

Original Article

Carcinoma cervix treated with Radiotherapy – our experience with emphasis on our concerns

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Abstract

Objective: Carcinoma cervix is the commonest cancer seen in our department. The purpose of this study is to discuss the unique problems we have encountered and address our concerns. **Materials and methods:** A retrospective analysis was done on 257 patients with carcinoma cervix seen between 1998 and 2005. A descriptive analysis was done wherein the proportion of patients coming from rural areas, the results of treatment and complications were brought out. **Results:** More than 50% (140/257) of the patients were from the rural areas. Sixty (23%) were defaulters and 197 (77%) completed the scheduled treatment. Forty four out of 197 (22%) received palliative RT and 153/197 (78%) who received curative treatment were analyzed. Status of 54 patients were unknown because 24 patients were from the camp and 30 patients were lost to follow-up. Thus, 78/99 (79%) patients were NED. **Conclusion:** A similar disease pattern and patient characteristics are expected in future. Communication with referring doctors, effective counseling of patients and relatives during treatment will hopefully bring down the default rates and the number of cases lost to follow up.

Key words: carcinoma cervix, concurrent chemoradiation.

Introduction

The incidence of cervical cancer is more than 30 per lakh population in Africa, Central China, South and Central America; 15-30/lakh in India and less than 15/lakh in the rest of the world. As per the population based cancer registry, the incidence of cervical cancer in India varies from 16.3 – 30.6/lakh. The highest is seen in Chennai, lowest in Delhi and the incidence in Bangalore is 21.7/lakh¹. In our department, cervical cancer forms

18.39% (257/1395 between 1998 and 2005) of the total number of cases.

Cervical cancer, being the second most common type among the women in developed countries, is currently estimated to be present in over one million women worldwide. Most of them have not been diagnosed nor do they have any access to treatment that could cure them or prolong their life. In 2005, there were over 500,000 new cases, of which more than 90% were in developing countries². It was responsible for 260,000 deaths in 2005, 95% of which occurred in developing countries. Over the next 10 years, deaths due to cervical cancer are projected to rise by almost 25%². Despite well established screening programs in the US, nearly half of the cervical cancers are seen in locally advanced stages³. The developing countries, the disease is usually advanced at the time of diagnosis and cervical cancer is the principal cause of death due to cancer in

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women³. In our hospital, 81% of the cervical cancers were seen in stage II B and beyond.

Need for the study

Carcinoma cervix is one of the commonest cancers seen in our department; the others being breast and head and neck cancers. More than eighty percent of the cervical cancers are locally advanced at the time of presentation. Concurrent chemo radiation and LDR brachytherapy with either BARC applicators or transperineal Syed-Neblett template is the protocol followed in our department. Our medical college has adopted a primary health centre at Kaiwara, a rural district where our faculty and students conduct regular camps. Out of the 257 patients that we saw over seven years, 140 (54.5%) were from rural background. We have encountered some unique problems with these groups of patients.

These patients are kept in wards for almost two months with stay, food, and investigations being done free and radiotherapy was done at concessional charges. Following treatment, it is very difficult to keep a track of these patients. In this retrospective analysis, we have tried to not only analyze the results of treatment but also to identify and address our concerns.

Materials and Methods

A total of 257 patients with carcinoma cervix were treated in our department between January 1998 and March 2005. Table 1 shows the stage wise distribution. Out of these, 60 (23%) patients defaulted during the treatment and 197 (77%) completed the scheduled treatment. Out of the 197 patients 150 (76%) were treated with radical intent and 47 (24%) with palliative radiation followed by symptomatic treatment. Three patients who showed good response to palliative radiation were converted to radical treatment. Thus, 153 (78%) patients who received curative treatment form the subjects of our study.

A dose of 46 Gy in 23#, 5#/week over 4.5 weeks was given for patients with radical intent. Midline shielding was done at 40 Gy, for patients who showed >50% central response using a central 5cm wide five HVL shielding. Out of the 153 patients, 83 also received weekly Cisplatin infusion 50mg over 3 hours with hydration for 4-6 cycles. Patients who received palliative RT of 30 Gy in 10# over 2 weeks were assessed 2 weeks later for tumor response.

Brachytherapy consisted of manual after loading intracavitary application or transperineal interstitial implantation using Cesium-137 or Iridium 192 sources respectively. A decision of either treatment was taken based on EUA (Evaluation Under Anesthesia) findings and availability of Iridium sources. The patients were also given Cisplatin infusion during brachytherapy.

Patients were followed up at 2 weeks at first, once a month for 3 months, one in 2 months for 6 months, once in 3 months for 2 years and once in 6 months later. The follow up period was from a minimum of 6 months to a maximum of 7 years. Every follow up included careful clinical examination to assess the tumor response and radiation reactions. Wherever necessary, investigations were done. Efforts were made to contact patients who were not coming for follow up by telephone or post. A descriptive statistical analysis was done.

Results

The results obtained are shown in table 1. Amongst the 153 patients treated radically, 24 (15.6%) were from the camp who could not afford to come to the hospital for follow up and they were advised regular follow up at their hometown. Thirty (19.6%) patients were lost to follow up. Thus amongst the 99 patients, 78 patients (78.8%) were disease free, ten (10%) patients had progressive disease, eight patients (8%) came back with local recurrence and three (3%) had distant metastasis. Amongst the ten patients with progressive disease, six patients were in stage IIIB (four had received chemo and two had not), two patients in stage III A (both had not received chemo) and two patients in stage IVA. Eight patients showed local recurrence – five in stage IIIB (all five had not received chemo, three patients recurred after one year, two recurred after three years); two patients belonged to stage IB and one patient in stage IV A (all three recurred after one year). Three patients showed distant failure – one was PO who came back with supraclavicular nodes. Two patients of IIIB developed bone metastasis and liver metastasis at the end of two years and one year respectively.

Amongst the 78 patients who were NED, 52 received chemotherapy and 26 had not received chemo. Sixteen patients had not received chemo because of age, other co-morbid conditions and 10 patients were treated during the first two years when chemotherapy was not routinely practiced. Table 2 shows stage wise distribution of patients who were disease free with and without chemotherapy.

Total number of camp patients was 24, out of which 15 received concurrent chemotherapy and nine did not receive chemotherapy. We could not get the information regarding these patients in spite of repeated mails.

The toxicities were assessed according to RTOG criteria. Acute toxicities: Five (5%) patients developed acute Grade II skin toxicity and 12 (12%) patients developed Grade III skin toxicity. Two (2%) patients developed Grade II rectal complication. One (1%) patient developed Grade II upper and lower GI complication

and one (1%) patient developed Grade II lower GI complication.

Late toxicities: One (1%) patient developed Grade II bladder complication, 11 (11%) patients developed rectal reactions, – Grade I-1; Grade II 4; Grade III – 5; Grade IV-1. A total number of 37 patients underwent interstitial implant. Amongst the 11 patients who developed late rectal reaction, 10 received interstitial implant. One patient who developed Grade II bladder complication also had received interstitial implant.

Table 1. Stage wise distribution of patients who were disease free against total number of patients analyzed.

Stage	Total number of patients	Total patients analyzed	Camp	Not followed up	Total	Total NED
IB	6	6	1	2	3	1
IIA	5	5	-	1	4	4
IIB	63	50	9	10	31	31
IIIA	5	4	2	-	2	-
IIIB	104	62	12	12	38	25
IVA	25	6	-	-	6	3
IVB	15	-	-	-	-	-
PO	34	20	-	5	15	14
Total	257	153	24	30	99	78

Table 2: Stage wise distribution of disease free patients with and without chemotherapy.

Stage	Received Chemo	Not received Chemo
IB	1	-
IIA	2	2
IIB	15	16
IIIB	21	4
IVA	1	2
PO	12	2
Total	52	26

Discussion

In our study 81% of the patients were in locally advanced stages. The role of radiotherapy increases with the increase in the stage of the disease. In developed countries 52% of the new cases of cancer receive radiotherapy. Because of the advanced stage at presentation, the patients with cancer in underdeveloped and developing countries will have a greater need for radiotherapy than those in the high income countries ⁴.

Radiotherapy remains an integral component of the standard treatment for majority of the cases, particularly those with bulky tumors more than 4 cm³. Despite the improvements in radiation equipment and techniques with better dose delivery during the past three decades,

the survival of patients with carcinoma of cervix in advanced stages remains low. This is attributed to the local failure³, which range from 4.5 – 25% and is the most common cause of death in these women³. Many attempts have been made to improve the outcome of radiotherapy, but none of these has been successful. The publication of five randomized trials in 1999, resulted in an alert by NCI in February 1999, suggesting that platinum based concurrent chemo radiation should be considered first line treatment with locally advanced cancer of the cervix. As a result, strategies involving combination therapy, especially the concurrent use of chemotherapy with radiotherapy, is beneficial³. Addition of chemotherapy to radiation therapy improved the progression free survival and overall survival by 16% and 12% respectively⁵. Thus concurrent chemotherapy and radiation therapy is the standard of care for local regionally advanced cervical cancer.

Cisplatin has been shown to be synergistic with radiotherapy administered once a week⁵. A systematic review and meta analysis of published trials using cytotoxic chemotherapy prior to radiotherapy found no benefit in overall survival and in addition toxicity increased⁶. Concomitant chemo radiation has the advantage of avoiding delay in starting radiation following neoadjuvant chemotherapy and at the same time is associated with lesser toxicity.

Several studies have demonstrated and expected increase in toxicity from the addition of chemotherapy, especially GI or hematological toxicity. A dosimetry study was done on 43 patients treated with concomitant chemo radiation (cisplatin) with the aim of investigating the correlation between the radiation dose to the rectum and the incidence of late rectal complication. At 40 months post-treatment, the group of patients receiving higher dose to the rectal reference point than the prescribed dose to point A, had serious grade 3 and 4 rectal complication (46% vs 14%)⁷. A systematic review and meta analysis of 19 trials carried out between 1980 and 2000, comprising 4580 patients by Green et al⁵ has shown a highly significant survival benefit with concomitant chemo radiation HR-0.71, p<0.00001, which represents a 12% absolute benefit in survival. In view of the consistency and the extent of survival benefit for chemo radiation, the additional acute toxicity is justified⁸ – grade 1 and 2 hematological toxicity was increased more than three fold and grades three and four toxicities increased to two fold. There was only a slight fall in hemoglobin and the other hematological toxicities were self limiting or resolved with medical

treatment. Gastrointestinal toxicity was twice as common with no difference in genitourinary, neurological, or skin toxicity.

In our hospital, 2% of the patients developed acute grade II rectal complication and 1% each developed grade II upper and lower GI complication. The late reactions included 1% with grade II bladder toxicity and 11% developed rectal reactions of grade I-IV.

Our concerns

1. Investigations: Uniform patterns of investigations were used in all patients. We were able to do the required investigations even in those from low socioeconomic status. The para aortic region was assessed only with abdominal ultrasound. Considering this, we had more number of advanced patients where we could have used a CT/MRI scan, but was not considered due to financial constraints.
2. Chemotherapy: Sixteen patients had not received chemo because of age, other co-morbid conditions and 10 patients were treated during the first two years when chemotherapy was not routinely practiced. In the initial four years, chemotherapy was used only in advanced stages and subsequently was made the standard protocol for all the patients. It was deferred only in patients with severe co-morbid diseases. All the patients were subjected to complete blood counts and renal function tests before each cycle of chemotherapy. Fifty two patients received four or more cycles of chemotherapy.
3. One fourth of the patients defaulted during treatment. An important observation was that we had more number of defaulters in the initial 2-4 years and in the subsequent years better compliance to treatment was noted once we made concurrent chemotherapy a protocol similar to what was observed by Saibishkumar et al⁹. We also noticed that 33/60 (55%) of the defaulted patients did show initial good response to external radiation but did not report for brachytherapy. It was interesting to know that the complete improvement in the presenting symptoms with external radiation was one of the reasons for non-compliance to brachytherapy.
4. Fifty four patients out of 153 (35.3%) constituted lost to follow up group. Among these 54 patients, we had 24 who were diagnosed at the primary health centre and were very poor to come to the hospital

at their own cost. We did try to contact them with a reply card but without any success.

5. The radiation induced morbidity was within the acceptable limits. We did not see any significant suprapubic fibrosis in spite of treating on telecobalt and most of our patients had a separation of more than 18cm. The reasons were that we did not use external beam therapy as the sole modality in any patient and we used four field treatments in obese patients. This shows that even with the available cobalt machine and brachytherapy, impressive results with acceptable toxicities can be achieved with careful planning especially in younger patients and in women with co-morbid conditions. Different Indian authors at various centers have shown the same⁹.

Conclusion, future thoughts / actions

We expect to face the same kind of disease pattern, patient characteristics, and the problems in future also. Better documentation as far as patient details, communicating with the referring doctors and effective counseling of patients and relatives throughout the course of treatment and during the follow up will probably bring down the defaulters and lost to follow up rates.

References

1. Nandakumar A, Gupta PC, Gangadharan P et al. Development of an atlas of cancer in India, First all India report, 2001-2002. Bangalore: National Cancer Registry Programme (ICMR), 2004.
2. World Health Organization. Comprehensive cervical cancer control: a guide to essential practice. Geneva: WHO, 2006.
3. Thomas GM. Improved treatment for cervical cancer-concurrent chemotherapy and radiotherapy. *N Engl J Med* 1999;340:1198-200.
4. Barton MB, Frommer M, Shafiq J. Role of radiotherapy in cancer control in low income and middle income countries. *Lancet Oncol* 2006;7:584-95.
5. Green JA, Kirwan JM Tierney JF et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet* 2001;358:781-6.
6. Tierney JF, Stewart LA, Parmar MK et al. Can the published data tell us about the effectiveness of neoadjuvant chemotherapy for locally advanced cancer of the uterine cervix? *Eur J Cancer* 1999;35:406-9.
7. Clark BG, Souhami L, Roman TN et al. Rectal complications in patients with carcinoma of cervix treated with concomitant cisplatin and external beam irradiation with high dose rate brachytherapy a dosimetric analysis. *Int J Radiat Oncol Biol Phys* 1994;28:1243-50.
8. Kirwan JM, Symonds P, Green JA et al A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer. *Radiother Oncol* 2003;68:217-26.
9. Saibishkumar EP, Patel FD, Sharma SC, Evaluation of late toxicities of patients with carcinoma of the cervix treated with radiotherapy: an audit from India. *Clin Oncol (R Coll Radiol)* 2006;18:30-7.