CMJ Original Research September 2019, Volume: 41, Number: 3
Cumhuriyet Tıp Dergisi (Cumhuriyet Medical Journal) 599-604
http://dx.doi.org/10.7197/cmj.vi.622642

Long-term results of 3-D brachytherapy treatment in locally advanced cervical cancer

Lokal ileri servis kanserinde 3D brakiterapi tedavisinin uzun dönem sonuçları

Özlem Yetmen Doğan, Makbule Eren

Sağlık Bilimleri University, Kartal Dr. Lütfi Kırdar Training and Research Hospital, Department of Radiation Oncology
Corresponding author: Özlem Yetmen Doğan, MD, Sağlık Bilimleri University, Kartal Dr. Lütfi Kırdar Training and Research Hospital, Department of Radiation Oncology
E-mail: dryetmen@gmail.com
Received/Accepted: July 20, 2019 /September 26, 2019
Conflict of interest: There is not a conflict of interest.

SUMMARY

In many advanced studies, image-guided 3D brachytherapy (BT) treatment has been shown to improve survival and reduce treatment-related toxicity in locally advanced cervical cancer. In this study, long-term treatment results, risky organ doses, and toxicity results of patients who were admitted to our clinic with the diagnosis of cervical cancer and treated with 3D brachytherapy were examined. Between 2012 and 2015, 152 inoperable cervical cancers were admitted, and long-term (> 12 months) follow-up of our clinic107 cases of inoperable cervical cancer was included in the study. After pelvic radiotherapy, pelvic MRI was performed, and target volumes were determined on CT. Volumes defined by the GEC-ESTRO guideline were, Gross tumor volume (GTV); residual tumor volume after external RT, High-risk clinical tumor volume (HRCTV); entire cervix and residual lesion, Intermediate-risk clinical tumor volume (IRCTV) low-risk volume and rectum, sigmoid and bladder contouring as risky organs, respectively. 3D brachytherapy treatment was performed with the microselectron device of 192 high-dose-rate (HDR) Ir 192 source.

The median age was 53 years, and the median follow-up was 45 months. All patients were diagnosed by biopsy, and 81.9% of these patients were diagnosed as squamous cell carcinoma. According to the stages;IB1 was 2 (2%), II was 65 (61%), III was 31 (29%), and IV was 9 (8%). 96% of the patients received cisplatin-based chemotherapy with pelvic 3 D RT. When 3D RT doses of all patients were examined; Median HRCTV was calculated as 90% 6 Gy, EQD2 value 84.7 Gy, IRCTV 95% 3.03 Gy. When we look at risky organ doses; The median rectum 2cc 2.4Gy, EQD2 58.4Gy value, median bladder 2cc 3.52Gy, EQD2 value was 68.8 Gy, median sigmoid 2cc 2.60 Gy, EQD2 value was found to be 60.3 Gy. During the follow-up period, 4 patients had a local recurrence, 11 patients had both local and distant metastasis, and 21 patients had only distant metastasis. The overall survival rate of 3 and 5 years was 78.1% and 72.2%. The 3 and 5-year local control rates were 87.4% and 77.3%, respectively. The survival rates of 3 and 5 years without distant metastasis were 66.5% and 61.2%. Rectovaginal fistula developed in 5 patients as late side effects and tumor progression was found in three of these patients.

In the treatment of locally advanced cervical cancer 3D BRT, the volumes defined by the GEC-ESTRO guidance are individual. Thanks to the development of imaging techniques during the treatment of these volumes, the survival rates have increased compared to the previous series, and a shallow rate of GIS and GUS side effects are observed.

Keywords: Cervical cancer, 3D brachytherapy, radiotherapy

Özlem Yetmen Doğan
Makbule Eren

ORCID IDs of the authors:
Ö.Y.D. 0000-0002-2733-0427
M.E. 0000-0002-7105-7165

ÖZET

Birçok çalışma, serviks kanserinde görüntü kılavuzluğunda 3D brakiterapi (BT) tedavisinin sağkalımı arttırdığı ve tedaviyle ilişkili toksisiteyi azalttığı gösterilmiştir. Bu çalışmada, kliniğimize serviks kanseri tanısıyla başvuran ve 3D brakiterapi ile tedavi edilen hastaların uzun dönem tedavi sonuçları, riskli organ dozları ve tedavi yan etkileri incelenmiştir.

2012-2015 yılları arasında 152 inopere servikal kanseri başvurmuştur, bu hastalardan kliniğimizde uzun süreli (> 12 ay) takibi olan 107 inopere servikal kanser vakası çalışmaya dahil edildi. Pelvik radyoterapiden sonra pelvik MRG yapıldı ve planlama BT'de hedef hacimleri belirlendi. GEC-ESTRO kılavuzunda tanımlanan hacimler, tüm tümör hacmi (GTV); RT sonrası rezidüel tümör hacmi, Yüksek riskli klinik tümör hacmi (HRCTV); tüm serviks ve rezidüel lezyon, Orta riskli klinik tümör hacmi (IRCTV) düşük riskli hacim ve rektum, sigmoid ve mesane, riskli organlar olarak kontürlendi. 3D brakiterapi tedavisi yüksek doz hızlı (HDR) Ir 192 kaynaklı mikroselektron cihazı ile tedavisi yapıldı.

Ortanca yaş 53, ortanca takip süresi 45 aydı. Tüm hastalara biyopsi ile tanısı kondu ve bu hastaların % 81.9'una skuamöz hücreli karsinom idi. Evrelere göre IB1 2 (% 2), II 65 (% 61), III 31 (% 29) ve IV 9 (% 8) idi. Hastaların% 96'sı pelvik 3D RT ile sisplatin bazlı kemoterapi aldı. Tüm hastaların 3D RT dozları incelendiğinde; Ortanca HRCTV% 90 6Gy, EQD2 değeri 84.7 Gy, IRCTV% 95 3.03 Gy olarak hesaplandı. Riskli organ dozlarına baktığımızda; Ortanca rektum 2cc 2.4Gy, EQD2 58.4Gy değeri, ortanca mesane 2cc 3.52Gy, EQD2 değeri 68.8 Gy, ortanca sigmoid 2cc 2.60 Gy, EQD2 değeri 60.3 Gy olarak bulundu. Takip süresince 4 hastada lokal nüks, 11 hastada hem lokal hem de uzak metastaz, 21 hastada sadece uzak metastaz mevcuttu. 3 ve 5 yıllık genel sağkalım oranı % 78.1 ve % 72.2 idi. Üç ve beş yıllık lokal kontrol oranları sırasıyla % 87.4 ve % 77.3 idi. Uzak metastazsız 3 ve 5 yıl sağkalım oranları % 66.5 ve % 61.2 idi. Beş hastada rektovajinal fistül geç yan etki olarak gelişti ve bu hastalardan üçünde tümör büyümesi nedeniyle geliştiği tespit edildi.

Lokal olarak ilerlemiş olan serviks kanseri 3D brakiterapi tedavisinde, GEC-ESTRO rehberliğinde tanımlanan tümör hacimleri bireyseldir. Bu tümör hacimlerinin belirlenmesinde görüntüleme tekniklerinin geliştirilmesi önemli bir yer tutmaktadır, bu gelişmeler sayesinde, sağkalım oranları önceki serilere kıyasla artmış olup çok az bir oranda GIS ve GUS yan etkileri gözlenmiştir.

Anahtarsözcükler: Serviks kanseri, 3D brakiterapi, radyoterapi

INTRODUCTION

The combination of concurrent radio-chemotherapy (RCT) followed by image-guided adaptive brachytherapy (IGABT) is a common treatment choice for locally advanced cervical cancer [1]. Several randomized trials demonstrated that RCT improves local, distant tumor control and survival compared with RT alone [2].There has been a significant evolution in brachytherapy over the last two decades. Recent external beam radiotherapy (EBRT) combination with IGABT studies [3-5] has shown promising results with high tumor local control rate. However, radiation-induced toxicity on the organ at risks (OARs),such as rectum, bladder, and vagina is still a significant problem. Serious side effects such as bowel obstruction can occur years after treatment and patients' quality of life effect negatively. Because of these effects GEC-ESTRO (Group Europé en de Curieth é rapie and the European Society for Radiotherapy and Oncology) made recommendation guidelines for target volume definition, dose planning reporting, and applicator reconstruction[5,6,7,8] . The correlation between OARs' and radiation dose parameters was analyzed in EMBRACE study [9]. Particular, the D0.1cm3,D1cc, and D2cm3 of rectum, bladder and sigmoid were used to establish dose-toxicity relationship. The studies found a clinical benefit of IGBRT 3 year local control (LC), cancer-specific survival (CSS) and overall survival (OS) rates of 91– 95%, 74– 87% and 65– 79% with reduced rate of treatment-related morbidity [10,11,12].

The GYN GEC-ESTRO working group described target volume delineation and also 3D image-based planning and 3D dose-volume parameters for brachytherapy of carcinoma cervix [6,7]. The magnetic resonance (MR) images were useful for specific gross disease and the OAR. The advantage of this method follows volumetric based planning, thus moving away from point A. Many centers are increasingly changing over to3D IGABT from 2D X-ray based plan. It has been shown that high-risk areas (cervix and residual disease at time of BT) had to get more than 87 Gy to attain local control rate of more than %90. This treatment method can be achieved with IGABT without any increase in radiation-induced morbidity [13,14]

Late GI and GUS toxicities have been the major problem in patients of cervical cancer treated with RCT and BT. The GEC-ESTRO group has described 3D image-based contouring of OARs and dose-volume histogram (DVH) parameters based on the contoured volume. They have recommended a minimum dose for the most irradiated tissue volume of 0.1 cm3 (D0.1cc), 1 cm3 (D1cc), and 2 cm3 (D2cc) for the OARs to be

reported [6,7,15,16]. Late rectal toxicity has been the primary concern in patients of cervical cancer. In the EMBRACE study they concluded that ıf the rectum got D2cc< 65 Gy, it has less frequent rectal morbidity [5].

In many radiation oncology departments, the CT simulator is very easy to reach. CT based BT as compared to MR-based BT is much feasible and practical because MR access is still difficult for most departments. The availability of CT contouring guidelines CT based IGABT has gained momentum.

Since 2012, we have followed 3D IGABT planning for carcinoma of the cervix as per the GEC-ESTRO guidelines. In this study, long-term treatment results, risky organ doses, and toxicity results of patients who were admitted to our clinic with the diagnosis of cervical cancer and treated with 3D brachytherapy were examined.

MATERIAL AND METHODS

Characteristics

Between 2012 and 2015, 152 consecutive patients with histopathologically proven cancer of the cervix were admitted at Department of Radiotherapy, Sağlık Bilimleri University, Kartal Dr. Lütfi Kırdar Training, and Research Hospital, and long-term (> 12 months) follow-up of our clinic107 cases was included in the study. Patients were staged as per the International Federation of Obstetrics and Gynecology (FIGO) staging system. The staging was done by clinical examination without anesthesia. Patients also had an abdomen MR, Positron emulsion tomography-CT, complete blood counts, and renal function tests before the start of the treatment. The gross disease extent before treatment was documented.

Radiotherapy Details

External Radiotherapy

All patients received external radiotherapy to the pelvis, to a dose of 45-50.4Gy in 25-28fractions, given once a day for 5days in a week. Radio-chemotherapy regime received once a week cisplatin 40 mg/m2. Patients with enlarged paraaortic nodes received pelvic-paraaortic region with concurrent radio-chemotherapy. The CT simulation was done for all patients. During the simulation, a bladder protocol was followed wherein the patient was first asked to empty her bladder and then made to drink 500 ml of water. CT simulation was done 45 min later. The same protocol was followed during treatment. CT images were transferred to the contouring workstation (Varian Eclipse—Palo Alto, CA). Target volumes were delineated based on established contouring guidelines [26–28]. If paraaortic nodes were found to be enlarged, then the nodal volume was extended to include the lower paraaortic nodes up to the renal hilum. The planning target volume (PTV) was obtained by combining the primary clinical target volume, and the nodal volume and expanding the combined volume by 7 mm. This margin was achieved based on our own data of set-up errors. Patients were treated by 3D conformal radiotherapy, and in all cases 95% of the PTV received ≥95% of the prescribed dose. Brachytherapy was scheduled within completion of external radiotherapy for all patients

Brachytherapy

Before BT treatment, all patients received pelvic MRI for disease response for external RT. All patients underwent BT under general anesthesia, and the disease response was documented. A central tandem was inserted into the uterine cavity if the cervical os could be sounded and dilated. Two fractions of HDR brachytherapy were delivered during a week. All patients underwent CT simulation following the implant. The bladder was filled with 50 ml of diluted contrast for delineation. The bladder, rectum, and sigmoid colon were contoured as the OARs on 3-mm axial slices.

BT contouring was performed according to the GEC-ESTRO recommendations, and target volume delineations were ; gross tumor volume (GTV), High-risk clinical target volume (HR-CTV) and intermediate-risk clinical volume (IR-CTV) ,OARs delineations were ;bladder, rectum and sigmoid colon and bowel were contoured.

All patients received a dose of 6 Gy×5 fractions such that the HRCTV received a total dose of 30Gy. BT treatment was performed with high dose rate (HDR) and Ir 192 source with microselectron device.

Follow-Up

Patients were seen 1,5 month after completing the therapy to assess any acute reactions. Subsequent follow-up was done at 3 months for the 3 years, every 6 months up to 5 years and annually thereafter. During each follow-up, clinical history and speculum and bimanual pelvic examination were done. Pelvic MR and PET-CT were taken after the 6 months of completing the treatment, because of to evaluate the residual tumor. Radiotherapy toxicities were graded as the EORTC-RTOG late toxicity criteria.

RESULTS

One hundred seven patients were enrolled for final analysis with a median follow up of 45 months (range: 15-65 months) from the completion of brachytherapy treatment. The median age was 53 (range :26-86 years).The FIGO stage distribution was as follows: stage IB was 2 (2%); stage IIB was 65 (61%);stage III was 31 (29%), and stage IVB was 9 (8%). One hundred-three 96% of the patients received cisplatin-based chemotherapy with pelvic 3 D RT. When 3D RT doses of all patients were examined; Median HRCTV was calculated as 90% 6 Gy, EQD2 value 84.7 Gy, IRCTV 95% 3.03 Gy. When we look at risky organ doses; The median rectum 2cc 2.4Gy, EQD2 58.4Gy value, median bladder 2cc 3.52Gy, EQD2 value was 68.8 Gy, median sigmoid 2cc 2.60 Gy, EQD2 value was found to be 60.3 Gy. There were no adverse events with respect to the bladder and sigmoid colon and hence, their toxicity, and dose correlation was not assessed.

At the end of the last, the follow-up, 64% (68/107) of the patients were alive with no local, loco-regional, or distant metastasis. 15 patients (14%) were alive with disease, 10 has distant metastasis,3 had loco-regional metastasis, and 2 had both loco-regional and distant metastasis. The 3 and 5-year local control rates were 87.4% and 77.3%, respectively. The overall survival rate of 3 and 5 years was 78.1% and 72.2%. The survival rates of 3 and 5 years without distant metastasis were 66.5% and 61.2%. Four patient had loco-regional metastasis, 3 of these patients were alive on palliative chemotherapy, 1 was died because of chemotherapy-related toxicity.21 patients had isolated distant metastasis; most of them had palliative chemotherapy. The most common distant metastasis were lung, liver, and bone.11 patient had both distant and loco-regional recurrences. At the end of the study, 24 patients were died because of disease progression.

The median number of completed chemotherapy cycles was five (range 3-7). Hematological toxicities were the main reason for uncompleted therapy. The most frequent grade 2-3 hematological toxicities were 37% leukopenia, 25% neutropenia, 18% thrombocytopenia, and 8% anemia.

Grade I-II acute proctitis developed only 23 patients who were managed conservatively. Acute grade I-II cystitis occurred 18 patient, and these patients were improved with medication. Five patients had rectovaginal fistula as late side effects. Three of them had a cervical tumor progression after the 12 months of brachytherapy. Two of them alive without disease immediate colostomy was performed after 8 and 10 months of the brachytherapy, and one of the patients with rectovaginal fistula had received 68.9 Gy to 2cm3 of the rectal volume, and the dose of the other to 2 cm3 rectum was 66.5 Gy. We did not observe Grade 3 -4 genitourinary side effects like urinary obstruction and fistulization.

DISCUSSION

In the intracavitary brachytherapy treatment has been historically delivered to point A. There are several limitations in prescribing to point A, although that 2D brachytherapy has proven to be effective in local control. The prescribed point A would always be at a fixed distance from the cervical os. There was no change in dose because of the size or shape of the residual mass at the time of brachytherapy. The patients' variations in anatomy and applicator positions were the other factors which were the need for changes doses to point A. The 2D planning system was on orthogonal X-rays, and there was no method for dose optimization.

The GEC-ESTRO guidelines announced the notion of 3D IGABT and 3D dose-volume parameters of the carcinoma cervix [5,6]. These recommendations of GEC-ESTRO were for MRI based BT. They concluded that long term results from these studies showed that D2cc for the rectum, sigmoid, and bladder have a significant estimated value in assessing late toxicity. Potter et al. have shown >85% local control and low treatment morbidity by using MR-based planning [14] In general, clinical experiences showed that IGABT has a suitable therapeutic ratio with %90> local control and with <5% morbidity rates. In the retro EMBRACE study demonstrated that local control rates 89% for stage III and 96% for stage II [17].

The recent studies have shown that MR has a superior tumor volume delineation than CT scan. We are using CT or MR suitable applicators for cervical cancer patients. But in our hospital, it is tough to have the appropriate localization to take an MR with the applicators inside the patient. Therefore, we use CT scan routinely in brachytherapy planning. Vishwanathan et al.[18] made a prospective trial that compared MR and CT based contouring. They concluded that cervical tumor contouring was superior in MR, but they noticed that no difference in OAR analysis.

The patients who had nodal failure was rare in our study. However, the outcome of these patients was inferior, and they might have distant metastasis after the treatment. Nomden et al. concluded that

node-positive patients had higher risk of developing distant metastasis and also had worse overall survival [19]. In our study we cannot find any survival difference with positive node patients than node-negative patients. The dominant pattern of failure was distant metastasis affecting 28% of the patients which are accordance with the literature [5,9,10,11].

During RCT, one of the most common acute side effects is hematopoietic [2]. In the lıterature,>grade 3 hematopoietic side effects occur about 30% of patients. In our study grade 2-3 haematological toxicities were, 37% leukopenia,25% neutropenia, 18% thrombocytopenia and 8% anaemia. Late grade 3-4 morbidity was 5% for urinary,8% for GI and 8% for vaginal toxicity were reported in the literature, but in our study, we only had 5% (5/107) grade 3-4 GI toxicity reported.

In the recent study 3 and 5 year local control and overall survival rates were 87.4% &77.3% and 78.1% &72.2%,respectively. These results are comparable to the published literature. Four retrospectives one prospective studies have demonstrated that IGABT improves local control than standard 2D BT. In these series, the 3 years LC improved from 64 – 76% to 85.5– 93.3%, while the three-year OS increased from 51– 63% to 65– 85.6% if IGABT was used [8,9,10]. These results showed that IGABT improved pelvic control and could be responsible for better survival rates.

CONCLUSION

Our results showed that IGABT with RCT should be the standard of treatment modality for locally advanced cervical cancer. The expected late side effects in 2D brachytherapy are significantly reduced in IGABT. 3D IGABT personalized treatment modality and BT planning and dose are tumor volume depended.3D CT based imaged BT is beneficial for delineating OAR and tumor volume.D2cc volume of the OARs correlates with late effects.

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