

Monthly palliative pelvic radiotherapy in advanced carcinoma of uterine cervix

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ABSTRACT

Background: Patients with locally advanced cervical cancer are often severely distressed with incessant vaginal bleeding, offensive discharge and pelvic pain and are in some instances beyond curative potential. At our institution we routinely use monthly palliative pelvic radiotherapy for these patients.

Methods and Material: One hundred patients treated between 2000 & 2004 were included in this analysis. Patients were treated with parallel-opposed pelvic portals with megavoltage radiation monthly up to a maximum of three fractions (10Gy/ fraction). Patients with good response after second fraction were considered for intracavitary brachytherapy delivering 30Gy to point A. Response was documented with regard to relief of bleeding, vaginal discharge and pelvic pain. The other aspects evaluated were patient compliance, disease response, toxicity and survival.

Results: Sixty-eight percent had FIGO stage IIIB, 12% had stage IVA and 14% had IVB disease. Twenty patients had metastatic disease. The median symptom duration was 5 months. Majority (67%) presented with vaginal bleeding, followed by discharge (69%) and pelvic pain (48%). All patients received at least one fraction of palliative pelvic radiotherapy. Sixty-one patients received the second fraction and 33 the third. Five patients received an intracavitary application. The overall response rates in terms of control of bleeding, discharge and pain were 100%, 49% and 33% respectively. The treatment was generally well tolerated with a median survival of 7 months.

Conclusions: Monthly palliative pelvic radiotherapy results in satisfactory control of symptoms in patients with locally advanced carcinoma of cervix with acceptable complications.

Key words: Palliative, Radiotherapy, Carcinoma, Cervix

INTRODUCTION

Cancer of the uterine cervix is the commonest malignancy affecting Indian woman.^[1] About two third of them presents with locally advanced disease. While definitive radiotherapy or concurrent chemoradiotherapy remains the mainstay of treatment for patients with locally advanced cervical cancer, a substantial number of patients are not suitable for radical treatment because of extensive pelvic disease and/ or metastatic spread. Patients in this group remain severely distressed with incessant vaginal bleeding, offensive discharge and crippling pelvic pain and are only suitable for palliative treatment aimed primarily at symptom control. Several institutions^[2,3,4,5,6] have reported the use of monthly pelvic radiotherapy for patients with advanced gynecological cancers with acceptable symptom control and toxicity rates. Although the reported 5years survival of patients with stage IIIB disease with bilateral hydronephrosis treated with radical chemoradiotherapy is 20-30%, we included these

patients with advanced disease in our monthly palliative radiotherapy protocol as they had extensive locoregional disease. These patients with advanced disease considered to be beyond curative potential were treated with palliative pelvic radiotherapy at monthly interval. We report our experience of patients treated with this palliative protocol over four years from January 2000 to January 2004.

MATERIALS AND METHODS

Patients receiving monthly palliative pelvic radiotherapy for locally advanced carcinoma of uterine cervix treated at Tata Memorial Hospital (TMH), Mumbai from January 2000 to January 2004 were included in this analysis. Although there are no specified guidelines for allocating patients with locally advanced carcinoma of cervix to receive palliative therapy, we formulated our institutional policy for treating such patients with palliative pelvic radiotherapy based on known adverse prognostic factors. The inclusion criteria

for this study were:

1. Histologically proven squamous cell carcinoma of cervix.
2. Patients without history of prior pelvic radiotherapy or chemotherapy.
3. Patients with frozen pelvis/ bilateral hydronephrosis due to disease/ metastatic disease or post-operative bulky recurrent disease.
4. Patients with symptoms like vaginal bleeding / discharge /pelvic pain.

All patients who fulfilled the above criteria were treated with parallel-opposed anterior-posterior and postero-anterior pelvic portals with megavoltage radiation monthly up to a maximum of three fractions. The radiotherapy dose was 10 Gy per fraction, prescribed at mid plane of pelvis. Portals were extended to encompass the inguinal lymph nodes if the disease involved them. All patients received prophylactic antiemetics & antidiarrhoeals.

Patient's with good response after the first two fractions of radiation were considered for a single intracavitary application of low dose rate (LDR) brachytherapy delivering a dose of 30Gy to point A. When ICA was done after the third fraction of external radiation, the ICA dose was reduced to 10Gy to point A.

Response was primarily assessed to document relief of bleeding, vaginal discharge and pelvic pain. We also evaluated patient compliance to radiotherapy, disease response, toxicity and survival. Response was graded according to percentage symptom relief (100%, 50%, 25%, & No Response/ Progressive Disease). Patient compliance was recorded as a percentage of patients who completed the planned course of treatment (i.e. external radiotherapy x 2 fractions followed by ICA or a third fraction of external radiotherapy). Acute gastrointestinal toxicity was graded using the common toxicity scoring criteria (CTC). Late toxicity for the pelvic subcutaneous tissue, the bowel and the bladder were graded according to RTOG criteria. Response of the primary tumor to radiation was also documented. The statistical analysis was done using SPSS software version 10.5. Survival was not the primary endpoint of this study. Survival was calculated from the date of registration to the date when last seen or the date of death.

RESULTS

We reviewed the records of 100 patients suffering from lo-

cally advanced or metastatic cervical cancer (Table 1). The median age at presentation was 55 years. Majority of the patients (68%) had FIGO stage IIIB disease. Eighty patients had locoregional disease at presentation. Six patients had post-operative bulky recurrent disease in the pelvis. Of the 20 patients with metastatic disease, thirteen had nodal metastasis only, and 6 had both nodal & pulmonary metastasis.

Symptom duration ranged from 1-12 months (Median 5 months). At presentation 76 patients complained of vaginal bleeding, 69 had offensive discharge and 48 complained of pelvic pain. Hemoglobin values ranged from 6.1gm/dl to 13.4gm/dl (Median value of 9.5 gm/dl). Sixteen patients had deranged renal function with serum creatinine above 2mg/dl.

All patients received at least one fraction of palliative pelvic radiotherapy with a median field size was 15 x 15 centimeter and a median prescription depth of 8 centimeters.

Patient Compliance

Though all patients received the first fraction of radiation, only 61 received the second fraction and 33 received the third fraction (Table 2). Four patients received intracavitary radiation after the completion of 2nd fraction of external radiation, while one patient received intracavitary radiation after the 3rd fraction of external radiation. Of the 39 patients who did not receive the second fraction of radiation, 6 had progressive disease, 30 absconded after the first fraction & 3 patients died of disease.

Of the 24 that did not receive either the third fraction or an

Table 1: Patient characteristics

No of patients	100
Age	30-80 years (Median:55 years)
Histology	Squamous Carcinoma 100%
Stage	FIGO Stage IIIB- 68% FIGO Stage IVA-12% FIGO Stage IVB- 14% Metastatic & Post op recurrence- 6%
Site of metastasis	Para-aortic nodes – 13 Para-aortic nodes with Lung metastasis-6 Liver-1
Hemoglobin	6.1g/dl – 13.4g/dl (Median: 9.5g/dl)
Duration of Symptoms	1month - 12 months (Median: 5 month)
Symptoms at Presentation	Bleeding: 76% Discharge: 69% Pelvic pain: 48%

Table 2: Patient compliance

Dose	No. of patients	%	Absconded (no information)	No further RT planed	Dead
10Gy x 1	100	100			
10Gy x 2	61/100	61	30	6	3
10Gy x 3	33/100	33	16	6	2
10Gy x 3+ICA &	1/100 &	1 &			
10Gy x 2 +ICA	4/100	4			

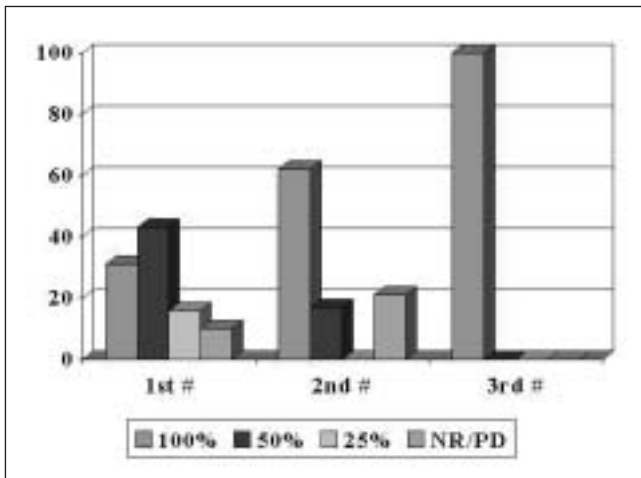


Figure 1: Radiotherapy fraction vs. control of bleeding

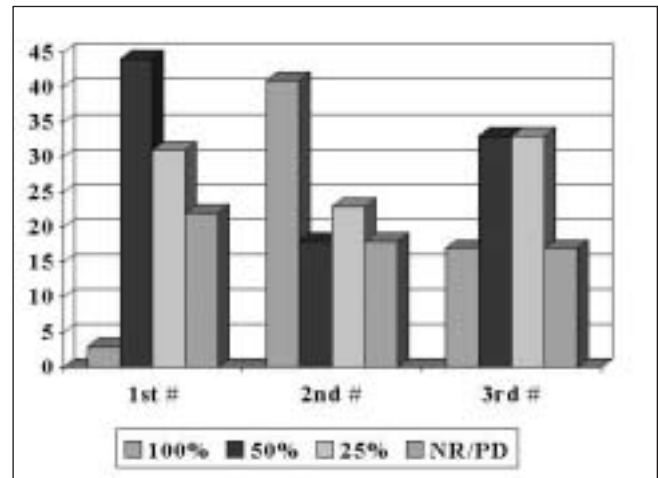


Figure 3: Radiotherapy fraction vs. pain relief

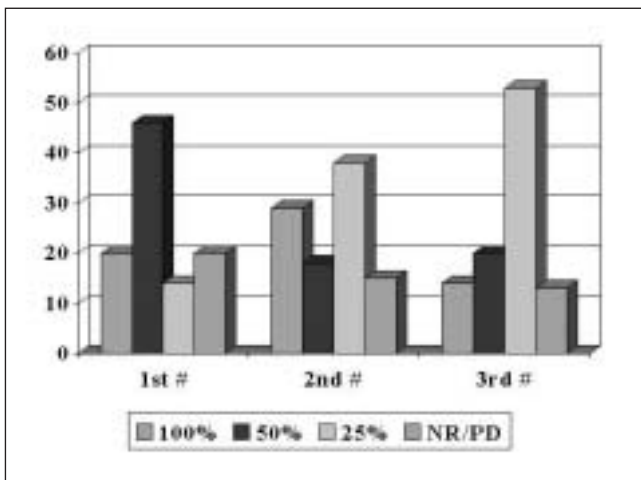


Figure 2: Radiotherapy fraction vs. control of discharge

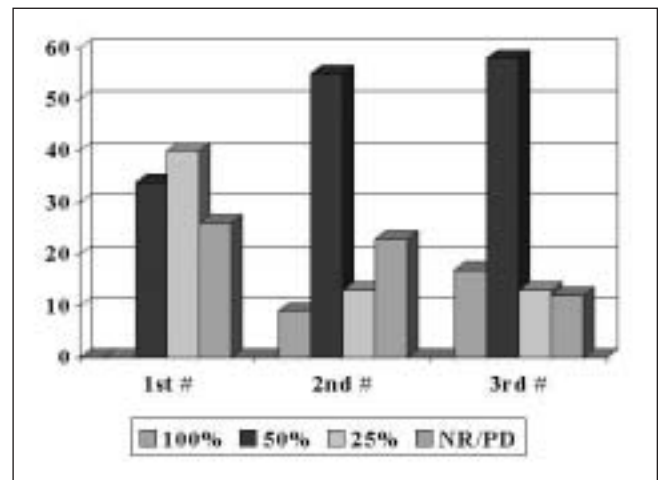


Figure 4: Radiotherapy fraction vs. disease response

intracavitary application, 2 patient died of disease, 6 had progressive disease and 19 were lost follow up.

Symptom Relief

Symptom relief (Figures 1-3) was evaluated and documented in all available patients after completion of each fraction of radiation. There was a steady increase in the percentage of patients relieved from bleeding with each fraction. A similar trend was noted for discharge and pain up to two fractions. Overall symptom relief for the entire group (excluding patients with no information), bleeding was controlled in 100 %, discharge in 49 % and pain 33 %.

Relief from Bleeding

After the first fraction of radiation 31% had complete response. The proportion of patients with complete response increased from 31% to 100% at the end of third fraction.

Relief from Discharge

Complete symptom relief after the first, second, and third

fractions were 20%, 29%, and 14% respectively.

Relief from Pain

Complete relief after the first, second, and third fractions were 3%, 41%, 17% respectively.

All patients tolerated radiation well. The acute toxicities were well controlled with symptomatic medical management. After the first fraction of radiation 13 patients developed grade I/II vomiting and 8 patients developed grade I/II diarrhea. Of the patients who received second fraction of radiation seven, & eight patients developed grade I/II vomiting and diarrhea respectively. Three patients developed grade III diarrhea after the second fraction of radiation. After the third fraction only two patients developed grade II vomiting and 4 developed grade II diarrhea.

Data available on late toxicity was very sparse and of the patients on whom the data available was only 4 developed subcutaneous fibrosis of anterior abdominal wall, 3 devel-

oped radiation cystitis and 3 developed radiation proctitis & bleeding per rectum.

Response

Complete response after the first, second, and third fractions and/or intracavitary application were 0%, 9%, and 17% respectively (Figure 4). After the first fraction, information on disease response was available for 70 patients. Of them 24 (34.2%) had partial response, 28 (40%) had poor response, 9 (12.8%) had no response, and 6 (8.5%) patients had progressive disease/ no response & 3 died of disease.

Of the 70 patients, 61 received 2nd fraction. After the second fraction no information was available on 16 patients. Information on response was available on 45 patients of whom 4 (8.8%) patient had complete response, 24 (53.3%) patient had a partial response and 6 (13.3%) patients had poor response. Nine (23%) patients had no response or progressive disease and 2 died of disease.

Thirty-three patients received the 3rd fraction and 4 received intracavitary brachytherapy. After the third fraction or the intracavitary application, 17% had complete response, 58% had partial response and 13% had poor response to treatment. Twelve percent of patient's had no response or progressive disease. One patient after the 3rd fraction achieved complete response & was treated with intracavitary brachytherapy (10Gy/single fraction).

The median duration of follow-up in our patients was 9 months. The maximum duration of survival in the entire cohort of patients treated was 27 months (2- patients). One of them was disease free at 27 months. There were 16 patients who survived for 6-12 months and 8 survived for more than a year.

DISCUSSION

A large number of patients with cervical cancer continue to be diagnosed with disease not suitable for radical treatment. Palliative treatment in these patients is a challenge and is primarily aimed at relief of symptoms and to maintain good quality of life.

Radiotherapy is an important component in treatment of both early and advanced cervical cancers. When used in patients with advanced disease it can effectively alleviate symptoms associated with the disease and achieve disease control in some patients. The use of single fraction palliative pelvic radiotherapy in advanced cervical cancer has been reported in a few institutional series.^[2,3,4,5,6]

The first report of the use of this treatment schedule was from the M. D. Anderson Cancer Center.^[2] They reported 111 patients with advanced gynecological malignancies, in-

cluding 77 patients with cervical cancer, treated over three decades. The authors reported 100% relief of bleeding and 63% relief of pain after three fractions of radiation, with a progressive increase in the symptom relief with increase in the number of fractions of radiation. This treatment protocol was also used by others^[3,5,6] with equally encouraging results. Based on these results we adopted a similar palliative radiotherapy protocol in the late 1990's for patients with advanced disease treated at our institution.

In our current series we recorded 100% relief of bleeding, 49% relief of vaginal discharge and 33% of pelvic pain. This was similar to reports from other institutions.^[2,3,4,5,6] There was a steady increase in the percentage of patients relieved from bleeding after each fraction although the maximum benefit was visible after the first two fractions. A dose response relationship was clearly apparent for the control of this symptom as was reported for patients treated at the M.D.Anderson cancer center.^[2]

Complete relief of vaginal discharge was seen in 49% of our patients. However the dose response relationship for the relief of vaginal discharge was only apparent up to the second fraction. Our rate of control of vaginal discharge is somewhat higher than that reported by Onsrud *et al*^[6] who reported a control rate of 39% for this symptom in their series from Norway. The difference could be due to large number of patients (42.1%) of endometrial cancer included in their study. Other institutions^[2,3,4,5] did not separately report the relief of this symptom.

Severe pelvic pain was a presenting symptom in 48% of our patients. At the end of treatment only 33% of our patients had complete pain relief. Maximum pain relief was apparent after the second fraction of radiation. This is in contrast to the higher rate of pain relief (63%) reported by Bowulware *et al.*^[2] In a report from the University of North Carolina^[5] the authors reported only 22% relief of pelvic pain using a similar palliative pelvic radiotherapy protocol. The possible reasons for poor response in terms of relief of pelvic pain could be due to poor tumor regression associated with hypofractionated radiation regimens and the associated pelvic inflammatory disease in many of these patients.

Vomiting and diarrhea were the main acute radiation related symptoms in our series. They were well controlled with symptomatic medical management. In view of poor patient compliance and follow-up we could not document late complications of treatment adequately. Only ten patients were documented to have clinically significant (grade III, IV) late toxicity in the form of subcutaneous fibrosis of anterior abdominal wall, radiation cystitis, and radiation proctitis. We anticipate higher rates of late complications with this schedule considering the large fraction size used. Spanos *et et* reported 11% grade III and 19% grade IV

gastrointestinal complications in patient receiving three fraction of pelvic radiotherapy (10Gy/fraction monthly) in advanced pelvic malignancies.^[8] In this study, out of 46 patients there were only 5 patients of carcinoma of cervix. The late gastrointestinal complication rate shown in this study was 25%, which was due to both radiation and misonidazole. However other RTOG studies^[9] using misonidazole have not demonstrated increased late complication rate associated with misonidazole and radiation therapy with conventional fraction. This study also concluded that the severity of complication increased with longer survival. It was 18% at less than six months and 40% at 6 to 12 months. Other studies have reported significantly increased late toxicities amongst patients with survival more than one year. Halle *et al* ^[5] also concluded that the palliative pelvic radiotherapy should be given only to those patients who are expected to survive less than a year.

The lower rate of complications reported in our series could be attributed to:

1. All the patients who achieved complete response after 2nd fraction were treated with intracavitary brachytherapy survived more. They did not receive the 3rd fraction of external beam radiation therapy.
2. Those who received the 3rd fraction, most of them were partial responder or non responder or were having progressive disease and they died of disease within 7 month.

The survival of our patients was similar to that of the patients in other series. We conclude that this treatment schedule provides adequate relief of local symptoms in patients with locally advanced and metastatic cervical cancer. Maximum symptom relief was apparent after two frac-

tions and the addition of a third fraction could probably be avoided in patients without significant bleeding. Late treatment related morbidity could be reduced by the use of optimal treatment technique and radiation energy. This treatment schedule seems suited for developing countries with relatively sparse infrastructure for radiotherapy where cervical cancer still remains the most common cancer among women.

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