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Palliative Split-Course pelvic radiotherapy for symptomatic cervical cancer

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ABSTRACT

Objective: Palliative pelvic RT effectively relieves significant health issues such as bleeding from the tumor, pain, discharge, or mass effect on the rectum genitourinary tract vessels and nerves in cervical cancer patients. There is no exact conclusion about an ideal palliative radiation treatment dose regimen. Thus we share the results of a commonly used split-course palliative pelvic RT regimen in our hospital.

Material and Methods: For a retrospective study, 9 patients records treated between 2015 and 2019 were reviewed. The dose of prescribed irradiation for the target was 20Gy in 5 daily fractions. An additional 20Gy in 5 fractions was delivered after a 2-week time for recovery. Symptomatic improvement and treatment-related toxicity during and after RT were assessed from handwritten clinician reports.

Results: Vast majority of patients enduring, and rapid symptomatic improvement was observed. Grade 3 to 5 treatment toxicity was not examined. Maximum acute toxicity was grade 1 GI or GU toxicity in 4 patients and G2 in two patients. Three patients had no acute side effects. All patients had complete symptom remission after treatment, one patient did not complete the second course of therapy due to deteriorating performance status, but local symptom relief was achieved.

Conclusion: Split course regimen effectively improved symptoms without significant toxicity. The integrated 2-week break allowed doctors to assess patients for increased dose palliative radiation and balanced therapeutic benefits with possible adverse effects. This regimen is a reasonable strategy for patients who do not tolerate definitive treatment.

Key words: cervical cancer, palliation, radiation, split course, 2-week break.

INTRODUCTION

Cancer of the cervix uteri (CC) is regarded as the 4th most common cancer type in women. In 2018, about 570000 newly diagnosed cases were registered, representing 66 percent of all gynecological cancers in females, about 90 percent of total cervical cancer CC related deaths occur in low- and middle-income countries (1). Diagnosing of CC at an early stage where access to successful care is available will dramatically increase the chances of survival. In many low economic counties, the disease is not diagnosed timely until cancer will reach an advanced stage or treatment is inaccessible; therefore, a high death rate induced by CC is observed. Multiple studies in developing countries clearly show that awareness is very low and the use of CC early detection screening programs as well (2-9). This lack of efficient screening programs also explains why more than 75 of women affected are at an advanced stage in developing countries while more than 75 of women affected are at an early stage in developed countries (10-12). Radical surgery with or without neoadjuvant chemotherapy or concomitant chemo-radiation will successfully treat early-stage cervical cancer (stage I to IIa). Chemo-radiotherapy or palliative chemotherapy with or without radiotherapy is mostly used to treat locally advanced CC (stages IIb to IVb) (13)

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The basic difficulty in the treatment of women with locally advanced cervical cancer (LACC) is the poor performance status of the patients. Because of poor tolerance for any type of therapy, treatment effects may be uncertain. In women with advanced or metastatic cervical cancer, symptoms such as vaginal bleeding or mass effects on the rectum, genitourinary tract, vessels, and nerves frequently require palliation. In the care of patients with pelvic symptoms who were unable to undergo intensive therapy, palliative RT is an important part of treatment and standard practice.

By the World Health Organization, palliative care is regarded as "an approach that improves the quality of life of patients and their families facing the problems associated with a life-threatening illness, through the prevention and relief of suffering employing early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual (14). For all stages of cancer treatment of a patient, this is correct; since the disease is not curable and life expectancy is limited, care priorities are based on symptom management and quality of life. In the palliative treatment of advanced CC, RT plays a crucial role, especially in hemostasis and pain control.

The main goal of palliative radiotherapy is to provide permanent and rapid improvement of symptoms while lessening acute or late side effects, resource use, and the frequency of cancer center visits (15). The other goals include tumor regression and a short period of rehabilitation. For palliative patients, a short course of radiotherapy delivering a high dose per fraction is preferred, as tumors do not need to be fully eradicated to achieve symptom improvement (16). Although palliative radiotherapy plays a very important role in the treatment of advanced cervical cancer, the optimum dose or fractionation schedule is not estimated.

For the gynecological malignancies palliation, several hypofractionated regimens have been recommended (17). Schemes vary from 30Gy/10 fractions to shorter 3.7Gy twice daily given in 4 fractions and a single 8Gy dose in one fraction. Many of these fractionation regimens can be repeated. Administration of palliative RT for gynecologic cancer may be delivered using the external beam approach and brachytherapy. The radiation fractionation regimen decision is based on many different factors, including tumor characteristics, radiological features, previous history of radiation therapy, and response to that intervention, patient's performance status, and estimated life expectancy. Ongoing or potential systemic therapy should be taken into consideration, as well. In decision making, physician choice and preparation often play an important role.

The most commonly used palliative pelvic RT scheme for cervical cancer has been the split course hypofractionated schedule at the EVEX Medical Corporation – Oncology Center. The idea is that in this challenging patient population, the first course of 20Gy delivered in five daily fractions offers a trial course to evaluate treatment tolerance. The first phase of treatment will be followed by a scheduled 2-week break, enabling patients to recover from acute adverse effects caused by the first phase of RT.

However, from either disease progression or intolerance to the first course of radiation during the break, a minority of patients would deteriorate. Patients who felt better could continue RT at the final total dose of 40Gy by completing the second phase of RT with 4Gy per fraction. This regimen thereby allows the identification of patients who may tolerate high-dose palliative RT after the initial dose. This approach has been well-tolerated in our practice. Most patients have benefited from the relief of pelvic symptoms while offering all patients an opportunity to receive the higher palliative radiotherapy trial course. In this study, we conducted a retrospective analysis to determine the overall efficacy of a split-course palliative radiotherapy protocol for symptom palliation.

MATERIAL and METHODS

Patient Population

Clinical reports were analyzed of all patients treated for cervical cancer with split course pelvic RT between May 2015 and May 2019. Nine patients were found in total with cervical cancer who underwent treatment with this regimen by checking the unit's disease-specific treatment reports built-in ARIA software. Histopathologically confirmed stage IVB cervical cancer had been diagnosed in all patients (Including squamous cell carcinoma, adenocarcinoma, or adenosquamous cell carcinoma).

Due to severe comorbidity, low-performance status, or metastatic illness, these patients were not suitable for radical treatment. History and physical examination included height, weight, body surface area, and The Eastern Cooperative Oncology Group Performance Status (ECOG) score. An initial examination was performed by a gyne-oncologist and radiation oncologist together. All patients had signed a treatment-specific informed consent before treatment.

Treatment

Chosen patients were treated with external beam RT using Clinic IX or True Beam (Varian Medical Systems) only. A megavoltage beam of 6 MV or greater, with a minimum source-axis distance of 100 cm and a minimum source-to-skin distance of 80 cm. Throughout the simulation and planning, methods were used to reduce small bowel irradiation, including full bladder or advanced physics planning for IMRT. The distal-most aspect of cervical-vaginal disease was marked using radio-opaque seeds. CT scan with or without MRI was used in treatment planning.

The tumor responsible for vaginal bleeding, mass effect, or pelvic pain identified by pelvic CT and/or MRI was outlined as the gross tumor volume (GTV). With a 1.0 margin, given the setup instability and organ movement, the planning target volume (PTV) was defined. The clinical target volume (CTV) was not defined due to care was given for palliative intent. Originally, it was planned that all patients would receive the full course of treatment with a maximum dose of 40Gy. All plans were generated in Eclipse (Varian Medical Systems): using a conformal 4-field technique with 16-MV photon beams or IMRT/VMAT technique with 6-MV photon beams.

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Daily image verification on the treatment unit was followed by prescribed treatment delivery. For the first course of RT, a dose of 20Gy in 5 fractions was approved.

All patients were treated once a day, five days a week, with a daily fraction size of 4Gy. Complete blood count analyses were performed weekly. Serum chemistry included creatinine and liver function tests. Transfusion was given if HGB <80 g/l. Patients were given a 2-week break after this first phase of palliative RT, during which patients and doctors jointly decided whether a patient should continue to the second course of palliative radiotherapy. Good performance status, the patient's ability to continue, stable cancer status of the treated tumor, and no distant progression were the indicators used to pick patients for the second phase of treatment, which included an extra 20Gy in 5 fractions.

Analyses

Symptom Palliation: Data regarding patient symptom improvement was obtained from clinician assessment reports performed during RT and clinic follow-up notes. All patients were followed-up via planned follow-up visits in the clinic if patients were able to come. If the patients' performance status had deteriorated and they could not come for follow-up checks, the clinic's administrative department started the interview process with a phone call to determine the vital status until the patient's death. The response to treatment, recurrence of disease, or survival is well beyond the context of this study.

Toxicity: At the monthly therapy reviews, at regular follow-up visits in two weeks and/or months following RT completion, toxicities were determined retrospectively from physician notes. The worst treatment-related toxicity observed during treatment or retrospectively analyzed was graded using the Common Terminology Criteria for Adverse Events v4.0 scale.

For the whole population of patients, only one clinician collected this data. A proportion of these charts was then evaluated by a group of physicians (resident a senior physician for each patient) to determine and validate the patients' toxicity score. Any discrepancy in scores was overcome by re-examining the patients' clinical charts, and the senior physician took the final decision.

RESULTS

Patient characteristics: Basic hallmarks of patients and diseases are outlined in Table 1. Patients were staged according to the 7th edition of the classification of the AJCC staging.

All the patients had stage IVB cervical cancer proven by pathology and radiological studies. None of the nine patients has ever undergone pelvis irradiation. The entire course of therapy was finished by eight patients, for a total of 40Gy. Because of low-performance status and severe comorbidities (acute hemorrhagic stroke during a 2-week break), only one patient was found not fit for the second phase of RT.

Symptom Palliation: Symptomatic improvement was measured in all cases with a cumulative follow-up of 12 months from the monthly treatment assessment clinical reports and from the follow-up charts to the final follow-up or until death. Table 2- shows that after finishing the complete course of palliative RT, patients had different symptomatic improvements. Bleeding and pain were palliated in most patients. 100% described symptom relief at the end of care in patients that had bleeding. In all patients, pelvic pain was relieved. All patients suffering from pelvic pain were prescribed non-steroidal anti-inflammatory medications or opioids during RT. These patients stopped or were able to decrease the pain drug dosage following completion of therapy. Palliation from vaginal discharge and mass effect was also reported in two weeks of treatment.

Toxicity: Table 3 - shows the treatment-induced acute and late toxicities. The majority of our patients well tolerated split course radiation. There was no grade 3, 4, or 5 RT side effects. Three patients showed no acute side effects at all. Diarrhea was the most frequent acute toxicity observed in 4 patients.

Table 1. Patient and Disease Characteristics

Demographics	Number (%), N = 9 (100%)
Age	
Median	66
Range	50-83
ECOG	
1	1 (12)
2	3 (33)
<2	5 (55)
Weight loss >5% of body weight	
Yes	4 (44)
No	1 (12)
Unknown	4 (44)
HGB	
>120 g/l	0
80 – 120 g/l	4 (44)
< 80 g/l	5 (56)
Histology	
Adenocarcinoma	2 (22)
Squamous cell carcinoma	6 (66)
Adeno-squamous carcinoma	1 (12)
Chemotherapy	
Prior	4 (44)
After	2 (22)
Prior to and after	2 (22)
No chemo	1 (12)
Prior Surgeries	
Yes	1 (12)
No	8 (88)

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Table 2. Palliation of Symptoms in Evaluable Patients

Symptom	Patients with Symptoms at Presentation Number (%),	Patients with Symptom Improvement in two weeks Number (%)	Patients with Symptom Improvement in 6 months Number (%)
Bleeding	8 (89)	8 (100)	8 (100)
Mass effect/obstruction	2 (22)	1 (50)	2 (100)
Vaginal discharge	8 (89)	3 (37)	5 (62)
Pelvic pain	5 (56)	4 (100)	5 (100)

Table 3. Treatment Toxicity by CTCAE v.4.0

	Grade 1	Grade 2	Grade 3,4 and 5
Acuity toxicity			0
Nausea/ Vomiting	2	1	
Diarrhea	2	2	
Anal mucositis	1	0	
Cystitis	2	0	
Vaginal mucositis	2	0	
Late toxicity			
Proctitis	2	0	0
Cystitis	1		
Vaginal stenosis	0		

DISCUSSION

The task frequently posed by radiation oncologists is to treat a patient with stage IVB or recurrent cervical carcinoma that has induced pelvic pain, mass effects, or bleeding. Conducted literature review confirms that numerous dose fractionation schedules have been tested (19, 22-30), but about RT dose and fraction size recommended for palliative pelvic RT, there is broad international heterogeneity (Table 4). Tumors respond quickly to radiation, and after a few days of treatment, bleeding stops. Several options can be useful if vaginal bleeding is the primary concern.

According to the Lonkhuijzen's descriptive analysis of eight papers reporting palliative care results, the evidence is not enough to prove the widespread presumption that better and durable palliation is accomplished with a higher dose administered in many smaller fractions. There is a strong need for a comparative study that will analyze various radiation fractionation schedules to determine an ideal palliative radiation regimen (18). Numerous regimens have been reported, with various fractionation schemes. Several studies have identified whole-pelvic palliative RT using single or multiple monthly doses of 10Gy. This treatment plan was generally well-tolerated, impacting vaginal bleeding and discharge after 2 or 3 fractions were reported (19-20). Late toxicity is poorly reported, and because of the large fraction size and wide irradiated area, the increased risk of late toxicities is a problem. In patients with different pelvic malignancies, RTOG 7905 research took this monthly fraction of 10Gy schedule concurrently with misonidazole (a hypoxic cell sensitizer).

A high incidence of late gastrointestinal (GI) complications (45 percent) were recorded, leading to the trial's premature termination (21).

The RTOG prospectively examined the use of a lower dose per fraction: 3.7Gy delivered twice a day to a total dose of 14.8Gy, repeated every month for up to three months. Spanos et al. reported on a phase II study of 142 patients with recurrent or metastatic disease in the pelvis using this fractionation and repeated at 3- to 6-week intervals for a total of three courses. The planned total tumor dose was 44.4Gy, and LDR intracavitary insertion (4,500 mg) was occasionally accompanied by 14.4 Gy EBRT dose with midline block. Twenty-seven patients lived for longer than one year. There were only two reported cases of grade 3 toxicity in the lower gastrointestinal tract. The research was extended to provide a phase III protocol randomizing 136 patients to rest for a short (2 weeks) or longer (4 weeks) time between split radiation courses. In patients with shorter rest intervals, there was a tendency towards increased acute toxicity (5 of 58 vs. 0 of 68; P = .07). In the two groups, late toxicity was not substantially distinct. The pelvic tumor response was 34 percent vs. 26 percent in both groups, reported as comparable. A 6 percent complication rate was reported by Spanos et al. in 290 patients treated under RTOG Protocol 8502. There was no late toxicity in any patient receiving <30Gy. No major variation in the occurrence of complications was observed for patients who had 2 or 4 weeks of rest (P = .47) (22-23). The weakness of this protocol is that the two days of treatment require at least a 6-hour interval between two daily fractions, which can be troublesome for the symptomatic patient.

It was impossible to compare the results from these studies, considering the patient sample variations (performance status spectrum, age, methods of symptom assessment, and measured outcomes). It appears that the highest control was achieved with bleeding. Pain palliation was correlated to the overall dose delivered. However, almost all these studies indicate that higher cumulative doses of RT could be considered in some patients to result in more effective palliation and potentially better overall survival. The latter is beyond the scope of our study. Therefore, in this population, which also has low-performance status or severe comorbidities, the proper selection of patients who may benefit more from a split course of RT is essential. In palliative care, balancing symptom improvement with RT side effects remains very important. We suggest that our treatment regimen prevents the overtreatment of very ill patients with the consequent toxicity and enables healing from the acute side effects of the first phase RT. This strategy allows the evaluation and identification of patients fit for escalated dose palliative RT after a trial dose of 20Gy. Further RT was continued only in patients who did not get worse after the 2-week break. Apparently, in most patients, split course RT offered symptom improvement. Treatment was well-tolerated, with mild and irregular events of toxicity over the planned 2-week break, both grade 1 or 2 GI and GU toxicity entirely resolved. Grade 3 or higher acute or late toxicity was not detected during radiation or within the six months after.

The scheduled break could provoke controversy as seen in patients undergoing curative-intent RT for other cancer forms the prolonged duration or delay of care can adversely affect local tumor control and disease-specific survival. Particularly because of short survival in patients treated with palliative intent, the goal of palliative RT regimens has centered on symptomatic improvement rather than local control of the tumor. Tumor local control or OS was not assessed in this study. Although understanding that symptom palliation can also be a feature of local tumor response. A significant portion of our patients has poor prognostic factors, including stage IVB disease, weight loss, and a higher ECOG score of performance status. The key reason for split course palliative RT is that the 2-week break allows the doctor to choose patients for the full dose palliative RT of 40 Gy. The retrospective nature of this clinical study did not allow us for precise measurement of the degree of improvement, new symptoms during RT, or span of palliation.

Indeed, findings from a retrospective analysis of clinical details, considering the possible subjectivity, patient selection, and bias implicit in this research design style, did not permit an objective comparison of efficiency. We retrieved data relating to whether the symptoms were improved during treatment and afterward. Symptom palliation and toxicity were analyzed mainly by doctors, and it is well known that physicians appear to overestimate or neglect the symptoms compared to patients. The analysis of the results could be influenced by the process by which these endpoints have been evaluated, as information was derived from clinical notes. For most studies oriented on palliative schedules, as this protocol, this issue of estimation is one of the main rationales. It should always be acknowledged that variables apart from the fraction size, including treatment volume and prior interventions, affect complication rates of radiation therapy.

CONCLUSION

We report that symptom palliation using this regimen is promising and posed minimal toxicities. There is clearly a need for well controlled studies with validated palliative and quality of life endpoints to determine the best fractionation schemes for palliative radiotherapy in cervical cancer. Therefore, we propose that these data may serve as the basis for the design of future prospective studies evaluating split-course palliative pelvic RT, with the incorporation of validated symptom inventory tools and a formal quality of life assessment.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

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