Рационална терапија
2018, Vol. X, No. 2, стр. 43-51 **UDK**: 615.849.099, 615.277.099
DOI: 10.5937/RACTER10-18049

Прегледни чланак/Review Paper

ACUTE RADIATION TOXICITY DURING AND AFTER CONCURRENT CHEMORADIOTHERAPY IN PATIENTS WITH LOCALY ADVANCED CERVICAL CANCER

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АКУТНА РАДИЈАЦИОНА ТОКСИЧНОСТ ЗА ВРЕМЕ И ПОСЛЕ ХЕМОРАДИОТЕРАПИЈЕ КОД ПАЦИЈЕНТКИЊА СА ЛОКАЛНО УЗНАПРЕДОВАЛИМ КАРЦИНОМОМ ЦЕРВИКСА УТЕРУСА

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Примљен/Received: 25.6.2018. Прихваћен/Accepted: 28.10.2018.

ABSTRACT

Cervical cancer takes an alarming 4th place among tumors in women and is a serious global problem of modern society. The gold standard in the treatment of locally advanced cervical cancer is based on concurrent chemoradiotherapy (external beam in combination with brachytherapy). However, during the treatment of cervical cancer, various forms of acute toxicity can occur, with the incidence of up to 84%. The most common adverse manifestations of this therapeutic approach include various hematologic, gastrointestinal, genitourinary and dermatologic problems.

Although most of the potential risk factors for acute radiation toxicity are primarily associated with certain features of therapeutic modalities, individual patient characteristics must also be taken into account. Knowledge of potential risk factors and early detection of patients with increased risk of acute radiation toxicity may significantly contribute to the administration of adequate corrective measures in order to prevent the occurrence of both acute and chronic toxicity, which is even more complex. Such an approach also leads to improvement of the quality of life of patients with locally advanced cervical cancer.

Key words: risk factors, acute radiation toxicity, locally advanced cervical cancer.

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САЖЕТАК

Карцином цервикса утеруса се налази на алармантном 4. месту међу малигним туморима код жена, и представља глобални проблем. Златни стандард у лечењу локално узнапредовалог карцинома цервикса утеруса је хеморадиотерапија (екстерно зрачење и брахитерапија). Међутим, за време лечења карцинома цервикса утеруса настају различити облици акутне токсичности, који укључују оштећења крвних лоза, гастроинтестиналне, генитоуринарне и дерматолошке проблеме.

Мада је већина потенцијалних фактора ризика за појаву акутне радијационе токсичности везана за поједине модалитете терапије, треба увек узети у обзир индивидуалне карактеристике пацијената. Познавање потенцијалних фактора ризика и рано откривање пацијената са повећаним ризиком од акутне радијационе токсичности може значајно допринети примени адекватних корективних мера које ће спречити и акутну и још комплекснију хроничну радијациону токсичност. Такав приступ доводи и до побољшања квалитета живота пацијената са локално узнапредовалим карциномом цервикса утеруса.

Кључне речи: локално узнапредовали карцином цервикса утеруса, акутна радијациона токсичност, фактори ризика.

INTRODUCTION

Growing trend of cervical cancer (CC) prevalence is a serious global problem of modern society. The current data suggests that this tumor has high mortality and morbidity and takes an alarming 4th place among tumors in women, accounting for 15% of all oncology patients[1,2,3]. In a lot of developing countries, CC remains major public health problem with high overall incidence and a higher frequency of advanced stages at the time when diagnosis is established[4]. Factors that cause the CC may be related to patient lifestyle and sexual habits, poor socio-economic status, poor prevention policy and the lack of organized screening[5]. Human papilloma virus is among the most important risk factors. Histologically, more than 90% of all cervical tumors are squamocellular, while adenocarcinoma makes 7-10%[6]. Due to the slow evolution and frequent lack of acute symptoms, in 70 to 90% of the patients the diagnosis is made when the disease is locally advanced[7]. With organized screening and advanced preventive measures, the incidence of CC decreases[8]. The disease is detected by gynecological examination, Papanicolau test, colposcopy, biopsy, or by using diagnostic imaging methods. In the early phase, the disease is usually asymptomatic, and later, abnormal vaginal bleeding, pelvic pain, and pain or discomfort during and after sexual intercourse can occur[9].

The disease staging is initially clinical, based on the gynaecological exam and results of the diagnostic visualization methods[1]. Tumor Nodus Metastasis (TNM) and Federation Internationale de Gynecologie et d'Obstetrique (FIGO) Classification are used for definitive disease staging[10]. Depending on the stage of the disease, CC patients are treated with surgery, chemotherapy and radiotherapy. Surgical treatment is used exclusively at early stages, when the tumor is limited to the cervix (FIGO Ia-IIa)[1].

The gold standard in the treatment of locally advanced CC (FIGO IIb to IVa) is based on concomitant chemo-irradiation (external beam in combination with brachytherapy) (11). Cisplatin is usually administered at a dose of 40 mg/m^2 once a week, for up to 6 cycles, during standard radiotherapy fractionated to a 5-day regimen[12]. This type of treatment prolongs the patient's overall survival by 5-8%, prolongs the interval to local recurrence of the disease by 5-9% and reduces the risk of disease progression by 40 to 60%[1,2,13]. The results of a recent meta-analysis, with the help of fixed-effects models, confirmed higher incidence of toxicity in patients who were treated with concurrent chemoradiotherapy (CCRT) compared to those treated exclusively with radiotherapy[6]. Cisplatin can cause severe side effects such as nausea, ototoxicity, neurotoxicity, and nephrotoxicity. Also, it is shown that the use of cisplatin particularly increases severity of acute hematological and gastrointestinal toxicity[14-17].

In a therapeutic setting, the cervix tolerates high radiation dose, and for this reason, the total dose delivered is increased by concomitant use of external beam RT and brachytherapy. There are different modalities of brachytherapy such as high-dose-rate (HDR) brachytherapy, low-dose-rate, middle-dose-rate, and pulse-dose-rate[18,19,20]. However, HDR is currently the most commonly used, because treatment time is the shortest and the most comfortable for the patients, compared to other modalities. Also, short treatment time ensures constant geometrical relation between applicator system, the radioactive source and anatomic structures, and gives an opportuity to precisely control the dose delivered to the tumor

and to the organs at risk. The American Brachitherapy Society recommends a dose less then 7.5 Gy[21]. Frequently used regimens are 6 Gy in 5 fractions, 5 Gy in 6 fractions and 5,5 Gy in 5 fractions[21]. Optimal brachitherapy treatment is administration of a single dose of 7 Gy in 4 fractions, after completing the external beam treatment[22].

The American Brachitherapy Society, the Radiation Therapy Oncology Group and the Gynecology Oncology Group also suggest that ideal duration of CCRT treatment is between 50 and 55 days, due to optimal compliance and treatment tolerance[23,24]. In developing countries, usually due to delays of intracavitary brachytherapy initiation, the treatment lasts for about 10 weeks on average[25]. Extended duration of treatment induces tumor regrowth, which results in worse disease control and shorter survival rates[23,24,25]. In terms of toxicity, gastrointestinal system is the most frequently affected[25].

ACUTE RADIATION TOXICITY - GENERAL ASPECTS

The term acute radiation toxicity refers to the toxicity observed during and shortly after radiotherapy or CCRT[26]. This adverse effects and morbidity can seriously affect the patient's quality of life[1,27]. Acute toxicity occurs from radiation induction to the 90th day, while late toxicity occurs months and years after radiotherapy has been completed[28]. The basic principle of radiotherapy is to apply the therapeutic tumoricidal radiation dose to the malignant tumor (target volume), and at the same time to spare the surrounding normal tissues (organs at risk)[29,30]. Previous studies have shown that 14 to 68% of patients with abdomen or pelvic tumors are treated with curative or palliative radiotherapy[25,31]. During the treatment, the incidence of anaemia, leukopenia, cystitis, diarrhoea and neuropathy rises to 84%, which is significantly more than after completion of the treatment[29,32-35]. Grade 3 and 4 toxicity occurs in 4 to 40% of patients and correlates with the target volume size, fractionation regimen, received dose and radiation techniques[25,35,36].

Radiation Therapy Oncology Group morbidity scoring criteria and Common Terminology Criteria for Adverse Events for radiological toxicity assessment have been used in studies related to toxicity in CC patients treated with CCRT[35,36]. In addition to these two scales, the Franco-Italian glossary, which has a system similar to the Radiation Therapy Oncology Group scale is also used, but in practice it is not widespread[36]. Creating a reliable and validated test, which could identify patients with an increased risk of radiation toxicity, using genetic and clinical factors, would significantly reduce the occurrence of early and late radiation complications[37].

It is known that certain radiotherapy factors such as the therapeutic dose, number of fractions, size, number and localization of radiation fields, and radiotherapy techniques can affect the acute radiation toxicity[25,38,39]. Due to high contact doses, brachytherapy has a significant effect on development of early and late postradiation toxicities, in particular those of grade 3 and 4[25,38,39,40]. The occurrence of acute radiation toxicity may depend on the biologically effective dose, the dose distribution heterogeneity received by the organs at risk and the effective volume[41, 42].

ACUTE RADIATION TOXICITY – MOST COMMON MANIFESTATIONS AND RISK FACTORS

Gastrointestinal toxicity

Gastrointestinal toxicity is the most common type of toxicity after whole pelvic iradiation[43]. Severe forms can be observed in 12 to 44% of patients during radiotherapy treatment, whether or not chemotherapy is also administered[44,45]. Small intestine radiation can cause diarrhea, pain, abdominal colic, loss of appetite, nausea and dehydration. Rectal toxicity is expressed in the form of diarrhea, tenesmus or rectal pain. Malnutrition is common in these patients[44].

Manifestations of acute gastrointestinal toxicity depend on the following: volume of the intestine that is involved in the 95% therapeutic isodose, height of the dose, doses that are registered at risk organs during brachytherapy (rectum, sigma, bladder), planning method (2D vs 3D), extended fields application, and treatment duration[46,47]. Increased frequency of the small intestine toxicity may be attributed to previous surgical, or laparoscopic interventions, adhesions, unsuccessful reperitonealization, vascular diseases, diabetes, pelvic inflammatory disease and age[48,49]. Prior surgical intervention in the abdomen or pelvis increases the risk of small bowel obstruction in patients who have received a dose of over 50 Gy[50]. Use of the IMRT technique affects a smaller volume of the small intestine compared to 3D conformal radiation therapy, and also causes less damage to the rectum[43]. Larger volume of the intestine is a risk factor for the

occurrence of grade 2 toxicity at the small intestine and severe diarrhea in patients suffering from gynecological cancer who had surgery in the abdomen[51].

Gastrointestinal toxicity in women is more frequent compared to men undergoing pelvic irradiation due to anatomical differences. Since entrance into the small pelvis is wider in women, larger volume of the intestine is irradiated[52]. The occurrence of high grade acute toxicity doubles the risk of late toxicity. The mechanism of connection between these factors is not fully understood, but it was noted in many studies. Possible explanation of this mechanism is the depletion of mucous stem cells that prevents cell renewal[48]. Risk factors for the occurrence of proctitis grade 2 or higher are younger age and higher dose received on the rectum[52]. Patients with cervical cancer have in 12 to 19% of cases a total cumulative rectal toxicity grade of over 2[50]. Unlike the male pelvis, which is characterized by a tight space between the prostate and the rectum (rectal faction, Denonville fascia), the female pelvis is characterized by a large space with a lot of free tissue in the rectovaginal area. The second anatomical difference is extent of the *cul de sac* extension along the vaginal and uterine posterior wall, that is variable[53]. Marnitz et al. confirmed that, during transcutaneous radiotherapy, hydrogel administration reduces the dose received by the anterior rectum wall by 50% and significantly reduces the risk of acute radiation toxicity[53].

The occurrence of acute radiation toxicity, especially gastrointestinal toxicity, can be contributed to the factors related to personal characteristics of the patient, age, race, genetics, clinical risk factors, general condition, lifestyle, smoking, application of other treatment forms, cardiovascular, renal, genitourinary, gastrointestinal or metabolic diseases [25,37,39,40,41,42,51]. Smoking is, however, an independent risk factor for late radiation toxicity occurrence in the small intestine[54]. It has been observed that toxicity is more common in socially maladjusted women, with poor nutritional status, with chronic diseases and insufficient medical supervision during treatment[55]. Furthermore, increased frequency of acute and chronic toxicity can be attributed to previous inflammatory disease of the pelvis, blood vessels, diabetes, atherosclerosis, collagenosis, or inflammatory bowel disease[56].

Genitourinary toxicity

The incidence of genitourinary toxicity in patients with cervical cancer treated by CCRT ranges from 17 to 40%[56]. Severe acute genitourinary toxicity can be found in 2 to 5% of cases and is 6 times more common when brachytherapy is applied[50]. Symptoms are the most commonly reported three weeks from the beginning of transcutaneous radiotherapy, with a peak in the fifth week, which coincides with the introduction of brachytherapy[55]. The risk factors for acute genitourinary toxicity associated with the treatment are: cumulative radiation dose, radiation volume, and modality of radiotherapy. The use of anticoagulant therapy and previous surgery can also contribute to toxicity in patients with cervical cancer[56]. Use of adjuvant radiotherapy causes more frequent bladder dysfunction, hydronephrosis, stress incontinence, and radiation cystitis[25,56]. Smoking is associated with fistula appearance in patients with genitourinary toxicity[56]. However, the use of CCRT does not increase rate of late genitourinary toxicity[46]. It has been reported that the incidence of urinary infections is significantly higher in patients with anemia treated with CCRT[57].

In a study conducted by Ferrigno and associates, in patients with pelvic tumors treated by IMRT and 3D conformal techniques, it was shown that the use of IMRT did not affect the frequency of acute genitourinary toxicity[44]. It is therefore important to examine which potential factors, in addition to those associated with radiotherapy techniques, affect the occurrence of this form of toxicity.

An increased incidence of acute gynecological radiation toxicity in young and obese patients with cancer of genital organs was noted, while urinary and gastrointestinal toxicity were not associated with obesity[58]. On the contrary, Smits et al. claim that obesity and a body mass index over 30 kg/m^2 are not associated with the larger of radiation toxicity[59].

Hematologic toxicity

During pelvic irradiation, the radiation dose affects the bone marrow. This leads to hematopoietic stem cell depletion, and erythrocyte, leukocyte and thrombocyte precursors are affected[60]. The hematologic toxicity is often a limiting factor for the application of CCRT[61]. Radiotherapy leads to reduction of the red bone marrow, which is responsible for hematopoiesis, while at the same time the yellow bone marrow becomes more dominant[61]. A study showed that

the frequency of hematologic toxicity, after administration of combined chemotherapy with cisplatin, ranges from 20 to 25%. Another study in India showed, on the contrary, that almost all patients (97.5%) had anemia under this treatment regimen. The same study showed that 50% of patients with leukopenia had diabetes. The occurrence of hematologic toxicity is not related to other forms of toxicity, and the authors believe that this is because the cause is different[57]. Toxicity is increased by expanded radiation fields, due to larger volume of the bone marrow irradiated[61]. It is the most often manifested in the form of red cells depletion and neutropenia of grade 3 or 4[57]. Patients with anemia and malnutrition have more side effects due to the treatment with combined chemoradiotherapy. With new radiotherapy methods such as IMRT, the hematologic toxicity rate is reduced and tolerance of chemotherapy improved[60]. Anemia and hypoxia in the course of radiation treatment affect both the tumor itself and the healthy tissue, reducing tolerance to radiation[57].

Frequency of neutropenia is higher when radiotherapy is combined with cisplatin[57]. During the CCRT, elderly patients have an increased incidence of hematologic toxicity, more frequent treatment breaks and complications, and also more high-grade complications[36,42]. However, Chakraborty and associates showed that elderly patients, treated with combined chemotherapy and Rapid Arc IMRT (Intensity-Modulated Radiation Therapy, IMRT) technique do not have a higher acute radiation toxicity rate than the younger ones[63].

Dermatologic toxicity

Risk factors for the occurrence of acute dermatologic toxicity are blood vessel diseases, smoking and poor nutritional status. Reactions are more frequent in patients with a larger body mass index. Grades 1 and 2 toxicities are encountered in about 10 to 50% of patients with gynecologic malignancies, while severe skin reactions in this region are rare. The reactions occur during the first two weeks of radiation, and they withdraw in 3 to 4 weeks after completition of radiation[50].

PREVENTIVE MEASURES

Heterogeneous symptoms and signs of acute radiation toxicity are usually consequence of neglecting the symptom appearance and the absence of a patient's reporting them to radiotherapist, usually until the moment when the high grade toxicity develops. Considering that the emergence of serious acute radiation toxicity is one of the most important drivers of chronic toxicity development, which often requires extensive interventions and expensive, long-term treatment, the early recognition of risk factors for the occurrence of acute radiation toxicity would enable timely and accurate identification and observation of patients at increased risk. The symptoms of acute radiation toxicity affect the quality of life of patients, survival rates are reduced and hospitalization is prolonged. The occurrence of severe forms of radiation toxicity following radiotherapy, such as intestinal obstruction, fistula formation and severe damage to the skin or mucous membranes, often requires surgical treatment.

A strategy for reducing gastrointestinal toxicity involves use of multiple radiation fields, to ensure the homogeneity and precision of the delivered dose. It is advised that radiotherapy courses are performed in patient lying in pronation, with a full bladder in order to displace the small intestine from the pelvis. Use of the modern radiation techniques significantly reduces acute and chronic radiation toxicity[50]. Moreover, with this form of radiotherapy planning it is possible to include all the surrounding lymph nodes and overcome anatomical differences, such as uterine retroversion[65]. For EBRT radiotherapy and brachytherapy planning it is ideal to use magnetic resonance imaging (MRI) because the anatomical levels are better defined, radiotherapy fields are determined more efficiently, adverse effects are reduced, and treatment tolerance is improved[1]. Planning of the IMRT technique, compared to 3D conformal or conventional radiotherapy, requires more time, knowledge and new technologies, but reduces toxicity to the surrounding tissues[44]. Adaptive Image Guided Radiation (IGRT) directs radiotherapy using the image coordinates of the real radiation treatment plan and includes time as a factor, during radiation, as the fourth dimension. By this method it is possible to reduce the dose received by the surrounding healthy tissues, while the target volume and regional lymph nodes receive a higher dose[7,50,64,65]. IMRT and Stereotactic Beam Radiation Therapy (SBRT) are highly sophisticated methods that, with extreme precision, destroy the cells of the primary tumor or metastases with minimum exposure of the surrounding healthy tissue[66].

Special attention should be paid to patients who undergo brachytherapy in terms of special preparation and care of the irradiated region.

Also, the appropriate diet should be followed. Ultrasound Guided Conformal Brachytherapy use provides good visualization of organs and 3D conformal planning in real time. In contrast to MR, it is a cheaper and more widely available diagnostic tool and has its place in smaller centers[67].

It has been shown that hydrogel application provides good separation between the rectum and the extraperitoneal cervical and upper parts of the vagina, and that the peritoneal part is fixed and there is no distention. This fact is also important in EBRT radiotherapy and brachytherapy[53]. Basu and associates placed hydroxypropyl methylcellulose gel between the vagina and rectum in a patient with cervical cancer, with no early or late irradiation complications[68]. However, these method needs to be improved.

Some studies have shown that analysis of molecular biomarkers can predict acute intestinal irradiation toxicity in these patients. It has been shown that there is a down regulation of the OPN cytokine fragment, thyroid hormone-binding protein, hepcidin (the acute phase protein), and the C1-INH fragment (an inhibitor of the complement system early activation) and that there is an upstream regulation of the fragment of the neurosecretory protein vascular growth factor in a patient with acute radiation toxicity[69].

The goal of all radiogenomic studies was to develop a strategy that would, with high sensitivity and specificity, identify patients who have an increased risk of the occurrence of acute and chronic radiation toxicity[37]. Analysis of the human genome isolated a single nucleotide polymorphism and identified aspecific chromosome region 11q14.3 that may be associated with the occurrence of acute gastrointestinal toxicity in patients undergoing prostate radiotherapy[37,50].

CONCLUSIONS

Modern concept of locally advanced cervical cancer treatment is based on concurrent chemoradiotherapy. However, during this kind of therapy, various manifestions of acute radiation toxicity can occur, i.e. gastrointestinal, hematologic, genitourinary, dermatologic or other forms. Although the most of the potential risk factors for the development of acute radiation toxicity are primarily associated with certain therapeutic modalities, individual patient characteristics must also be taken into account in this regard. Known potential risk factors and early detection of risk factors for the acute radiation toxicity may contribute to better individualization of the treatment. New clinical studies are needed, based on analysis of the importance of known, but also many other, insufficiently defined potential risk factors for the acute radiation toxicity in patients with local advanced cervical cancer.

ЛИТЕРАТУРА

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018. PP
2. Wang JQ, Wang T, Shi F, Yang YY, Su J, Chai YL, Liu Z. A Randomized Controlled Trial Comparing Clinical Outcomes and Toxicity of Lobaplatin- Versus Cisplatin-Based Concurrent Chemotherapy Plus Radiotherapy and High-Dose-Rate Brachytherapy for FIGO Stage II and III Cervical Cancer. Asian Pac J Cancer Prev 2015;16(14): 5957-61.
3. Zhang Y, Yang Z, Zhou Y, Pan J, Liu Y. Efficacy of concurrent single-agent chemotherapy using radiotherapy in patients with cervical cancer: a meta-analysis. Int J ClinExp Med 2015;8(6): 8661-73.
4. Fu ZZ, Li K, Peng Y, Zheng Y, Cao LY, Zhang YJ et al. Efficacy and toxicity of different concurrent chemoradiotherapy regimens in the treatment of advanced cervical cancer: A network meta-analysis. Medicine (Baltimore) 2017;96(2): e5853.
5. Depuydt CE, Beert J, Bosmans E, Salembier G. Human Papillomavirus (HPV) virion induced cancer and subfertility, two sides of the same coin. Facts Views Vis Obgyn 2016;8(4): 211-2.
6. Meng XY, Liao Y, Liu XP, Li S, Shi MJ, Zeng XT. Concurrent cisplatin-based chemoradiotherapy versus exclusive radiotherapy in high-risk cervical cancer: a meta-analysis. Onco Targets Ther 2016;9:1875-88.
7. Krusun S, Pesee M, Supakalin N, Thamronganantasakul K, Supaadirek C,Padoongcharoen P. Treatment interruption during concurrent chemoradiotherapy of uterine cervical cancer; analysis of factors and outcomes. Asian Pac J Cancer Prev 2014;15(14): 5653-7.
8. PP Royal-Preyra B, Bowes D, Bahl G, Joseph P, Nolan M, Ymeri H et al. Long-term Outcomes and Late Effects of Definitive Chemoradiotherapy in Patients with Cervical Cancer in Nova Scotia. Cureus 2015;7(10): e343.
9. Liu Y, Yu J, Qian L, Zhang H, Ma J. Extended field intensity-modulatedradiotherapy plus concurrent nedaplatin treatment in cervical cancer. Oncol Lett 2016;11(5):3421-7.PP
10. FIGO Committee on Gynecologic Oncology. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. International Journal of Gynecology and Obstetrics 2009;105: 103–4.
11. Li Z, Yang S, Liu L, Han S. A comparison of concurrent chemoradiotherapy and radiotherapyin Chinese patients with locally advanced cervical carcinoma: a multi-center study. Radiat Oncol 2014;9: 212.
12. Kalaghchi B, Abdi R, Amouzegar-Hashemi F, Esmati E, Alikhasi A. Concurrent Chemoradiation with

Weekly Paclitaxel and Cisplatin for Locally Advanced Cervical Cancer. Asian Pac J Cancer Prev 2016;17(S3):287-91.

13. Mazeron R, Gilmore J, Dumas I, Champoudry J, Goulart J, Vanneste B et al. Adaptive 3D image-guided brachytherapy: a strong argument in the debate on systematic radical hysterectomy for locally advanced cervical cancer. Oncologist 2013;18(4): 415-22.
14. Reducing Uncertainties About the Effects of Chemoradiotherapy for Cervical Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 18 Randomized Trials Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration J Clin Oncol 2008; 26(35): 5802–12.
15. Yoon HI, Cha J, Keum KC, Lee HY, Nam EJ, Kim SW et al. Treatment outcomes of extended-field radiation therapy and the effect of concurrent chemotherapy on uterine cervical cancer with para-aortic lymph node metastasis. Radiat Oncol 2015; 10:18.
16. Chen CC, Wang L, Lin JC, Jan JS. The prognostic factors for locally advanced cervical cancer patients treated by intensity-modulated radiation therapy with concurrent chemotherapy. J Formos Med Assoc 2015;114(3): 231-7.
17. Kirwan JM, Symonds P, Green JA, Tierney J, Collingwood M, Williams CJ. A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer. Radiother Oncol 2003;68(3): 217-26.
18. Dutta S, Nguyen NP, Vock J, Kerr C, Godinez J, Bose S et al. International Geriatric Radiotherapy Group. Image-guided radiotherapy and -brachytherapy for cervical cancer. Front Oncol 2015;5:64.
19. Kaidar-Person O, Abdah-Bortnyak R, Amit A, Nevelsky A, Berniger A, Bar-Deroma R et al. Tolerance of the vaginal vault to high-dose rate brachytherapy and concomitant chemo-pelvic irradiation: Long-term perspective. Rep Pract Oncol Radiother 2013;19(1):56-61.
20. Petit A, Floquet A, Lasbareilles O, Stoeckle E, Chemin A, Kind M et al. Pulsed-dose-rate brachytherapy for uterine cervix carcinoma: 10 years of experience with 226 patients at a single institution. Brachytherapy 2013;12(6): 542-9.
21. Viswanathan AN, Beriwal S, De Los Santos JF, Demanes DJ, Gaffney D, Hansen J et al; American Brachytherapy Society. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: high-dose-rate brachytherapy. Brachytherapy 2012;11(1):47-52.
22. Haie-Meder C, Pötter R, Van Limbergen E, Briot E, De Brabandere M, Dimopoulos J et al; Gynaecological (GYN) GEC-ESTRO Working Group. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol 2005;74(3):235-45.
23. Diaz J, Yu D, Micaily B, Ferriss JS, Hernandez E. Radiation therapy with concurrent chemotherapy for locally advanced cervical carcinoma: outcome analysis with emphasis on the impact of treatment duration on outcome. Obstet Gynecol Int 2014;2014:214351.
24. Pathy S, Kumar L, Pandey RM, Upadhyay A, Roy S, Dadhwal V et al. Impact of Treatment Time on Chemoradiotherapy in Locally Advanced Cervical Carcinoma. Asian Pac J Cancer Prev 2015;16(12):5075-9.
25. Roszak A, Wareńczak-Florczak Z, Bratos K, Milecki P. Incidence of radiation toxicity in cervical cancer and endometrial cancer patients treated with radiotherapy alone versus adjuvant radiotherapy. Rep Pract Oncol Radiother 2012;17(6): 332-8.
26. Halperin E, Wazer D, Perez C, Brady L. Perez and Brady's Principles and Practice of radiation oncology. Sixth edition. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins 2013.
27. PJ Zhou J, Chen QH, Wu SG, He ZY, Sun JY, Li FY et al. Lymph node ratio may predict the benefit of postoperative radiotherapy in node-positive cervical cancer. Oncotarget 2016;7(20): 29420-8.
28. Cihoric N, Tapia C, Krüger K, Aebersold DM, Klaeser B, Lössl K. IMRT with FDG-PETCT based simultaneous integrated boost for treatment of nodal positive cervical cancer. Radiat Oncol 2014;9:83.
29. Liberman D, Mehus B, Elliott SP. Urinary adverse effects of pelvic radiotherapy. Transl Androl Urol 2014;3(2): 186-95.
30. Hernández-Moreno A, Vidal-Casariego A, Calleja-Fernández A, Kyriakos G, Villar-Taibo R, Urioste-Fondo A et al. Chronic enteritis in patients undergoing pelvic radiotherapy: prevalence, risk faktors and associated complications. Nutr Hosp 2015; 32(5): 2178-83.
31. Qin Q, Huang Q, Zhong Q, Fan X, Chen D, Wang L. Clinical risk factors for late intestinal toxicity after radiotherapy: A systematic review protocol. Syst Rev 2013;2:39.
32. Varghese SS, Ram TS, Pavamani SP, Thomas EM, Jeyaseelan V, Viswanathan PN. Concurrent chemo-irradiation with weekly cisplatin and paclitaxel in the treatment of locally advanced squamous cell carcinoma of cervix: a phase II study. J Cancer Res Ther 2014;10(2): 330-6.
33. Muecke R, Micke O, Schomburg L, Buentzel J, Glatzel M, Baaske D et al. Impact of treatment planning target volumen (PTV) size on radiation induced diarrhoea following selenium supplementation in gynecologic radiation oncology--a subgroup analysis of a multicenter, phase III trial. Radiat Oncol 2013; 8:72.
34. PJ 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): 1341-6.
35. PJ National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Revised Version 4.03 June, 2010.
36. Chinnachamy AN, Chopra S, Krishnatry R, Kannan S, Thomas B, Mahantshetty U et al. Evaluation of interobserver and interscale agreement in assessing late bowel toxicity after pelvic radiation in patients with carcinoma of the cervix. Jpn J Clin Oncol 2013;43(5): 508-14.
37. Kerns SL, Kundu S, Oh JH, Singhal SK, Janelsins M, Travis LB et al. The Prediction of Radiotherapy Toxicity Using Single Nucleotide Polymorphism-Based Models: A Step Toward Prevention. Semin Radiat Oncol 2015;25(4): 281-91.

38. Kuku S, Fragkos C, Mc Cormack M, Forbes A. Radiation-induced bowel injury: the impact of radiotherapy on survivorship after treatment for gynaecological cancers. Br J Cancer 2013;109(6): 1504-12.
39. Bentzen SM. Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. Nat Rev Cancer 2006;6: 702–13.
40. Huscher A, Bignardi M, Magri E, Vitali E, Pasinetti N, Costa L et al. Determinants of small bowel toxicity in postoperative pelvic irradiation for gynaecological malignancies. Anticancer Res 2009;29(11): 4821-6.
41. Beskow C, Agren-Cronqvist AK, Lewensohn R, Toma-Dasu I. Biological effective dose evaluation and assessment of rectal and bladder complications for cervical cancer treated with radiotherapy and surgery. J Contemp Brachytherapy 2012;4(4): 205-12.
42. Tharavichtikul E, Meungwong P, Chitapanarux T, Chakrabandhu S, Klunklin P, Onchan W et al. The association of rectal equivalent dose in 2 Gy fractions (EQD2) to late rectal toxicity in locally advanced cervical cancer patients who were evaluated by rectosigmoidoscopy in Faculty of Medicine, Chiang Mai University. Radiat Oncol J 2014;32(2): 57-62.
43. Julie DA, Oh JH, Apte AP, Deasy JO, Tom A, Wu AJ et al. Predictors of acute toxicities during definitive chemoradiation using intensity-modulated radiotherapy for anal squamous cell carcinoma. Acta Oncol 2016;55(2): 208-16.
44. Ferrigno R, Santos A, Martins LC, Weltman E, Chen MJ, Sakuraba R et al. Comparison of conformal and intensity modulated radiation therapy techniques for treatment of pelvic tumors. Analysis of acute toxicity. Radiat Oncol 2010;5:117.
45. Xu B, Guo Y, Chen Y, Lu H, Tang T, Yue Z et al. Is the irradiated small bowel volume still a predictor for acute lower gastrointestinal toxicity during preoperative concurrent chemo-radiotherapy for rectal cancer when using intensity-modulated radiation therapy? Radiat Oncol 2015;10:257.
46. Marnitz S, Wlodarczyk W, Neumann O, Koehler C, Weihrauch M, Budach V. Which technique for radiation is most beneficial for patients with locally advanced cervical cancer? Intensity modulated proton therapy versus intensity modulated photon treatment, helical tomotherapy and volumetric arc therapy for primary radiation - an intraindividual comparison. Radiat Oncol 2015;10:91.
47. Chopra S, Dora T, Chinnachamy AN, Thomas B, Kannan S, Engineer R et al. Predictors of grade 3 or higher late bowel toxicity in patients undergoing pelvic radiation for cervical cancer: results from a prospective study. Int J Radiat Oncol Biol Phys 2014;88(3):630-5.
48. Jereczek-Fossa BA, Badzio A, Jassem J. Factors determining acute normal tissue reactions during postoperative radiotherapy in endometrial cancer: analysis of 317 consecutive cases. Radiother Oncol. 2003;68(1):33-9.
49. Hafiz A, Abbasi AN, Ali N, Khan KA, Qureshi BM. Frequency and Severity of Acute Toxicity of Pelvic Radiotherapy for Gynecological Cancer. J Coll Physicians Surg Pak 2015;25(11):802-6.
50. Chen SW, Liang JA, Hung YC, Yeh LS, Chang WC, Lin WC et al. Late toxicities in concurrent chemoradiotherapy using high-dose-rate intracavitary brachytherapy plus weekly cisplatin for locally advanced cervical cancer: a historical cohort comparison against two previous different treatment schemes. Eur J Gynaecol Oncol 2010;31(5):504-9.
51. Huang EY, Sung CC, Ko SF, Wang CJ, Yang KD. The different volume effects of small-bowel toxicity during pelvic irradiation between gynecologic patients with and without abdominal surgery: a prospective study with computed tomography-based dosimetry. Int J Radiat Oncol Biol Phys 2007;69(3):732-9.
52. Yang TJ, Oh JH, Son CH, Apte A, Deasy JO, Wu A et al. Predictors of acute gastrointestinal toxicity during pelvic chemoradiotherapy in patients with rectal cancer. Gastrointest Cancer Res 2013;6(5-6):129-36.
53. Noyes WR, Hosford CC, Schultz SE. Human collagen injections to reduce rectal dose during radiotherapy. Int J Radiat Oncol Biol Phys 2012;82(5):1918-22.
54. Chopra S, Krishnatry R, Dora T, Kannan S, Thomas B, Sonawone S et al. Predictors of late bowel toxicity using three different methods of contouring in patients undergoing post-operative radiation for cervical cancer. The Br J Radiol 2015;88(1055):20150054.
55. Kumaran A, Guruvare S, Sharan K, Rai L, Hebbar S. Chemoradiation related acute morbidity in carcinoma cervix and correlation with hematologic toxicity: a South Indian prospective study. Asian Pac J Cancer Prev 2014;15(11): 4483-6.
56. Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet 1997;350(9077): 535-40.
57. Gangopadhyay A, Das J, Nath P, Biswas J. Haemoglobin levels may predict toxicities in patients on pelvic chemoradiation for carcinoma of the cervix-experience of a regional cancer centre. E cancer medical science 2014;8:431.
58. PJ Dandapani SV, Zhang Y, Jennelle R, Lin YG. Radiation-Associated Toxicities in Obese Women with Endometrial Cancer: More Than Just BMI? Scientific World Journal 2015;2015:483208.
59. Ha Smits A, Mc Grane J, Lopes A, Kent E, Bekkers R, Massuger L et al. Radiation-related toxicities and outcomes in endometrial cancer: are obese women at a disadvantage? Int J Clin Oncol 2017.
60. Klopp AH, Moughan J, Portelance L, Miller BE, Salehpour MR, Hildebrandt E et al. Hematologic toxicity in RTOG 0418: a phase 2 study of postoperative IMRT for gynecologic cancer. Int J Radiat Oncol Biol Phys. 2013;86(1): 83-90.
61. Carmona R, Pritz J, Bydder M, Gulaya S, Zhu H, Williamson CW et al. Fat composition changes in bone marrow during chemotherapy and radiation therapy. Int J Radiat Oncol Biol Phys 2014;90(1):155-63.
62. Singh D, Latha H, Kapoor A, Mayilvaganan A, Jakhar SL, Kumar HS. Necessity of CT-MRI based treatment planning for cervical tumors with retroverted uterus: A case report with review of literature. J Cancer Res Ther 2015;11(3):662.
63. Chakraborty S, Geetha M, Dessai S, Patil VM. How well do elderly patients with cervical cancer tolerate definitive radiochemotherapy using RapidArc? Results from an institutional audit comparing elderly versus younger patients. E cancer medical science 2014;8: 484.
64. Tharavichitkul E, Wanwilairat S, Chakrabandhu S, Klunklin P, Onchan W, Tippanya D et al. Image-gui-

ded brachytherapy (IGBT) combined with whole pelvic intensity-modulated radiotherapy (WP-IMRT) for locally advanced cervical cancer: a prospective study from Chiang Mai University Hospital, Thailand. J Contemp Brachytherapy 2013;5(1): 10-6.

65. Sagae S, Monk BJ, Pujade-Lauraine E, Gaffney DK, Narayan K, Ryu SY et al; Gynecologic Cancer InterGroup Cervix Cancer brainstorming day. Advances and Concepts in Cervical Cancer Trials: A Road Map for the Future. Int J Gynecol Cancer 2016;26(1): 199-207.
66. Orecchia R, Surgo A, Muto M, Ferrari A, Piperno G, Gerardi MA et al. VERO® radiotherapy for low burden cancer: 789 patients with 957 lesions. E cancer medical science 2016;10: 677.
67. Narayan K, van Dyk S, Bernshaw D, Khaw P, Mileshkin L, Kondalsamy-Chennakesavan S. Ultrasound guided conformal brachytherapy of cervix cancer: survival, patterns of failure, and late complications. J Gynecol Oncol 2014;25(3): 206-13.
68. Basu S, Manir KS, Basu A, Ghosh K. Rectal separation using hydroxypropyl methylcellulose in intracavitary brachytherapy of cervical cancer: an innovative approach. J Contemp Brachytherapy 2016;8(5): 399-403.
69. Chai Y, Wang J, Gao Y, Wang T, Shi F, Su J et al.Identification of biomarkers for radiation-induced acute intestinal symptoms (RIAISs) in cervical cancer patients by serum protein profiling. J Radiat Res 2015;56(1): 134-40.