



Research Article

OUTCOME ANALYSIS OF CERVICAL CANCER PATIENTS WITH PARA-AORTIC LYMPH NODE METASTASES

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ABSTRACT

Background: With an estimated 122,844 new cases in 2012, and 67,000 deaths cervical cancer is a major cause of morbidity and mortality for Indian women. Because of technical, manpower and financial constraints about 80% of these cases present in a locally advanced stage of the disease; often with metastases to the paraaortic lymph nodes. **Aim:** This study was done to assess the outcome of the cervical cancer patients with paraaortic lymph nodes treated with concurrent chemoradiation followed by brachytherapy in respect to various prognostic factors. **Materials and Method:** The study included 30 cervical cancer patients with paraaortic lymph nodes treated from February 2008 to January 2010 at Mahavir Cancer Sansthan, Patna. Overall disease free survival and its relation to various factors including age, number and size of nodes, response to treatment and number of chemotherapy cycles taken was evaluated. **Results:** The 3year DFS was 46.66%, with distant metastasis in 40% of the patients. Response to treatment was the most significant factor affecting survival followed by size of nodes and number of chemotherapy cycles taken. **Conclusion:** To improve the prognosis of such patients surgical debulking of bulky nodes and adjuvant chemotherapy to decrease distant metastasis can be tried.

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INTRODUCTION

Background

Cervical cancer is the fourth most common cancer affecting women worldwide, the most common cancer in women in several less developed countries, and now the second most common cancer in India. Almost 85% of the global burden of cervical cancer is in areas with lower levels of development, and more than one fifth of all new cases are diagnosed in India. With an estimated 122,844 new cases of cervical cancer in the year 2012, which accounted for 23% of all the cancers in females and 67,000 deaths it is still a major cause of morbidity and mortality for Indian women especially from rural background. [1] Global evidence has shown that the key to reduce cervical cancer morbidity and mortality is early detection coupled with timely treatment of cervical precancerous lesions. [2] Because of technical, financial and manpower constraints cervical cancer screening is not being used widely in India. It has been estimated that in India, even with a major effort to expand cytology screening services, it will not be possible to screen even one-fourth of the population once in a lifetime in the near future. [3-4] So, over 80% of the cases report for treatment in fairly advanced stages of the disease, that is FIGO stage IIB to IV. [5] In general, the incidence of lymph node metastasis is directly correlated with the stage of the disease. It has been established that cervical cancer spreads in a progressive but predictable pattern and many patients with locally advanced carcinoma of cervix

harbour paraaortic metastasis. The Gynaecologic Oncology Group (GOG) demonstrated paraaortic disease in 5% of stage I, 16% of stage II, and 25% of stage III patients. [6] Lymph node metastasis, pelvic and/or paraaortic, have a major negative impact on the survival of the patient. [7] Besides, many studies have also shown a direct relationship between survival and the number and size of lymph node metastases. [8-10] The standard treatment in patients of cervical cancer with high common iliac and/or para aortic lymph nodes has been Extended field radiotherapy with concurrent weekly Cisplatin based chemotherapy followed by brachytherapy. Published trials do suggest improved outcome although at the expense of increased toxicity. [11-14]

Majority of the patients coming to our cancer centre have a rural background and locally advanced cervical cancer is one of the most common cancer seen in our patients. Most of these patients belong to low socio economic group and cannot afford newer conformal radiotherapy techniques recommended for treating metastases to paraaortic nodes. Hence this study was done to assess the treatment outcome, the prognostic factors and the pattern of failure seen in these patients treated with conventional radiotherapy techniques.

Aim

The aim of this study was

1. To assess disease free survival in locally advanced cervical cancer patients with high common iliac and/or para aortic lymphadenopathy treated with

extended field radiotherapy and concurrent weekly chemotherapy followed by brachytherapy.

2. To assess the pattern of failures in these patients.
3. To assess various prognostic factors associated with 3-year disease free survival in these patients.

MATERIAL AND METHODS

The study included 30 biopsy proven cervical cancer patients with radiological evidence of either high common iliac and/or paraaortic lymph nodes treated from February 2008 to January 2010 at Mahavir Cancer Sansthan, Patna. The inclusion criteria included patients who completed their planned treatment with extended field radiotherapy, concurrent weekly chemotherapy followed by high dose rate brachytherapy, availability for follow-up for at least three years or until disease progression.

All the patients received extended field external radiation to the para-aortic region and pelvis with concurrent weekly cisplatin followed by intracavitary irradiation. External radiation was delivered to the pelvic and paraaortic regions to a total dose of 45Gy/25# in 5 weeks with a fraction size of 1.8Gy/day, 5 days a week by AP-PA parallel opposing beams on a Cobalt 60 machine with customised blocks. Then the pelvic field was boosted with an additional dose of 5.4Gy in 3 fractions to a total dose of 50.4Gy in 5.5 weeks. Cisplatin (40 mg/m²) was given weekly with external radiation for a maximum of five doses. This was followed by intracavitary irradiation after a gap of 3-5 days. Three applications of high dose rate brachytherapy were done. The dose given per fraction was 6-7Gy depending upon the bladder and rectal dose. The overall treatment time was 56-60 days. Patients were evaluated weekly for acute toxicity during radiotherapy and for late toxicity during follow up as per Radiation Therapy Oncology Group (RTOG) morbidity scoring criteria. Response to treatment was assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) Criteria. The patients were kept on regular follow-up at an interval of 3 months for the 1st two years and 6 monthly for subsequent years.

Disease free survival was calculated from the 1st day of starting radiotherapy to the day of disease progression or last follow up. Various factors including age, number and size of the para aortic lymph nodes, response to treatment at first follow-up and number of chemotherapy cycles taken by the patients were evaluated as prognostic factors for disease free survival. Survival analyses was done using Graph Pad prism 7.02 version.

RESULTS

The age range of the study population was 38 to 65 years. 15 out of 30 (50%) of the patients were less than or equal to 50 years, and the remaining 50% were more than 50 years of age. The median age was 51 years. It was seen that 36.6% patients had stage IIB, 6.6% had stage IIIA and 56.6% had stage IIIB disease. The most common tumour histology was squamous cell carcinoma (83.3%) followed by adenocarcinoma (13.3%) and adenosquamous carcinoma (3.33%).

Out of the 30 patients 3 (10%) had high common iliac lymph node involvement and rest 27 (90%) patients had para-aortic nodes involvement. Out of these 30 patients 11 (36.66%) had single nodes whereas 19 (63.33%) had multiple nodes. Again

63.33% of the paraaortic nodes were less than 2 cm. in size whereas 36.66% were more than 2 cm. The largest node seen was 4cm x 3.5 cm. in size. Regarding the location most of the nodes (90%) were situated either at the level of renal hilum or just below it. The highest level seen was a paraaortic node around T 12 vertebrae.

All of the patients received concurrent weekly Cisplatin at a dose of 40mg/m². It was seen that 77% of the patients took 4-5 cycles of concurrent Cisplatin. This was followed by 13.33% of the patients taking 3 cycles and 10% taking only 2 cycles of chemotherapy. Acute toxicity was the most common cause for non-compliance to the planned 5 cycle of chemotherapy. Most of the toxicities seen in these patients were either haematological or gastrointestinal.

At the first follow-up, complete local response was found clinically in 26 (86.66%) patients; whereas both clinical and nodal complete response was seen in only 21(70%) of the patients. 5 patients (16.66%) who had no evidence of disease on clinical examination showed residual nodal disease on imaging.

The median disease free survival was found to be 22 months. [Fig.1] The 3year disease free survival rate was found to be 46.66%. 12 out of 30 patients (40%) developed distant metastases. 6 out of 30 (20%) patients had an in-field locoregional failure. Supraclavicular lymph node was the most common site of failure in 6 patients followed by lung in 3 patients, mediastinal nodes in 2 patients, brain in 1 patient and ascites in 1 patient.

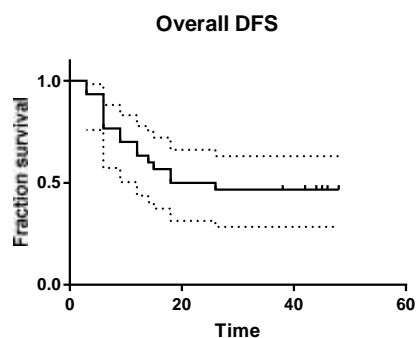


Figure 2 Kaplan Meier Survival Plot showing overall DFS

On subset analysis, 3 year DFS was found to be 40% in patients who were 50 years or younger as compared to 53.33% in the patients more than 50 years of age (p value = 0.59). Patients with single lymph nodes showed 54.54% 3 year DFS as compared to 42.10% in patients with multiple lymph nodes. (p value = 0.90) [Fig 2].

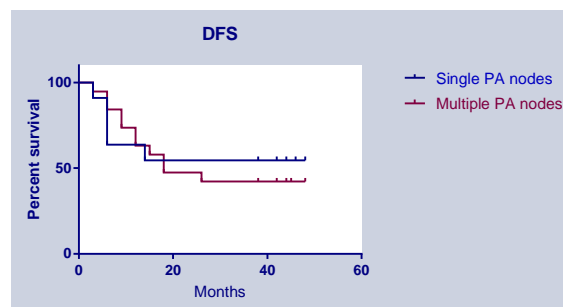


Figure 1 Kaplan Meier Survival Plot according to number of paraaortic lymph nodes

However, size of the involved lymph node was found to be a significant prognostic factor with 63.15% patients showing disease free survival at 3 years with less than 2 cm sized node compared to only 18.18% in patients with more than or equal to 2 cm (p value = 0.029) [Fig 3].

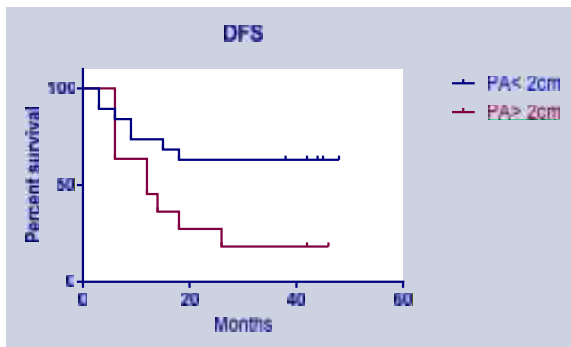


Figure 3 Kaplan Meier Survival Plot according to size of paraaortic lymph nodes

The most significant prognostic factor for 3 year DFS was found to be the response to therapy at first follow up. Patients with a complete response, clinically and radiologically had a much better survival than those who had a residual disease at the first follow up. The 3 year DFS was 53.84% and 66.66% in patients showing complete response clinically and radiologically respectively as compared to no survival at 3 years in patients with a residual disease (p value < 0.0001). [Fig. 4 & 5]

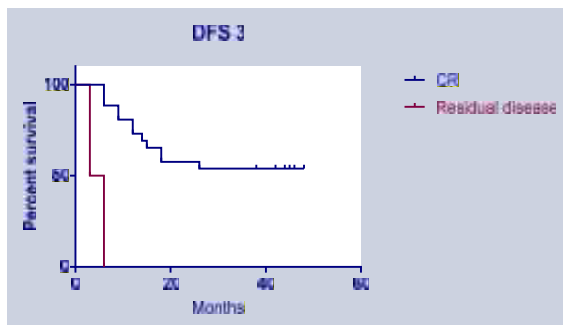


Figure 4 Kaplan Meier Survival Plot according to Clinical Response at first follow up

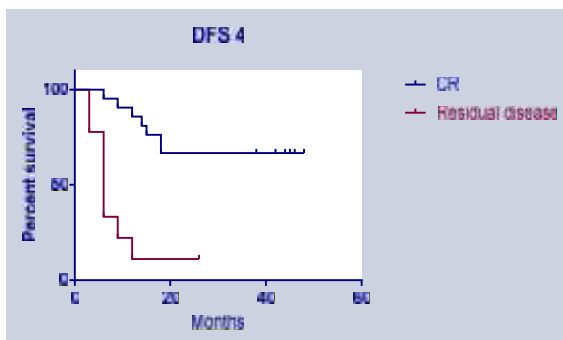


Figure 5 Kaplan Meier Survival Plot according to Imaging Response at first follow up

Similarly, disease free survival also showed an increasing trend with the number of concurrent weekly chemotherapy. [Fig.6] The 3year survival was 64.28%, 44.44%, 25% and 0 in patients taking 5, 4, 3 and 2 cycles of concurrent weekly Cisplatin with external beam radiation. The log rank test for trend was significant (p value = 0.03).

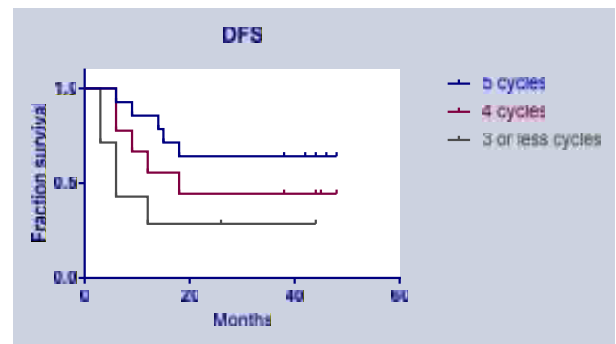


Figure 6 Kaplan Meier Survival Plot according to number of Chemotherapy cycles

DISCUSSION

The age of the patients ranged from 38 to 65 years with a median age of 51 years. This is in accordance with data from cancer registries in developing countries which suggest that about 80 to 90 percent of confirmed cervical cancer cases occur among women aged 35 years or older. The incidence increases with age and reaches a maximum in women in their 50s and 60s. [15] Stage IIIB was the most common stage seen in our patients as the chances of having metastases in paraaortic lymph nodes have been proven to be directly related to the stage of the disease, with a reported incidence of 33% to 43% among stage III patients in various studies. [16 - 17]

The presence of positive paraaortic nodes has a deleterious influence upon survival, more pronounced than the finding of positive pelvic nodes. Others have also noted a lower survival for patients with common iliac metastases as compared to patients with other pelvic sites involvement. [18] In the Sakuragi *et al.* experience, patients with positive common iliac nodes had a similar survival curve as patients with aortic metastases. A multivariate analysis of prognostic variables in the GOG group study for carcinoma of cervix treated with radiation therapy showed the presence of paraaortic nodes as the most important predictor of survival. [8]

Extended field radiation therapy (EFRT), treating the pelvic and paraaortic nodal area in continuity has been shown to improve survival in cervical cancer patients with involved paraaortic nodes. There have been several retrospective studies addressing this particular scenario. Silberstein *et al* initially reported on the use of extended field radiation therapy in the treatment of cervical carcinoma. Patients received 6000cGy in 6 weeks to the paraaortic lymph nodes by means of a 360 degree rotational Co 60 technique. Three of the six patients survived 3 or more years after completion of radiation therapy. [19] Piver *et al* treated 31 patients with biopsy confirmed para-aortic nodes. The 5 year survival with no evidence of disease was 9.6%. [20] Berman *et al* reported on a series of 98 patients treated with extended field radiation. The median survival was reported to be 15.2 months. The 3 year survival for patients was 25%. [6] Lovechio JL and co-workers reported on a series of 36 patients treated with a course of EFRT. The 5 year actuarial survival rate was 50%, with a median survival time of 29 months. [21] Nori *et al* evaluated 127 patients from 1971- 1980 who underwent pre-treatment laparotomy. 31 were found to have para-aortic nodes and 27 patients received extended field radiotherapy. The 5 year survival was 29%. [22] Goodman *et al* reported the

results of a number of studies demonstrating an overall 30% - 40% survival in patients with paraaortic metastasis treated with extended field radiation. [23]

Given the ability of extended field radiation therapy to sterilise nodal disease and the success of concurrent chemoradiotherapy in pelvic confined disease combining cytotoxic chemotherapy with EFRT was the next step in improving the outcome of patients with positive para-aortic nodes. In our study, at the first follow-up, complete local response was found clinically in 86.66% patients; whereas both clinical and nodal complete response was seen in only 70% of the patients. 16.66% patients who had no evidence of disease on clinical examination showed residual nodal disease on imaging. The median survival was found to be 22 months. The 3year disease free survival rate was found to be 46.66%.

A similar GOG 125 study by Varia *et al* on 86 cervical carcinoma patients with para-aortic metastases treated with extended field radiation with concomitant 5-FU and cisplatin during weeks one and five of external beam showed three-year overall survival rate of 39%. [11] Chung *et al* did a prospective study in 63 patients to investigate the toxicity and efficacy of integrating EFRT, HDR brachytherapy, and concurrent and adjuvant cisplatin based chemotherapy for locally advanced cervical cancer. The observed rates at 5-year of locoregional control, freedom from distant metastasis, and overall survival were 86%, 81% and 77% respectively. Use of higher dose in the form of boost and 2 cycles of adjuvant chemotherapy in this study could be the possible cause of higher survival than that seen in our patients. [17]

In our study 40% of the patients developed distant metastases and 20% had an in-field locoregional failure. The study by Varia *et al* for the Gynecologic Oncology Group showed that overall, 41.9% of the patients developed distant metastasis with or without pelvic failure, and 31.4% of the patients developed pelvic failure with or without distant metastasis. [11] In a retrospective study by Grigsby *et al*, of 24 patients with paraaortic nodal metastasis there was no regional failure, with distant metastases being most common site of failure. [24] The observations of the aforementioned trials are similar to the findings of our study. Distant metastasis remains the major problem apart from the pelvic or pelvic/paraaortic control. This may be explained in part by the fact that occult metastasis that could not be detected by conventional diagnostic studies might be present in some patients, thus limiting the impact of improved pelvic and paraaortic control on survival.

The most common site of distant metastases seen in our patients was supraclavicular lymph nodes. This is in accordance with the fact that carcinoma of the cervix metastasizes in a predictable pattern, with tumour usually spreading from the primary cervical tumour to the pelvic nodes, paraaortic nodes, and left supraclavicular nodes, and then ultimately to extranodal distant sites (haematogenous spread).

On subset analysis, 3 year DFS was found to be 40% in patients who were 50 years or younger as compared to 53.33% in the patients more than 50 years of age though the p value was insignificant. Some authors have noted decreased survival in women younger than 35 or 40 years, who have a greater frequency of poorly differentiated tumour. [25]

However other reports have shown that age is not a prognostic factor in carcinoma of cervix. [26]

In our study, patients with single lymph nodes showed 54.54% 3 year DFS as compared to 42.10% in patients with multiple lymph nodes. (p value = 0.90). However, size of the involved lymph node was found to be a significant prognostic factor with 63.15% patients showing disease free survival at 3 years with less than 2 cm sized node compared to only 18.18% in patients with more than or equal to 2 cm (p value = 0.029).

Though not found to be a significant prognostic factor in our study, a direct relationship has been noted in most studies between the number of positive pelvic nodes and survival; the higher the number of nodal metastases, the lower the survival. [8,27] Similarly, the size of tumour deposits in lymph nodes bears a direct relationship to the overall size of the node and has an impact upon survival. Husseinzadeh *et al* reported that median OS for patients with microscopic and macroscopic nodal metastasis was 30 and 21 months, respectively. The 2- and 5-year OS for the entire group was 35 and 12%, respectively. The 2- and 5-year OS with microscopic metastasis to periaortic nodes were 50% and 12%, respectively, compared with survival of 22% at 2 years and 11% at 5 years, respectively, in those with macroscopic nodal metastasis. [28] Besides, number and size, the level of involvement of the aortic area appears to have a correlation with survival. Vigliotti *et al* observed a 31% 5- year survival for patients with aortic metastases at L3-L4 level, but it decreased to 10% for patients with L1-L2 metastases. [10]

The most significant prognostic factor for 3 year DFS in our study was found to be the response to therapy at first follow up. The 3 year DFS was 53.84% and 66.66% in patients showing complete response clinically and radiologically respectively as compared to no survival at 3 years in patients with a residual disease (p value < 0.0001). Vigliotti *et al*. also noted a direct relationship between size of residual aortic disease and survival. The 5-year survival rate for patients with no visible disease was 50%, with small residual disease 33%, with moderate-size residual tumour 23%, and with massive residual tumour 0%. [10]

Similarly, in our study disease free survival also showed an increasing trend with the number of concurrent weekly chemotherapy. The 3year survival was 64.28%, 44.44%, 25% and 0 in patients taking 5, 4, 3 and 2 cycles of concurrent weekly Cisplatin with external beam radiation. The log rank test for trend was significant (p value = 0.03). In the study by Saad *et al* in 22 patients diagnosed with para-aortic nodes, the pelvic and periaortic control was significantly improved with the addition of concurrent cisplatin-based chemotherapy to EFRT. For the 11 patients who underwent CRT, 10 (91%) had their pelvic and periaortic disease controlled, whereas 4 (36%) developed distant metastasis as compared to the 10 patients who underwent RT alone, 5 (50%) had their pelvic and periaortic disease controlled, whereas 4 (40%) developed distant metastasis. The fact that occult submicroscopic metastasis that could not be detected by conventional diagnostic studies might be present in some of the patients with paraaortic lymph nodes further supports the role of concurrent chemotherapy in these patients. [29]

CONCLUSION

Locally advanced cervical cancer patients have a high propensity of having paraaortic lymph nodes. Some of these patients can also have mediastinal and/or supraclavicular lymph nodes at the time of initial diagnosis, which are not detected on conventional imaging. So, the use of new functional imaging modalities like PET-CT can be useful in these cases. Further, cervical cancer patients harbouring paraaortic nodes can be effectively treated with extended field radiation and concurrent weekly platinum based radiotherapy. However, nodal and distant failures remain the grey area in these cases. To further improve on the prognosis of such patients surgical debulking of bulky nodes, increase in the radiation dose in the form of boost by new conformal radiotherapy techniques and adjuvant chemotherapy to decrease distant metastasis can be tried.

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