

Original Research Article

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

J. Kannan, Amit Saklani, Srigopal Mohanty*, Kiranmayee Narapaneni,
Deepak George, N. Ingersal

Department of Medical Oncology, Government Royapettah Hospital and Kilpauk Medical College, Chennai, India

Received: 13 November 2021

Revised: 07 December 2021

Accepted: 13 December 2021

***Correspondence:**

Dr. Srigopal Mohanty,

E-mail: drsrigopal17@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

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. $P \leq 0.05$ 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.⁷⁻⁹ 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, hydroureteronephrosis, 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 fourth 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 hydroureteronephrosis 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	Number (%)
Duration of symptoms (in months)	
Median	2
Range	1-36
Histopathology	
Squamous	1277 (96.7)
Adeno	30 (2.3)
Adeno squamous	10 (0.7)
Sarcoma	3 (0.2)
Neuroendocrine	1 (0.1)
Grade	
Low	328 (24.8)
Intermediate	916 (69.4)
High	77 (5.8)
Stage (FIGO)	
I	45 (3.4)
IIA	77 (5.8)
IIB	450 (34.1)
IIIA	18 (1.4)
IIIB	438 (33.2)
IIIC	126 (9.5)
IVA	113 (8.5)
IVB	54 (4.1)
Sites of distant metastasis	
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 N (%)	Univariate analysis P value	Multivariate analysis 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.

Parameters	Distant metastasis N (%)	Univariate analysis P value	Multivariate analysis P value
Absent	13 (1.2)		
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)		

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 parametrial 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.² 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, IIB, III, IVA consists of concurrent chemoradiotherapy (including brachytherapy).^{11,12} 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 regimens are platinum (cisplatin) based doublets.¹³ Addition of bevacizumab to platinum based chemotherapy has shown to prolong survival in metastatic cervical cancer patients.¹⁴ The 5 years survival in localized and metastatic cervical cancer are 91.5% and 16.5% respectively.¹⁵ Prognosis of single site metastasis is similar irrespective of sites of metastases.¹⁶ 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.¹⁷⁻¹⁸ 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.¹⁹ 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.¹⁹⁻²² 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.²³ 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.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3):209-49.
2. Bobdey S, Sathwara J, Jain A, Balasubramaniam G. Burden of cervical cancer and role of screening in India. *Indian J Med Paediatric Oncol.* 2016;37(4):278-85.
3. World health Organization (WHO). International Agency for Research on Cancer. India factsheet. Lyon: IARC; 2018. Available at: <https://gco.iarc.fr/today/data/factsheets/populations/>

- 356-india-fact-sheets.pdf. Accessed on 25 August 2021.
4. Monica, Mishra R. An epidemiological study of cervical and breast screening in India: district level analysis. *BMC Women's Health.* 2020;20:225.
 5. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, et al. ICMR-NCDIR-NCRP investigator group. Cancer statistics 2020: reports from national cancer registry programme, India. *J Glob Oncol.* 2020;6:1063-75.
 6. Ramkumar B, Mohanty S, Narapaneni K, Saklani A, Kannan J. Cervical cancer among 39 years or younger females in south India; a retrospective study. *Int J Sci Res.* 2021;10(7):15-7.
 7. Dunyo P, Effah K, Udofia EA. Factors associated with late presentation of cervical cancer cases at a district hospital: a retrospective study. *BMC Public Health.* 2018;18(1):1156.
 8. Shankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, et al. HPV screening for cervical cancer in rural India. 2009;360(14):1385-94.
 9. Thulaseedharan JV, Frie KG, Samkaranarayanan R. Challenges of health promotion and education strategies to prevent cervical cancer in India: a systematic review. *J Educ Health Promot.* 2019;8:216.
 10. Bhatla N, Aoki D, Sharma DN, Shankaranarayanan R. Cancer of the cervix uteri. *Int J Gynaecol Obstet.* 2018;143(2):22-36.
 11. Chuang LT, Temin S, Camacho R, Duaenas-Gonzalez D, Feldman S, Gultekin M, et al. Management and care of women with invasive cervical cancer: American Society of Clinical Oncology resource stratified clinical practice guideline. *J Glob Oncol.* 2016;2(5):311-40.
 12. Petignat P, Roy M. Diagnosis and management of cervical cancer. *BMJ.* 2007;335 (7623):765-8.
 13. Scatchard K, Forrest JL, Flubacher M, Cornes P, Williams C. Chemotherapy for metastatic and recurrent cervical cancer. *Cochrane Database Syst Rev.* 2012;10(10):CD006469.
 14. Tewari KS, Sill MW, Long HJ, Penson RT, Huang H, Ramondetta LM, et al. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med.* 2014;370:734-43.
 15. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer.* 2013;49:1374-403.
 16. Zhou S, Peng F. Patterns of metastases in cervical cancer: a population based study. *Int J Clin Exp Pathol.* 2020;13(7):1615-23.
 17. Yin Z, Tang H, Li L, Ni J, Yuan S, Lou H, Chen M. Impact of sites versus number of metastases on survival of patients with organ metastasis from newly diagnosed cervical cancer. *Cancer Manag Res.* 2019;11:7759-66.
 18. Zhang Y, Guo Y, Zhou X, Wang X, Wang X. Prognosis for different patterns of distant metastases in patients with uterine cervical cancer: a population based analysis. *J Cancer.* 2020;11(6):1532-41.
 19. Liu X, Meng Q, Wang W, Zhou Z, Zhang F, Hu K. Predictors of distant metastasis in patients with cervical cancer treated with definitive radiotherapy. *J cancer.* 2019;10(17):3967-74.
 20. Wang W, Liu X, Meng Q, Zhang F, Hu K. Normogram predicting survival and patterns of failure in patients with cervical cancer treated with concurrent chemoradiotherapy: A special focus on lymph nodes metastases. *PLoS one.* 2019;14(4):e0214498.
 21. Cheng S, Li Y, Zhang M, Tong T. PET/CT imaging analysis of recurrent sites and patterns of spread following modified radical surgery (type B) for stage Ib-IIa cervical cancer. *Oncol letters.* 2018;16(3):3623-27.
 22. Stock RG, Chen AS, Karasek K. Patterns of spread in node positive cervical cancer: the relationship between local control and distant metastases. *Cancer J Sci Am.* 1996;2(5):256-62.
 23. Fortin I, Jurgenliemk-Schulz I, Mahantshetty U, Haie-Meder C, Hoskin P, Segedin B, et al. Distant metastases in locally advanced cervical cancer pattern of relapse and prognostic factors: early results from the EMBRACE study. *Int J radiat Oncol Biol Phys.* 2015;93(3):S8-9.

Cite this article as: Kannan J, Saklani A, Mohanty S, Narapaneni K, George D, Ingersal N, et al. The pattern of distant metastasis and clinicopathological factors associated with de-novo metastatic cervical cancer: a retrospective analysis. *Int J Res Med Sci* 2022;10:191-5.