Original Research Article

The pattern of distant metastasis and clinicopathological factors associated with de-novo metastatic cervical cancer: a retrospective analysis

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ABSTRACT

Background: Metastatic cervical cancer carries poor prognosis. The factors associated with distant metastasis in newly diagnosed cervical cancer patients are not clear.

Methods: A retrospective analytical study was performed to study the pattern of distant metastasis, and to evaluate the factors associated with de-novo metastatic cervical cancer. Univariate and multivariate analysis (by MANOVA) were used to evaluate the association. P≤0.05 was considered significant.

Results: Out of 1321 newly diagnosed cervical cancer patients, 54 (4.1%) had de-novo metastatic disease and most of which (81%) were found at single site. Common sites of distant metastasis were non-regional nodes, followed by liver, lung, peritoneum and bone. Univariate analysis showed the factors associated with de-novo metastasis were non-squamous subtype, high grade histology, bulky primary tumor (>4 cm), pelvic/para-aortic lymphadenopathy, and hydroureteronephrosis. Multivariate analysis revealed the factors associated with de-novo metastasis were bulky primary tumor (>4 cm), high grade histology, pelvic/para aortic lymphadenopathy, hydroureteronephrosis.

Conclusions: Newly diagnosed cervical cancer patients with bulky primary tumor, high grade histology, pelvic or para aortic lymphadenopathy, hydroureteronephrosis are associated with higher risk of de-novo distant metastasis.

Keywords: Cervical cancer, Distant metastasis, Pattern, risk factors

INTRODUCTION

Cervical cancer is the fourth most common cancer among women globally, and second most common cancer among women in India.1 It contributes to 6-29% of all cancers among women in India.2 India contributes to nearly one quarter of the global cervical cancer incidence and one third of global cervical cancer mortality.3,4 Majority cervical cancer (60 to 70%) patients are diagnosed in advanced stage.5,6 Advanced stage at diagnosis in developing countries is due to lack of public awareness and regular screening practices.5,9 The correct estimation of incidence of metastatic cervical cancer may sometimes be underscored due to incomplete metastatic work up particularly in resource limited settings. In view of paucity of data on de novo metastatic cervical cancer, the present study was undertaken to find the pattern of distant metastases, and to evaluate the clinicopathological factors associated with distant metastasis in newly diagnosed cervical cancer to risk stratify patients, who are at higher risk of having distant metastasis at diagnosis.

METHODS

A retrospective analytical study was conducted in the department of Medical oncology, Government
Royapettah hospital attached to Kilpauk medical college, Chennai. Convenience sampling method was followed to select 1321 cervical cancer patients registered in the hospital between January 2016 and December 2020. Data was retrieved from the institutional cancer registry in a predesigned proforma after obtaining permission from Institutional ethical committee.

Data was collected for clinicopathological variables like age, co-morbidity, performance status, family history, symptoms, duration of presentation, histopathology, tumor size, pelvic and para-aortic lymphadenopathy, hydroureronephrosis, and site of distant metastasis. Staging was performed as per the federation of international obstetrics and gynecology staging system for cervical cancer 8th edition. 2017.10

Statistical package for social sciences (SPSS) statistical software version 23.0 was used for data analysis. Univariate and multivariate analysis (with 95% confidence interval) were used for evaluating association between de-novo metastasis and different clinicopathological parameters. P≤0.05 was considered statistically significant.

**Inclusion criteria**

Patients with newly diagnosed cervical cancer registered in the hospital in the period from January 2016 to December 2020 were included in the study.

**Exclusion criteria**

Patients received cervical cancer treatment prior to registration in our hospital, were excluded from the study.

**RESULTS**

The median age of diagnosis was 53 years. Most patients were diagnosed with good performance status; 98.8% of patients were diagnosed with Eastern Co-operative Oncology Group performance status 1 to 2. Bleeding and discharge per vagina were the two most common presenting symptoms. Squamous cell carcinoma was the commonest histopathological subtypes. Three forth of patients presented with symptoms for 2 months or more duration. Early stage cervical cancer without parametrial involvement was observed in only 9.2% of patients, whereas majority patients were diagnosed in advanced stage. Forty five percent patients were diagnosed with bulky primary tumor. Pelvic lymphadenopathy, para-aortic lymphadenopathy, and hydroureronephrosis were observed in 213 (16.1%), 52 (3.9%), and 255 (19.3%) patients respectively. The clinicopathological characteristics of the study population are illustrated in the Table 1. De-novo metastasis was found in 54 (4.1%) patients, out of which single site metastases was present in 44 (81%) patients. Common sites of distant metastasis were in the following order; non-regional lymph nodes > liver > lung > peritoneum > bone.

### Table 1: Baseline clinicopathological characteristics of the study population.

| Parameters         | Number (%)       |
|--------------------|------------------|
| **Age (in years)** |                  |
| Median             | 53               |
| Range              | 26-86            |
| **ECOG**           |                  |
| I                  | 1045 (79.1)      |
| II                 | 260 (19.7)       |
| III                | 16 (1.2)         |
| IV                 |                  |
| **Co-morbidities** |                  |
| Diabetes           | 164 (12.4)       |
| Hypertension       | 131 (9.9)        |
| Coronary artery disease | 21 (1.6)     |
| Hepatitis B        | 16 (1.2)         |
| Hepatitis C        | 4 (0.3)          |
| HIV                | 21 (1.6)         |
| Hypothyroid        | 26 (2.0)         |
| Hyperthyroid       | 1 (0.1)          |
| Positive family history | 20 (1.5)   |
| **Symptoms**       |                  |
| Bleeding PV        | 1281 (96.9)      |
| Discharge PV       | 1258 (95.2)      |
| Pain abdomen       | 1110 (84.0)      |
| Back pain          | 357 (27.0)       |
| Neck swelling      | 3 (0.2)          |

Continued.
### Parameters

| Duration of symptoms (in months) | Number (%) |
|----------------------------------|------------|
| Median                           | 2          |
| Range                            | 1-36       |

### Histopathology

| Histopathology        | Number (%) |
|-----------------------|------------|
| Squamous              | 1277 (96.7)|
| Adeno                 | 30 (2.3)   |
| Adeno squamous        | 10 (0.7)   |
| Sarcoma               | 3 (0.2)    |
| Neuroendocrine        | 1 (0.1)    |

### Grade

| Grade | Number (%) |
|-------|------------|
| Low   | 328 (24.8) |
| Inter| 916 (69.4) |
| High  | 77 (5.8)   |

### Stage (FIGO)

| Stage (FIGO) | Number (%) |
|--------------|------------|
| I            | 45 (3.4)   |
| IIA          | 77 (5.8)   |
| IIB          | 450 (34.1) |
| IIIA         | 18 (1.4)   |
| IIIIB        | 438 (33.2) |
| IIIC         | 126 (9.5)  |
| IVA          | 113 (8.5)  |
| IVB          | 54 (4.1)   |

### Sites of distant metastasis

| Sites of distant metastasis | Number (%) |
|-----------------------------|------------|
| Non regional nodes          | 20 (37.0)  |
| Liver                       | 16 (29.6)  |
| Lung                        | 11 (20.4)  |
| Peritoneum                  | 10 (18.5)  |
| Bone                        | 8 (14.8)   |

**Table 2: Factors associated with distant metastasis evaluated by univariate and multivariate analysis (95% confidence interval).**

| Parameters                    | Distant metastasis | Univariate analysis | Multivariate analysis |
|-------------------------------|--------------------|---------------------|-----------------------|
|                               | N (% )             | P value             | P value               |
| **Histopathology**            |                    |                     |                       |
| Squamous                      | 51 (4.0)           | 0.018               | 0.915                 |
| Adeno                         | 2 (6.9)            |                     |                       |
| Adeno squamous                | -                  |                     |                       |
| Sarcoma                       | 1 (50)             |                     |                       |
| Neuroendocrine                | -                  |                     |                       |
| **Grade**                     |                    |                     |                       |
| Low                           | 4 (1.2)            | 0.000               | 0.000                 |
| Intermediate                  | 31 (3.4)           |                     |                       |
| High                          | 19 (25.0)          |                     |                       |
| **Tumor size**                |                    |                     |                       |
| ≤4 cm                         | 10 (1.4)           | 0.000               | 0.000                 |
| >4 cm                         | 44 (7.4)           |                     |                       |
| **Parametrium**               |                    |                     |                       |
| Not involved                  | 1 (0.8)            | 0.054               | 0.060                 |
| Involved                      | 53 (4.4)           |                     |                       |
| **Pelvic lymphadenopathy**    |                    |                     |                       |
| Present                       | 41 (18.9)          | 0.000               | 0.000                 |

Continued.
Univariate analysis showed the clinicopathological factors associated with distant metastasis were bulky primary tumor, non squamous histology, high grade histology, pelvic/para aortic lymphadenopathy, and hydroureteronephrosis (Table 2). Whereas on multivariate analysis; all of the above factors, except histopathological subtype and parametrical involvement, were found independently to be associated with distant metastases (Table 2).

**DISCUSSION**

Cervical cancer continues to be a major public health problem in developing countries. Disease stage at diagnosis significantly affects the treatment plan and survival outcome. The management of early stage cervical cancer (IA1, IA2, IB1, IIA) usually consists of surgery with or without adjuvant radiotherapy depending upon the risk factors, while the treatment of stage IB2, II B, III, IVA consists of concurrent chemoradiotherapy (including brachytherapy). Metastatic cervical cancer carries a poor prognosis. The treatment intention in metastatic cervical cancer is purely palliative, which takes into account the performance status, co morbidity, toxicities associated with the treatment modality before planning any treatment. The preferred chemotherapy regimen are platinum (cisplatin) based doublets. Addition of bevacizumab to platinum based chemotherapy has shown to prolong survival in metastatic cervical cancer patients. The 5 years survival in localized and metastatic cervical cancer are 91.5% and 16.5% respectively. Prognosis of single site metastasis is similar irrespective of sites of metastases. Previous study have reported that oligometastasis, bone only metastasis, single organ metastasis, non liver metastasis (compared to liver metastasis) in cervical cancer are associated with better overall survival. The present study showed the incidence of denovo metastatic cervical cancer to be 4.1%. Previous study have reported the commonest metastatic sites in cervical cancer patients were lungs > non regional lymph nodes > liver > bone. Common sites of distant metastasis in the present study were in the following orders; non regional lymph nodes > liver > lung > peritoneum > bone. Although the data on denovo metastatic cervical cancer and risk factors associated with distant metastasis in these patients are not clear, previous studies have reported the factors associated with distant metastasis and poor survival in treated patients of cervical cancer were non squamous histology, pelvic or para aortic nodal involvement. However one study have reported larger primary tumor volume and high grade histology to have higher risk of developing distant metastasis after definitive treatment in cervical cancer patients. In the present study, the factors associated with denovo metastatic cervical cancer evaluated by univariate analysis were non squamous subtype, high grade histology, bulky primary tumor (>4 cm), pelvic and para-aortic lymphadenopathy, hydroureteronephrosis. However on multivariate analysis, the factors significantly associated with distant metastasis were bulky primary tumor, high grade histology, pelvic or para-aortic lymphadenopathy, and hydroureteronephrosis. Limitation of the study was its retrospective nature, whereas to our best knowledge this is the largest study on clinicopathological characteristics of de-novo metastatic cervical cancer.

**CONCLUSION**

The study showed that denovo metastasis is observed in 4.1% of cervical cancer patients, and most of which presents as single site metastasis. Higher rates of distant metastasis was observed in newly diagnosed cervical cancer patients with bulky primary tumor, high grade histology, pelvic/para aortic lymphadenopathy, hydroureteronephrosis, which warrants thorough metastatic work up in these cohorts before planning treatment.

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| Parameters                              | Distant metastasis | Univariate analysis | Multivariate analysis |
|-----------------------------------------|--------------------|---------------------|-----------------------|
| Absent                                  | N (%)              | P value             | P value               |
| **Para-aortic lymphadenopathy**         |                    |                     |                       |
| Present                                 | 11 (21.2)          | 0.000               | 0.000                 |
| Absent                                  | 43 (3.4)           |                     |                       |
| **Hydroureteronephrosis**               |                    |                     |                       |
| Present                                 | 20 (7.8)           | 0.001               | 0.001                 |
| Absent                                  | 34 (3.2)           |                     |                       |
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