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Concurrent chemoradiation in locally advance carcinoma cervix (Figo stage IIB tO IVA)

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Abstract
Aim: to assess concurrent chemoradiation in locally advance carcinoma cervix (figo stage iib to iva).
Material and method: All patients underwent a thorough clinical examination, complete haemogram, biochemical workup, chest x-ray and ultrasound abdomen and pelvis. Staging was done as per Revised FIGO 2009. External Radiotherapy with Cobalt 60 teletherapy machine is given. Two field or four field box technique is used. Daily treatment is given from Monday to Friday. Total dose of radiotherapy given is 50 gy in 25 fractions. Manual after loading Caesium 137 BARC applicaters are used. Two ovoid and one tandem technique is used. Total dose given is 22 to 25 gy. Single session is given after external radiotherapy. The American Brachytherapy Society recommends that intracavitary applicators insertions be performed under analgesia/ anesthesia to allow examination, insertion and packing.
Result: Out of total cases 38 i.e.76% had complete response, 7 i.e. 14 % had partial response and 5 i.e.10 % lost for follow up. Out of total cases, the toxicities studied i.e. the skin toxicity, vomiting and diarrhoea was 40% to 50% which was under grade 2.
Conclusion: The compliance to treatment was good. The acute toxicities to combined treatment were within acceptable limits. Our observations indicate that concurrent chemo radiotherapy using cisplatinum in advanced carcinoma of the cervix, is a feasible approach towards better locoregional response.

Keywords: Carcinoma Cervix, Chemoradiation

Introduction
While carcinoma of cervix ranks second after those of Breast, Colorectum and Endometrium in developed countries, it is the leading cancer among females of developing countries35. The disease frequently presents as large tumours of advanced stage38. It constitutes 40% of all female malignancies in our country [2] Over 80% of patients reported to FIGO (International federation of gynaecological oncology) with invasive cancer were treated by radiotherapy. This high frequency is mainly due to multiparity, poor genital hygiene, low socio-economic conditions, early marriage, non-circumcision in the male Hindu population. Management of microscopic, but invasive disease confined to the cervix (FIGO stage IA) is very effective, with simple hysterectomy for giving greater than 95% five year survival [3].
Most patient with early disease, however present as stage IB or IIA, and are treated by radical radiotherapy or radical surgery. For such patients five year survival is between 80% to 90%8. Radical hysterectomy (removal of uterus with draining lymph nodes) has become standard management for the majority of early cervical cancer, but radiation therapy was increasingly employed for bulky FIGO stage I and II tumours (more than four centimeters), which accounts for one third of the incidence but half the relapses, as tumour size has been shown to be an important prognostic variable [1].
Most HPV infections in young females are temporary and have little long term significance.70% of infections are gone in 1 year and 90% in 2 years. Almost all are gone after that21. But when infections persist in 5% to 10% of infected women there is high risk of developing cervical precancer (lesions on the cervix), which can progress to invasive cervical cancer. This process usually takes 15-20 years, providing many opportunities for detection and treatment of the pre-cancerous condition, often with high cure rates [4].
More than 30 to 40 types of HPV are typically transmitted through sexual contact and infect the anogenital region.

Some sexually transmitted HPV types may cause genital warts. Persistent infection with "high-risk" HPV types different from the ones that cause warts-may progress to precancerous lesions and invasive cancers42. HPV infection is a cause of nearly all cases of cervica cancers45; however most infections with these types do not cause disease.

Material and Method

This study was conducted in the Department of Obstetrics and Gynecology in association with Radiotherapy Department at Krishna Institute of Medical Sciences (Deemed University), Karad from May 2009 to May 2011. In the current study 50 patients with locally advanced carcinoma cervix (FIGO stage IIb to IVa) are studied.

All patients underwent a thorough clinical examination, complete haemogram, biochemical workup, chest x-ray and ultrasound abdomen and pelvis. Staging was done as per Revised FIGO 2009. External Radiotherapy with Cobalt 60 teletherapy machine is given. Two field or four field box technique is used. Daily treatment is given from Monday to Friday. Total dose of radiotherapy given is 50 gy in 25 fractions. Manual after loading Caesium 137 BARC applicaters are used. Two ovoid and one tandem technique is used. Total dose given is 22 to 25 gy. Single session is given after external radiotherapy. The American Brachytherapy Society recommends that intracavitary applicators insertions be performed under analgesia/ anesthesia to allow examination, insertion and packing. Here we use short general anesthesia or sedation depending onpatients compliance with routine use of analgesia in the form of Inj. Voveron (diclofenac sodium) 75 mg deep intramuscular. In the chemotherapy cisplatin in the dose of 40mg/meter square every week for 4 to 6 cycles is given. Cases are followed after 6 weeks and 3 months.

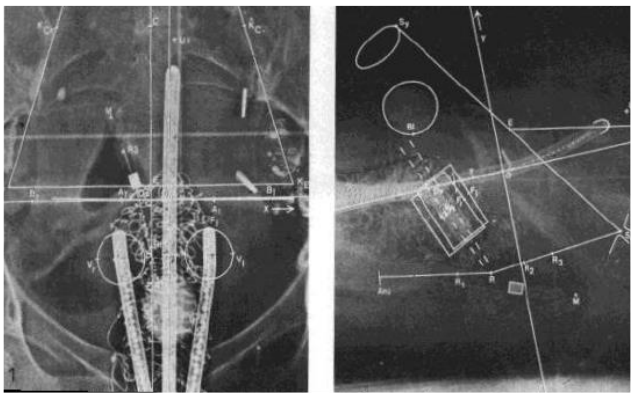

Fig. 1: Simulation X-ray I/C Brachytherpy

Result

Out of total cases 28 i.e. 56% are from 51 to 60 age group and 14 cases i.e. 28% are from 41 to 50 age group. Out of total cases 41,i.e. 82% are from rural area and 9,i.e. 18%are from urban area. Out of total cases, 30 i.e. 60% had white pv disharge and pv bleeding as common complaint. Out of total cases 21 i.e.42% are moderatetly differentiated squamous cell carcinoma and 18 i.e.36% well differentiated squamous cell carcinoma. Out of total cases 33 i.e. 66% are from stage IIIb and 16 i.e. 32% are from sage IIb. Out of total cases 38 i.e.76% had complete response, 7 i.e. 14 % had partial response and 5 i.e.10 % lost for follow up. Out of total cases, the toxicities studied i.e. the skin toxicity, vomiting and diarrhoea was 40% to 50% which was under grade 2.

Discussion

In my study at Krishna Institute of Medical Sciences, 50 carcinoma cervix patients were included. Though it was difficult to draw concrete conclusions with the results of the study, due to the small number of patients and short period of follow up and an analysis of various parameters of patients data and results correlated with the literature available are presented. Incidence of cervical cancer – incidence of cervical cancer is thirty four percent per one lakh population in India as a whole, 42 per lakh in south India [5].

At our institute – Krishna Institute of Medical Sciences, Karad it is 20 % of all the cancers reported and 40 % of all female cancers. Age - Age of our patients varied from 36 to 60 years with mean age of 51 years. Of which 56% belong to age group of 51-60 years of age group and 28% belong to 41 - 50 years of age group and 16 % belong to 31-40 years of age group. The world literature reports that more than 50% of patients with carcinoma cervix reports before the age of 50 years and these patients are seen with locally advanced disease. The modern concept of genesis and spread of carcinoma of cervix is in 4 phases: Induction phase- 15 – 30 years; In-situ phase- 5 – 10 years; Invasive phase- 1 – 5 years; Dissemination phase- 1 – 5 years Socio-economic status – Most of our patients come from lower and lower middle socioeconomic group. They have more number of children and their genital hygiene is poor. Majority of patients are from rural areas.

Following are the common complaints that the patients present with at the time of diagnosis. White discharge per vagina. White discharge associated with back ache.

Bleeding per vagina. Back ache, pain abdomen. Post coital bleeding.

Menstrual cycle status, age at marriage and parity – all patients attained menarche between 13 – 14 years, 12/50 were premenopausal and 38/50 were post-menopausal amounting to 24% and 76% respectively. All the patients has early marriage between 9 years and 17 years. As the literature, early marriage is found to be one of the etiological factor in cancer cervix as encountered in our study also [6].

Out of total patients 92% were multiparous, 6% were primipara and 2% i.e. one case was nulliparious. In multiparous patients the number of children were ranging from 3 – 9 children, average being 4. Thus multiparity is found in our study group as reported in literature. Clinical staging – the incidence of cervical cancer in our country is 40%, 70% of these cases belong to stage III, 25% to stage I and II and 5% to stage IV. In our study 66% cases were among stage III, 32% to stage II and 2% to stage IV.

Histopathological study 96% were squamous cell carcinoma of cervix, only 2 cases i.e. 4% were adenocarcinoma of cervix. Well differentiated, moderately differentiated, poorly differentiated all categories were found in our study. Majority belonged to moderately differentiated squamous cell carcinoma i.e. 42%.

Radiotherapy- In radiotherapy, total dose of 72-75 Gy was given to poin A using both external and internal radiation.

Chemotherapy- Cisplatin in the dose of 40mg/meter square every week for 4 to 6 cycles is given [7]. The use of cisplatinum along with radiotherapy in cervical carcinoma has shown varying response rates. In our study a complete response of 76% and a partial response of 14% is achieved. Choo *et al.* (1983) achieved a complete response rate of 55% which is less than the complete response rate observed in our patients. They have used cisplatinum at a dose of 25mg/m2

weekly once till the completion of intracavitary treatment. Carolyn *et al*. (1988) achieved a complete response rate of 81% which is higher than the complete response rate seen in our study. They have used cisplatinum in a dose schedule of 20 mg x 5 days for three cycles. Gynaec Oncology Group, in over 800 patients of Gynaecological malignancies have used cisplatinum in three dose schedules - 50mg/m2, 100mg/m2, 20mg/m2 x 5 days every 3 weeks. The overall response rate is around 23%. They have documented the activity of cisplatin as well as it's independence of response from dose and schedule of the drug. Blake *et al* 1983, have achieved complete response of 89% which is higher than that observed in our study. This is probably due to the higher dose used - 120mg/m of cisplatinum. Weiss *et al* 1988, have achieved a response rate of 25% with cisplatin +5 Fluroracil which is less than that observed in our study with cisplatin alone [8].

In 1999 keys *et al*. reported the results of the gog -123 study in which 369 patients with bulky stage IB disease and without any evidence of paraaortic lymph node metastasis were radomized between weekly cisplatin(40mg/m2) and radiation versus radiation only. At a median follow up of 36 months, local response and distal metastasis rates were 9% and 21% and 12% and 16% respectivly, both in favor of concomitant arm.

Rose *et al* in 1999 reported the results of GOG- 120 trials in which a course of standard pelvic radiotherapy was combined with one of the three concurrent chemotherapy regimens (cisplatin alone, cisplatin with 5-FU with hudroxyurea, hydroxyurea alone) in patients with FIGO IIB-IVA. At a median follow up of 35 months, survival curves for the two cisplatin groups were almost identical and both were statistically superior to the survival curve of the hydroxyurea alone group.

The National Cancer Institute (USA) alert in February in 1999 stated that concomitant chemoradiotherapy should be considered for all patients with cervical cancer, based on evidence from five randomised controlled trials (RCTs) [9]. In 2003, Aich Ranen Kanti *et al* reported the results of 867 patients with untreated ca cervix FIGO stage IIB –IVA were treated with concomitant chemoradiation with cisplatin and gemcetabine and the complete local control rate was 67% at 3 months after completion of treatment, which was subsequently reduced to 60% at the median follow up of 10.5 months, which showed the promising results of it. The other aspect of the study was the toxicity [10]. In our study we have mainly studied acute toxicity. Mainly skin and intestinal toxicities, vomiting and diarrhea has been studied [11]. They were graded according to CTC (National Cancer Institute-Common Toxicity Criteria) criteria. Most of them were grade o and grade 1 which were manageable with antiemetic medication and there were no interruption either for chemotherapy or for radiotherapy. Aich Ranen Kanti *et al.* in 2003 observed 25% and 63% grade 0 and grade 1 toxicity respectively for nasea and vomiting which was 35% and 50 % in our study. They have also observed 25% and 54% grade 0 and grade 1 toxicity respectively for diarrhea, which was 16% and 62% in our study [12].

Choo *et al*. 1983 observed that 30% of their patients who received cisplatinum developed leukopenia which needed temporary interruption in radiation. Although myelosuppression was noted in our study, it was not severe enough to cause delay in completion of therapy. In conclusion, with the use of single agent cisplatin concurrent with radiation therapy, the response noted appears to be superior when compared to that observed with radiotherapy alone. Although there were some toxicities, they did not result in any delay in the completion of treatment either Chemotherapy or Radiotherapy. Many of the carcinoma cervix cases treated in the dept used only radiation therapy as a treatment modality before 2005 [13]. Retrospctive analysis had shown 71% had complete response, 9% had partial response and toxicities were 30% to 35% which was under grade 2. There was marginal clinical improvement in local response by adding chemotherapy but was not statistically significant.

Conclusion

In our study of concurrent cisplatin (at 40mg/m2 for 4 to 6 cycles) with radiotherapy (external + intracavitary) application, we have found an excellent locoregional response for locally advanced carcinoma cervix (IIB-IVA) The compliance to treatment was good.

The acute toxicities to combined treatment were within acceptable limits. Our observations indicate that concurrent chemo radiotherapy using cisplatinum in advanced carcinoma of the cervix, is a feasible approach towards better locoregional response.

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