Role of Hyperfactionated external beam radiotherapy in stage IIB to III and postoperative cases of carcinoma cervix: an evaluation

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Citation

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Abstract

OBJECTIVE – To investigate the tolerance to and response rate with hyperfractionated external radiotherapy in stages IIB to III and postoperative cases of carcinoma uterine cervix.METHODS- A prospective study of carcinoma uterine cervix FIGO stage IIB to III and postoperative cases was undertaken. A total of 22 patients were studied (12 in study group and 10 in control group).Control group was treated by conventional fractionation-60Gy/30fractions (f), 2Gy/f, 5days/week for 6 weeks.Study group was treated in hyperfractionation schedule 72Gy/60f,5days/week over 6weeks. Two fractions of 120cGy per day were given at interval of 6 hours.RESULTS – Patients enrolled in this study ,13.6% had stage IIB ,4.5% stage IIIA,22.7% stage IIIB and 59.1% postoperative cases. No severe acute toxicity was observed but moderate acute reactions were high. The commonest site of complication was small bowel where severe toxicity occurred slightly higher in study group than control group. Complete response was 80% and 91.7% in control and study group respectively.CONCLUSION - Hyperfractionated radiotherapy as compared to conventional radiotherapy has produced clinically better tumor control in stages IIB to III and postoperative cases without enhancing normal tissue damage.

INTRODUCTION

Carcinoma uterine cervix is the most common malignancy in Indian women. It constitutes 38.52% of all cancers in Indian women. It is most frequent cause of death attributable to malignancies in developing countries. The majority of patients present in late stages and the 5-year survival rates are dismal.

AIMS AND OBJECTIVES

Hyperfractionated radiation therapy permits higher total doses of radiation without increasing toxic effects to normal tissue.

The aims and objectives of the study is to evaluate the tolerance and response rate with hyperfractionated external beam radiation therapy in stages IIB to III and postoperative cases of carcinoma cervix.

MATERIAL AND METHODS

Between June 2007 to May 2008 previously untreated cases o carcinoma cervix stages IIB to III and postoperative cases were included in this study. All cases were biopsy proven. Pretreatment evaluation included history taking and physical examination for staging including hematological, liver and kidney function tests.

X-ray chest, ultrasonography, CT Scan and intravenous pyelogram were also done.

Total 10 patients were enrolled in control group and 12 patients in study group. External beam radiotherapy was delivered to the whole pelvis using CO-60 beam at 60 cm SSD. Control group was treated by conventional fractionation which consisted of delivering 60Gy in 30 fractions(f), 2Gy/f, and 5days/wk for 6weeks.

Study group was treated in hyperfractionation schedule delivering 72Gy in 60 fractions 5days/weeks over 6weeks. Two fractions of 120 cGy were given at 6 hours interval.

OBSERVATIONS AND RESULTS

Figure 1

Table I: PATIENT CHARACTERISTICS

Parameters	Control group	Study group
Age		
Median	45 years	45 years
Range	(32-60) years	(35-60) years
Parity		
Median	6	6
Range	(2-13)	(4-8)
Stage		
IIB	1(10%)	2(17%)
IIIA	1(10%)	-
IIIB	2(20%)	3(25%)
Postoperative	6(60%)	7(58.1%)
Histopathology		
Squamous Cell Carcinoma	9(90%)	11(91.7%)
Adenosquamous Carcinoma	1(10%)	1(8.3%)

Figure 2

Table II: DISTRIBUTION ACCORDING TO SYMPTOMS, RESPONSE RATE AND COMPLICATIONS

CLINIACAL PRESENTATIONS	Control Group	Study Group
1.Watery discharge per vaginum	9(90%)	8(67%)
2.Blood mixed discharge/P.V. bleeding	8(80%)	8(67%)
3.Pelvic pain	5(50%)	5(41%)
RESPONSE RATE		
1.Complete Response	8(80%)	11(91.7%)
2.Partial Response	1(10%)	1(8.3%)
3. No Response	-	-
4. Progressive	-	-
5.Recurrence	1(10%)	-
COMPLICATIONS		
1.Skin desquamation	2(20%)	3(25%)
2.Gastritis	2(20%)	3(25%)
3.Diarrhea	1(10%)	6(50%)
4.Urinary complaints	4(40%)	3(25%)
5.Tenesmus	2(20%)	2(17%)
6.Rectal bleeding	1(10%)	1(8%)

DISCUSSION

Since 1980s a growing trend of research to improve radiation efficiency in control of malignant tumors with equal or less complications, has advocated a move away from traditional radiotherapeutic fractionation. In clinical practice, depending on the dose fractionation schedule, either acute reactions or late sequelae of therapy may be dose limiting [1,2].

To observe an increase in the tolerance of normal late responding tissues by fractionation, interval between fractions must be long enough to allow for complete recovery of sublethal damage of normal tissues but not tumors. Tumors and acute responding tissue are expected to repair the sublethal damage around the same time, longer than late responding tissues[3,4]. However, the recovery of sublethal damage of normal acute responding tissues should be more efficient than tumors because chronically hypoxic cells of tumors are unable to or totally incapable of repairing sub lethal damage[5].

Survival curves of mammalian cells exposed to ionizing radiation display the characteristic pattern of initial shoulder followed by straight line. This type of curves has been mathematically represented by a linear quadratic model, where is linear and is quadratic component of cell killing. The ratio / is the dose in Gray at which linear and quadratic components of cell killing are equal[5]. Late responding tissues have a low / ratio (practically, /=3Gy); acute responding tissues, on the other hand, present a higher /ratio (assumed as /=10Gy).

Among tumors squamous cell carcinoma of uterine cervix has a high /ratio, whereas most normal pelvic tissues which usually limit increase of dose in the pelvis have a low /ratio.

These characteristics, theoretically qualify squamous cell carcinoma of cervix for hyperfractionated radiotherapy treatment. But the practical problem is to assess the feasibility and ideal dose of hyperfractionation schedule in this tumor.

One of the earliest published work on hyperfractionation radiotherapy of pelvic tumors was by Cox and colleagues on a phase I/II RTOG protocol. This prospective one arm study evaluated 50 patients with advanced T3 or T4 or T2N + bladder cancer between April 1983 and June 1986. All patients were submitted to hyperfractionated radiotherapy in the whole pelvis, with 1.2Gy fractions at minimum interval of 4hours, upto the dose the dose of 50.4Gy[6]. Fields were later reduced and total dose ranged from 60Gy in 9 patients, 64.8Gy in 15 patients to 69.9Gy in 26 patients. Similar group has been given60Gy by traditional radiotherapy to pelvis.The authors concluded that tolerance of normal pelvis tissue to that of hyperfractionated treatment was good enough to justify its application to other pelvic tumors.

The first published clinical study on hyperfractionation in

carcinoma cervix was a work by Indian group, Varghese and colleagues in 1992[7]. The study compared 15 patients in hyperfractionation with other 15 patients exposed to traditional radiotherapy. Hyperfractionation was given 1.2Gy per fraction (f), whole pelvic irradiation 2f/day with interval of 6 hours. A total tumor dose (T.T.D.) of 60Gy/50f over 5weks was delivered. The control group received 50Gy/25f, 2Gy/f over 5weeks, all 30 patients than, underwent one intracavitary insertion of low dose Cesium-137.The article reports that 8weeks after treatment all acute normal tissue reactions had subsided without any sequelae.

A second published article on hyperfractionated radiotherapy in carcinoma cervix was reported by Komaki and colleagues in 1994[8]. This study was prospective one arm Phase I/II trial by RTOG. It evaluates late effects of 71 patients with carcinoma cervix classified as bulky stage IB,II,III and IV.

Hyperfractionation was done with doses of 1.2Gy to the whole pelvis twice daily at 4-6hrs interval, 5days/weeks. The whole pelvis received doses ranging from 24-48Gy. Following external radiation one or two intracavitary application with Cesium-137 delivered a total minimum dose of 85Gy to Point A.

Third study was published by Faria and colleague in 1996[9]. The study evaluated tolerance to and survival rate with hyperfractionated external radiotherapy only in patients with stages IIIB carcinoma of uterine cervix. Total 23 patients underwent hyperfractionated external radiotherapy without brachytherapy. Hyperfractionation was given with 1.2Gy dose twice daily at 6 hours interval,5days/week, to whole pelvis upto 72Gy within 30 days. This is the only published study which gave the highest total dose with hyperfractionation. The result suggest futher increase of total in pelvis with hyperfractionataed irradiation may be possible.

Tumor recurrence pattern suggest the need for improved control in the pelvis perhaps by a further increase in the total dose permitted by hyperfractionation. Metastasis in the paraaortic lymph nodes can be addressed by extending the volume irradiated to encompass the nodes.

CONCLUSION

Hyperfractionated schedule as compared to conventional radiotherapy had produced clinically better tumor control without enhancing normal tissue damage. The results of the study group are definitely better than patients treated with conventional schedule. Further study is required with a larger sample size to give a definite opinion regarding the role of hyperfractionated radiotherapy in stage IIB to III and in post operative cases of carcinoma cervix.

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