

Radical Radiotherapy of Locally Advanced Cervix Uteri Carcinoma

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Abstract

External beam radiotherapy with concomitant platinum-based chemotherapy followed by brachytherapy is defined as radical radiotherapy of cervix uteri carcinoma. Radical radiotherapy is the gold standard treatment for locally advanced cervix uteri carcinoma. The rates of survival and treatment-related adverse events in patients with cervix uteri carcinoma are affected by both stage of disease and treatment. Both should be optimal in proportion to the available facilities. Here, recommendations from the current literature are presented.

Keywords: Brachytherapy, Cervix cancer, Chemotherapy, Radiotherapy

Cervix uteri carcinoma is the most common gynecological cancer worldwide. In addition, it is the fourth most common malignancy and the fourth leading cause of cancer-related death in women [1]. The most common histopathological subtype is squamous cell carcinoma (85%). Non-squamous cell carcinoma is less common and is associated with poor prognosis. From 36% to 50% of cervix uteri carcinoma patients are diagnosed in a locally advanced stage (International Federation of Gynecology and Obstetrics [FIGO] stage IB2-IVA) [2]. Based on the results of five randomized-controlled trials, locally advanced cervix uteri carcinoma (LACC) is treated with radical radiotherapy (RT) [3-7]. Radical RT includes external beam radiotherapy (EBRT) with concomitant platinum-based chemotherapy (CHT) followed by brachytherapy (BRA) [8].

The diagnosis of invasive carcinoma should be confirmed histopathologically with a punch biopsy of grossly visible tumor, or conization of non visible tumor or dilation and curettage for repetitive nondiagnostic materials before staging workup [9]. The FIGO staging system is used for cervix uteri carcinoma and was revised in 2018. While FIGO-2018 does not standardize any imaging technique, lymph node biopsy, or surgical assessment and recommends using them for staging based on the available local resources, it allows under-resourced physicians to continue staging with clinical assessment,

including physical examination, biopsy, endoscopy, and conventional imaging techniques (X-ray, intravenous pyelography, and barium enema) [10].

Staging should be accurate to facilitate appropriate treatment, which can improve local control and survival. Adverse events are also reduced secondary to correct staging [11]. Staging is divided into three categories, i.e., clinical, radiological, and surgical staging. The accuracy of clinical staging decreases from 85% to 21% with increasing stage [12]. Therefore, if available, cross-sectional imaging techniques are strongly recommended for staging [10]. Computed tomography (CT) is widely available but its poor soft tissue resolution represents a limitation for local staging (tumor size, parametrial invasion, and so forth) of cervix uteri carcinoma. The absolute agreement between clinical staging and CT staging is 28.30%. While CT shows no superiority over clinical assessment in local staging, it allows more accurate FIGO staging as it can detect urinary obstruction (FIGO III-B), lymph node involvement (FIGO III-C1 and C2), bladder/rectum invasion (FIGO IV-A), and extrapelvic metastasis (FIGO IV-B) [13,14]. Magnetic resonance imaging (MRI) has high soft tissue contrast and resolution, and therefore is superior to both CT and clinical assessment for local staging [15-18]. Unfortunately, lymph node involvement is determined by size and shape in both CT and MRI, and both techniques show low sensitivity in assessment of the lymph nodes. Positron emission

tomography (PET)-CT is superior to MRI for evaluating nodal involvement because of its high sensitivity. In addition, PET-CT is recommended for detecting extrapelvic metastases. PET-CT prompts changes in the RT field and treatment plan in 34% and 23% of patients, respectively. While PET-MRI is superior to PET-CT only in local staging, it is not superior in detecting regional lymph node involvement and extrapelvic metastasis [19]. Due to the complementary roles of MRI and PET-CT, also known as trimodality staging workup, FIGO and the National Comprehensive Cancer Network (NCCN) recommend both MRI and PET-CT for pretreatment assessment of cervix uteri carcinoma [10-12, 19]. Unfortunately, surgical staging determines metastasis in 10–15% of patients who do not have paraaortic node metastasis based on staging with PET-CT. In the absence and presence of pelvic lymph node metastasis, the risk for paraaortic lymph node metastasis is 5% and 25–30%, respectively. Therefore, surgical staging is recommended particularly for patients with pelvic lymph node metastasis [20].

EBRT is used to reduce the macroscopic tumor volume and eradicate subclinical disease with acceptable toxicity in patients with LACC. The optimal RT technique for cervix uteri carcinoma has yet to be determined. Although there are no recommendations that two-dimensional (2D) RT should not be used, because this may be the only method available in low- and middle-income countries, three-dimensional conformal radiotherapy (3D-CRT) is considered the gold standard in patients with LACC [21,22]. However, 3D-CRT causes significant early adverse events in the gastrointestinal (GI) and genitourinary (GU) tracts and the hematopoietic system, which causes treatment interruptions [23,24]. Interruption of RT negatively affects prognosis. A higher radiation dose can be prescribed with intensity-modulated radiation therapy (IMRT), increasing target volume coverage and protecting the organs at risk (OAR) [21]. Therefore, the use of IMRT in patients with cervix uteri carcinoma has increased gradually over the last decade [25]. As of 2020, a limited number of studies have compared 2D-RT and 3D-CRT (non-IMRT) techniques with IMRT in patients with LACC [24,26-29]. A meta-analysis showed that early GIS, early GUS, and late GUS adverse events were less common in the IMRT group, and there were no differences between the IMRT and non-IMRT groups in terms of overall survival (OS) or disease-free survival (DFS) [30]. A recent report indicated that the incidence of hematological toxicity in patients with LACC receiving concomitant radiochemotherapy was reduced with pelvic bone marrow-sparing IMRT [31,32].

CHT is administered concomitantly with RT to increase radiosensitivity. Concomitant cisplatin (DDP) ± fluorouracil (FU) is the standard regimen in radical RT of LACC. DDP can be administered via the

intravenous bolus route, weekly (40 mg/m²), triweekly (70–75 mg/m²), or every 4 weeks (50 mg/m²) [3-7]. The use of non-weekly regimens was evaluated in two groups, i.e., single DDP and DDP-based multiagent CHT regimens. The results of two meta-analyses examining this difference indicated that weekly single-DDP causes less hematological toxicity than non-weekly DDP ± multiagent CHT with no differences in survival rates, but the local recurrence rates were lower with triweekly single DDP [33,34]. In patients for whom DDP is contraindicated, although tumor response and survival rates are lower than DDP, usage of carboplatin (weekly; AUC 2) is recommended [35].

BRA is an integral part of radical RT in patients with LACC, and delivers high (>80 Gy) radiation doses to the tumor, while sparing the OAR [36]. In parallel with EBRT, significant advances have been made in BRA image guidance techniques, treatment planning technologies, and application systems. Image guidance techniques in BRA are designated as 2D if using plain radiography, two and a half dimensional (2.5D) if using ultrasonography (USG), and 3D if using CT or MRI. The 2D-BRA technique is also referred to as the conventional technique and is based on two points representing doses to the paracervical triangle (Point A) and pelvic wall (Point B) in accordance with the Manchester system. Unfortunately, the 2D-BRA technique does not take into account tumor size and changes (or variation) in adjacent OAR. Therefore, tumor control rates are decreased in large tumors and the risk of developing adverse events are increased in small tumors [37,38]. In BRA, USG can be performed through both transabdominal and transrectal routes [39]. Although both USG techniques require operator experience and expertise, both are economical, widely available, portable, and have real-time applicability in the BRA room with relatively short application times. Neither can be used to assess target volume coverage, OAR, residual tumor, vaginal extension, or cumulative dose to the sigmoid colon. Therefore, USG should be used together with MRI for BRA planning [38,40]. BRA planning with CT is also increasing in parallel with the increase in use of CT simulators in radiation oncology departments. Contouring OAR with CT is not different from MRI. However, as mentioned in the staging paragraph as MRI has higher soft tissue contrast and resolution than CT, the guidelines recommend using CT together with MRI (T2 weighted sequence) in BRA planning to increase both local control and survival without increasing early and late adverse events. MRI can be used in two methods for BRA planning. BRA planning CT with applicators followed by fusion with pelvic MRI, or pelvic MRI with MRI-compatible applicators followed by fusion with BRA planning CT [41-43]. Second, BRA can be applied at a low dose rate (LDR) or high dose rate (HDR). There were no differences between LDR-BRA and HDR-BRA in terms of local control and survival. In LDR-BRA,

the healthcare personnel performing the application are exposed to radiation, the treatment period is long (days for LDR vs. minutes for HDR) and pulmonary embolism due to prolonged hospitalization is more common. Therefore, HDR-BRA is preferred at present [44]. Third, different applicators are used in BRA according to the patient's anatomy and tumor characteristics. The most commonly used are tandem ovoid (TO) with vaginal packing and tandem ring (TR) with a rectal retractor. While there are no differences in tumor treatment outcome between the two types of applicator, the OAR radiation exposure is lower with the use of TR and a rectal retractor compared to TO and vaginal packing. Therefore, if the patient's anatomy and tumor characteristics are suitable, TR and a rectal retractor should be used [45-47]. In addition, HDR-BRA can be applied as an interdigitated or sequential form [48]. However, the total treatment time (radiochemotherapy + BRA) should not exceed 8 weeks [49].

Adverse events (early or late) increase with combined treatments such as radical RT of cervix uteri carcinoma that includes EBRT with concomitant CHT followed by BRA. The most commonly seen early adverse events are seen both in hematopoietic and gastrointestinal systems [50]. Most of them are self-limited and are treated symptomatically. Intraoperative complications in BRA are vaginal laceration and uterine perforation. Uterine perforation risk is reported between 1.75% and 13.7% in the literature. In uterine perforation, the tandem is removed and prophylactic antibiotics are administered [51]. Late adverse event rates (5-9.5% in 3 years) were reduced with the use of 3D treatment planning techniques including both with EBRT and BRA. The most common late adverse events occur in the rectum (eg.: bleeding, perforation and fistula), small intestine (eg.: obstruction, necrosis, perforation and fistula) and bladder (eg.: hematuria and contracted bladder). More rare adverse events are pelvic insufficiency fracture, vaginal stenosis, lymphedema and neuropathy [52-60].

As mentioned before, EBRT with concomitant platinum-based CHT followed by BRA is defined as radical RT of cervix uteri carcinoma. This combination treatment scheme is applied as a standard at Ondokuz Mayıs University Oncology Center to all patients with locally advanced cervix uteri carcinoma without contraindications. In 2019, we presented our results of radical RT of 64 patients with local-advanced cervix uteri carcinoma. All of the patients were treated with 3D-CRT and concomitant cis-platinum-based CHT (40 mg/m²) followed by 3D intra-cavitary HDR-BRA. According to our results, 3-year PFS and OS rates were 67.5 and 76.9%, respectively. Our survival results were compared with the results of 3D-planned radical RT that was published in

the literature in Table 1. Additionally, in our study, while grade 3 early adverse effects were detected only in the hematopoietic system at a rate of 3.1% in the early period, no grade 4 and higher early adverse events and any late adverse events were detected [50].

Author	Three year DFS (%)	Three year OS (%)
Nomden et al. [52]	71	65
Lakosi et al. [53]	85	81
Rijkmans et al. [54]	83	86
Pötter et al. [55]	75	68
Lindegaard et al. [56]	87	79
Sturdza et al. [57]	79	74
Kawashima et al. [58]	81	94
Choong et al. [59]	78	77
Oh et al. [60]	72	84
Serarslan et al. [50]	67	76
Abbreviations: DFS: Disease Free Survival; OS: Overall Survival		

Table 1: Results of treatments including three-dimensional radical radiotherapy plannings.

Follow-up and surveillance are as important as treatment. Patients should be followed up in terms of tumor response and adverse events. After radical RT, it is recommended to perform the first control imaging between months 3 and 6. Imaging results have prognostic significance. Follow-up in cases of complete response or further treatment in cases of non-response are planned according to the tumor response [61-63].

Declaration of Conflict of Interest

None.

Authors' contributions

AS and DM were responsible for the overall study concept. AS, DM and REY were responsible for treatments. AS, DM and REY collected the clinical data AS, DM and REY provided technical and material support. AS, DM and REY analyzed the data and wrote the manuscript. All authors reviewed, edited, and approved the final manuscript.

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