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EFFECT OF CONCURRENT CHEMO-RADIOTHERAPY IN THE MANAGEMENT OF CERVICAL CANCER: A PROSPECTIVE STUDY

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ABSTRACT

The present study was conducted to evaluate the effect of concurrent chemo-radiotherapy in the management of cervical cancer. The ability of radiotherapy to cure locally advanced cervical cancer is limited by the size of the tumor, because the doses required to treat large tumors exceed the limit of toxicity in normal tissue. Concurrent chemotherapy inhibits the repair of sub lethal damage from radiation, synchronizes cells to a particularly radiosensitive phase of the cell cycle, and is cytotoxic in vitro. The present study was conducted on 150 patients satisfying inclusion and exclusion criteria, the maximum number of patients are from stage-I has a frequency of 99% and a minimum number of patients are from stage IV with a frequency of 50%. Post-Operative patients has a frequency of 95%, stage II has a frequency of 90%, stage III has a frequency 85%. The results obtained from our studies show that early stage cervical cancer (<IIB) shows a better outcome of treatment of advanced stages (≥IIB). In the treatment of advanced stages (≥IIB), concomitant radio chemotherapy shows significant results in terms of complete tumor regression.

KEYWORDS: Chemo-Radiotherapy, Cytotoxic, Tumor.

INTRODUCTION

Cancer that forms in tissues of cervix (the organ connecting the uterus and vagina). It is usually a slow-growing cancer that may not have symptoms but can be found with regular Pap tests (a procedure in which cells are scraped from the cervix and looked at under a microscope). Cervical cancer is almost always caused by Human Papilloma Virus (HPV) infection.[1] Concurrent chemotherapy inhibits the repair of sub lethal damage from radiation, synchronizes cells to a particularly radiosensitive phase of the cell cycle, and is cytotoxic in vitro.[2,3,4]

CANCER STAGING SYSTEMS: A number of staging systems are used for cancer. The classification of the International Federation of Gynecology and Obstetrics (FIGO), which is based on tumor size and the extent of spread of disease in the pelvis and distant organs, is recommended for staging invasive cervical cancer.

Stage 0: Carcinoma in situ, cervical intraepithelial neoplasia Grade III.
This is not considered invasive cancer, since the lesion has not gone beyond the basement membrane.

Stage I: Carcinoma confined to the cervix. Extension to the uterus is disregarded.

• IA: Microinvasive carcinoma, strictly confined to the cervix. Can only be diagnosed by microscopy; it is not clinically visible. It is classified into 2 stages, IA1 and IA2

• IB: Carcinoma strictly confined to the cervix and clinically visible; or a microscopic lesion greater than IA2. It is classified into 2 stages, IB1 and IB2

Stage II: Carcinoma confined to the cervix. Extension to the uterus is disregarded. It is classified into 2 stages, IIA and IIB

- IIA: Spread beyond the cervix, including upper two-thirds of the vagina, but not to tissues around the uterus (parametria). 5-year survival with optimal treatment: ~75%.
- IIB: Spread beyond the cervix, with parametrial invasion, but not as far as the pelvic wall or the lower third of the vagina. 5-year survival with optimal treatment: ~65%.

Stage III: Tumor extends to pelvic wall or involves lower third of the vagina, or causes hydronephrosis or non-functioning kidney.

- IIIA: Invasion of the lower third of the vagina, with no extension to the pelvic wall. 5-year survival with optimal treatment: ~30%.

- IIIB: Extension to the pelvic wall, or hydronephrosis or nonfunctioning kidney. 5–year survival with optimal treatment: ~30%.

Stage IV: Tumor has spread
- IVA: Spread to involve the mucosa of the bladder or rectum. 5-year survival with optimal treatment: ~10%.
- IVB: Spread to distant organs, such as extrapelvic lymph nodes, kidneys, bones, lungs, liver and brain. 5-year survival with optimal treatment: <5%.[5]

TREATMENT

RADIATION THERAPY: Radiation therapy plays a central role in the treatment of most invasive cervical cancers. It is mainly used for cases with bulkier tumors (stage IB and IIA through to IVB) and those with extensive involvement of lymph nodes seen on laparotomy (without hysterectomy).[6]

Types of radiotherapy

There are two broad groups of radiation treatment, which differ in terms of position of the source of radiation relative to the patient:
1. Teletherapy, in which the source of radiation is distant from the patient;
2. Brachytherapy, in which small radioactive sources are placed in cavities within the body. Curative treatments are based on a combination of pelvic teletherapy and intravaginal brachytherapy.

CHEMOTHERAPY

Chemotherapy is not a primary mode of treatment for cervical cancer, but it may be used concurrently with surgery or radiation to treat bulky tumors. Cisplatin is the most commonly used drug and is included in the WHO's Model List of Essential Medicines. The benefits of adding cisplatin to radiotherapy in developing country settings has not been proven.

SURGICAL

Curative surgery in cervical cancer aims to remove the primary tumour, with all its extensions, in a single operation. The main surgical procedures are radical hysterectomy and pelvic lymphadenectomy, although simple hysterectomy and trachelectomy are indicated in specific cases.

METHODOLOGY

This study was conducted in inpatients of tertiary care hospital which contain departments such as General medicine, Cardiology, Neurology, Gynecology, Orthopaedics.

Study design: The study was Prospective and Retrospective Observational Study.

Study duration: The study was conducted over a period of 6 months.

Inclusion criteria: Patients aged 18 years or above, with moderate or severe head injury were recruited. All the patients with Glasgow coma scale(GCS) of less than 15. The above study criteria are enrolled into the study.

Exclusion criteria: Exclusion criteria included severe renal, liver, lung or cardiovascular disease, poor mental state due to drug or alcohol abuse, concomitant stroke, pregnancy or lactation, life-threatening multiple trauma, signs of brain stem failure, status epilepticus and grand mal fits**,** Patients with normal GCS.[15]

Sources of data
- Patients who are admitted in hospital.
- Inpatient clinical case notes.
- Generic name of the drug.
- Route of administration.
- Frequency of administration.
- Interacting with nursing staff.
- Interacting with healthcare professionals.

Data collection and assessment of the study results/observations: A suitable data collection form was designed to collect required information and analyse the data. The data collection form included the information related to patient demographics such as age, weight, sex along with diagnostic information, generic name of the drug, the ROA, frequency and related information. The analysis was done by prospective method which included the details like patients information, prescribing pattern of cerebrolysin its role in TBI its clinical outcome.

Procedure of the study: All the data present in documentation forms including demographic details of the patient, history, diagnosis, treatment. This data which was collected on daily basis by following each patient in Neuro department, who are prescribed with cerebrolysin and were further evaluated for benefical effect of cerebrolysin.

Data analysis: The data was analyzed based on information obtained from case sheets.
- Age wise
- Gender wise
- Drug discontinuation
- Drug interactions
- Inappropriate prescription

RESULTS

The study "The effect of concurrent chemo-radiotherapy in the management of cervical cancer: A prospective study" was conducted in Sushrutha cancer hospital. A total number of 150 patients with cervical cancer.

AGE-WISE DISTRIBUTION OF TOTAL STUDY POPULATION

The study population was divided into various groups according to their age and stages.

Table 1: Age-wise distribution of total study population.

AGE	Stage I	Stage II	Stage III	Stage IIIB/IV	Stage IV	Post-OP
20-30	-	15	5	1	-	3
31-40	-	17	15	2	1	2
41-50	3	17	24	3	1	2
51-60	-	8	15	1	1	2
61-70	1	2	5	1	2	-
71-80	-	-	1	-	-	-

Age-wise distribution of total study population, 24 patients were between 20-30 years age group, 37 patients were between 31-40 years of age group, 50 patients were between 41-50 years of age group, 27 patients were between 51-60 years of age group, 11 patients were between 61-70 years of age group, 1 patient was between 71-80 years of age group.

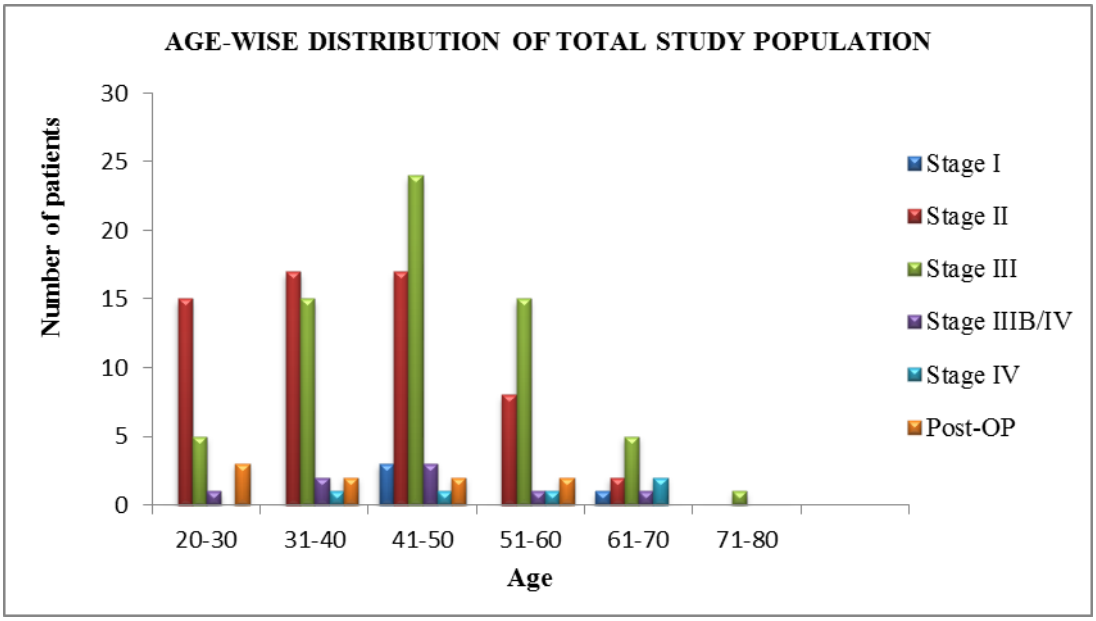

Figure 1: Age-wise distribution of total study population.

DISTRIBUTION OF PATIENTS ACCORDING TO THE STAGE

Table 2: Distribution of patients according to the stage.

Stage	Number of patients	Percentage (%)
IB	4	2.66
IIA	4	2.66
IIB	54	36
IIIA	4	2.66
IIIB	62	41.33
IVA/B	5	3.33
IIIB/IV	8	5.33
PO	9	6

It shows the distribution of patients according to their stages. Out of 150 patients, 41.33% of patients were observed in stage IIIB. The least number of patients were observed in stage IB, IIA, IIIA with a frequency of 2.66% each. 62 patients were affected with stage IIIB, frequency of 41.33%, 54 patients are with stage IIB with a frequency of 36%, 9 patients fall in Post Operative, 8 patients affected with stage IIIB/IV with 5.33%, 5 patients were observed in stage IVA/B with a frequency of 3.33%. 4 patients were observed with stage IB, IIA, IIIA with a frequency of 2.66% each.

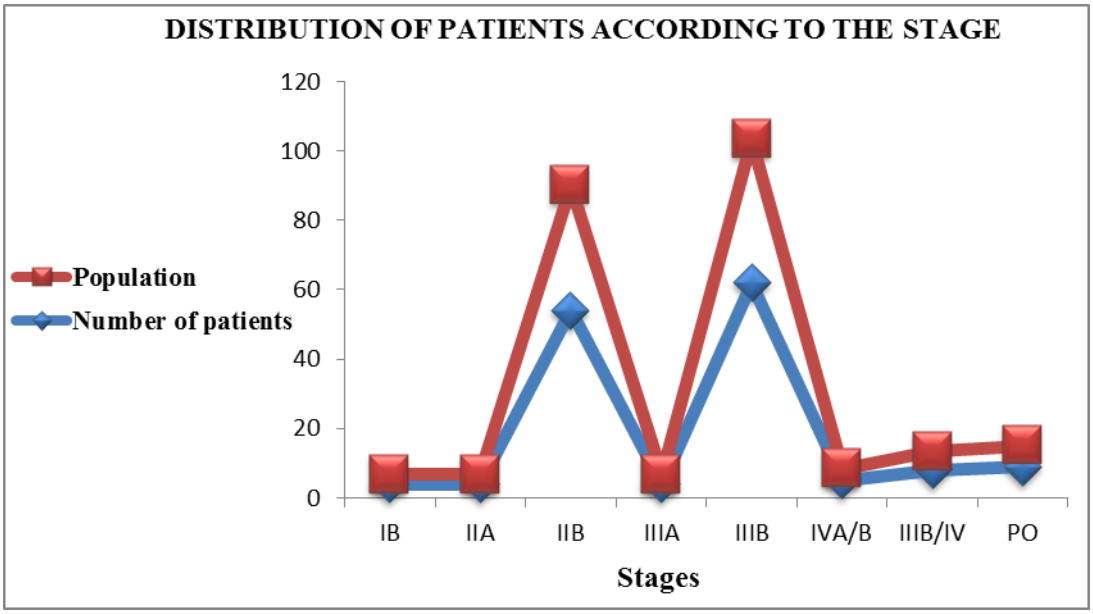

Figure 2: Distribution of patients according to the stage.

DISTRIBUTION OF PATIENTS ACCORDING TO THE FAMILY HISTORY

Table 3: Distribution of patients according to paternal history of cervical cancer.

Paternal	Number of patients	Percentage (%)
Grandmother	67	44.66

Table 4: Distribution of patients according to maternal history of cervical cancer.

Maternal	Number of patients	Percentage (%)
Grandmother	17	11.33
Mother	54	36
Sister	12	8

This graphical presentation represents the distribution of patients according to their family history, Out of 150 patients, 67 patients (44.66%) had a paternal history of cervical cancer (i.e. grandmother). From maternal history of cervical cancer (i.e. grandmother, mother, and sister) had a frequency of 55.34%, from which 17 patients had a history from grandmother (11.33%) and 12 patients had a history from sister (8%).

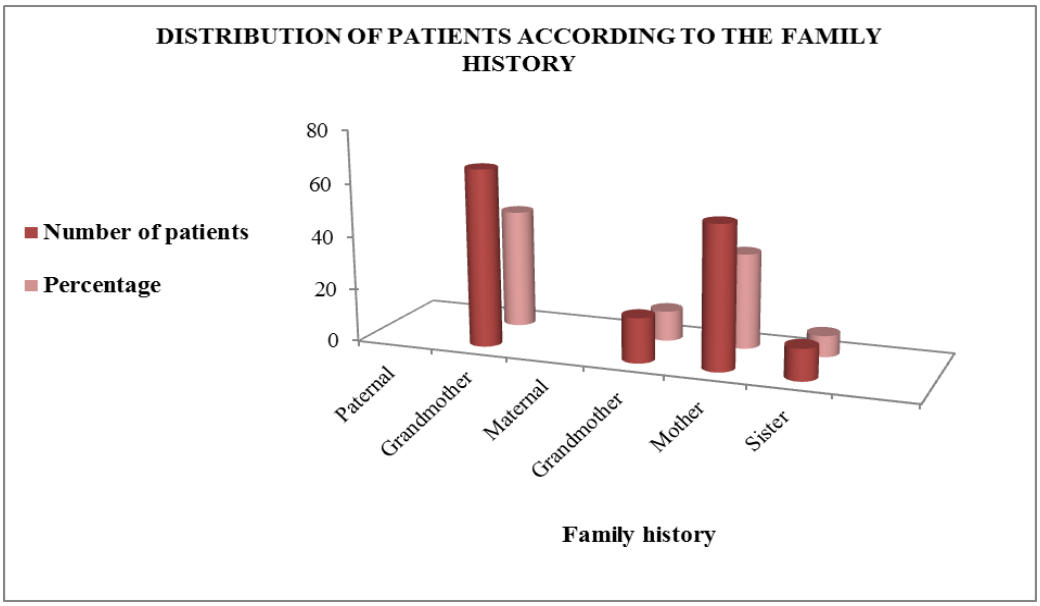

Figure 3: Distribution of patients according to the family history.

DISTRIBUTION OF PATIENTS ACCORDING TO THE CAUSE

Table 5: Distribution of patients according to the cause.

Factors	Number of patients	Percentage (%)
Early pregnancy	82	54.66
Late pregnancy	26	17.33
Post menopausal	18	12
Hysterectomy	24	16

This graphical presentation provides the information on distribution of patients according to the cause of the disease. Among 150 study population, 54.66% of patients had a cause of early pregnancy and a least number of patients had a cause of post menopausal with frequency 12%. And late pregnancy and post menopausal had frequency 17.33% and 12% respectively.

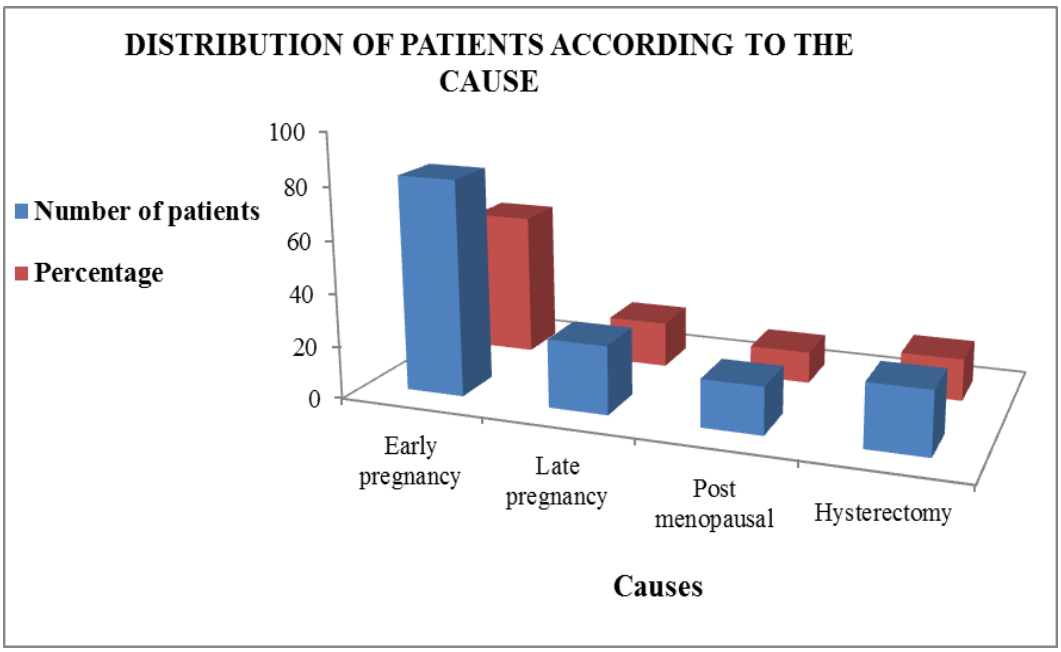

Figure 4: Distribution of patients according to the cause.

DISTRIBUTION OF PATIENTS ACCORDING TO THE DIAGNOSIS

Table 6: Distribution of patients according to keratinizing sqaumous cell carcinoma.

Stages	Number of patients	Percentage (%)
I	2	1.33
II	16	10.66
III	18	12
IV	3	2
Post-Operative	7	4.66

Table 7: Distribution of patients according to non-keratinizing sqaumous cell carcinoma.

Stages	Number of patients	Percentage (%)
I	1	0.66
II	35	23.33
III	39	26
IV	2	1.33
IIB/IV	8	5.33
Post-Operative	2	1.33

Here the patients are placed based on their diagnostic criteria, from this data the of patients are placed under non-keratinizing and keratinizing with the frequency of 23.33% of stage II and 10.66% of stage II respectively. Whereas 1.33% of patients with stage I are placed in keratinizing and non-keratinizing and 1.33% of stage IV and post-operative respectively.

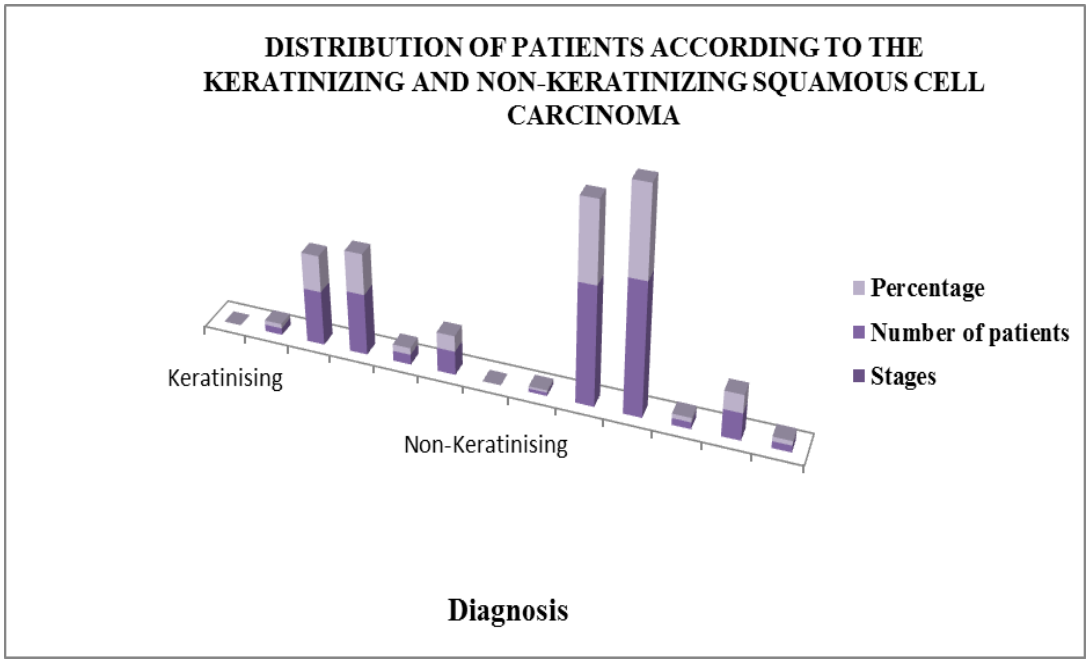

Figure 5: Distribution of patients according to the Keratinizing and Non-Keratinizing.

Table 8: Distribution of patients according to Adenocarcinoma, Basoloid squamous cell carcinoma, Exophytic papillary squamous carcinoma.

Types	Stage I	Stage II	Stage III	Stage IV	Percentage(%)
Adenocarcinoma	-	2	7	-	6%
Basoloid squamous cell carcinoma	-	4	-	-	2.66%
Exophytic papillary squamous carcinoma	1	3	-	-	2.66%

This table shows the information on other diagnostic characteristics other than keratinisng and non-keratinisng squamous cell carcinoma. Where the remaining patients are placed under other types diagnostic characteristics, from which 6% of patients had a adenocarcinoma of stage I and II. Whereas the basoloid squamous cell carcinoma of stage II and exophytic papillary squamous carcinoma of stage I and II has a frequency of 2.66%.

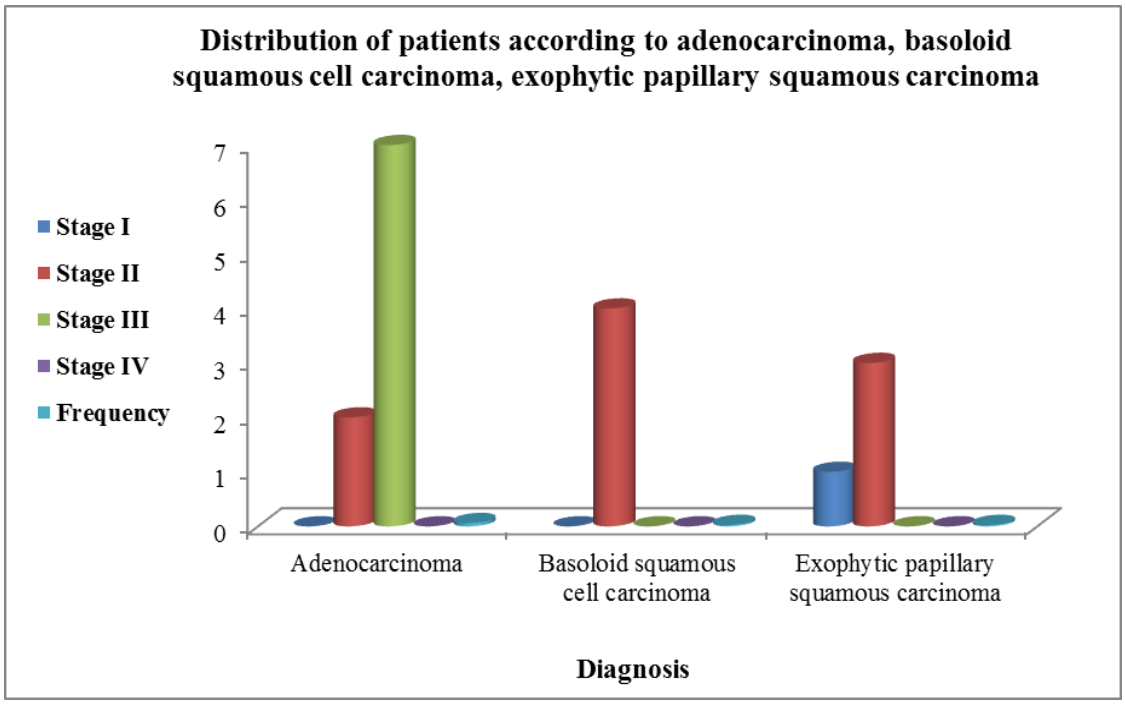

Figure 6: Distribution of patients according to Adenocarcinoma, Basoloid squamous cell carcinoma, Exophytic papillary squamous carcinoma.

DISTRIBUTION OF PATIENTS ACCORDING TO THE TYPES OF TREATMENT PLANNED

Table 9: Distribution of patients according to the types of treatment planned.

Types	Number of patients	Percentage (%)
Radical	115	76.66
Intent radical	14	9.33
Palliative	15	10
Pre-Operative	2	1.33
Post-Operative	2	1.33
Prophylactic	-	-
Pre-OP+ Surgical+ Post-OP	2	1.33

This graphical presentation provides the information on the distribution of patients according to the types of treatment planned. The data which is extracted from 150 patients provides 76.66% of patients are administered with radical type of treatment and 1.33% of patients are given with pre-operative, post-operative and pre-operative + surgical+ post-operative type of treatment. No patients are prescribed for prophylactic treatment. 10% of patients underwent palliative therapy and 9.33% of patients underwent intent radical therapy.

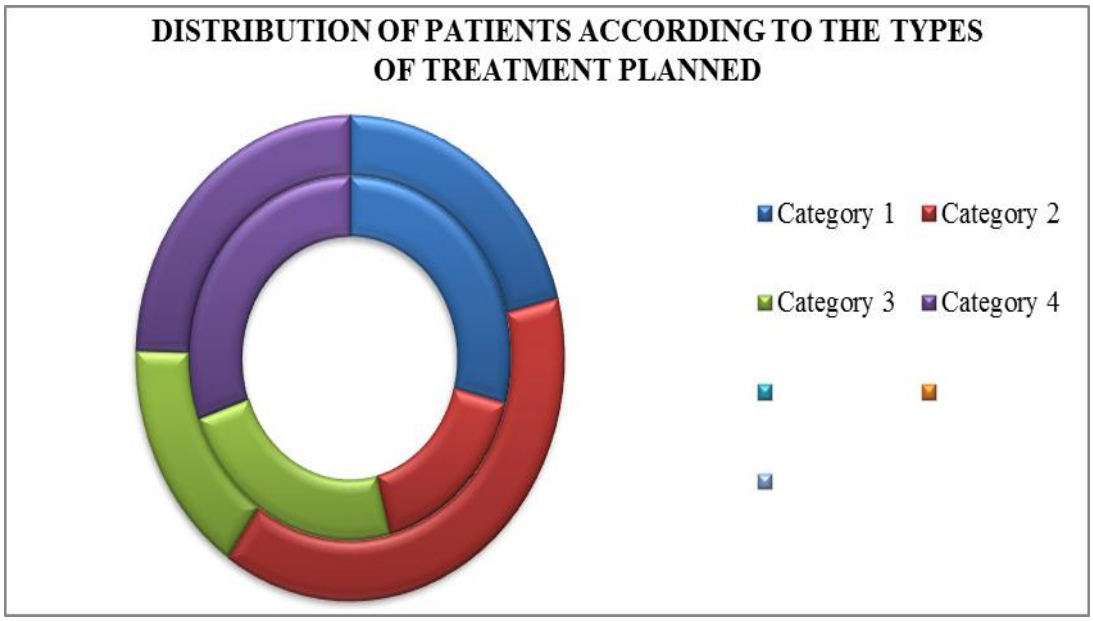

Figure 7: Distribution of patients according to the types of treatment planned.

DISTRIBUTION OF PATIENTS ACCORDING TO THE MENESTRUAL HISTORY

Table 10: Distribution of patients according to the menstrual history.

Factors	Number of patients	Percentage (%)
Irregular menses	89	59.33
Regular menses	1	0.66
Post-menopausal	46	3.66
Presence of watery discharge	6	4
Presence of white discharge	4	2.66
Foul smell pelvic discharge	4	2.66

It shows a graphical presentation on distribution of patients based on their menstrual history. From the data provided the out of 150 patients, 59.33% of patients had irregular menses, 0.66% of patients had regular menses, 2.66% of patients had a presence of white discharge and foul smell pelvic discharge. 4% of patients had presence of watery discharge and 3.66% of patients had post-menopausal.

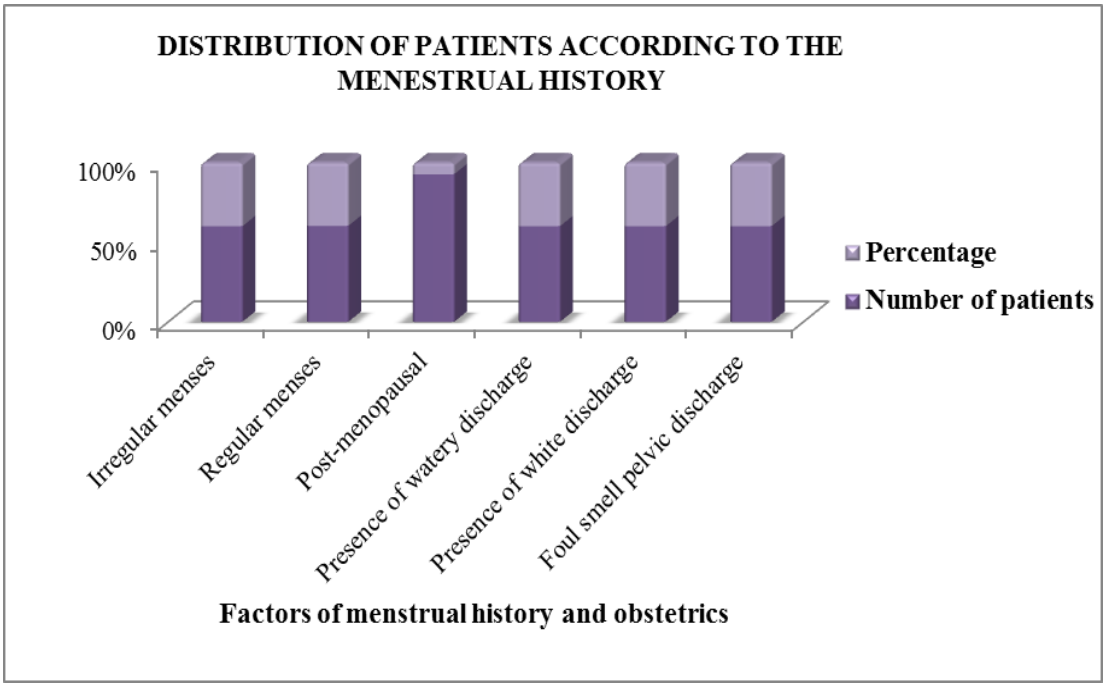

Figure 8: Distribution of patients according to the menstrual history.

DISTRIBUTION OF PATIENTS ACCORDING TO TREATMENT

Table 11: Distribution of patients according to chemotherapy.

Stage	Chemotherapy	Percentage (%)
IB	1	0.66
IIA	-	-
IIB	-	-
IIIA	-	-
IIIB	-	-
IVA/B	-	-
Post-Operative	1	0.66

This data provides the information on the distribution of patients according to treatment of chemotherapy alone. Only one patient of stage IB administered with chemotherapy alone with the frequency of 0.66% and one patient of post-operative with the frequency of 0.66%.

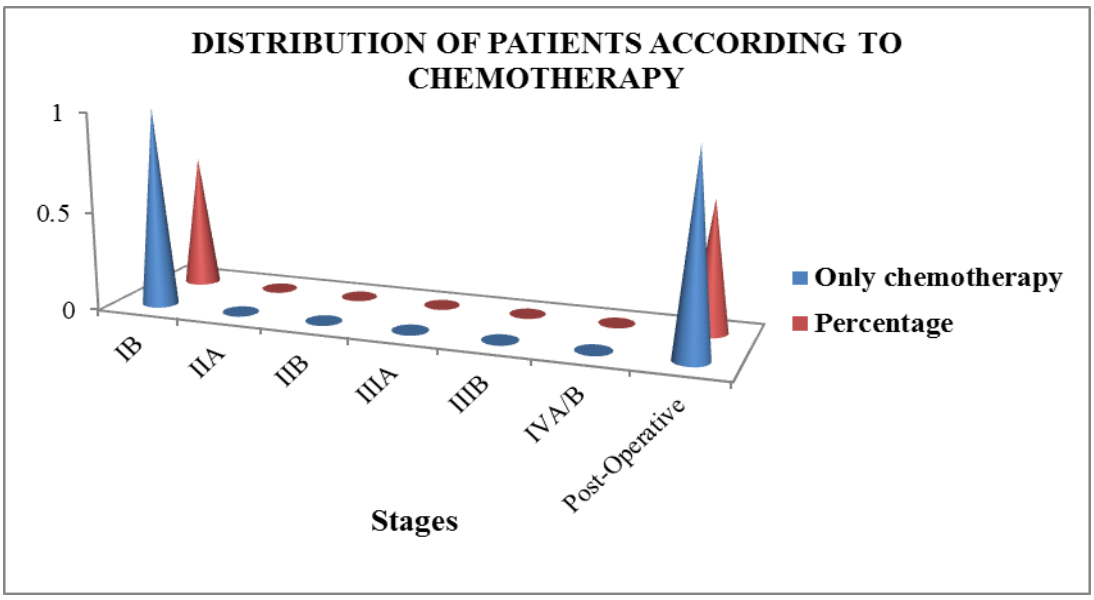

Figure 9: Distribution of patients according to chemotherapy.

Table 12: Distribution of patients according to chemotherapy and radiation therapy.

Stage	Chemotherapy+ Radiation therapy	Percentage (%)
IB	2	1.33
IIA	3	2
IIB	48	32
IIIA	1	0.66
IIIB	50	33.33
IIIB/IV	2	1.33
Post-Operative	7	4.66
IVA/B	-	-

Here the patients are distributed based on the therapy of chemotherapy combined with radiation therapy. From these data 50 patients of stage IIIB are administered with this type of therapy with the frequency of 33.33% and 1 patient of stage IIIA had a frequency of 0.66%. Whereas the stage IIA and post-operative had a frequency of 2% and 4.66% respectively. The stage IIB had a frequency of 32%. Stage IB and IIIB/IV had a frequency of 1.33%.

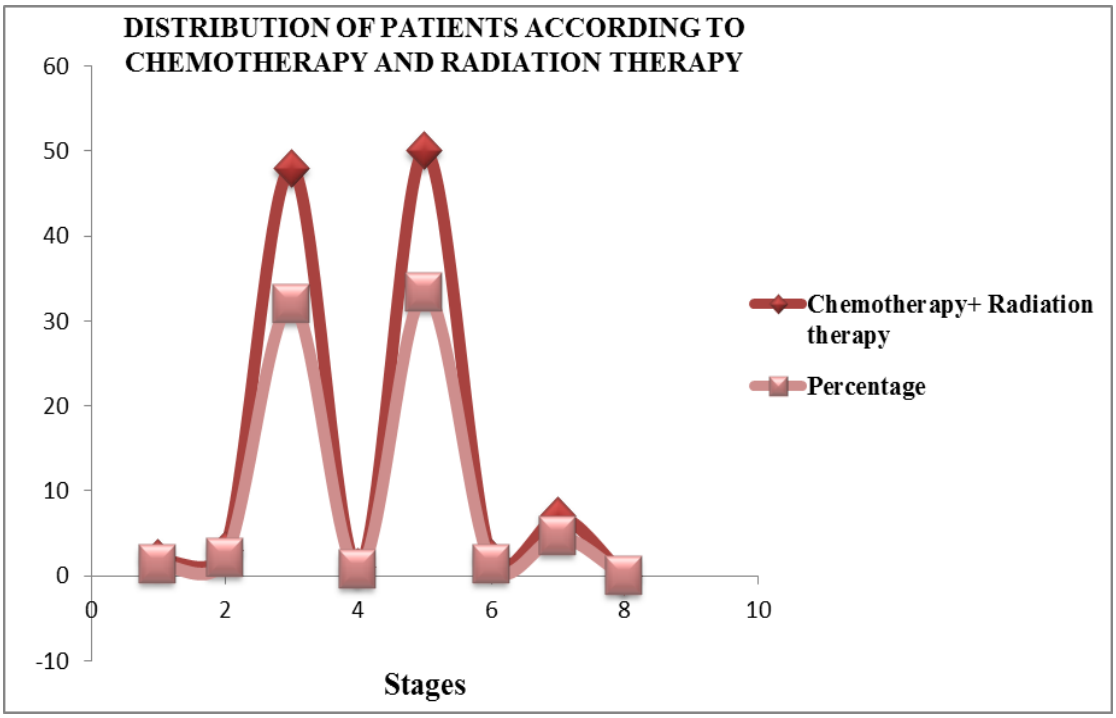

Figure 10: Distribution of patients according to chemotherapy and radiation therapy.

Table 13: Distribution of patients according to radiation therapy.

Stage	Radiation therapy	Percentage (%)
IB	2	1.33
IIA	1	0.66
IIB	2	1.33
IIIA	8	5.33
IIIB	9	6
IIIB/IV	6	4
IVA/B	5	3.33
Post-Operative	2	1.33

Here the patients are distributed based on the therapy of radiation therapy alone. From this data 8 patients of stage IIIA had a frequency of 5.33% and 1 patient of stage IIA had a frequency of 0.66%. Stage IB, IIB and post operative had a frequency of 1.33%. Whereas stage IIIB and IIIB/IV had a frequency of 6 and 4 respectively. 3.33% of IVA/B had undergone radiotherapy alone.

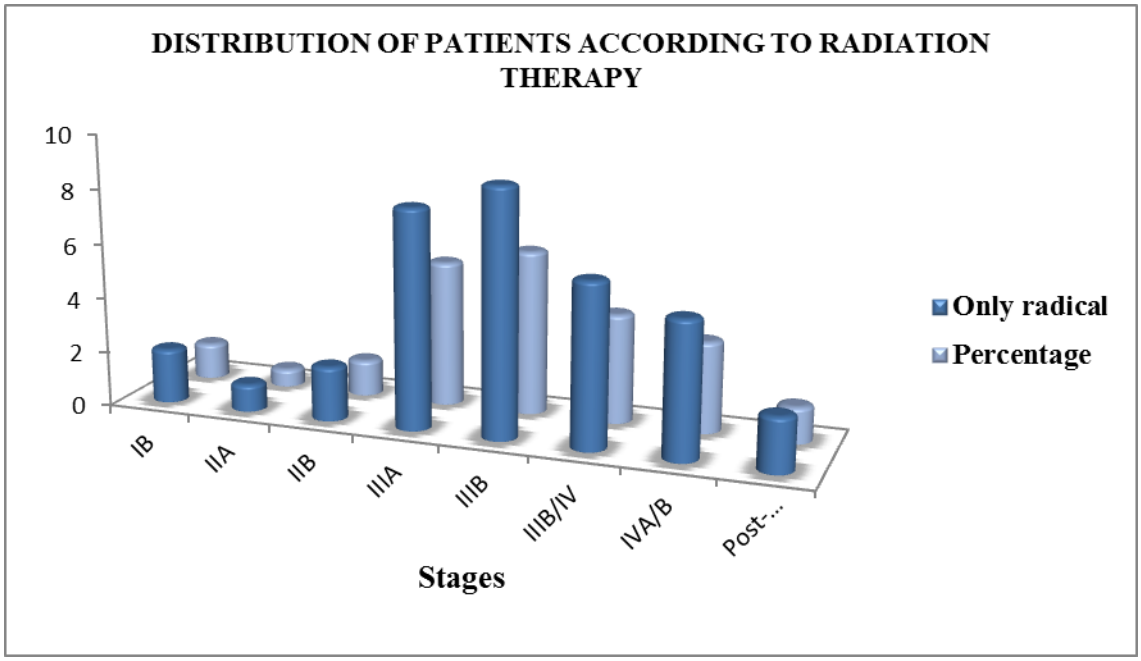

Figure 11: Distribution of patients according to radiation therapy.

Table 14: Distribution of patients based on response to cancer therapy.

Stages	Number of Patients	Complete Response	Partial Response
Stage IB	5	5	-
Stage IIA	5	4	1
Stage IIB	60	52	8
Stage IIIA	9	7	2
Stage IIIB/IV	71	44	24

Here the patients are distributed based on response to cancer therapy. Most of patients had complete response to cancer therapy (i.e, chemotherapy alone (or) radiation alone (or) chemo-radiotherapy, based on their stage). Minimum number of patients had partial response to cancer therapy.

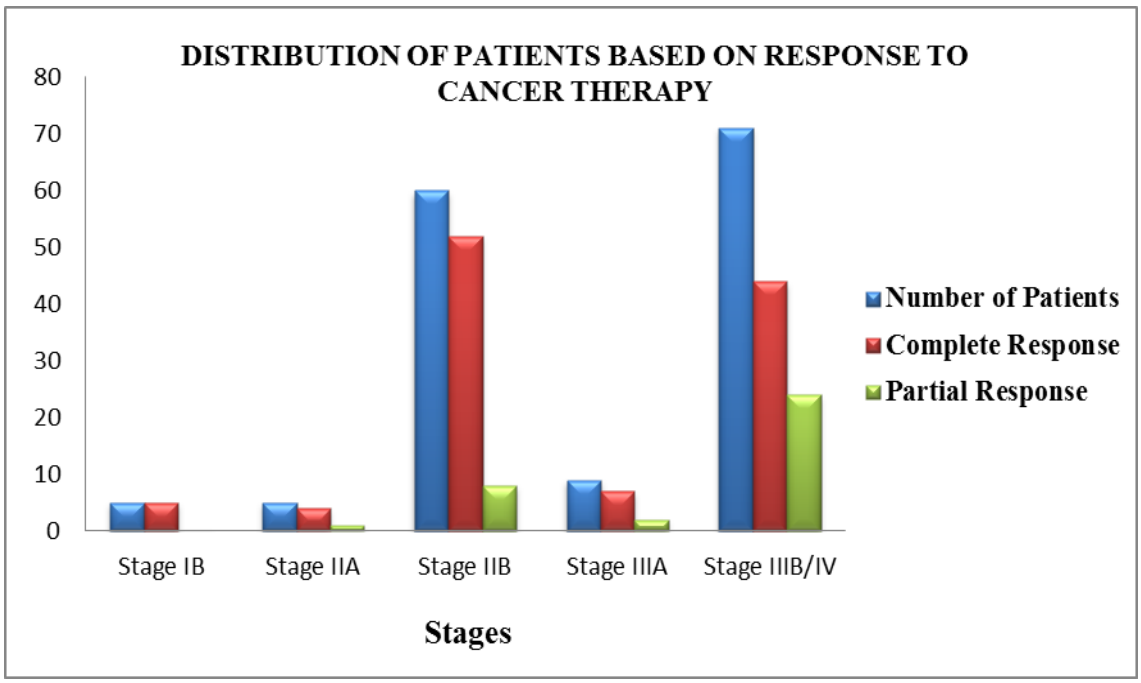

Figure 12: Distribution of patients based on response to cancer therapy.

DISCUSSION

A combination of external beam treatment with brachytherapy is used to increase the dose to the tumor with reduced dose to the organs at risk. High Dose Rate (HDR) brachytherapy is now accepted for cervical cancer treatment.[7] The currently recommended treatment approach in radical, curative-intent radiotherapy of cervical cancer consists of 3 elements: external-beam radiotherapy of the primary tumor with pelvic and - if involved - paraaortic lymph nodes to a total dose of 45-50 Gy, intracavitary brachytherapy and concomitant chemotherapy with cisplatin with weekly doses of 40 mg/m2. Typical brachytherapy dose concepts (in combination with external beam radiotherapy doses of 45 to 50 Gy) contained 3-5 fractions with doses of 5-7 Gy each.[8,9] The duration from the initiation of treatment to completion is typically between 8-10 weeks in many large studies. The ideal OTT of the entire course of EBRT and brachytherapy should be kept within 7-8 weeks to offset accelerated tumor repopulation that may occur during prolonged treatment breaks.[10] From this analysis, we conclude that clinical stage continues to be the strongest prognostic factor in patients with carcinoma of the uterine cervix.[11]

CONCLUSION

It is well known that intracavitary radiotherapy (ICR), either alone or in combination with external-beam radiotherapy (EBRT) is an essential component of the radiation treatment of uterine cervical cancer. Although low-dose-rate (LDR) brachytherapy has been successfully applied to the management of such patients, several radiation oncologists have experience of using high-dose-rate (HDR) brachytherapy with promising clinical results over the past 4 decades. The only clinical prognostic factor for advanced cervical carcinoma is the clinical stage of the disease. The results obtained from our studies show that early stage cervical cancer (<IIB) shows a better outcome of treatment of advanced stages (≥IIB). In the treatment of advanced stages (≥IIB), concomitant radio chemotherapy shows significant results in terms of complete tumor regression. Our study concludes Radio-chemotherapy gives better treatment results in patients with cervical cancer and higher overall survival rates than radiotherapy alone.

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