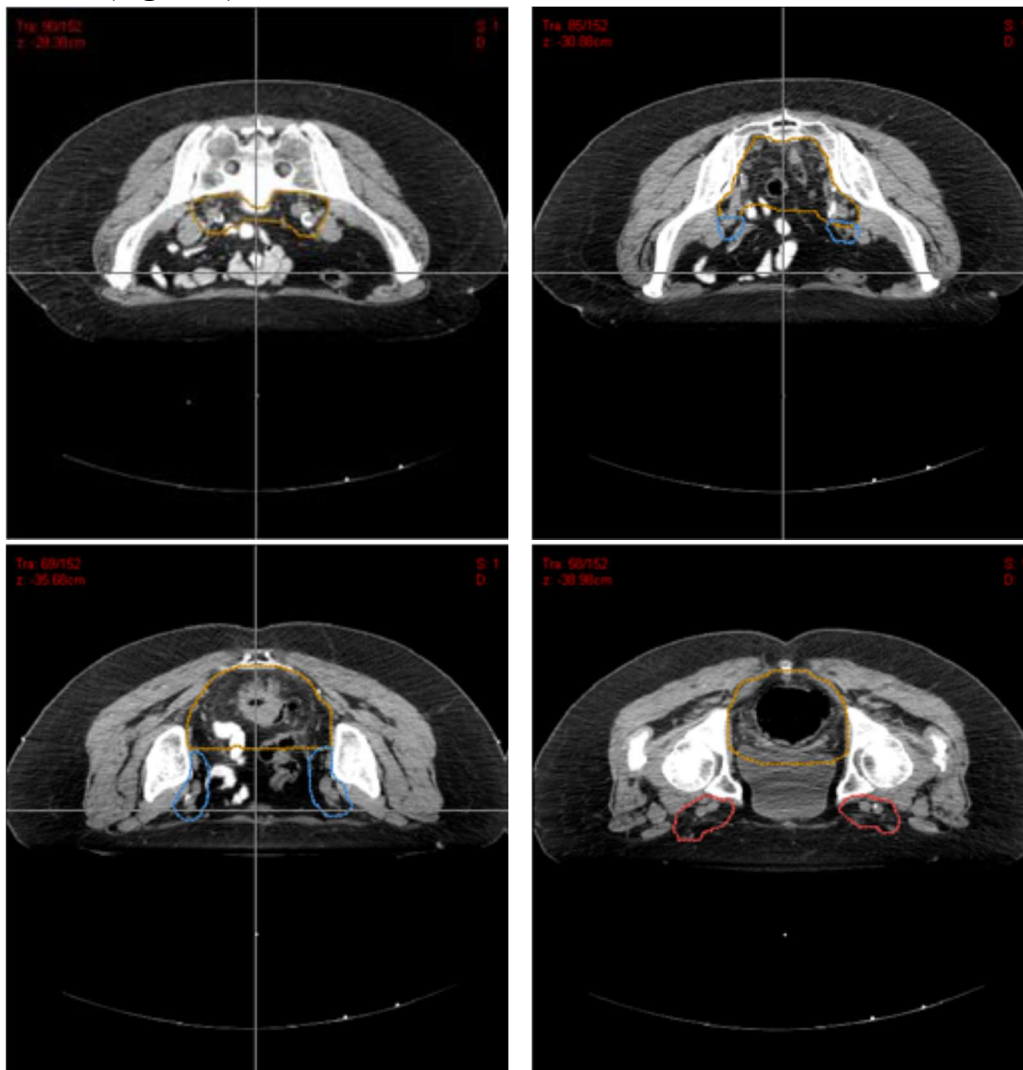
Radiation Treatment Fields (CTV)

Target volumes for rectal cancer differ substantially from those appropriate for gynecologic or genitourinary cancer. The most striking differences arise from the need for proper coverage of the peri-rectal and pre-sacral regions. The rectum and its associated mesentery are avoidance structures for GYN malignancy, but represent first echelon drainage for rectum.

- Radiation therapy fields had include the tumor or tumor bed and mesorectum with an adequate margin, the pre-sacral nodes, and the internal iliac nodes.
- The external iliac nodes have been included for T4 tumors involving anterior structures.
- The inguinal nodes have been included for lower tumors involving the anal canal or the anal margin or advanced disease with lower third vaginal involvement.

- Pelvic nodal CTV contours: 7mm around vessels, carving out bowel, bladder and bone. (based by RTOG consensus)
- The ischial fossa were included in RT field if tumor invasion to this area.
- For postoperative patients treated by abdominoperineal resection, the perineal included within the fields.
- Different CTV to create PTV margin have been considered for motion target (rectum) and motionless target (pelvis nodal) (10 mm)

Brown = CTVA (peri-rectal, pre-sacral, internal iliac), Blue = CTVB (external iliac), Red = CTVC (inguinal).



Elective Clinical Target Volumes in Anorectal Cancer: An RTOG Consensus Panel Contouring Atlas R Myerson, M Garofalo, Iel Naqa, R Abrams, A Apte, W Bosch, P Das, L Gunderson, T Hong, J Kim, C Willett, L Kachnic.

Radiation dose

- Once daily, 5 fractions per week, 45 Gy 1.8Gy per fraction.
- For patients with very close or positive margins after resection, especially for patients with T4 we have gave as an additional boost, 10 Gy external beam radiation.

Constraints of OAR

- Small bowel: 48 Gy (max)
- Femoral heads: 45 Gy (max)
- Bladder: 70 Gy (<20%)

GFR as represent of renal function was evaluated before treatment with: (Glomerular Filtration Rate) Cockcroft-Gault, CreatClear (ml/min) = $\text{Sex} * ((140 - \text{Age}) / (\text{SerumCreat})) * (\text{Weight} / 72)$

- Additional examinations were urological ultra sound examination in the beginning, after three, six, and 9-12 months of treatment, and urine sediment.
- At 3 and 6 months urea (s), creatinine (s), GFR (Cockcroft-Gault) were analyzed.
- From 9 up to 12 months cystoscopy have been analyzed to the indicated patients, who had G1 and G2 GU-AEs.

Statistical analysis - Testing of qualitative data was done with X2– test, quantitative data that did not have a normal distribution with the Kruskal -Wallis test and Mann - Whitney test. Testing of quantitative data that had normal distribution was done with One Way ANOVA and T - test. Verification of tests was made with 99.7% confidence level ($P < 0.01$) and the reliability of 95% ($P < 0.05$). Data processing was done with the SPSS statistical package. The data obtained are presented in tables and graphs. The following statistical parameters were calculated: index structure, arithmetic mean, standard deviation, minimum and maximum values.

After 3DCRT, patients were followed up between 3 and 6 months with next parameters: urea (s-serum), creatinine (s), GFR (Cockcroft-Gault), and urological echo and urine sediments. Image studies were done when specific complaints occurred.

Urinary Toxicity:

- acute urinary toxicity was considered three months of the end of 3DCRT,
- late urinary toxicity was considered after 9 up to 12 months of the end of 3DCRT, and was graded according to test on Table-1.-
- Cystoscopy (twenty cases) have been performed to the patients who had G1 and G2 GU AEs at 9 up to 12 months from the end of 3DCRT. Cystoscopy results have been analyzed divided all patients in to the two groups, cystoscopy performed group and control group.
- Information about patient complaint was obtained by physician interview. During the treatment were used questioner about urological problems of patients.

Questioner

Adverse Event:	Date of Treatment:	Course Number:
Date of onset:	Grade at onset:	
Date of first change in grade:	Grade:	
Date of next change in grade:	Grade:	
Date of next change in grade:	Grade:	
Date of next change in grade:	Grade:	
Date of next change in grade:	Grade:	
Date of next change in grade:	Grade:	
Did adverse event resolve?	Yes _____	No _____
If so, date of resolution of adverse event:		
Date of last observation (if prior to recovery):		
Reason(s) observations stopped (if prior to recovery):		
Was patient retreated?	Yes _____	No _____
If yes, was treatment delayed for recovery?	Yes _____	No _____
Date of next treatment?		
Reduced for next treatment?	Yes _____	No _____

Additional comments:

If module is being activated for new adverse event not currently in CTC, please provide definitions for adverse event grading:

Grade 0 = _____

Grade 1 = _____

Grade 2 = _____

Grade 3 = _____

Grade 4 = _____

RESULTS

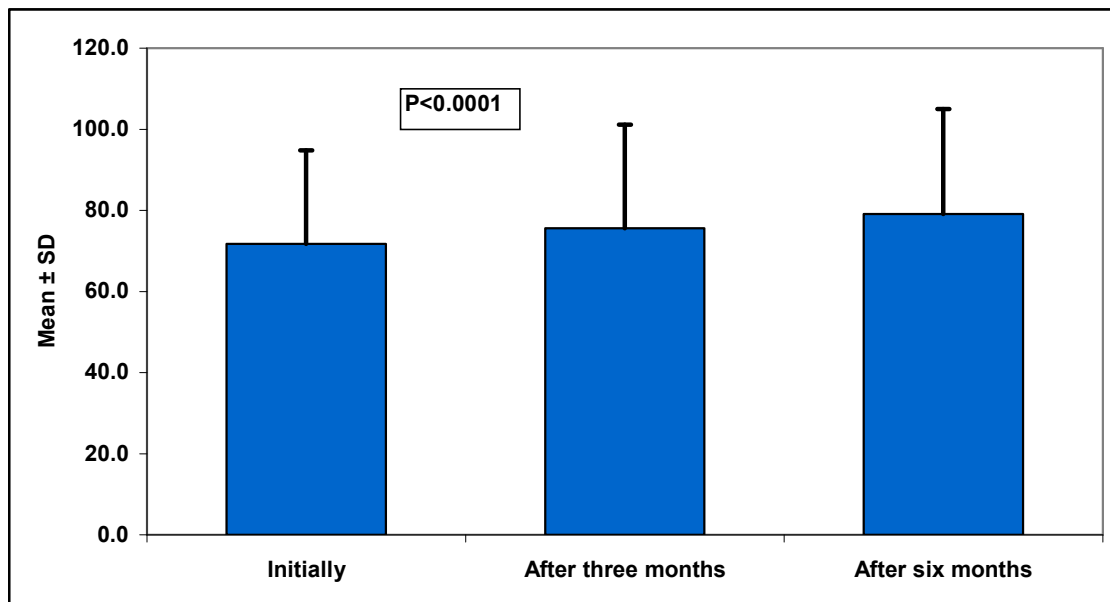
The research included 75 patients with pelvic tumors of which 53 or 70.7% were female and 22 or 29.3% of male (Table 1). The average age of the patients involved in the research was 57.5 years (SD \pm 11.2 years) range 33-77 years. The average age of the female patients involved in the research was 56.1 years (DS \pm 11.1 years), range 33 – 77 years. The average age of the male patients involved in the research was 60.8 years (DS \pm 11.1 years), range 37 – 74 years. With Man- Whitney test we couldn't reach significant statistic between the average ages by gender. (U'=720, P=0.112 therefore P>0.05).

Of the 75 patients involved in the research 30 or 40.0% were Rectal cancer, 28 or 37.3% were cervical cancer and 17 or 22.7% were endometrial cancer. All male patients involved had rectal cancer.

Table 8. GFR at the baseline of the therapy, after three and six months

	GFR		
	Baseline	After three months	After six months
N	75	75	75
Mean	71.7	75.6	79.1
SD	23.1	25.6	25.9
Repeated Measures ANOVA	F = 10.58, P<0.0001		
Tukey - Kramer Multiple Comparisons test	Initially vs. After three months, P<0.05 Initially vs. After six months, P<0.001 Three months vs. Six months, P>0.05		

Graphic 3. GFR at the baseline of the therapy, after three AND six months

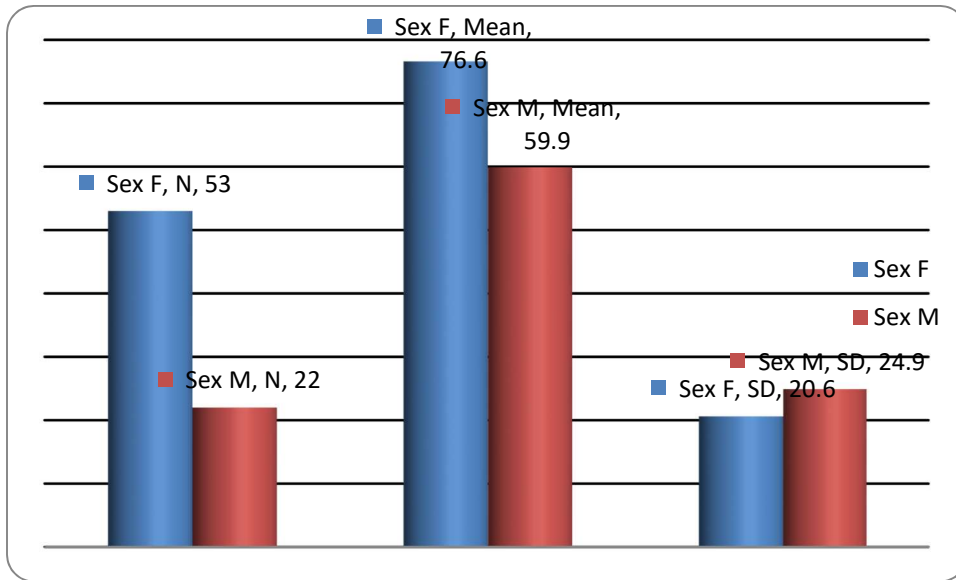


The average value of GFR in the baseline of the therapy was 71.7 ml/min (SD± 23.1 mmol/L), three months after baseline of the therapy was 75.6 ml/min (SD ± 25.6) and six months after receiving the therapy was 79.1 ml/minL (SD ± 25.9 mmol/L). With repeated measures ANOVA we have reached an important significant statistic between the average value of GFR after using the therapy (F=10.58, P<0.0001). With Tukey-Kramer Multiple Comparisons test we have reached a significant statistic between the values of GFR at the baseline of the treatment vs. three months after using the therapy the baseline of the treatment vs. three months after using the therapy (P<0.05), baseline of treatment vs. six months after using the therapy (P<0.001) while we have not reached the difference between values of GFR three months vs. six months after (table 8 and graphic 3).

Table 9. GFR at the baseline of the therapy by gender

GFR Baseline	Sex		Total
	F	M	
N	53	22	75
Mean	76.6	59.9	71.7
SD	20.6	24.9	23.1
Unpaired T-test	T=3.01, P=0.003		

Graphic 4. GFR at the baseline of the therapy by gender

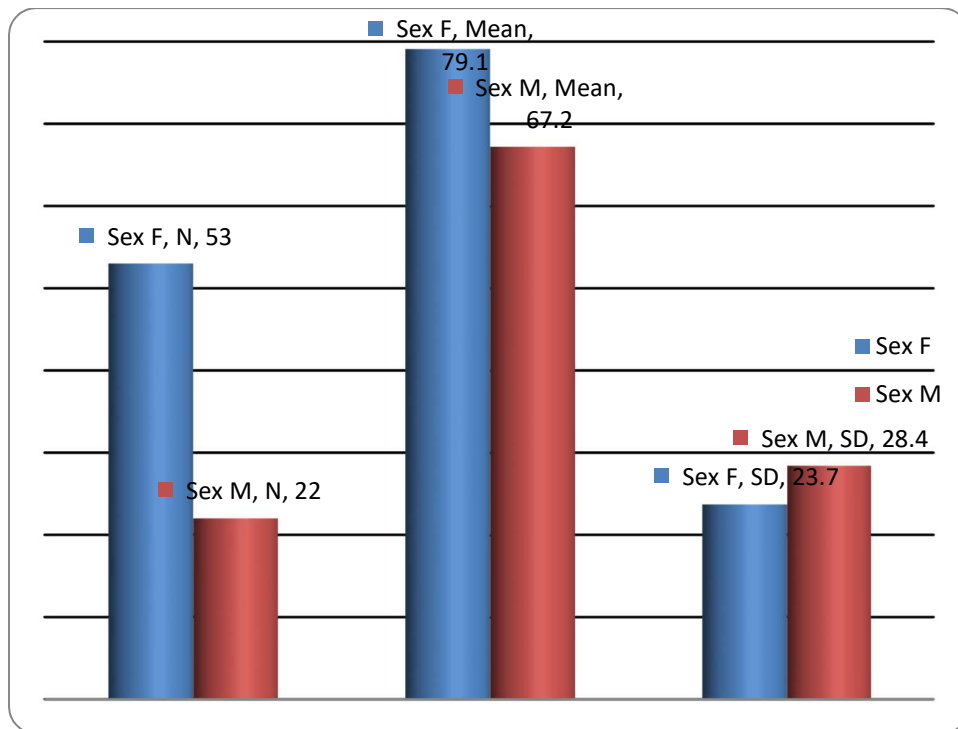


The average value of GFR in the therapy on female patients was 76.6 (SD± 20.6), while males was 59.9 (SD ± 24.9). With Unpaired T-test we have reached an important significant statistic between the average value of GFR by gender (T=3.01, P=0.003), (table 9 and graphic 4).

Table 10. GFR three months after baseline of the therapy by gender

GFR after three months	Sex		Total
	F	M	
N	53	22	75
Mean	79.1	67.2	75.6
SD	23.7	28.4	25.6
Unpaired T-test	T=1.86, P=0.066		

Graphic 5. GFR three months after baseline of the therapy by gender



The average value of GFR three months after baseline of the therapy on female patients was 79.1 (SD± 23.7), while the average value of GFR on males was 67.2 (SD±28.4). With Unpaired T-test we have not reached an important significant statistic between the average value of GFR by gender (T=1.86, P=0.066), (table 10, graphic 5).

Table 11. GFR six months after baseline of the therapy by gender

GFR after six months	Sex		Total
	F	M	
N	53	22	75
Mean	81.5	73.4	79.1
SD	24.0	29.8	25.9
Unpaired T-test	T=1.239, P=0.219		

The average value of GFR six months after baseline of the therapy on female patients was 81.5 (SD± 24.0), while the average value of GFR on males was 73.4 (SD ± 29.8). With Unpaired T-test we have not reached an important significant statistic between the average value of GFR by gender (T=1.239, P=0.219), (Table 11).

Table 12. GFR three months after baseline of the therapy by age group

GFR after three months	Age group				
	30-39	40-49	50-59	60-69	70+
N	7	10	22	25	11
Mean	102.0	94.9	79.3	65.1	57.6
SD	14.6	12.1	22.1	24.7	23.8

The average value of GFR three months after baseline of the therapy at patients of age group 30-39 years was 102.0 (SD± 14.6) at age group 40-49 years was 94.9 (SD ± 12.1), 50-59 years was 79.3 (SD ± 22.1), 60-69 years was 65.1 (SD ± 24.7) while at the age group of patients over 70 years was 57.6 (SD ± 23.8), (Table 12).

Table 13. GFR six months after baseline of the therapy age group

GFR after six months	Age group				
	30-39	40-49	50-59	60-69	70+
N	7	10	22	25	11
Mean	103.8	100.1	78.9	71.5	62.1
SD	13.5	12.1	23.0	23.1	31.7

The average value of GFR six months after baseline of the therapy at patients of age group 30-39 years was 103.8 (SD± 13.5), at age group 40-49 years was 100.1 (SD ± 12.1) 50-59 years was 78.9 (SD ± 23.0), , 60-69 years was 71.5 (SD ± 23.1) while at the age group of patients over 70 years was 62.1 (SD ± 31.7), so, from Mean value its seen that it is better GFR at the youngest age group (Table 13).

Table 14. GFR at the baseline of the therapy at patients who have received under or over 50 Gy

GFR Baseline	Dose	
	under 50 Gy	over 50 Gy
N	40	35
Mean	67.4	76.7
SD	23.3	22.1
Unpaired T-test	T=1.765, P=0.082	

The average value of GFR in the baseline of the therapy at patients who have received less than 50 Gy was 67.4 (SD± 23.3) while at those who have received more than 50 Gy was 76.7 (SD ± 22.1). With Unpaired T-test we have not reached an important significant statistic between the average value of GFR by dose (T=1.765, P=0.082), (Table 14).

GFR three months after baseline of the therapy at patients who have received less or more than 50 Gy

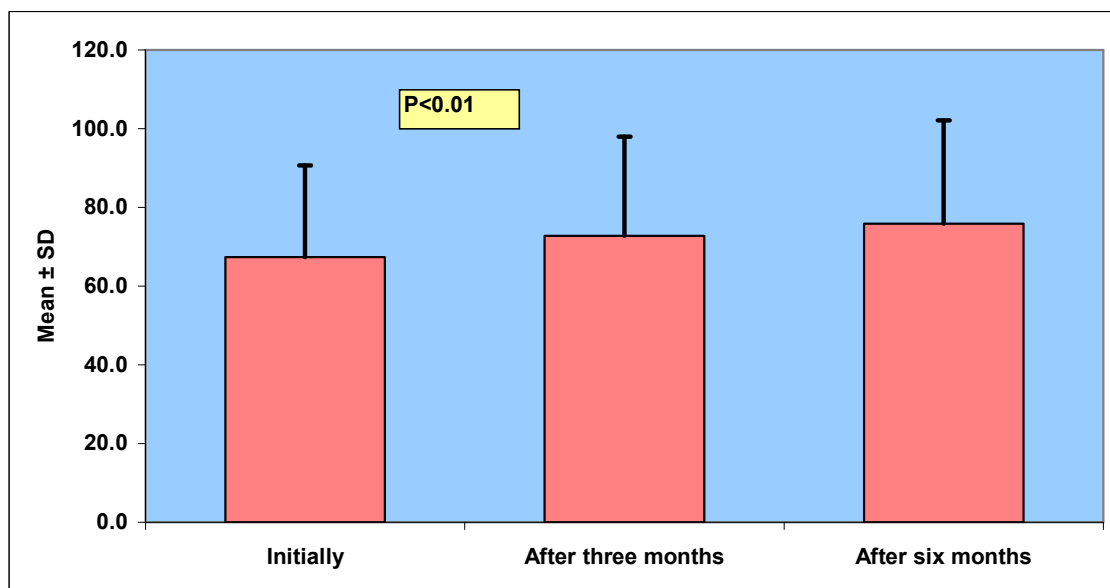
The average value of GFR three months after baseline of the therapy at patients who have received less than 50 Gy was 72.8 (SD± 25.2), while at those who have received more than 50 Gy was 78.8 (SD ± 26.0). With Unpaired T-test we have not reached an important significant statistic between the average value of GFR by dose (T=1.021, P=0.310).

Also GFR six months after baseline of the therapy at patients who have received under or over 50 Gy the average value of GFR six months after baseline of the therapy at patients who have received less than 50 Gy was 75.8 (SD± 26.3), while at those who have received more than 50 Gy was 82.9 (SD ± 25.3). With Unpaired T-test we have not reached an important significant statistic between the average value of GFR by dose (T=1.176, P=0.243).

Table 15. GFR at the baseline of the therapy, after three and six months at patients with dosage under 50 Gy

	GFR under 50 Gy		
	Baseline	After three months	After six months
N	40	40	40
Mean	67.4	72.8	75.8
SD	23.3	25.2	26.3
Repeated Measures ANOVA	F = 7.48, P=0.001		
Tukey - Kramer Multiple Comparisons test	Initially vs. After three months, P<0.05 Initially vs. After six months, P<0.001 Three months vs. Six months, P>0.05		

Graphic 6. GFR at the baseline of the therapy, after three and six months at patients with dosage under 50 Gy

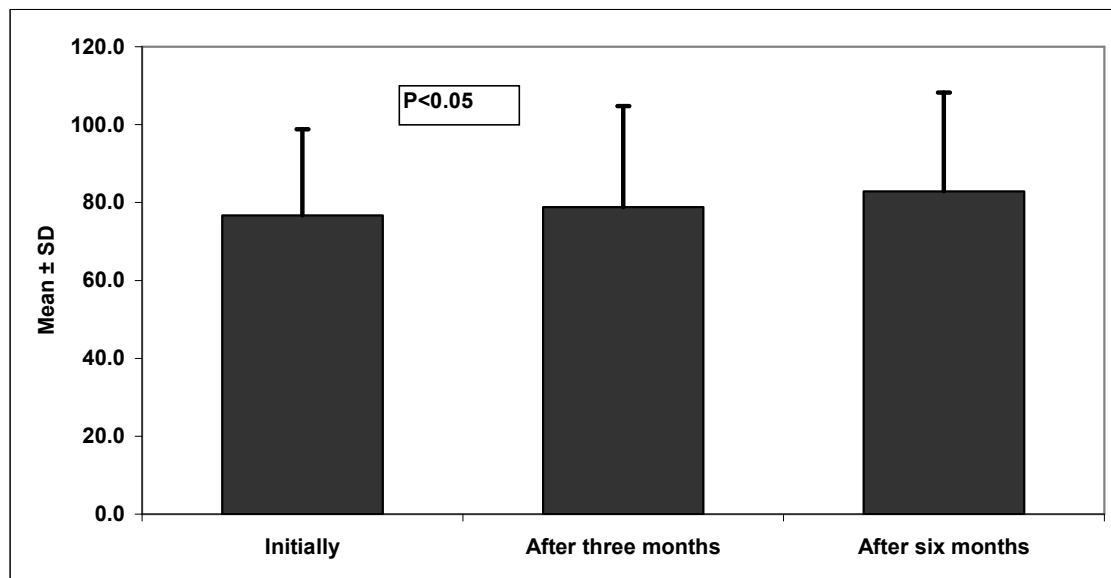


With repeated measures ANOVA we have reached an important significant statistic between the average value of GFR after using the therapy at patients with dosage under 50 Gy ($F=7.48$, $P<0.001$). With Tukey-Kramer Multiple Comparisons test we have reached a significant statistic between the values of GFR at the baseline of the treatment vs. three months after using the therapy. The baseline of the treatment vs. three months after using the therapy ($P<0.05$), baseline of treatment vs. six months after using the therapy ($P<0.001$) while we have not reached the difference between values of GFR three months vs. six months after (table 15 and Graphic 6).

Table 16. GFR at the baseline of therapy, after three and six months at patients with dosage over 50 Gy

	GFR and RT over 50 Gy		
	Baseline	After three months	After six months
N	35	35	35
Mean	76.7	78.8	82.9
SD	22.1	26.0	25.3
Repeated Measures ANOVA	F = 3.56, P=0.033		
Tukey - Kramer Multiple Comparisons test	Initially vs. After three months, $P>0.05$ Initially vs. After six months, $P<0.05$ Three months vs. Six months, $P>0.05$		

Graphic 7. GFR at the baseline of therapy, after three and six months at patients with dosage over 50 Gy

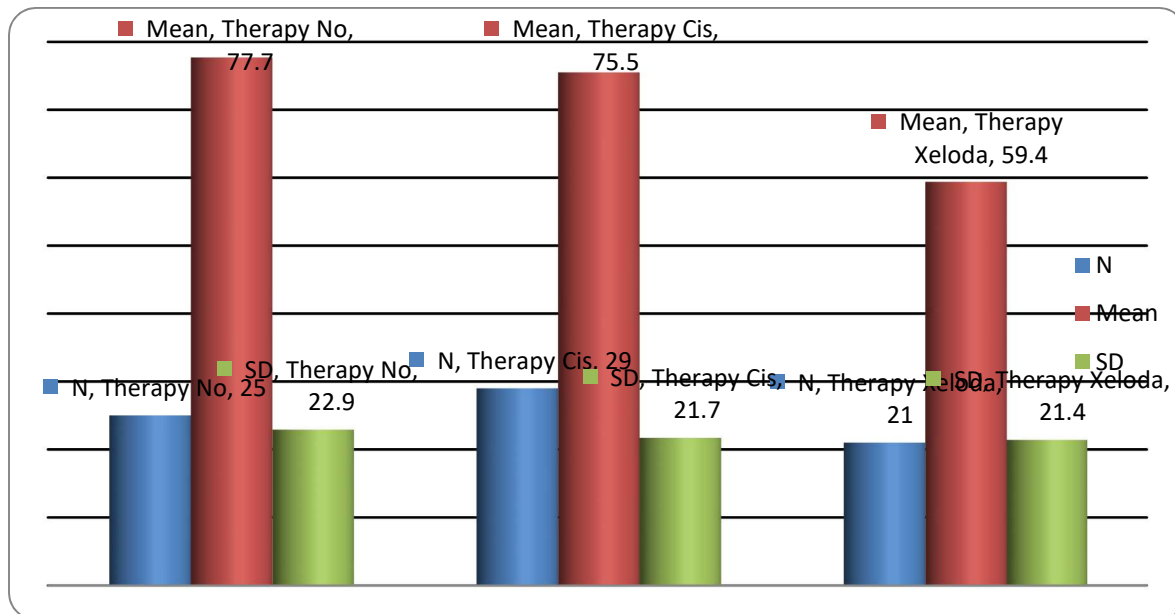


With repeated measures ANOVA we have reached an important significant statistic between the average value of GFR after using the therapy at patients with dosage over 50 Gy ($F=3.56$, $P=0.033$). With Tukey-Kramer Multiple Comparisons test we have reached a significant statistic between the values of GFR at the baseline of the treatment and six months after using the therapy ($P<0.05$), (table 16 and graphic 7)

Table 17. GFR at the baseline of therapy according type of Chemotherapy

GFR Baseline	Therapy		
	No	Cisplatin	Capecitabine
N	25	29	21
Mean	77.7	75.5	59.4
SD	22.9	21.7	21.4
One Way ANOVA	F = 4.61, P=0.01		
Tukey - Kramer Multiple Comparisons test	No therapy vs. Cisplatin, P>0.05 No therapy vs. Capecitabine, P<0.05 Cisplatin vs. Capecitabine, P<0.05		

Graphic 8. GFR at the baseline of therapy according to type of Chemotherapy



The average value of GFR at the start of therapy in those who have not received chemotherapy 77.7 (SD± 22.9) at those whom it is applied Cisplatin was 75.5 (SD ± 21.7) and at those in whom was applied Capecitabine was 59.4 (SD ± 21.4). With One Way ANOVA we have reached an important significant statistic between mean values of GFR according to the type of therapy applied ($F=4.61$, $P=0.01$). With Tukey-Kramer Multiple Comparisons test we have also reached an important significant statistic between the average values of GFR in the early treatment of patients without therapy vs. Capecitabine ($P<0.05$), Cisplatin vs. Capecitabine ($P<0.05$) while we did not find a difference between the GFR average values without therapy vs. Cisplatin ($P>0.05$), (table 17 and graphic 8).

Table 18. GFR three months after baseline of therapy at patients according to type of Chemotherapy

GFR after three months	Therapy		
	No	Cisplatin	Capecitabine
N	25	29	21
Mean	79.4	78.6	66.8
SD	30.3	20.8	24.5
One Way ANOVA	F = 1.74, P=0.18		
Tukey - Kramer Multiple Comparisons test	No therapy vs. Cisplatin, P>0.05 No therapy vs. Capecitabine, P>0.05 Cisplatin vs. Capecitabine, P>0.05		

The average value of GFR three months after baseline of therapy in those who have not received chemotherapy was 81.2 (SD± 30.3), at those whom it is applied Cisplatin was 78.6 (SD ± 20.8) at those in whom was applied Capecitabine was 66.8 (SD ± 24.5). With One Way ANOVA we have not reached an important significant statistic between mean values of GFR according to the type of therapy applied (F=1.74, P=0.18). With Tukey-Kramer Multiple Comparisons test we have not reached an important significant statistic between the average values of GFR in the early treatment of patients without therapy vs. Capecitabine (P>0.05), Cisplatin vs. Capecitabine (P>0.05) also we did not find a difference between the GFR average values without therapy vs. Cisplatin (P>0.05), (Table 18).

Table 19. GFR six months after baseline of therapy at patients according to type of Chemotherapy

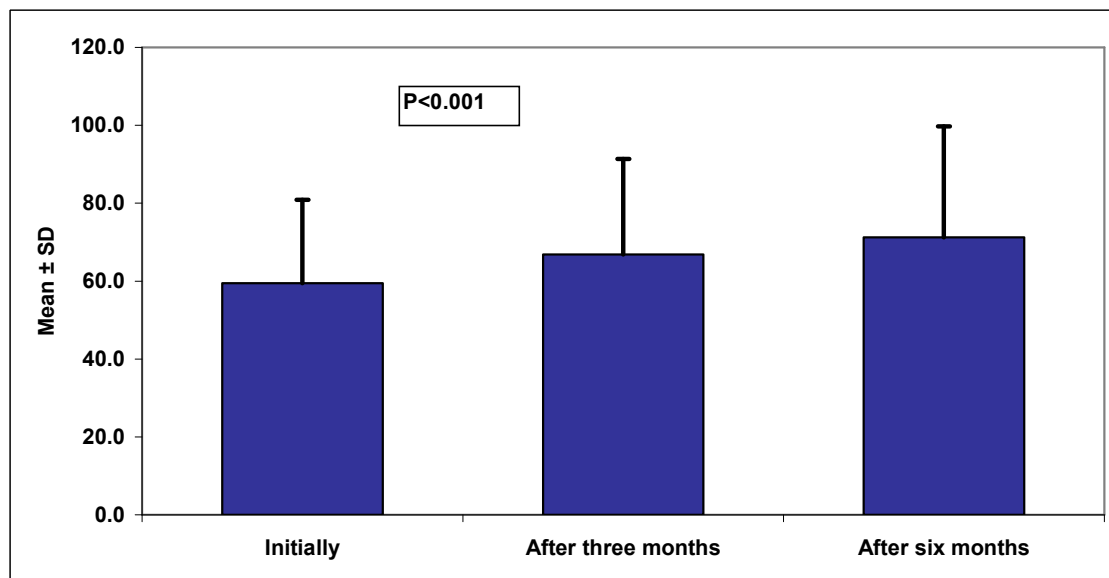
GFR after six months	Therapy		
	No	Cisplatin	Capecitabine
N	25	29	21
Mean	81.2	83.1	71.2
SD	30.3	18.4	28.5
One Way ANOVA	F = 1.41, P=0.249		
Tukey - Kramer Multiple Comparisons test	No therapy vs. Cisplatin, P>0.05 No therapy vs. Capecitabine, P>0.05 Cisplatin vs. Capecitabine, P>0.05		

The average value of GFR six months after baseline of therapy in those who have not received chemotherapy was 81.2 (SD± 30.3), at those whom it is applied Cisplatin was 83.1 (SD ± 18.4) at those in whom was applied Capecitabine was 71.2 (SD ± 28.5). With One Way ANOVA we have not reached an important significant statistic between mean values of GFR according to the type of therapy applied (F=1.41, P=0.249). With Tukey-Kramer Multiple Comparisons test we have also not reached an important significant statistic between the average values of GFR in the early treatment of patients without therapy vs. Capecitabine (P>0.05), Cisplatin vs. Capecitabine (P>0.05) also we did not find a difference between the GFR average values without therapy vs. Cisplatin (P>0.05), (Table 19).

Table 20. GFR at the baseline of therapy, after three and six months at patients with Capecitabine

	GFR - Capecitabine		
	Baseline	After three months	After six months
N	21	21	21
Mean	59.4	66.8	71.2
SD	21.4	24.5	28.5
Repeated Measures ANOVA	F = 8.38, P=0.0009		
Tukey - Kramer Multiple Comparisons test	Initially vs. After three months, P<0.05 Initially vs. After six months, P<0.001 Three months vs. Six months, P>0.05		

Graphic 9. GFR at the baseline of therapy, after three and six months at patients with Capecitabine



With repeated measures ANOVA we have reached an important significant statistic between the average value of GFR after using the therapy at patients that was applied Capecitabine (F=8.38,

P<0.001). With Tukey-Kramer Multiple Comparisons test we have reached a significant statistic between the values of GFR at the baseline of the treatment vs three months after applying Capecitabine therapy (P <0.05), at the baseline of the treatment vs. six months after using the therapy Capecitabine (P<0.001), while we have not reached difference between values of GFR three months after vs. six months after (Table 20 and graphic 9).

Table 21. GFR at the baseline of therapy, after three and six months at patients with Cisplatin

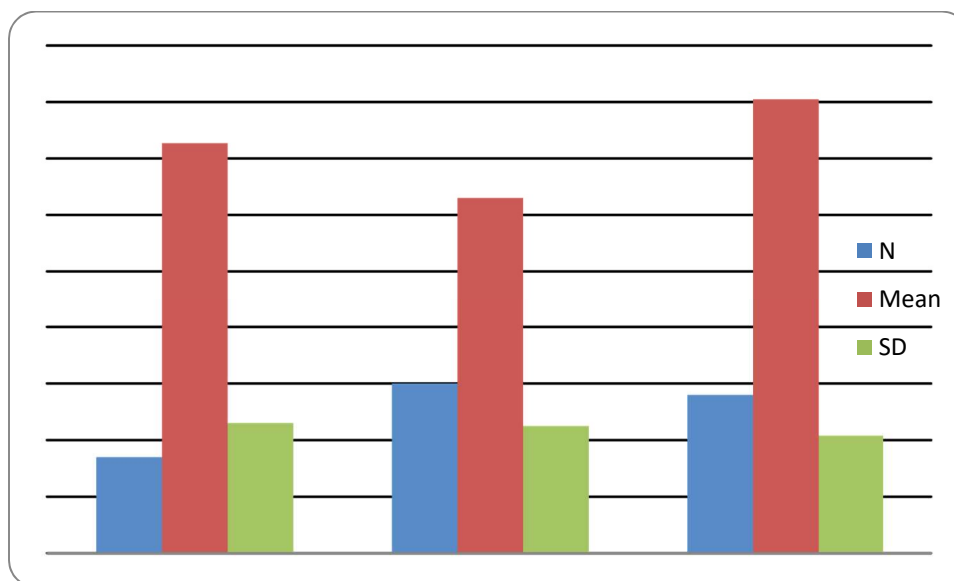
	GFR Cisplatin		
	Baseline	After three months	After six months
N	29	29	29
Mean	75.5	78.6	83.1
SD	21.7	20.8	18.4
Repeated Measures ANOVA	F = 5.32, P=0.0076		
Tukey - Kramer Multiple Comparisons test	Initially vs. After three months, P>0.05 Initially vs. After six months, P<0.01 Three months vs. Six months, P>0.05		

With repeated measures ANOVA we have reached an important significant statistic between the average value of GFR after using the therapy at patients that was applied Cisplatin (F=5.32, P=0.0076). With Tukey-Kramer Multiple Comparisons test we have reached a significant statistic between the values of GFR at the baseline of the treatment vs six months after applying Cisplatin therapy (P<0.01), (Table 21).

Table 22. GFR at the baseline of therapy at patients according to their diagnosis

GFR Baseline	Diagnosis		
	Endometrial Cancer	Rectal Cancer	Cervical Cancer
N	17	30	28
Mean	72.7	63.0	80.5
SD	23.0	22.5	20.8
Kruskal-Wallis test	KW = 9.33, P=0.009		
Dunn's Multiple Comparisons test	Endometrial cancer vs. Rectal cancer, P>0.05 Endometrial cancer vs. Cervical cancer, P>0.05 Rectal cancer vs. Cervical cancer, P<0.01		

Graphic 10. GFR at the baseline of therapy at patients according to their diagnosis



The average value of GFR at the baseline of the therapy at patients with endometrial cancer was 72.7 (SD± 23.0), at those with rectal cancer was 63.0 (SD ± 22.5) and those with Cervical Cancer was 80.5 (SD ± 20.8). With Kruskal-Wallis test we have reached an important significant statistic between mean values of GFR according to the type of disease (KW=9.33, P=0.009). With Dunn's Multiple Comparasions we have reached an important significant statistic between mean values of

GFR at the baseline of treatment to patients diagnosed with Rectal cancer vs. Cervical cancer, $P < 0.01$, (Table 22 and graphic 10).

Table 23. GFR three months after baseline of therapy at patients according to their diagnosis

GFR after three months	Diagnosis		
	Endometrial Cancer	Rectal Cancer	Cervical Cancer
N	17	30	28
Mean	71.4	70.1	83.9
SD	27.5	25.8	22.7
One Way ANOVA	F = 2.48, P=0.09		
Tukey - Kramer Multiple Comparisons test	Endometrial Cancer vs. Rectal Cancer, $P > 0.05$ Endometrial Cancer vs. Cervical Cancer, $P > 0.05$ Rectal Cancer vs. Cervical Cancer, $P > 0.05$		

The average value of GFR three months after baseline of the therapy at patients with Endometrial Cancer was 71.4 (SD \pm 27.5), at those with Rectal Cancer was 70.1 (SD \pm 25.8) and those with Cervical Cancer was 83.9 (SD \pm 22.7). With One Way ANOVA we have not reached an important significant statistic between mean values of GFR according to the type of disease (F= 2.48, $P = 0.09$). With Tukey-Multiple Comparisons we have not reached an important significant statistic between mean values of GFR at the baseline of the treatment at patients with Endometrial Cancer vs. Rectal Cancer ($P > 0.05$), Endometrial Cancer vs. Cervical Cancer ($P > 0.05$) and also we didn't find any difference between values of Rectal Cancer vs. Cervical Cancer ($P > 0.05$), (Table 23).

GFR six months after baseline of therapy at patients according to their diagnosis - The average value of GFR three months after baseline of the therapy at patients with Endometrial Cancer was 72.3 (SD \pm 29.7), at those with Rectal Cancer was 74.6 (SD \pm 27.1) and those with Cervical Cancer was 88.1 (SD \pm 19.7). With One Way ANOVA we have not reached important significant statistic between mean values of GFR according to the type of disease (F= 2.85, $P = 0.06$). With Tukey-Multiple Comparisons we have not reached an important significant statistic between mean values of GFR at the baseline of the treatment at patients with Endometrial Cancer

vs. Rectal Cancer ($P>0.05$), Endometrial Cancer vs. Cervical Cancer ($P>0.05$) and also we didn't find any difference between values of Rectal vs. Cervical Cancer ($P>0.05$).

Table 24. GFR at the baseline of therapy, after three and six months at patients with Endometrial Cancer

	GFR Endometrial Cancer		
	Baseline	After three months	After six months
N	17	17	17
Mean	72.7	71.4	72.3
SD	23.0	27.5	29.7
Repeated Measures ANOVA	F = 0.08, P=0.921		

With repeated measures Anova we have not reached an important significant statistic between the average value of GFR after applying the therapy at patients with Endometrial Cancer ($F=0.08$, $P>0.921$), (Table 24).

Table 25. GFR at the baseline of therapy, after three and six months at patients with Rectal Cancer

	GFR Rectal Cancer		
	Baseline	After three months	After six months
N	30	30	30
Mean	63.0	70.1	74.6
SD	22.5	25.8	27.1
Repeated Measures ANOVA	F = 8.50, P=0.0006		
Tukey - Kramer Multiple Comparisons test	Initially vs. After three months, P<0.05 Initially vs. After six months, P<0.001 Three months vs. Six months, P>0.05		

With repeated measures ANOVA we have reached an important significant statistic between the average value of GFR after applying the therapy at patients with Rectal Cancer (F=8.50, P<0.001). With Tukey-Kramer Multiple Comparisons test we have reached a significant statistic between the values of GFR at the baseline of the treatment vs three months after therapy (P<0.05), baseline of therapy vs six months after applying the therapy (P <0.001), while we did not reach a difference between values of GFR three months and six months after, (Table 25).

Table 26. GFR at the baseline of therapy, after three and six months at patients with Cervical Cancer

	GFR Cervical Cancer		
	Baseline	After three months	After six months
N	28	28	28
Mean	80.5	83.9	88.1
SD	20.8	22.7	19.7
Nonparametric Repeated Measures ANOVA	F= 13.07, P=0.0015		
Dunn's Multiple Comparisons test	Initially vs. After three months, P>0.05 Initially vs. After six months, P<0.001 Three months vs. Six months, P>0.05		

With Nonparametric repeated measures ANOVA (Friedman test) we have reached an important significant statistic between the average values of GFR after applying the therapy at patients diagnosed with Cervical Cancer (F=13.07, P<0.001). With Dunn's Multiple Comparisons test we have reached an important significant statistic between the values of GFR at the baseline vs. six months after therapy (P<0.001), (Table 26).

Table 27. GFR at the baseline of therapy at patients with dosage under or over 50 Gy (with or without comorbidity)

GFR Baseline	Comorbidity		Total
	No	Yes	
N	59	16	75
Mean	76.4	54.4	71.7
SD	21.4	21.1	23.1
Unpaired T-test	T=3.67, P=0.0005		

The average values of GFR at the baseline of therapy to patients without comorbidity was 76.4 (SD±21.4), while at patients diagnosed with associated diseases was 54.4 (SD ± 21.1). With unpaired T-test we have reached an important significant statistic between the average values of GFR by the presence of associated diseases (T=3.67, P=0.0005), (Table 27).

Table 28. GFR six months after baseline of therapy at patients with dosage under or over 50 Gy

GFR after six months	Comorbidity		Total
	No	Yes	
N	59	16	75
Mean	83.0	64.8	79.1
SD	22.7	32.1	25.9
Unpaired T-test	T=2.6, P=0.011		

The average values of GFR three months after baseline of therapy to patients with comorbidity was 64.8 (SD± 32.1) while at patients without associated diseases was 83.0 (SD ± 22.7). With Unpaired T-test we have reached an important significant statistic between the average values of GFR by the presence of associated diseases (T=2.6, P=0.011), (Table 28).

Table 29. GFR at the baseline of therapy, after three and six months at patients with Comorbidity

	GFR with comorbidity		
	Baseline	After three months	After six months
N	16	16	16
Mean	54.4	57.7	64.8
SD	21.1	24.3	32.1
Repeated Measures ANOVA	F = 2.60, P=0.09		

With repeated measures ANOVA we have not reached an important significant statistic between the average values of GFR after applying the therapy at patients with associated diseases ($F=2.60$, $P>0.05$), (Table 29).

Table 30. GFR at the baseline of therapy, after three and six months at patients without comorbidity

	GFR without comorbidity		
	Baseline	After three months	After six months
N	59	59	59
Mean	76.4	80.4	83.0
SD	21.4	23.9	22.7
Repeated Measures ANOVA	F = 8.33, P=0.0004		
Tukey - Kramer Multiple Comparisons test	Initially vs. After three months, P<0.05 Initially vs. After six months, P<0.001 Three months vs. Six months, P>0.05		

With repeated measures ANOVA we have reached an important significant statistic between the average values of GFR after applying the therapy at patients without associated diseases ($F=8.33$, $P=0.0004$). With Tukey-Kramer Multiple Comparisons test we have reached an important significant statistic between the values of GFR at the baseline of treatment vs. three months after therapy ($P<0.05$), beginning of treatment vs. six months after applying the therapy ($P<0.001$) while we have not reached difference between the values of GFR three months vs. six months after (Table 30).

Table 31. Comparison between the chemotherapy treatments in patients at baseline, 3 and 6 months

Difference GFR 3 months- GFR Initially	Chemotherapy	
	Yes	No
N	50	25
Average GFR	68.7	77.7
SD	22.8	22.9
Min	14.8	22.5
Max	105.7	123.8
T-test	T=1.60, P=0.113	

At 50 patients that was ordained chemotherapy while at 25 of them no. The average difference of GFR three months after compared to baseline of treatment was higher at the group that was not applied chemotherapy compared to the group with chemotherapy but without an important significant statistic (T-test = 1.60, P=0.113 therefore $P>0.05$), (Table 31).

Table 32. Levels of GFR six months after compared to three months after baseline of treatment at patients according to usage of chemotherapy

Difference GFR 6 months – GFR 3 months	Chemotherapy	
	Yes	No
N	50	25
Average	73.7	79.4
DS	22.9	30.3
Min	14.0	15.6
Max	106.2	126.6
Mann-Whitney test	U'=724, P=0.268	

The average of GFR six months after compared to three months after baseline of treatment was higher at the group that was not applied chemotherapy compared to the group with chemotherapy but without an important significant statistic. (Table 32).

Table 33. Levels of GFR six months after compared to GFR at the baseline of therapy at patients according to usage of chemotherapy

Difference GFR 6 months – GFR Initially	Chemotherapy	
	Yes	No
N	50	25
Average	78.1	81.2
DS	23.7	30.3
Min	10.6	13.2
Max	110.2	127.5
T-test	T=0.49, P=0.624	

Six months after baseline of therapy compared to baseline of therapy average of GFR was higher at the group that was not applied chemotherapy compared to the group with chemotherapy but without an important significant statistic (T- test = 0.49, P=0.624 therefore P>0.05), (Table 33).

Table 34. GFR at baseline of treatment by treatment modality

Category of treatment dose group	N	GFR Baseline				One Way ANOVA
		Average	SD	Min	Max	
1	22	75.5	22.5	27.3	105.7	F=2.25 P=0.07
2	21	59.4	21.4	14.8	98.6	
3	7	75.4	20.4	45.7	100.6	
4	12	76.6	24.6	37.6	123.8	
5	13	78.7	22.1	22.5	102.4	
Total	75	71.7	23.1	14.8	123.8	

Category 1: Radiotherapy over 50 Gy plus chemotherapy (Cisplatin).

Category 2: Radiotherapy under 50 Gy plus chemotherapy (Capecitabine).

Category 3: Radiotherapy under 50 Gy plus chemotherapy (Cisplatin).

Category 4: Radiotherapy under 50 Gy.

Category 3: Radiotherapy over 50 Gy.

At the baseline of treatment we did not reach an important significant statistic between the average values of GFR by method of treatment (F=2.25, P=0.07 therefore P>0.05), (Table 34).

Table 35. GFR three months after treatment by treatment modality

Category of treatment dose group	N	GFR after three months				One Way ANOVA
		Average	SD	Min	Max	
1	22	78.3	22.6	19.4	106.2	F=0.85 P=0.497
2	21	66.8	24.5	14.0	99.2	
3	7	79.4	15.0	54.6	98.8	
4	12	79.2	29.9	25.3	126.6	
5	13	79.6	31.9	15.6	120.1	
Total	75	75.6	25.6	14.0	126.6	

Three months after baseline of treatment we did not reach an important significant statistic between the average values of GFR by method of treatment (F=0.85, P=0.497 therefore P>0.05), (Table 35).

Table 36. GFR six months after treatment by treatment modality

Category of treatment dose group	N	GFR after six months				One Way ANOVA
		Average	SD	Min	Max	
1	22	84.0	19.5	37.6	110.2	F=0.71 P=0.581
2	21	71.2	28.5	10.6	107.2	
3	7	80.1	15.3	60.0	104.3	
4	12	81.5	27.4	43.2	127.5	
5	13	81.0	33.9	13.2	121.5	
Total	75	79.1	25.9	10.6	127.5	

Six months after baseline of treatment we did not reach an important significant statistic between the average values of GFR by method of treatment ($F=0.71$, $P=0.581$ therefore $P>0.05$), (Table 36).

Table 37. Acute toxicity of GU Tract according to the RTOG scoring system at 3 and 6 months

Gender	No	G 0		G 1		G 2		G 3		G 4	
Follow up		months		months		months		months		months	
		3	6	3	6	3	6	3	6	3	6
F	53	41	35	10	11	2	5	0	2	0	0
M	22	18	14	1	4	3	2	0	2	0	0

From 75 patients involved in research at 3 months follow up, GU AEs grade 1 and grade 2 are 16 patients or 21.33%.

Whereas follow up on 6 months GU AEs grade 1 and grade 2 are 22 patients or 29.33%.

Grade 3 GU AEs are 4 patients or 5.33%.

Table 38. Demographic data of patient with radiotherapy by group at 9 -12 months

	Group with cystoscopy		Control group		P-value
	N	%	N	%	
Total	20	100.0	55	100.0	0.349
F	12	60.0	41	74.5	
M	8	40.0	14	25.5	
Age group					
30-39	1	5.0	6	10.9	0.787
40-49	3	15.0	7	12.7	
50-59	9	45.0	13	23.6	
60-69	6	30.0	19	34.5	
70+	1	5.0	10	18.2	
Diagnosis					
Endometrial Cancer	3	15.0	14	25.5	0.628
Rectal Cancer	9	45.0	21	38.2	
Cervical cancer	8	40.0	20	36.4	

From 75 of the patients that radiotherapy was applied because of rectal, endometrial or cervical cancer, only 20 or 26.7% of them have had indications of cystoscopy, they were identified as cystoscopy group, while 55 or 73.3% of them were identified as control groups and did not have indications of cystoscopy. According to gender both of the frequently groups were female patients so we have not reach an import significant statistic ($P>0.05$). Also according to group and diagnosis of patients we did not reach any important significant statistic ($P>0.05$), (Table 38).

Table 39. Dose and type of therapy by groups at 9-12 months

	Group with cystoscopy		Control group		P-value
	N	%	N	%	
Total	20	100.0	55	100.0	
Dose					
over 50 Gy	8	40.0	27	49.1	0.663
under 50 Gy	12	60.0	28	50.9	
Chemotherapy					
0	5	25.0	20	36.4	0.589
Cisplatin	8	40.0	21	38.2	
Capecitabine	7	35.0	14	25.5	
Radiotherapy					
RT+Ch	15	75.0	35	63.6	0.518
RT	5	25.0	20	36.4	

Radiotherapy was applied at both groups and did not reach any significant difference by doses, type of radiotherapy applied alone or combined with chemotherapy ($P>0.05$). (Table 39).

Table 40. Patients with cystoscopy changes by gender and grades, diagnosis and therapy

	Male		Female		P-value
	N	%	N	%	
Total	8	100.0	12	100.0	
Grade					
I	6	75.0	4	33.3	0.171
II	2	25.0	8	66.7	
Diagnosis					
Endometrial Cancer	-	-	3	25.0	0.012
Rectal Cancer	8	100.0	1	8.3	
Cervical cancer	-	-	8	66.7	
Dose					
over 50 Gy	-	-	8	66.7	0.012
under 50 Gy	8	100.0	4	33.3	
Chemotherapy					
0	2	25.0	3	25.0	0.016
Cisplatin	-	-	8	66.7	
Capecitabine	6	75.0	1	8.3	
Radiotherapy					
RT+Chemo	6	75.0	9	75.0	0.999
RT	2	25.0	3	25.0	

We have also analyzed impact of the gender on the cystoscopy group based by grades and type of therapy. (Table 40)

At male patients changes on the cystoscopy often were first grade while at female patients second grade but without significant difference ($P>0.05$). We had only one case with rectal carcinoma at female patients.

In all cases at male patients we used doses under 50 Gy, at female patients 33.3% of doses under 50 Gy were used and get significant difference ($P<0.05$). Male patients in 75% of cases were used chemotherapy while at female patients 66.7%, without significant difference ($P>0.05$). Combined radio/chemotherapy are used same at both genders.

Table 41. Dose and type of therapy by grades

	Grade I		Grade II		P-value
	N	%	N	%	
Total	10	100	10	100	
Dose					
over 50 Gy	2	20.0	6	60.0	0.169
under 50 Gy	8	80.0	4	40.0	
Cisplatin/Capecitabine					
0	3	30.0	2	20.0	0.175
Cisplatin	2	20.0	6	60.0	
Capecitabine	5	50.0	2	20.0	
Radiotherapy					
RT+Ch	7	70.0	8	80.0	0.999
RT	3	30.0	2	20.0	
X2-test or Fisher exact test					

On 20.0% of patients with Grade I toxicity it's used doses over 50 Gy, while 60% of patient with Grade II its used doses over 50 Gy, but since the sample its small we did not find statistical significance ($P=0.169$). Even according to the type of therapy by grades we did not find statistical significance ($P=0.175$). Radiotherapy or combined Radio and chemo therapy regardless the grade was used in similar structure and we did not find statistical significance ($P=0.999$), (Table 41).

DISCUSSION

Glomerular filtration rate (GFR) is the rate (volume per unit of time) for clearance of particular waste product by the kidney. Approximately 120 mL are formed per minute. The GFR is a direct measure of renal function. It is reduced before the onset of symptoms of renal failure and is related to the severity of the structural abnormalities in chronic renal disease. The GFR can predict the signs and symptoms of uraemia, especially when it falls below 60 mL/min. Unfortunately it is not an ideal index, being difficult to measure directly, and is sometimes insensitive for detecting renal disease.

The GFR varies according to renal mass and correspondingly to the body mass. GFR is conventionally corrected for body surface area (which equates with renal mass), which in normal humans is approximately 1.73m^2 and represents an average value for normal young men and women. When the GFR is corrected for body surface area, a normal range can be derived to assess renal impairment.

According to the new KDIGO (guidelines for chronic kidney disease (CKD) progression) there are 5 stages of chronic kidney disease: 90-120 mL/min – I, 60-90 mL/min – II, 30-60 – III, 15-30 – IV, <15 mL/min – V for dialysis treatment.⁷⁰ The normal corrected GFR is 80-120 mL/min/ 1.73 m^2 , impaired renal function is 30-80 mL/min/ 1.73 m^2 and renal failure is less than 30 mL/min/ 1.73 m^2 . The corrected GFR is approximately 8% lower in women than in men, and declines with age at an annual rate of 1 mL/min/ 1.73 m^2 from the age of 40.

Chronic kidney disease (CKD) and cancer are connected in a number of ways in both directions: cancer can cause CKD either directly or indirectly through the adverse effects of therapies, CKD may conversely be a risk factor for cancer, and both may be associated because they share common risk factors, often toxins. Cancer as a cause or a risk factor for chronic kidney disease. The most frequent situation in which nephrologists have to face CKD in patients with cancer is that following the assessment of kidney function for dosage adjustment before chemotherapy. Because CKD, defined by an estimated glomerular filtration rate (eGFR) < 60 mL/min/ 1.73 m^2 , is common, with a prevalence of about 4% in the adult population aged 20 years and older, reaching 30% or more in the elderly, it is expected to be also common in patients with any type of cancer. In the Renal Insufficiency and Anticancer Medications (IRMA) Study, Launay-Vacher et al showed that among 4,684 participants with cancer, aged an average of 58 yrs, 12% had an eGFR < 60 mL/min/ 1.73 m^2 using the abbreviated MDRD equation, and 20% with the Cockcroft-Gault formula. Association, however, does not mean causation, and the cure of most cancers is unlikely to improve the course of CKD. The issue here is that of the prevention of adverse drug effect from over dosage due to renal impairment. In contrast, cancer-associated glomerulopathies are scarce, but more likely causally-related events. In a comprehensive review of paraneoplastic glomerulopathies, Ronco pointed the heterogeneity of this entity and the diversity of both glomerular injuries and cancers that have been reported. Most often, associations are described as case reports or case series making risk assessment difficult. Clinical remission of the glomerulopathy after cancer removal or chemotherapy in many of the reported cases, however,

provides indirect evidence for a causal link between these diseases. Membranous nephropathy (MN) is by far the most frequent type of glomerulopathy associated with solid tumors, but minimal change disease, membranoproliferative glomerulonephritis, extracapillary glomerulonephritis and IgA nephropathy were also reported. Compared with the general population, kidney transplant recipients have a three- to four-fold increase in overall cancer risk, and relative risks higher than three for about 20 specific tumors. After dialysis, cancer risk increases 10 to 80% according to studies, with relative risks significantly higher than the general population for about ten cancer sites. There is emerging evidence for an excess risk of cancer in patients at early CKD stages.⁷¹

A cystoscopy is used to allow visualization of the inner surfaces of the urinary tract. In our study cystoscopy have been recommended for following conditions:

Urinary tract infections

Blood in the urine (hematuria)

Loss of bladder control (incontinence)

Painful urination, chronic pelvic pain.

Creatinine clearance at the baseline of treatment has been to the largest number of patients between 60-90 ml / min. Males after the first 3 months have increased borderline of significance for 7ml unlike by women that is 2,5ml / min.

In our study, the average value of GFR three months after baseline of the therapy on female patients was 79.1 (SD± 23.7), while the average value of GFR on males was 67.2 (SD ± 28.4). With Unpaired T-test we have not reached a statistical significance between the average value of GFR by gender T=1.86, P=0.066, the average value of GFR six months after baseline of the therapy on female patients was 81.5 (SD± 24.0), while the average value of GFR on males was 73.4 (SD ± 29.8). With Unpaired T-test we haven't reached an important significant statistic between the average value of GFR by gender (T=1.239, P=0.219).

Principles of radiation therapy for cervical cancer

Definitive Radiation Therapy for patients with an intact cervix (eg, those who do not have surgery), the primary tumor and regional lymphatics at risk are typically treated with definitive EBRT to a dose of approximately 45 Gy (40–50 Gy). The volume of the EBRT would depend on the nodal status as determined surgically or radiographically. The primary treatment of early-stage cervical cancer is either surgery or RT. Surgery is typically reserved for early-stage disease and smaller lesions, such as stage IA, IB1, and selected IIA1.⁷² Although chemo-radiation is tolerated, acute and long-term side effects have been reported.⁷³⁻⁷⁵ Some oncologists prefer concurrent single-agent Cisplatin chemo-radiation over Cisplatin plus 5-FU chemo-radiation, because the latter may be more toxic.^{7,8} Concurrent carboplatin or nonplatinum chemo-radiation regimens are options for patients who may not tolerate Cisplatin-containing chemoradiation.^{3,73,76} When concurrent

chemo-radiation is used, the chemotherapy is typically given when the external-beam pelvic radiation is administered.⁸

In our study from 29 patient that had diagnosed with cervical cancer, 17 from them were treated with Cisplatin chemo-radiation where the radiotherapy giving dose were over 50 Gy. Other 12 patients, just 2 of them was treated with radiotherapy alone, that means 10 patients were treated with Cisplatin chemo radiation where the radiation dose were under 50 Gy.

In our data findings to those patients with repeated measures ANOVA we have reached an important significant statistic between the average value of GFR after using the therapy at patients that was applied Cisplatin ($F=5.32$, $P=0.0076$). With Tukey-Kramer Multiple Comparisons test we have reached a significant statistic between the values of GFR at the baseline of the treatment vs six months after applying Cisplatin therapy ($P<0.01$). The value of GFR was improved mostly because of infusive support therapy on the day of Cisplatin application and good result of primary disease.

Annual incidence rates for urinary AEs actually increase between years three and five post-RT, from 18% to 28%, respectively.⁴ Minor (grade 1 or 2) AEs are more common than major AEs; 44% develop acute (90 days after RT) minor urinary AEs, and 7-9.5% develop late minor AEs.^{17,77,78}

In our study 3 months after RT, urinary AEs with minor grade 1 and 2 to the patients that taken chemo radiotherapy with Cisplatin diagnosed with cervical cancer were 34.8%. This findings are within worldwide data and mostly they develop because of anatomy structure of pelvic, closeness of treated area with urethra.

The posterior bladder and insertion point of the ureters lie directly anterior to the cervix, making these areas most susceptible to injury. The most common major urinary AEs (grade 3 or above) are ureteral stenosis, vesicovaginal fistula, and hematuria.¹⁷

In our study with major urinary AEs (grade 3 or above) at first 3 months there is no evidence, but after 6 months we had 4 patients from total treated patients that had grade 3 manifested with ureteral stenosis followed with hematuria and local pain. On those 4 cases was seen that those findings are more because of the progression of primary disease then adverse effect of radio chemo therapy treatment.

Post-RT ureteral strictures are difficult to manage, in contrast to the ureter injured during gynecologic surgery, which can be reimplanted into the bladder with success rates over 90%.^{79,80} The stenotic ureter after RT is typically managed with repeated stenting; reimplantation is often not possible due to an ischemic distal segment. Stents must be exchanged every three months under anesthesia and may cause infections, bladder pain, urinary frequency and urgency. When prolonged stenting is not tolerated, urinary diversion or nephrectomy may be required.^{81,82,83}

Because of the small number of the patients with grade 3 or 4 in our study, this findings are not real and not enough for farther investigation in this direction and we cannot do comperation with findings on literatures.

RT principles has been a widely used modality in the treatment of patients with endometrial cancer, it clearly improves locoregional control. Tumor-directed RT refers to RT directed at sites of known or suspected tumor involvement and may include EBRT and/or brachytherapy.⁸⁴

The uterus resides within the peritoneum directly posterior to the bladder, thus most AEs following RT involve the bladder and bowel. Contrary to RT for cervical cancer, ureteral stricture is rare and urinary AEs in general are much less common. Only one small series reported a 6% rate of grade 4 ureteral stricture with hydronephrosis after HDR-BT.⁸⁵ The PORTEC-1 and 2 trials, with median follow-ups of 52 and 45 months, respectively, demonstrated no severe urinary AEs.^{27,86} Late AEs of any grade occurred in 25% of patients who underwent RT vs. 6% in patients who only received surgery ($P<0.0001$). GU AEs were most common, 68% of which were grade 1.

In our study after 3 months follow up to the patients diagnosed with endometria cancer only 17.6% appear with minor urinary AEs grade 1 and 2. Even with the small sample, our data correspond with other data finds in literature.

Urinary AEs following RT for rectal cancer are due to the close proximity of the rectum to the bladder, as well as its blood and nerve supply. One trial reported urinary AEs such as frequency, cystitis, incontinence, urinary retention, and ureteral stricture. Severe late urinary AEs were rare (4%) but AEs were potentially severe, with one patient requiring daily catheterization for grade 3 urinary retention, one requiring nephroureterectomy for a grade 4 stricture, and two requiring urinary diversion for grade 4 incontinence.⁸⁷ Another trial with a median follow-up of 85 months demonstrated incontinence at least twice weekly in 25% of patients.⁸⁸ Surgery itself may play an important role in the development of urinary dysfunction due to autonomic nerve damage, still one study with a mean follow up of 15 years found that although urinary incontinence was common in both irradiated and non-irradiated patients, it was significantly more so in those who received RT (45% vs. 27%, $P=0.023$).⁸⁹ Additionally, a retrospective study of 535 patients compared TME + RT vs. TME (Total Mesorectal Excision) only, and found all grades of urinary incontinence to be more common in the TME+RT group (36% vs. 24%, $P=0.007$).⁹⁰ Though most studies do not track urinary AEs in the setting of RT for rectal cancer, the studies do demonstrate that RT has a significant impact on urinary function with potentially severe AEs, although these are rare. Preoperative RT has been found to have fewer severe AEs of any system when compared with postoperative RT (27% vs. 40% acute and 14% vs. 24% late) and one study even found improved overall survival with preoperative treatment.⁴²⁻⁴⁴

In our study 30 patients are diagnosed with rectal cancer, 30% have had minor urinary AEs grade 1 and grade 2 on 3 up to 6 months follow up. It is seen that from all involved diagnosis in the

research patient with rectal cancer had higher percentage of minor urinary AEs because of higher number of patients and it is within other findings in literature.

Various trials did not find any relation between the percentage of bladder volume receiving a certain radiation dose and late urinary toxicity.⁹¹⁻⁹³ Kuban et al.⁹⁴ postulated that the dose-volume relation is confounded by changes in bladder volume throughout therapy, making it difficult to be evaluated. However, Pinkawa et al.⁹⁵ reported that the mean bladder volume can be kept at the same level at the time of the initial treatment planning and during the treatment, if patients are asked to have a full bladder. Boersma et al.⁹³ analyzed the radiation dose of certain bladder volumes of 130 patients with pelvic cancer treated with 3DCRT in a dose-escalating protocol. The 2-year actuarial incidence of Grade 3 or higher genitourinary complications was 8% and 21% using the RTOG/EORTC (European Organization for Research and Treatment of Cancer) and the SOMA/LENT (Late Effect of Normal Tissue) toxicity scales, respectively. They investigated whether the absolute bladder wall volume irradiated by various dose levels of radiation correlated with the actuarial incidence of late bladder complications. Although the crude figures indicated a trend towards higher complication rates with larger irradiated volumes, actuarial analysis did not demonstrate any significant effect. The total radiation dose and the maximum dose applied to the bladder wall did not correlate with the incidence of late bladder complications either.

According to the method of treating in our study we did not find difference of appearing urinary AEs.

Our data regarding the frequency of severe toxicities are similar to those of other series, despite the fact that a direct comparison of toxicities is difficult due to the existence of many modified versions of the classification, and modifications of grading scales. Similarities were found between our results, the RTOG 9413⁹⁶ analysis, and the GETUG-01 (Genitourinary Tumor Group)⁹⁷ prospective study. The diversity in the diagnostics could be created by individual physicians due to the subjectivity of the scoring system, when the same toxicity could be graded differently. The analysis of GU toxicity is difficult, due to interference with pre-existing dysfunction, age-related diseases, and previous urological surgery.^{98,99} We have to remember that some of these pre-existing symptoms could have been erroneously interpreted as acute or even late GU toxicity. On the other hand, late bladder damage can occur with a long latency time, potentially resulting in the underestimation of the real severity of late toxicity.¹⁰⁰

In our study we do not have patients with pre-existing urinary dysfunction, obstruction or previous urological surgery. According to the table 5, 21.3% of patients involved on research had associated disease, 5.3% Diabetes Mellitus, 6.7% Diabetes Mellitus and Hypertension, and 9.3% of them Hypertension.

So, the development of acute 3DCRT- induced GU damage was generally mild and none of the patients had an interruption of radiotherapy due to toxicity side effects.

The risk of acute GU reactions depended preferentially on the age of patients, in agreement with the results demonstrated by Jereczek-Fossa *et al.*¹⁰¹

It mean that also in our study better GFR is seen to the patients at youngest age group. The average value of GFR three months after baseline of the therapy at patients of age group 30-39 years was 102.0 (SD± 14.6) at age group 40-49 years was 94.9 (SD ± 12.1), 50-59 years was 79.3 (SD ± 22.1), 60-69 years was 65.1 (SD ± 24.7) while at the age group of patients over 70 years was 57.6 (SD ± 23.8)

The average value of GFR six months after baseline of the therapy at patients of age group 30-39 years was 103.8 (SD± 13.5), at age group 40-49 years was 100.1 (SD ± 12.1) 50-59 years was 78.9 (SD ± 23.0), , 60-69 years was 71.5 (SD ± 23.1) while at the age group of patients over 70 years was 62.1 (SD ± 31.7).

The biological variables and different clinical decisions based on patient age could participate on the final outcome. These molecules are ligands of the NK (Natural Killer) cell activation receptor NKG2D (The Natural Killer Group 2D) ¹⁰², and can stimulate NK cell functional maturation. Originally, the primary mechanism of RT in cancer reduction has been considered the neoplastic cell DNA damage. However, Takeshima *et al.* have found that tumor-specific CTL (Cytotoxic T Cell), which were induced in the draining lymph nodes and tumor tissue of mice by RT, are fundamental to the inhibition of cancer growth.¹⁰³ The immunological evaluation performed during 3DCRT showed a positive correlation of the number of activated NK cells and the proportion of terminally differentiated tumor targeted cytotoxic effectors with GU toxicities. Both of these subpopulations returned to normal values or decreased after completing RT. In contrast, T lymphocytes were decreased during RT and normalized after its completion; while NKT (Natural Killer T) cells were down-regulated in all time periods. The acute GU and late GU toxicities significantly increased the T cell proportion, NK cell-mediated cytotoxicity, and cytotoxic T cell numbers. We assume that these changes are caused by stress conditions induced by RT-damaged and GU toxicity-affected tissues, eliciting stimulation of cytotoxic cells (NK and CTLs). These RT effects could be due to inflammation following increased apoptotic/necrotic events in the involved tissues. The surface expression or extracellular release of stress proteins (e.g. MICs-Macrophage Inhibitory Cytokine, Hsp70-Heat Shock Protein 70), following tumor cell damage by RT, can play a key role in immune system modulation.¹⁰⁴

External beam RT

The incidence of RTOG grade 1 and grade 2 urinary AEs after external beam radiation therapy (EBRT) is reported to be 20-43% and 7-19%, respectively, with a follow-up of up to 10 years. ¹⁰⁵⁻¹⁰⁸ Mild symptoms can resolve either spontaneously or with treatment within 42 months after EBRT.¹⁰⁷ Grade 3 urinary AEs occur at a rate of 5-13%. Radiation cystitis with gross macroscopic hematuria is the most common grade 3 AE of EBRT. ¹⁰⁸⁻¹¹²

In our study EBRT incidence of grade 1 and grade 2 urinary AEs is 26.66% with a follow up 9 to 12 months with symptoms as microscope hematuria that have been seen in urine examination,

intermittent macroscopic hematuria, and moderate frequency of nocturia, dysuria and urgency for urination. Our findings are within the data reported in other literature.

Peeters *et al.* randomized 669 patients to receive 68 and 78 Gy radiation doses by 3-D conformal radiotherapy (CRT) and compared early and late urinary AEs for both treatment arms. In their analysis there was no statistically significant difference between dose escalations with respect to urinary AEs ($P=0.3$). The 3-year cumulative risk for RTOG grade ≥ 2 urinary AEs was 28.5% for the 68 Gy arm and 30.2% for the 78 Gy arm. Nonetheless, patients experienced more early and late gastro-intestinal toxicity with higher radiation dose.¹¹²

Furthermore, grade 2 and grade 3 acute urinary AEs were strong predictors for the development of late AEs ($P \leq 0.03$). Based on our research on this topic, we have not found any evidence, also in medical science paper we couldn't find more data for this issue.

In pelvic malignancies bladder filling status has largely been the matter of debate.

George *et al.*¹¹³ and Pinkawa *et al.*¹¹⁴ recommended a full bladder for treatment of gynecological malignancies, as the dose-volume-load to bladder and cranially displaced sigmoid colon/small bowel loops can be reduced significantly.

However; Pinkawa in another study¹¹⁵ found that bladder wall displacements are reduced significantly ($P < 0.01$) at superior and anterior border while treating empty bladder compared to full bladder and also there is less variability in bladder volume in an empty bladder state.

The ideal bladder filling status has not been ensured by any study so far.

The bladder protocols may vary from institution however most institute follow a consistent bladder filling protocol of voiding urine 15 min prior to both imaging and treatment, same it was applied in our study.

Data for radiation therapy and rectal cancer

Urinary AEs have not been properly evaluated in the setting of RT for rectal cancer. The only trial that describes urinary AEs mentions “bladder problems” in 2–4%.⁴² Given the close proximity of the bladder as well as its blood and nerve supply to rectum, there is likely to be an additive effect of RT and surgery causing increased risk of bladder dysfunction, although the lower doses of RT used for colorectal cancer may mitigate this effect.

In our study 12% of patients have had grade 1 and grade 2 Urinary AEs. The reason is that majority of patients had rectal cancer which includes 40% of total (table 3). Another reason is that the large number of patients in this group were previously operated (22 operated patients from total 30).

The acute side effects of pelvic radiation therapy for rectal cancer are mainly the result of gastrointestinal toxicity, are self-limiting, and usually resolve within 4 to 6 weeks of completing treatment.¹¹⁶

An analysis of patients treated with postoperative chemotherapy and radiation therapy suggests that these patients may have more chronic bowel dysfunction than do patients who undergo

surgical resection alone.¹¹⁷ A Cochrane review highlights the risks of increased surgical morbidity as well as late rectal and sexual dysfunction in association with radiation therapy.¹¹⁶ Improved radiation therapy planning and techniques may minimize these acute and late treatment-related complications. These techniques include the following:^{44,118-121}

1. The use of high-energy radiation machines.
2. The use of multiple pelvic radiation fields.
3. Prone patient positioning.
4. Customized patient molds (belly boards) to exclude as much small bowel as possible from the radiation fields and immobilize patients during treatment.
5. Bladder distention during radiation therapy to exclude as much small bowel as possible from the radiation fields.
6. Visualization of the small bowel through oral contrast during treatment planning so that when possible, the small bowel can be excluded from the radiation field.
7. The use of 3-dimensional or other advanced radiation planning techniques.

In Europe, it is common to deliver preoperative radiation therapy alone in one week (5 Gy × five daily treatments) followed by surgery one week later, rather than the long-course chemo-radiation approach used in the United States. One reason for this difference is the concern in the United States for heightened late effects when high radiation doses per fraction are given.¹²²

In our study patients were treated at prone and supine position as described in materials and method, giving 1,8 Gy per fraction up to 45 Gy total. In this group of patient we have reached significant statistic between the average value of GFR at patients with rectal cancer on follow up 3 and 6 months after treatments comparing with GFR at the baseline. Analyses confirmed that the treatment with Capecitabine and radiotherapy improved local treatment of rectal cancer without increasing the rate of late treatment – related side effects. It is because also for use of computerized software used to conform the dose to the shape of target in 3D.

With repeated measures ANOVA we have reached an important significant statistic between the average value of GFR after applying the therapy at patients with Rectal Cancer (F=8.50, P<0.001). With Tukey-Kramer Multiple Comparisons test we have reached a significant statistic between the values of GFR at the baseline of the treatment vs three months after therapy (P<0.05), baseline of therapy vs six months after applying the therapy (P <0.001), while we did not reach a difference between values of GFR three months and six months after.

Data for radiation therapy and cervical cancer

Cervical cancer tends to be a disease of younger women, with a median age of 48 years⁴². In the absence of cancer register and poorly collected data in our country the median age of patient could not be exactly determined. In our study from cervical cancer patient's median age were 51 years. Radical hysterectomy and primary radical RT are equivalent in Stage IB to IIA disease, and RT is integral to the treatment of more advanced disease (\geq IIB).^{123,124} Radical RT is delivered as 40–50 Gy EBRT plus 20–40 Gy HDR-BT for total doses to the cervix of up to 90 Gy. Overall, 53% of women receive RT within 6 months of diagnosis.¹²⁵ Eifel et al. reported that minor grade 1 or 2 urinary tract complications occurred most often during the first 3 years after treatment.¹²⁶ The risk of developing grade 1 and 2 AEs following RT for cervical cancer has been reported to be 28%¹²⁷ and increases by an additional 17.4% at 5 years.¹²⁶

In our study after one year 10.7% have develop grade 1 and 2 urinary AEs effects following RT for cervical cancer. The reason is small number of patient with this diagnose and short time follow up.

Patients who survived 3 years after treatment had a 7.7% probability of a major (grade 3) complication from RT. At 5 years, the risk of a major complication was 9.3% and there was a subsequent continuous risk of \sim 0.34% per year, resulting in an actuarial risk of major complications of 11.1% at 10 years, 13% at 15 years and 14.4% at 20 years.^{17,126,128} Grade 3–4 urinary AEs occur in 1.3–14.5% in series with at least 3 years of follow-up.¹²⁷⁻¹²⁹ Case reports demonstrate that spontaneous bladder rupture can occur as much as 30 years after RT for cervical cancer.^{130,131} Ureteral stricture and radiation cystitis are the most common urinary complications. The ureters insert into the posterior wall of the bladder just anterior to the cervix. A systematic review found that 14 of 17 trials of RT plus systemic chemotherapy did not routinely record late AEs.¹³²

In our study we have not reached significance of appearance of the urinary AEs effect in connection with method of treatment and applied dose. It is as a consequence of the small number of patients involved in the study and the impossibility among groups comperation. But we have reached an important significant statistic between the average values of GFR after applying the therapy at patients diagnosed with cervical cancer after six months of follow up. Mature analyses confirm that the addition Cisplatin to radiotherapy significantly improved the survivor rate of women with locally advanced cervical cancer without increasing the rate of late treatment related sides effects. It is also because the low dose to normal tissues such a bladder (conformal avoidance).

Data for radiation therapy and endometrial cancer

HDR-BT and/or 3D-CRT have an important role in adjuvant therapy for high-risk disease or salvage therapy for a local recurrence after hysterectomy.¹³³ Low-grade AE with radiation for endometrial cancer was reported in 11–16% of the patients.^{27,28,134} Grade 1 urinary AEs effects

after one year follow up in the endometrial cancer in our study is 4%. This is because of the small sample sizes and short follow up. The majority of those tend to be grade 1. With median follow-up of 52 and 68 months, the PORTEC and GOG99 trials noted no grade 3–4 urinary AEs.^{27,28} Likewise, many other cohort series report severe urinary AEs to be nonexistent or rare with pelvic EBRT or BT for endometrial cancer.^{134,135} However, the longest median follow-up in any of these series is only 5.5 years. Indeed, only one case series reports any significant rate of severe urinary AEs: a 6% incidence of ureteral stricture after HDR-BT.⁸⁵ The lower rate of urinary AEs after uterine RT compared to cervical RT may be due to differences in follow-up, in anatomic position relative to the ureters or the lower doses of EBRT delivered as adjuvant therapy after hysterectomy rather than high doses of BT+EBRT used as sole therapy in cervical cancer.

According to our research the results are approximately same with results based on published study in other countries, because mostly the way of treatment is same with other referents countries to what we did comparison. The potential reasons why our study results are deficient is that in the research were involved small number of patients, short time follow up and lacking cooperation with other specialties in treating these patients and their monitoring. Damage to renal function in these patients with severe malignancies is certainly an additive deterioration factor that determines the outcome. Long-term follow-up is hardly feasible due to the unpredictable course of the underlying disease. It is therefore difficult to distinguish the changes that result from the development of the underlying disease of the unwanted AEs.

CONCLUSION

1. Kidney function expressed through GFR according to the gender initially was with low average to male patient, diagnosed with Rectal Cancer, comparing to females patients diagnosed with same diagnoses and with Endometrial Cancer and Cervical Cancer.
2. The value of GFR was improved at three and 6 months after initiation of the treatment at patients diagnosed with Rectal Cancer who received dose under 50 Gy, concurrent with Capecitabine. That means: depending on the stadium of the disease, in our study patient to whom treatment was RT (under 50 Gy) + Capecitabine 825mg/m^2 , twice daily for 5 days/week during EBRT was better option that positively influenced in improvement of GFR value.
3. There is no type of treatment method applied in our study that has affected the deterioration of kidney function.
4. The type of treatment method applied (EBRT or/and chemotherapy) in patients with Endometrial Cancer did not affect the changes in renal function in the period before the onset and during follow-up of 6 months. Initial GFR have not changed through follow up.
5. We have reached improvement average of GFR value after six months of follow up at patients diagnosed with Cervical Cancer to whom treatment was RT+ concurrent weekly Cisplatin. Correctly calculated dose of Cisplatin (40 mg/m^2) maximum five cycles individually to all patients, have not affected GFR value at patients with locally advanced or high-risk Cervical Cancer where this treatment was applied. Cisplatin to radiotherapy significantly improved control of locally advanced Cervical Cancer without increasing the rate of late treatment related sides effects.
6. We have reached improvement average values of GFR at Rectal Cancer vs. Cervical Cancer. Addition of Capecitabine at patients diagnosed with Rectal Cancer treated concurrently with radiotherapy significantly improved local control of Rectal Cancer without increasing the rate of late treatment related side effects.
7. We have reached improvement average values of GFR at patient to whom was given capicitabine vs to the patient that have no other chemotherapy applied. That means Capecitabine have not affected GFR value, and is not nephrotoxic.
8. The average values of GFR at the baseline of therapy to patients without comorbidity was significantly better comparing with patients diagnosed with associated diseases. It means that the patients with other comorbidity's such as hypertension and diabetes mellitus initially had worsted GFR value.

9. Treated group from Rectal Cancer had significant improvement of GFR after three and six months of starting the treatment, in comparison to other groups diagnosed with Cervical and Endometrial Cancer. These improvements were caused by:
 - Gender (Most of patients were males with initially low average value of GFR),
 - Young average age,
 - Pelvic anatomy where the bladder is less involved in the radiation field during rectal radiotherapy treatment,
10. Positive impacts at GFR value and in urinary AEs within the allowed limit, at patients with Rectal Cancer, Endometrial Cancer and Cervical Cancer are also from:
 - Computerized software used to conform the dose to the shape of the target in 3D, multi leaf collimator,
 - Low dose to normal tissues such as bladder (conformal avoidance),
 - Adequate margins for organ motion during treatment.
11. Minor urinary AEs effects (acute and late) have had no effects on the kidney function expressed with GFR to all patients involved in research.
12. Minor grade 1 and 2 adverse side effects are relatively frequent. In patients at three months urinary AEs were 21.33% and at six months were 29.33%. Higher percentage 34.8% of urinary AEs grade 1 and 2 was at patients diagnosed with Cervical Cancer, treated concurrently with Cisplatin chemo-radiotherapy, comparing to groups diagnosed with Endometrial and Rectal Cancer.
13. Grade 3 AEs represented with 5.33% after six months have been appeared according to locally advanced cancer and progression of the underlying disease after treatment.
14. Patients who have had most common side effects were those who initially had anemia, hypertension, diabetes, dehydrated patient who had difficulty coping with treatment.
15. With X²-test and Fisher exact test after one year of follow up we have reached important statistical significant results between the groups of patient treated with doses under 50 Gy and over 50 Gy. This was because of the small number of patients into groups and categories, according to different diagnoses and way of treatment.
16. Patients that have performed cystoscopy have had slight or occasional damage to the walls of the bladder and they have not need any treatment.

17. Complications of the urinary tract more frequently are seen 1 year after treatment in worldwide study, the results of this study are limited because of: small numbers of patients into groups, short follow up to detect and evaluate the late AEs of urinary tract.
18. Our study dates are within average of worldwide dates.

Recommendations from this study are:

- This issue need multidisciplinary approach;
- It is important that the possible complications of RT to be recognized by providers and properly to be managed;
- Drinking of plenty fluids at least double of their normal intake, avoid drinking lots of tea, coffee or alcohol can help reducing acute urinary toxicity;
- The use of IMRT (Intensity-Modulated Radiation Therapy), IGRT (Image-Guided Radiation Therapy) as most sophisticate procedures are the best choice for better treatment and less side effects through systems;
- Biologically optimized radiotherapy is an exciting new development.

ABBREVIATION

RT – Radiotherapy

Gy – Grey

AEs – Adverse Effects

UICC – Union for International Cancer Control

CFRT – Conformal Radiotherapy

GI – Gastro Intestinal

GU – Genitourinary

HPV – Human Papilloma Virus

EBRT – External Beam Radiotherapy

CT – Computer Tomography

MRI – Magnetic Resonance Imaging

PET – Positron Emission Tomography

IMRT – Intensity Modulated Radiation Therapy

CIS – Carcinoma In Situ

ICBT – Intracavitary Brachytherapy

BT – Brachytherapy

LV – Lymph Vascular

LVSI – Lymph Vascular Space Invasion

GOG – Gynecology Oncology Group

PORTEC – Post Operative Radiation Therapy in Endometrial Carcinoma

HIR – High Intermediate Risk

HDR – High Dose Rate

LDH – Low Dose Rate

3D CRT – 3D Conformal Radiotherapy

FAP – Familial Adenomatous Polyposis

HNPCC – Hereditary Nonpoliposis Colorectal Cancer

DFS – Disease Free Survival

OS – Overall Survival

CCRT – Concurrent Chemo Radiotherapy

LVI – Lymph Vascular Invasion

PNI – Peri Neural Invasion

TME – Total Mesorectal Excision

T – Tumor

N – Nodal Status

M – Metastasis

DNA - Deoxyribonucleic Acid

GFR – Glomerular Filtration Rates

RTOG – Radiation Therapy Oncology Group

PGUM – Pretreatment Genitourinary Morbidity

pTNM – Pathological TNM classification

ICRU – International Commission on Radiation Units and Measurements

DRR – Digital Reconstruction Radiograph

TPS – Treatment Planning System

LN – Lymph Node

L – Lumbal

S – Sacral

AP – Antero Posterior

PA – Postero Anterior

GTV – Gross Tumor Volume

CTV – Clinical Target Volume

ITV – Internal Target Volume

PTV – Planning Target Volume

OAR – Organ at Risks

MLC – Multi Leaf Collimator

DVH – Dose Volume Histogram

PALN – Para Aortal Lymph Node

GYN – Gynecology

KDIGO - Kidney Disease: Improving Global Outcomes

CKD – Chronic Kidney Disease

IRMA – Renal Insufficiency and Anti Cancer Medications

MDRD – Modification of Diet in Renal Disease

HDR-BT – High Dose Rate Brachytherapy

EORTC - European Organization for Research and Treatment of Cancer.

SOMA/LENT – Late Effect of Normal Tissue - scale

GETUG – Genitourinary Tumor Group

NK – Natural Killer

NKG2D - The Natural Killer Group 2D

CTL – Cytotoxic T Cell

NKT – Natural Killer T

MIC – Macrophage Inhibitory Cytokine

HSP70 – Heat Shock Protein 70

REFERENCES

1. New Techniques in Radiation therapy Moderator: Dr S C Sharma Department of Radiotherapy PGIMER Chandigarh
2. Xh. Bicaj et al. ONKOLOGJIA, ALB-MED, ISBN 978-9951-460-17-0, page 206-208, 2014- Prishtina.
3. Wong LC, Ngan HY, Cheung AN, et al. Chemoradiation and adjuvant chemotherapy in cervical cancer. *J Clin Oncol* 1999;17:2055- 2060. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10561258>.
4. Georg P, Boni A, Ghabuous A, et al. Time course of late rectal- and urinary bladder side effects after MRI-guided adaptive brachytherapy for cervical cancer. *Strahlenther Onkol* 2013;189:535-40. [PubMed]
5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Cervical Cancer, Version 1.2018 — October 25, 2017.
6. Mendivil AA, Rettenmaier MA, Abaid LN, et al. Survival rate comparisons amongst cervical cancer patients treated with an open, robotic-assisted or laparoscopic radical hysterectomy: A five year experience. *Surg Oncol* 2016;25:66-71. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26409687>.
7. Gaffney DK, Erickson-Wittmann BA, Jhingran A, et al. ACR Appropriateness Criteria(R) on Advanced Cervical Cancer Expert Panel on Radiation Oncology-Gynecology. *Int J Radiat Oncol Biol Phys* 2011;81:609-614. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21215531>.
8. Monk BJ, Tewari KS, Koh W-J. Multimodality therapy for locally advanced cervical carcinoma: state of the art and future directions. *J Clin Oncol* 2007;25:2952-2965. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17617527>.
9. Gien LT, Beauchemin MC, Thomas G. Adenocarcinoma: a unique cervical cancer. *Gynecol Oncol* 2010;116:140-146. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19880165>
10. Baalbergen A, Veenstra Y, Stalpers LL, Ansink AC. Primary surgery versus primary radiation therapy with or without chemotherapy for early adenocarcinoma of the uterine cervix. *Cochrane Database Syst Rev* 2010:CD006248. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20091590>.
11. Park JY, Kim DY, Kim JH, et al. Outcomes after radical hysterectomy in patients with early-stage adenocarcinoma of uterine cervix. *Br J Cancer* 2010;102:1692-1698. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20531414>.
12. Wo JY, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. *Int J Radiat Oncol Biol Phys* 2009;73:1304-1312. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19306747>.
13. Pahisa J, Martinez-Roman S, Martinez-Zamora MA, et al. Laparoscopic ovarian transposition in patients with early cervical cancer. *Int J Gynecol Cancer* 2008;18:584-589. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18476952>.

14. Morice P, Juncker L, Rey A, et al. Ovarian transposition for patients with cervical carcinoma treated by radiosurgical combination. *Fertil Steril* 2000;74:743-748. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11020517>.
15. Randomised study of radical surgery versus radiotherapy for stage Ib–IIa cervical cancer. Landoni F, Manco A, Colombo A, et al *Lancet* 1997;350:535–540.
16. American Brachytherapy Society. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: General Principles. 2012. Accessed on May 9, 2016.
https://www.americanbrachytherapy.org/guidelines/Guidelines_Carcinoma_Cervix_Part1.pdf
17. Eifel PJ, Levenback C, Wharton JT, Oswald MJ. Time course and incidence of late complications in patients treated with radiation therapy for FIGO stage IB carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1995;32:1289-1300. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7635768>.
18. Lewis SA. Everything you wanted to know about the bladder epithelium but were afraid to ask. *Am J Physiol Renal Physiol*. 2000;278(6):F867–F874. [PMID: 10836974]
19. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017;67:7-30. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28055103>.
20. Van den Bosch T, Coosemans A, Morina M, et al. Screening for uterine tumours. *Best Pract Res Clin Obstet Gynaecol* 2011. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22078749>.
21. Kitchener HC, Trimble EL. Endometrial cancer state of the science meeting. *Int J Gynecol Cancer* 2009;19:134-140. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19258955>.
22. Dinkelspiel HE, Wright JD, Lewin SN, Herzog TJ. Contemporary clinical management of endometrial cancer. *Obstet Gynecol Int* 2013;2013:583891. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23864861>.
23. Obermair A, Youlden DR, Young JP, et al. Risk of endometrial cancer for women diagnosed with HNPCC-related colorectal carcinoma. *Int J Cancer* 2010;127:2678-2684. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20533284>.
24. Ueda SM, Kapp DS, Cheung MK, et al. Trends in demographic and clinical characteristics in women diagnosed with corpus cancer and their potential impact on the increasing number of deaths. *Am J Obstet Gynecol* 2008;198:218 e211-216. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18226630>.
25. Benedetti Panici P, Basile S, Salerno MG, et al. Secondary analyses from a randomized clinical trial: age as the key prognostic factor in endometrial carcinoma. *Am J Obstet Gynecol* 2014;210:363 e361-363 e310. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24361787>.

26. Doll KM, Tseng J, Denslow SA, et al. High-grade endometrial cancer: revisiting the impact of tumor size and location on outcomes. *Gynecol Oncol* 2014;132:44-49. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24183734>.
27. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage- 1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet* 2000;355:1404-1411. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10791524>.
28. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 2004;92:744-751. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14984936>.
29. Creutzberg CL, Nout RA, Lybeert ML, et al. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. *Int J Radiat Oncol Biol Phys* 2011;81:e631-638. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21640520>.
30. ASTEC/EN.5 Study Group, Blake, P., Swart, A.M., et al. (2009). Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRS ASTEC and NCIC CTG EN.5 randomized trials): pooled trial results, systematic review, and meta-analysis. *Lancet*. 373(9658), 137-146. doi: 10.1016/S0140-6736(08)61767-5.
31. Balch GC, De Meo A, Guillem JG: Modern management of rectal cancer: a 2006 update. *World J Gastroenterol* 12 (20): 3186-95, 2006. [[PUBMED Abstract](#)]
32. Baxter NN, Garcia-Aguilar J: Organ preservation for rectal cancer. *J Clin Oncol* 25 (8): 1014-20, 2007. [[PUBMED Abstract](#)]
33. Guillem JG, Cohen AM: Current issues in colorectal cancer surgery. *Semin Oncol* 26 (5): 505-13, 1999. [[PUBMED Abstract](#)]
34. Seitz U, Bohnacker S, Seewald S, et al.: Is endoscopic polypectomy an adequate therapy for malignant colorectal adenomas? Presentation of 114 patients and review of the literature. *Dis Colon Rectum* 47 (11): 1789-96; discussion 1796-7, 2004. [[PUBMED Abstract](#)]
35. MacFarlane JK, Ryall RD, Heald RJ: Mesorectal excision for rectal cancer. *Lancet* 341 (8843): 457-60, 1993. [[PUBMED Abstract](#)]
36. Enker WE, Thaler HT, Cranor ML, et al.: Total mesorectal excision in the operative treatment of carcinoma of the rectum. *J Am Coll Surg* 181 (4): 335-46, 1995. [[PUBMED Abstract](#)]
37. Sauer R, Liersch T, Merkel S, et al.: Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol* 30 (16): 1926-33, 2012. [[PUBMED Abstract](#)]

38. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9202. *J Clin Oncol* 2006; 24:4620-4625.
39. American Cancer Society. *Cancer Facts & Figures 2013*. Atlanta: American Cancer Society; 2013.
40. Ramsey S, Tepper JE. Rectal cancer radiotherapy. *Cancer J*. 2007;13:204-9. [PubMed]
41. Elliott SP, Jarosek SA, Virnig BA. Unpublished analysis of SEER public use file. 1992-2006.
42. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004;351:1731-40. [PubMed]
43. Martling A, Holm T, Johansson H, et al. The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. *Cancer* 2001;92:896-902. [PubMed]
44. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997;336:980-7. [PubMed]
45. Compton CC, Greene FL: The staging of colorectal cancer: 2004 and beyond. *CA Cancer J Clin* 54 (6): 295-308, 2004 Nov-Dec. [PUBMED Abstract]
46. Gunderson LL, Sargent DJ, Tepper JE, et al.: Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. *J Clin Oncol* 22 (10): 1785-96, 2004. [PUBMED Abstract]
47. McLeod HL, Murray GI: Tumour markers of prognosis in colorectal cancer. *Br J Cancer* 79 (2): 191-203, 1999. [PUBMED Abstract]
48. Gryfe R, Kim H, Hsieh ET, et al.: Tumor microsatellite instability and clinical outcome in young patients with colorectal cancer. *N Engl J Med* 342 (2): 69-77, 2000. [PUBMED Abstract]
49. Ballek NK, Gonzalez CM. Reconstruction of radiation-induced injuries of the lower urinary tract. *Urol Clin North Am* 2013;40:407-19. [PubMed]
50. Bolus NE. Basic review of radiation biology and terminology. *J Nucl Med Technol* 2001;29:67-73; test 76-7.
51. Tibbs MK. Wound healing following radiation therapy: a review. *Radiother Oncol* 1997;42:99-106. [PubMed]
52. Mundy AR, Andrich DE. Posterior urethral complications of the treatment of prostate cancer. *BJU Int* 2012;110:304-25. [PubMed]
53. Kidney: Function and Anatomy, Diagram, Conditions, and Health Tips
<https://www.healthline.com/human-body-maps/kidney>
54. Dos Santos NA, Carvalho Rodrigues MA, Martins NM, dos Santos AC. Cisplatin-induced nephrotoxicity and targets of nephroprotection: an update. *Arch Toxicol* 2012;86:1233-50. DOI: <http://dx.doi.org/10.1007/s00204-012-0821-7>.
55. Pabla N, Dong Z. Cisplatin nephrotoxicity: mechanisms and renoprotective strategies. *Kidney Int* 2008;73:994-1007. DOI: <http://dx.doi.org/10.1038/sj.ki.5002786>.

56. GENERAL RADIOLOGY, Radiation Cystitis: Acute and Chronic, Apr 7, 2017
<https://radiologykey.com/radiation-cystitis-acute-and-chronic/>
57. Amdur RJ, Parsons JT, Fitzgerald LT, et al. Adenocarcinoma of the prostate treated with external-beam radiation therapy: 5-year minimum follow-up. *Radiother Oncol.* 1990;18(3):235–246. [PMID: 2120741]
58. Duncan W, Williams JR, Kerr GR, et al. An analysis of the radiation related morbidity observed in a randomized trial of neutron therapy for bladder cancer. *Int J Radiat Oncol Biol Phys.* 1986;12(12):2085–2092. [PMID: 3539897]
59. Pilepich MV, Krall JM, Sause WT, et al. Correlation of radiotherapeutic parameters and treatment related morbidity in carcinoma of the prostate--analysis of RTOG study 75-06. *Int J Radiat Oncol Biol Phys.* 1987;13(3):351–357. [PMID: 3494005]
60. Pilepich MV. Radiation Therapy Oncology Group studies in carcinoma of the prostate. *NCI Monogr.* 1988;7:61–65. [PMID: 3173504]
61. Quilty PM, Duncan W, Kerr GR. Results of a randomised study to evaluate influence of dose on morbidity in radiotherapy for bladder cancer. *Clin Radiol.* 1985;36(6):615–618. [PMID: 4064546]
62. Quilty PM, Duncan W. Primary radical radiotherapy for T3 transitional cell cancer of the bladder: an analysis of survival and control. *Int J Radiat Oncol Biol Phys.* 1986;12(6):853–860. [PMID: 2424878]
63. Sack H, Nosbuesch H, Stuetzer H. Radiotherapy of prostate carcinoma: results of treatment and complications. *Radiother Oncol.* 1987;10(1):7–15. [PMID: 3671775]
64. Sakurai M, Saijo N, Shinkai T, et al. The protective effect of 2-mercapto-ethane sulfonate (MESNA) on hemorrhagic cystitis induced by high-dose ifosfamide treatment tested by a randomized crossover trial. *Jpn J Clin Oncol.* 1986;16(2):153–156. [PMID: 3090314]
65. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys.* 1995;31(5):1341–1346. [PMID: 7713792]
66. Marks LB, Carroll PR, Dugan TC, et al. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. *Int J Radiat Oncol Biol Phys.* 1995;31(5):1257–1280. [PMID: 7713787]
67. De Vita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology (9th edition) De Vita, V.T., Lawrence, T.S. and Rosenberg S.A. Lippincott, Williams and Wilkins, 2011
68. Radiotherapy to the bladder. Oxford university hospital, NHS trust, the radiotherapy department.
69. Feldman AS, et al. Etiology and evaluation of hematuria in adults.
<http://www.uptodate.com/home>. Accessed July 10, 2015.

70. KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) volume 76 | SUPPLEMENT 113 | AUGUST 2009 Supplement to Kidney International
<http://www.kidney-international.org>
71. Nephrol. 2010; 23(3): 253–262.PMCID: PMC4823382
PMID: 20349418
72. ACOG practice bulletin. Diagnosis and treatment of cervical carcinomas. Number 35, May 2002. American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet 2002;78:79-91. Available at:<http://www.ncbi.nlm.nih.gov/pubmed/12197489>.
73. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol 2008;26:5802- 5812. Available at:<http://www.ncbi.nlm.nih.gov/pubmed/19001332>.
74. King M, McConkey C, Latief TN, et al. Improved survival after concurrent weekly cisplatin and radiotherapy for cervical carcinoma with assessment of acute and late side-effects. Clin Oncol (R Coll Radiol) 2006;18:38-45. Available at:<http://www.ncbi.nlm.nih.gov/pubmed/16477918>.
75. Tan LT, Zahra M. Long-term survival and late toxicity after chemoradiotherapy for cervical cancer--the Addenbrooke's experience. Clin Oncol (R Coll Radiol) 2008;20:358-364. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18395427>.
76. Cetina L, Garcia-Arias A, Uribe MdJ, et al. Concurrent chemoradiation with carboplatin for elderly, diabetic and hypertensive patients with locally advanced cervical cancer. Eur J Gynaecol Oncol 2008;29:608-612. Available at:<http://www.ncbi.nlm.nih.gov/pubmed/19115688>
77. Lorvidhaya V, Tonusin A, Changwiwit W, et al. High-dose-rate afterloading brachytherapy in carcinoma of the cervix: an experience of 1992 patients. Int J Radiat Oncol Biol Phys 2000;46:1185-91. [PubMed]
78. Pinn-Bingham M, Puthawala AA, Syed AM, et al. Outcomes of high-dose-rate interstitial brachytherapy in the treatment of locally advanced cervical cancer: long-term results. Int J Radiat Oncol Biol Phys 2013;85:714-20. [PubMed]
79. Rafique M, Arif MH. Management of iatrogenic ureteric injuries associated with gynecological surgery. Int Urol Nephrol 2002;34:31-5. [PubMed]
80. Williams SK, Leveillee RJ. Expanding the horizons: robot-assisted reconstructive surgery of the distal ureter. J Endourol 2009;23:457-61. [PubMed]
81. Maier U, Ehrenbock PM, Hofbauer J. Late urological complications and malignancies after curative radiotherapy for gynecological carcinomas: a retrospective analysis of 10,709 patients. J Urol 1997;158:814-7. [PubMed]
82. Parliament M, Genest P, Girard A, et al. Obstructive ureteropathy following radiation therapy for carcinoma of the cervix. Gynecol Oncol 1989;33:237-40. [PubMed]

83. Gellrich J, Hakenberg OW, Oehlschlager S, et al. Manifestation, latency and management of late urological complications after curative radiotherapy for cervical carcinoma. *Onkologie* 2003;26:334-40. [PubMed]
84. Klopp A, Smith BD, Alektiar K, et al. The role of postoperative radiation therapy for endometrial cancer: Executive summary of an American Society for Radiation Oncology evidence-based guideline. *Pract Radiat Oncol* 2014;4:137-144. Available at:<http://www.ncbi.nlm.nih.gov/pubmed/24766678>.
85. Nguyen TV, Petereit DG. High-Dose-Rate Brachytherapy for Medically Inoperable Stage I Endometrial Cancer. *Gynecologic Oncology* 1998;71:196-203. [PubMed]
86. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet* 2010;375:816-23. [PubMed]
87. Engels B, Tournel K, Everaert H, et al. Phase II study of preoperative helical tomotherapy with a simultaneous integrated boost for rectal cancer. *Int J Radiat Oncol Biol Phys* 2012;83:142-8. [PubMed]
88. Brændengen M, Tveit KM, Bruheim K, et al. Late patient-reported toxicity after preoperative radiotherapy or chemoradiotherapy in nonresectable rectal cancer: results from a randomized Phase III study. *Int J Radiat Oncol Biol Phys* 2011;81:1017-24. [PubMed]
89. Pollack J, Holm T, Cedermark B, et al. Late adverse effects of short-course preoperative radiotherapy in rectal cancer. *Br J Surg* 2006;93:1519-25. [PubMed]
90. Bruheim K, Guren MG, Skovlund E, et al. Late side effects and quality of life after radiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys* 2010;76:1005-11. [PubMed]
91. Storey MR, Pollack A, Zagars G, Smith L, Antolak J, Rosen I: Complications from radiotherapy dose escalation in prostate cancer: preliminary results of a randomized trial. *Int J Radiat Oncol Biol Phys*. 2000; 48: 635-42.
92. Koper PC, Jansen P, van Putten W, van Os M, Wijnmaalen AJ, Lebesque JV, et al.: Gastro-intestinal and genito-urinary morbidity after 3D conformal radiotherapy of prostate cancer: observations of a randomized trial. *Radiother Oncol*. 2004; 73: 1-9.
93. Boersma LJ, van den Brink M, Bruce AM, Shouman T, Gras L, te Velde A, et al.: Estimation of the incidence of late bladder and rectum complications after high-dose (70-78 GY) conformal radiotherapy for prostate cancer, using dose-volume histograms. *Int J Radiat Oncol Biol Phys*. 1998; 41: 83-92.
94. Kuban D, Pollack A, Huang E, Levy L, Dong L, Starkschall G, et al: Hazards of dose escalation in prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys*. 2003; 57: 1260-8.
95. Pinkawa M, Fishedick K, Asadpour B, Gagel B, Piroth MD, Eble MJ: Low-grade toxicity after conformal radiation therapy for prostate cancer—impact of bladder volume. *Int J Radiat Oncol Biol Phys*. 2006; 64: 835-41.

96. A Phase III Trial Comparing Whole Pelvic Irradiation Followed by a Conedown Boost to Boost Irradiation Only and Comparing Neoadjuvant to Adjuvant Total Androgen Suppression (TAS) 2011.
97. Pommier P, Chabaud S, Lagrange JL, Richaud P, Lesaunier F, Le PE, Wagner JP, Hay MH, Beckendorf V, Suchaud JP, Pabot du Chatelard PM, Bernier V, Voirin N, Perol D, Carrie C: Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01.
J Clin Oncol 2007, 25:5366-5373. PubMed Abstract | Publisher Full Text
98. Liu M, Pickles T, Berthelet E, Agranovich A, Kwan W, Tyldesley S, McKenzie M, Keyes M, Morris J, Pai H: Urinary incontinence in prostate cancer patients treated with external beam radiotherapy.
Radiother Oncol 2005, 74:197201. PubMed Abstract | Publisher Full Text
99. Sandhu AS, Zelefsky MJ, Lee HJ, et al. Long-term urinary toxicity after 3-dimensional conformal radiotherapy for prostate cancer in patients with prior history of transurethral resection. Int J Radiat Oncol Biol Phys. 2000;48(3):643–647. [PMID: 11020559]
100. Peeters ST, Hoogeman MS, Heemsbergen WD, Hart AA, Koper PC, Lebesque JV: Rectal bleeding, fecal incontinence, and high stool frequency after conformal radiotherapy for prostate cancer: normal tissue complication probability modeling.
Int J Radiat Oncol Biol Phys 2006, 66:11-19. PubMed Abstract | Publisher Full Text
101. Jerezek-Fossa BA, Jassem J, Badzio A: Relationship between acute and late normal tissue injury after postoperative radiotherapy in endometrial cancer.
Int J Radiat Oncol Biol Phys 2002, 52:476-482. PubMed Abstract | Publisher Full Text
102. Nausch N, Cerwenka A: NKG2D ligands in tumor immunity.
Oncogene 2008, 27:5944-5958. PubMed Abstract | Publisher Full Text
103. Takeshima T, Chamoto K, Wakita D, Ohkuri T, Togashi Y, Shirato H, Kitamura H, Nishimura T: Local radiation therapy inhibits tumor growth through the generation of tumor-specific CTL: its potentiation by combination with Th1 cell therapy.
Cancer Res 2010, 70:2697-2706. PubMed Abstract | Publisher Full Text
104. De Maio A: Extracellular heat shock proteins, cellular export vesicles, and the Stress Observation System: A form of communication during injury, infection, and cell damage: It is never known how far a controversial finding will go! Dedicated to Ferruccio Ritossa. Cell Stress Chaperones 2010.
105. Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. JAMA 2005;294:1233-9. [PubMed]
106. Zelefsky MJ, Wallner KE, Ling CC, et al. Comparison of the 5-year outcome and morbidity of three-dimensional conformal radiotherapy versus transperineal permanent iodine-125 implantation for early-stage prostatic cancer. J Clin Oncol 1999;17:517-22. [PubMed]

107. Zelefsky MJ, Cowen D, Fuks Z, et al. Long term tolerance of high dose three-dimensional conformal radiotherapy in patients with localized prostate carcinoma. *Cancer* 1999;85:2460-8. [PubMed]
108. Lawton CA, Won M, Pilepich MV, et al. Long-term treatment sequelae following external beam irradiation for adenocarcinoma of the prostate: analysis of RTOG studies 7506 and 7706. *Int J Radiat Oncol Biol Phys* 1991;21:935-9. [PubMed]
109. Crook J, Lukka H, Klotz L, et al. Systematic overview of the evidence for brachytherapy in clinically localized prostate cancer. *CMAJ* 2001;164:975-81. [PubMed]
110. Williams SG, Millar JL, Duchesne GM, et al. Factors predicting for urinary morbidity following 125iodine transperineal prostate brachytherapy. *Radiother Oncol* 2004;73:33-8. [PubMed]
111. Peeters ST, Heemsbergen WD, Koper PC, et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 2006;24:1990-6. [PubMed]
112. Peeters ST, Heemsbergen WD, van Putten WL, et al. Acute and late complications after radiotherapy for prostate cancer: results of a multicenter randomized trial comparing 68 Gy to 78 Gy. *Int J Radiat Oncol Biol Phys* 2005;61:1019-34. [PubMed]
113. Georg P, Georg D, et al. Factors influencing bowel sparing in intensity modulated whole pelvic radiotherapy for gynaecological malignancies. *Radiother Oncol* 2006;80:19-26.
114. Pinkawa M, et al. Dose-volume histogram evaluation of prone and supine patient position in external beam radiotherapy for cervical and endometrial cancer. *Radiother Oncol* 2003;69:99-105.
115. Pinkawa M, et al. Bladder extension variability during pelvic external beam radiotherapy with a full or empty bladder. *Radiother Oncol* 2007;83:163-7.
116. Wong RK, Tandan V, De Silva S, et al.: Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma. *Cochrane Database Syst Rev* (2): CD002102, 2007. [PUBMED Abstract]
117. Kollmorgen CF, Meagher AP, Wolff BG, et al.: The long-term effect of adjuvant postoperative chemoradiotherapy for rectal carcinoma on bowel function. *Ann Surg* 220 (5): 676-82, 1994. [PUBMED Abstract]
118. Dahlberg M, Glimelius B, Pahlman L: Improved survival and reduction in local failure rates after preoperative radiotherapy: evidence for the generalizability of the results of Swedish Rectal Cancer Trial. *Ann Surg* 229 (4): 493-7, 1999. [PUBMED Abstract]
119. Guerrero Urbano MT, Henrys AJ, Adams EJ, et al.: Intensity-modulated radiotherapy in patients with locally advanced rectal cancer reduces volume of bowel treated to high dose levels. *Int J Radiat Oncol Biol Phys* 65 (3): 907-16, 2006. [PUBMED Abstract]

120. Koelbl O, Richter S, Flentje M: Influence of patient positioning on dose-volume histogram and normal tissue complication probability for small bowel and bladder in patients receiving pelvic irradiation: a prospective study using a 3D planning system and a radiobiological model. *Int J Radiat Oncol Biol Phys* 45 (5): 1193-8, 1999. [[PUBMED Abstract](#)]
121. Gunderson LL, Russell AH, Llewellyn HJ, et al.: Treatment planning for colorectal cancer: radiation and surgical techniques and value of small-bowel films. *Int J Radiat Oncol Biol Phys* 11 (7): 1379-93, 1985. [[PUBMED Abstract](#)]
122. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al.: Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 93 (10): 1215-23, 2006. [[PUBMED Abstract](#)]
123. Cancer Facts & Figures 2009. American Cancer Society; Atlanta: 2009.
124. Cowan RA, McBain CA, Ryder WD, et al. Radiotherapy for muscle-invasive carcinoma of the bladder: results of a randomized trial comparing conventional whole bladder with dose-escalated partial bladder radiotherapy. *Int J Radiat Oncol Biol Phys*. 2004; 59:197–207. [PubMed: 15093917]
125. Kaufman DS, Winter KA, Shipley WU, et al. Phase I-II RTOG study (99–06) of patients with muscle-invasive bladder cancer undergoing transurethral surgery, paclitaxel, cisplatin, and twicedaily radiotherapy followed by selective bladder preservation or radical cystectomy and adjuvant chemotherapy. *Urology*. 2009; 73:833–837. [PubMed: 19100600]
126. Elliott, SP.; Jarosek, SA.; Virnig, BA. Unpublished analysis of SEER public use file. 1992–2006.
127. McIntyre JF, Eifel PJ, Levenback C, Oswald MJ. Ureteral stricture as a late complication of radiotherapy for stage IB carcinoma of the uterine cervix. *Cancer*. 1995; 75:836–843. [PubMed: 7828135]
128. Takeshi K, Katsuyuki K, Yoshiaki T, et al. Definitive radiotherapy combined with high-dose-rate brachytherapy for Stage III carcinoma of the uterine cervix: retrospective analysis of prognostic factors concerning patient characteristics and treatment parameters. *Int J Radiat Oncol Biol Phys*. 1998; 41:319–327. [PubMed: 9607347]
129. Kapp KS, Stuecklschweiger GF, Kapp DS, Poschauko J, Pickel H, Hackl A. Carcinoma of the cervix: analysis of complications after primary external beam radiation and Ir-192 HDR brachytherapy. *Radiother Oncol*. 1997; 42:143–153. [PubMed: 9106923]
130. Elliott SP, Meng MV, Elkin EP, McAninch JW, Duchane J, Carroll PR. Incidence of urethral stricture after primary treatment for prostate cancer: data from CaPSURE. *J Urol*. 2007; 178:529– 534. discussion [PubMed: 17570425]

131. Nishimura T, Suzuki K, Iijima M, et al. Spontaneous rupture of bladder diverticulum after postoperative radiotherapy for carcinoma of the uterine cervix: a case report. *Radiat Med.* 2000; 18:261–265. [PubMed: 11247004]
132. Green JA, Kirwan JM, Tierney JF, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet.* 2001; 358:781–786. [PubMed: 11564482]
133. Small W Jr, Du Bois A, Bhatnagar S, et al. Practice patterns of radiotherapy in endometrial cancer among member groups of the gynecologic cancer intergroup. *Int J Gynecol Cancer.* 2009; 19:395– 399. [PubMed: 19407566]
134. Kucera H, Vavra N, Weghaupt K. Benefit of external irradiation in pathologic stage I endometrial carcinoma: a prospective clinical trial of 605 patients who received postoperative vaginal irradiation and additional pelvic irradiation in the presence of unfavorable prognostic factors. *Gynecol Oncol.* 1990; 38:99–104. [PubMed: 2191908]
135. Irwin C, Levin W, Fyles A, Pintilie M, Manchul L, Kirkbride P. The role of adjuvant radiotherapy in carcinoma of the endometrium-results in 550 patients with pathologic stage I disease. *Gynecol Oncol.* 1998; 70:247–254. [PubMed: 9740699]