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ACUTE TOXICITY PROFILE OF CONCURRENT CHEMORADIATION IN CARCINOMA CERVIX WITH THE INTEGRATION OF BRACHYTHERAPY DURING EXTERNAL BEAM RADIATION THERAPY

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ABSTRACT

Background: Concurrent chemoradiation with weekly cisplatin is the treatment of choice in a case of carcinoma cervix. Prolonging treatment time is detrimental to disease control. When brachytherapy is scheduled during external beam radiation therapy (EBRT), treatment time can be shortened significantly thereby improving local control. As the delivery of radiation with brachytherapy is uniform and spares normal tissues it reduces the acute toxicities. In this study, we aimed to study the acute toxicities associated with this unique scheduling of brachytherapy along with EBRT. **Methods:** Fifty patients with carcinoma cervix between stage IIA to IIIB treated at our institution with chemo-radiation were included in the study. Concurrent chemotherapy was delivered using weekly cisplatin (40mg/m2) for 5 cycles. EBRT was delivered using four field box technique. HDR brachytherapy was introduced after 3rd week of EBRT. Brachytherapy was delivered in 3 fractions each 8.5Gy at the end of the 3rd, 4th, and 5th week. Acute RTOG toxicities were assessed during the treatment and one week post treatment. **Results:** The median age of the study population is 45 years. Eighty four percent of patients received 4 or more cycles of concurrent chemotherapy, whereas 16% of patients received only 3 cycles of concurrent chemotherapy. Most common toxicity observed in the current study population is diarrhea followed by vomiting. Most toxicities are of RTOG grade 0 or 1 and none of the patients developed grade 4 toxicity. Only two patients developed grade 3 diarrhea and one patient developed grade 3 neutropenia. **Conclusion:** Integrating brachytherapy schedule along with EBRT decreases overall treatment time with an acceptable acute toxicity profile.

KEYWORDS : Brachytherapy, toxicity and EBRT

Introduction

Cancer cervix is the second most common cancer reported in Indian women and accounts for more than 77000 (9.1%) deaths related to cancer in India(356-India-Fact-Sheets.Pdf, n.d.). Despite the incidence of cancer cervix is on decreasing trend in the last decade, cancer cervix is still a major health care problem in India with a prevalence of 42/100,000 population(356-India-Fact-Sheets.Pdf, n.d.). About 60% of patients in India present with loco-regional disease and require curative chemoradiotherapy (Chapter8 Cancer Cervix Uteri.Pdf, n.d.).

Curative chemoradiotherapy includes weekly cisplatin, external beam radiotherapy (EBRT) and brachytherapy. Over the years, the EBRT has been standardized and brachytherapy experienced many variations. Currently, HDR intracavitary radiation therapy for cancer cervix has now been widely used and well established because of its various advantages. Integrations of EBRT and brachytherapy are possible with HDR, thus reducing treatment duration and potentially better tumor control.

Many studies showed that the overall treatment time prolongation was associated with increased pelvic recurrences and decreased survival in patients with cancer cervix(Perez et al., 1996),(Perez et al., 1995),(Song et al., 2013). This can be avoided by designing shorter treatment regimens. One such strategy to decrease the treatment time is to integrate brachytherapy schedule concurrently with external beam radiation therapy(Vedasoundaram et al., n.d.). Historically shortening the treatment time using different dose schedules in EBRT resulted in increased acute toxicity. But dose distribution of brachytherapy is more conformal and avoids organs at risk thereby lowering acute toxicity. This study is aimed at reporting acute toxicity of a new treatment schedule where brachytherapy is scheduled concurrently with external beam radiation therapy.

Materials and Methods

Fifty patients with cancer cervix (squamous cell carcinoma) of Stage IIA to IIIB (without the involvement of the lower 1/3rd of the vagina) were included in the study. All patients require to have normal renal, hepatic parameters and Eastern Cooperative Oncology Group (ECOG) performance score of zero to two. Patients who are not fit for HDR brachytherapy after receiving 30Gy of EBRT were excluded from the study and treated according to institute protocol. All study patients received concurrent weekly cisplatin 40mg/m2 along with EBRT. A dose of 50Gy in 25 fractions was delivered using 3DCRT technique and a midline shield is introduced after 46Gy of EBRT. Brachytherapy was introduced after 30Gy i.e., at the end of 3rd week of EBRT and a total of 25.5 Gy is delivered in three fractions at the end of 15th, 20th and 25th fraction of EBRT. Both EBRT and Brachytherapy were not delivered not same day. Total duration of therapy was about 5 weeks. Acute toxicities were measured according to RTOG toxicity criteria once weekly during the course of EBRT and up to one month after completion of treatment. After the completion of treatment, follow up examination was done every two months for 6 months. At every visit, each patient was clinically evaluated for local control of disease and examined for any evidence of distant metastasis

Results

Patient characteristics

The data of 50 patients were analyzed. The median age of the patients was 45 years (range 30-60). All belong to ECOG performance status (PS) 0 or 1. Most patients belong to stage IIB (44%) followed by stage IIIB (32%). Eight four percent of patients completed at least 4 cycles of weekly cisplatin.

Table1- Patient characteristics (n=50)

Age	Years
Median	45
Range	35-60
ECOG PS	% of patients
0	32%
1	68%
Stage	% of patients

IIA	24
IIB	44
IIIB	32
No of cycles of Cisplatin	% of patients
3	16
4	40
5	44

Status of Acute RTOG Toxicity

The patients who underwent treatment were analyzed for acute RTOG toxicity and the grade of toxicity was documented weekly, and the single maximum grade of toxicity for each of the toxicity parameter that the patient developed at the end of EBRT was documented.

Table 2- Status of acute toxicity

Parameter	Status of toxicity	Frequency	Percentage
Skin	Grade 0	42	84
	Grade 1	8	16
	Grade 2	0	0
	Grade 3 or above	0	0
Vaginal mucosa	Grade 0	34	68
	Grade 1	12	24
	Grade 2	4	8
	Grade 3 or above	0	0
UGI	Grade 0	14	34
	Grade 1	27	54
	Grade 2	9	18
	Grade 3 or above	0	0
Vomiting	Grade 0	23	46
	Grade 1	18	36
	Grade 2	9	18
	Grade 3 or above	0	0
LGI	Grade 0	15	30
	Grade 1	20	40
	Grade 2	13	26
	Grade 3	2	4
	Grade 4	0	0
Diarrhea	Grade 0	20	40
	Grade 1	15	30
	Grade 2	13	26
	Grade 3	2	4
	Grade 4	0	0
Neutropenia	Grade 0	38	76
	Grade 1	6	12
	Grade 2	5	10
	Grade 3	1	2
	Grade 4	0	0
Anemia	Grade 0	49	98
	Grade 1	1	2
	Grade 2 or above	0	0
Thrombocytopenia	Grade 0	47	94
	Grade 1	3	6
	Grade 2 or above	0	0

Status of skin and vaginal mucosal toxicity:

Total 8 (16%) patients who developed skin toxicity were of grade1 and no patient developed grade 2 or more skin toxicity. Overall, 16 (32%) patients developed vaginal mucositis. Out of 16 patients who developed vaginal mucositis, 12 were grade 1 toxicity, and 4 were grade 2 toxicity.

Status of UGI toxicity

Overall Upper GI toxicity (anorexia, nausea vomiting and abdominal discomfort) is given below. 54% had grade1, and 18% had grade 2. Most common UGI toxicity observed was vomiting. Of those who had vomiting 18 patients had grade 1, 9 patients had grade 2 requiring oral anti-emetics and none developed grade 3 or more toxicity. Vomiting was seen usually 1 day after administration of chemotherapy suggesting that cisplatin a highly emetogenic drug also contributed to the development of vomiting.

Status of LGI toxicity

Overall lower GI toxicity (altered bowel frequency, diarrhea, rectal discomfort and bleeding) is given below.40% had grade 1, 26% had grade 2 and 4% had grade 3 toxicity. Diarrhea was the most common toxicity observed. Of the 30 patients who had diarrhea 15 had grade 1, 13 had grade 2 requiring oral fluid and parasympatholytic drugs to control diarrhea and 2 had grade 3 toxicity requiring parenteral support. 15 patients who had grade 2 or 3 diarrhea the toxicity was seen after 1st HDR brachytherapy application.

Status of hematological toxicity

Overall, 12 patients developed hematological toxicity of some grade. Neutropenia (N=12) was the most common hematological toxicity seen; only 1 patient developed anemia and 3patients developed thrombocytopenia. The patients who developed anemia or thrombocytopenia also developed neutropenia. There was no isolated anemia or thrombocytopenia observed.

Out of 12 patients who developed neutropenia 6 were of grade1, 5 were of grade 2 and only one patient developed grade 3 toxicity.

DISCUSSION

The radiation treatment for cancer cervix consists of both external beam radiation therapy and brachytherapy. Multiple studies have shown that treatment time prolongation greater than 8weeks resulted in increased local failures and decreased overall survival. Whereas shortening of treatment time improves overall survival and decreases local recurrences. It can be achieved by hypofractionation of EBRT dose, but it will increase the acute toxicities. As brachytherapy dose distribution is more uniform than EBRT, it helps in sparing the organs at risk.

Acute toxicity:

Shortening of treatment time is expected to increase the acute toxicities. But the majority of toxicities that occurred in our study were grade 1 or grade 2 toxicities and very few grade 3 toxicities. There was no grade 2 or more skin toxicity in our study whereas Keys (3.8% grade 3), Pearcey (2.4% grade 3) and Rose (0.6% grade 3) showed some grade 3 skin toxicity(Keys et al., 1999; Pearcey et al., 2002; Rose et al., 1999).

There was no grade 2, 3 and 4 genitourinary toxicity in our study whereas Keys (grade 2- 23.5%, 3 -7.7%, 4 -1.1%) and Rose (grade 1-6.3%, 2- 3.4%, 3 -1.7%, 4 -1.1%) showed higher toxicity for all the grades compared with our study(Keys et al., 1999; Rose et al., 1999). Only grade 1 toxicity was seen in our study. The occurrence of grade 1 toxicity was 22% in our study.

Only 4% patients developed grade 3 gastrointestinal toxicity in our study, and none was of grade 4. Keys et al, observed grade 3 toxicities of 26.8% and grade 4 toxicities of 4.9%(Keys et al., 1999). Rose et al reported 4.5% of grade 3 GI toxicities in their study which is comparable to our study(Rose et al., 1999).

Even hematological toxicities were low in our study, only 10% patients developed grade 2 neutropenia, and 2% patients developed grade 3, whereas rose et al reported a grade 2 neutropenia of 14.8% and 11.9% of grade 3 neutropenia.

Overall, the incidence of grade 3 or more toxicity in our study was low or comparable to historical data. It shows that shortening of treatment time interval to less than 6 weeks is not associated with an increase in acute toxicities. Out of 50 patients, one patient developed local recurrence. It is evident from the study that decreased overall treatment time duration results in good local control. On follow up one patient developed distant liver metastasis.

Conclusion:

Overall treatment time can be shortened by scheduling brachytherapy along with EBRT and this integration of brachytherapy into EBRT is associated with an acceptable acute toxicity profile.

References:

1) 356-india-fact-sheets.pdf. (n.d.). Retrieved April 11, 2022, from https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf
2) Chapter8CancerCervixUteri.pdf. (n.d.). Retrieved April 11, 2022, from https://ncdirindia.org/All_Reports/Report_2020/resources/Chapter8CancerCervixUteri.pdf
3) Keys, H. M., Bundy, B. N., Stehman, F. B., Muderspach, L. I., Chafe, W. E., Suggs, C. L., Walker, J. L., & Gersell, D. (1999). Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. The New England Journal of Medicine, 340(15), 1154–1161. https://doi.org/10.1056/NEJM199904153401503
4) Pearcey, R., Brundage, M., Drouin, P., Jeffrey, J., Johnston, D., Lukka, H., MacLean, G., Souhami, L., Stuart, G., & Tu, D. (2002). Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 20(4), 966–972.
5) Perez, C. A., Grigsby, P. W., Castro-Vita, H., & Lockett, M. A. (1995). Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. International Journal of Radiation Oncology, Biology, Physics, 32(5), 1275–1288. https://doi.org/10.1016/0360-3016(95)00220-S
6) Perez, C. A., Grigsby, P. W., Castro-Vita, H., & Lockett, M. A. (1996). Carcinoma of the uterine cervix. II. Lack of impact of prolongation of overall treatment time on morbidity of radiation therapy. International Journal of Radiation Oncology, Biology, Physics, 34(1), 3–11. https://doi.org/10.1016/0360-3016(95)00169-7
7) Rose, P. G., Bundy, B. N., Watkins, E. B., Thigpen, J. T., Deppe, G., Maiman, M. A., Clarke-Pearson, D. L., & Insalaco, S. (1999). Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. The New England Journal of Medicine, 340(15), 1144–1153. https://doi.org/10.1056/NEJM199904153401502
8) Song, S., Rudra, S., Hasselle, M. D., Dorn, P. L., Mell, L. K., Mundt, A. J., Yamada, S. D., Lee, N. K., & Hasan, Y. (2013). The effect of treatment time in locally advanced cervical cancer in the era of concurrent chemoradiotherapy. Cancer, 119(2), 325–331. https://doi.org/10.1002/cncr.27652
9) Vedasoundaram, P., Vandanasetti, S., Periasamy, K., & Kandasamy, S. (n.d.). Measurement of Cervical Regression and Optimizing Brachytherapy Schedule Concurrently with External Beam Radiation Therapy in Cervical Carcinoma. Cureus, 11(8), e5316. https://doi.org/10.7759/cureus.5316