

Original Research Article

Analysis Of Pelvic Lymph Nodal Metastasis In Operable Cases Of Cancer Cervix-A One Year Cohort Study at a Regional Cancer Centre.

Abstract:

Objective: To study the incidence of nodal metastasis in early stage operable cases of cancer cervix and to correlate the nodal metastasis with different parameters like stage, degree of differentiation, lympho-vascular space invasion (LVSI) and deep stromal invasion.

Materials and Methods: This is an observational study conducted in Department of Gynec Oncology, Acharya Harihar Regional Cancer Centre & SCB Medical College ,Cuttack. from September 2013 to August 2014. The incidence of Lymph node positivity, Degree of differentiation, Deep Stromal invasion and Lymphovascular space invasion(LVSI) were analysed in 80 patients who underwent Wertheim's Radical hysterectomy for early stage operable cancer cervix which includes stage I A to II A. **Results:** The mean age of patients with early stage Cervical cancer was 52.5 years. Post menopausal bleeding was the most common clinical presentation . 17.5% patients had lympho-vascular invasion and pelvic lymph node involvement where as 20% had stromal invasion. None of the patients had vaginal margin involvement. Majority of cases belonged to Stage I B (57.5%) , followed by Stage II A (40%) and only 2.5% had Stage I A. Most of the cases (85%) were reported to have squamous cell carcinoma on histopathological examination

Discussion: Patients with Lymph node positivity , positive vaginal margin, parametrial positivity (1 out of 3 high risk factors) received chemo-radiation. Patients with lesion size more than 4 cm, LVSI, Deep stromal invasion (2 out of 3 intermediate risk factors) received radiation only as per all international protocols.

Conclusion: The incidence of lymph node metastasis in cancer cervix patients is quite significant mostly found in stage IB2,IIA2 but found to be less in stage I A. We are of opinion that Wertheim's Radical hysterectomy along with bilateral pelvic lymphadenectomy is an effective mode of treatment in patient with early stage cancer cervix which is required for risk stratification as per post operative histopathological analysis to decide adjuvant therapy in form of Radiotherapy alone or combination of Radiation and Chemotherapy for the better survival rate of patients.

INTRODUCTION:

Cervical cancer is the leading cause of cancer mortality in India, accounting for 17 percent of all cancer deaths among women age 30 to 69 years. At current incidence rates, the World Health Organization (WHO) estimates that the annual burden of new cases in India will increase to nearly 225,000 by 2025[1]. Multi-factorial causation, potential for prevention, and the sheer

threat it poses make cervical cancer an important disease for in-depth studies. Metastasis to lymph nodes indicate poor prognosis[2]. According to International Federation of Gynecology and Obstetrics (FIGO) staging system for cervical cancer, [3] cervical carcinoma confined to the cervix (disregard extension to the corpus) is classified as Stage I. Invasive carcinoma diagnosed only by microscopy; stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less; vascular space involvement, venous or lymphatic, does not affect classification and is I A, further sub-classified as I A 1 and I A 2. Clinically visible lesion confined to the cervix or microscopic lesion greater than I A 2 is classified as I B further divided into I B 1 and I B 2. In Stage II, cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina. II A means tumor without parametrial invasion, and II B involves parametrium. Early stage cancer cervix includes I and II A. Lymph node metastasis develops in 15–25% of early-cervical cancer patients [4]. With involvement of pelvic lymph nodes, the long term survival is considerably reduced[5]. The five year survival in this group of patients is approximately 60% [6]. Patients with common iliac or para-aortic node involvement had less five year survival rate compared to patients with only pelvic node involvement (external iliac, hypogastric, or obturator). Early stage cervical cancers (IA-IIA) are treated by radical hysterectomy and bilateral pelvic lymphadenectomy. Depending on the intermediate & high risk factors for recurrence adjuvant treatment is given. 5-Year survival rate of patients with positive nodes ranges from 20% to 74%. Information on the lymph node (LN) status is necessary to determine the treatment strategy [8]. Our aim of study is to evaluate the incidence of lymph node metastasis in early stage operable cases of Cervical cancer and its correlation with various risk factors.

MATERIALS AND METHODS:

This is an observational cohort study, conducted in Acharya Harihar Regional Cancer Centre, Cuttack, a recognized regional cancer center affiliated to government medical college at Cuttack in the state of Orissa, India. After obtaining approval from the regional ethics and research committee, Lymph node positivity, Degree of differentiation, Deep Stromal invasion and LVSI were analysed in 80 patients who underwent Wertheim's Radical hysterectomy for early stage cancer cervix, from September 2013 to August 2014. Patients were appropriately staged by clinical and radiological examination before surgical procedure. Routine chest radiographs were taken and assessed. Pearson chi square test with Yates correction for continuity and Fischer exact test were used to analyse the data in SPSS Version 20.

RESULTS:

Among the 80 patients in the study group, the mean age of patients was 52.5 and ranged from 31-68 years. Both lymph node positivity and cancer cervix incidence were highest in the (51-60) years age group (Table 1). Multiparous patients had a higher lymph node involvement and vascular invasion.

Table -1: Correlation of various variables with lymph node metastasis

<u>PATHOLOGICAL STAGE</u>	<u>NO OF PATIENTS (N=80)</u>	<u>LYMPH NODE POSITIVE(N=14)</u>	<u>P value</u>
<u>IA</u>	2(2.5%)	0	
<u>IB</u>	46(57.5%)	8(17.3%)	Stage IB vs IIA<0.0001
<u>IIA</u>	32(40%)	6(18.7%)	
<u>AGE(in years)</u>	NO. OF PATIENTS	NO. OF LYMPH NODE METASTASIS	
<u>31-40</u>	8(10%)	11(13.75%)	
<u>41-50</u>	12(15%)	12(15%)	
<u>51-60</u>	36(45%)	45(56.25%)	
<u>61-70</u>	24(30%)	12(15%)	
<u>HISTOLOGY</u>	NO. OF PATIENTS	NO. OF LYMPH NODE METASTASIS	
<u>SQUAMOUS</u> <u>1)WDSCC *</u>	10	2(20%)	NOT SIGNIFICANT
<u>2)MDSCC **</u>	56	9(16%)	
<u>3)PDSCC ***</u>	2	1(50%)	

<u>4)ADENO</u>	12	2(16.6%)	
<u>SURGICAL FINDINGS</u>	NO. OF PATIENTS		
<u>POSITIVE VAGINAL MARGIN</u>	0		
<u>POSITIVE PELVIC LYMPH NODES</u>	14(17.5%)		
<u>LYMPHOVASCULAR INVASION</u>	14(17.5%)		
<u>STROMAL INVASION</u>	16(20%)		

* well differentiated squamous cell carcinoma

** Moderate differentiated squamous cell carcinoma

*** poorly differentiated squamous cell carcinoma

The presenting complaints in decreasing order of frequency were Post menopausal bleeding(47.5%),white discharge(22.5%),irregular bleeding per vaginum(22.5%) and postcoital bleeding(7.5%).

Table 2:Correlation Of Metastatic Lymph Nodes With LVSI and Deep stromal invasion

PARAMETERS	LYMPHNODE METASTASIS (POSITIVE)	TOTAL NUMBER OF PATIENTS WITH LYMPH	Pvalue

		NODE POSITIVE	
LVSI(Lymphovascular Space Invasion)		14	P<0.005
Absent (66)	4(6%)		
Present (14)	10(71.4%)		
DEEP STROMAL INVASION		14	P<0.0001
Absent (64)	8(12.5%)		
Present (16)	6(37.5%)		

DISCUSSION:

Cervical cancer is the most common cause of death among all gynecological cancers worldwide. It is the most common gynecological cancer among Indian women.[9] In spite of being a developing nation, screening of cervical cancer by pap smear is on a steady rise over past years resulting in increasing detection of early cervical cancer in India. The patients with early detection of cervical cancer are ideal candidates for primary surgical treatment with radical hysterectomy and pelvic lymphadenectomy [10]with fair survival without needing any adjuvant therapy. Ernst Wertheim was the pioneer of radical hysterectomy , which included the removal of Uterus, cervix, parametrium and adequate tumor margin with pelvic lymph nodes, which he described in the year 1898. Time and again with many modifications suggested that the procedure remains the treatment of choice for early cervical cancer[11]. But there are also some early cases with various risk factors like tumor size, Lymphovascular Space Invasion, Stromal Invasion and lymph node status where positivity demands adjuvant treatment in form of Radiation alone or Chemo radiation in spite of radical surgery so considered as poor prognostic factors[12,13,14]

Radical hysterectomy with pelvic lymphadenectomy is indicated in Stage I. Lymph nodal involvement is significant in Stage IA2 or Stage IB1 cervical cancer [6,7] Though Chemo radiation or combined therapy is suggested for Stage IB2 or Stage IIA2 cervical cancer, Radical hysterectomy with pelvic lymphadenectomy is performed in selected cases[15,16,17]. Radical hysterectomy, in combination with adjuvant therapies, is an efficient mode of treatment for pelvic lymph nodal metastatic patients with stage IB-IIA cervical cancer.[18] Locally advanced

cervical cancer, FIGO stage equal or more than IB1 is treated with chemotherapy and external beam radiotherapy followed by brachytherapy.[19] In metastatic para-aortic nodal involvement radiotherapy is extended ,therefore accurate assessment of the extent of the disease is very important for planning the most appropriate treatment.

Radical surgery alone has low morbidity, enables more accurate prediction of prognosis and may be the sufficient in most patients with lymph node-negative early stage cervical cancer.[6]With a primary radical hysterectomy, stage IB1 cervical cancer patients have a significantly better survival rate than those with stage IB2.[20] In about two-thirds of pelvic lymph node positivity with stage IB cervical cancer cases, surgery alone could provide equal or better survival (without the toxicity of chemoradiotherapy), than any kind of multimodality treatment alternatives.[21] Para-aortic node metastasis appears to occur secondarily to wide-spread pelvic lymph node metastasis. [22,23] Terada KY et al stated that,for patients undergoing radical hysterectomy as primary treatment, postoperative adjuvant radiotherapy did not significantly improve survival. [7]. Radical hysterectomy with modifications has currently achieved lower morbidity due to its frequent usage and advancement of surgical equipments and techniques like Laparoscopy and Robotics.Our study has similar results with various results of other studies([Table 3](#))

Table -3: Comparison with other studies

<u>Patient Characteristics</u>	<u>Our Study</u> <u>N=80</u>	<u>Schorge et al</u> <u>[24]</u> <u>N=171</u>	<u>Landoni et al</u> <u>[15]</u> <u>N=343</u>	<u>Jena, Amitabh, et al [25]</u>	<u>Rajshekar S., et al.[26]</u> <u>N=601</u>
<u>Median age</u> <u>(Years)</u>	52.5	46	47	49.5	49
<u>Clinical stage</u>					
<u>I A</u>	2.5%	-	-	6.3%	-
<u>I B</u>	57.5%	91%	88%	30%	88.4%
<u>II A</u>	40%	9%	12%	51.2%	11.6%

<u>Cell type</u>					
<u>Squamous</u>	85%	73%	83%	91%	87%
<u>Adeno</u>	15%	16%	14%		10%
<u>Small cell</u>			3%		
<u>Clear cell</u>					
<u>Adenosquamous</u>				2.5%	
<u>Pelvic nodes positive</u>	17.5%	–	13%	12.5%	18.5%
<u>Lymphovascular invasion</u>	17.5%	45%	–	7.5%	17%
<u>Deep stromal invasion</u>	20%	42%	–	3.75%	70%

In our study, a significant number of patients in IB(17.3 %) and IIA(18.7%) had lymph node metastasis which correlated well with that of other studies. But the number of lymph node metastasis was more in well differentiated carcinoma rather than moderately differentiated which was not significant which may be due to proper lymph node dissection in those moderately differentiated carcinoma patients. Also the highest incidence of lymph node metastasis was found in age group 51-60 years where the maximum number of patients present. We had 14 patients with lymphovascular space invasion but there were 4 patients who didn't have lymphovascular space invasion but had lymph node metastasis. Same was also for deep stromal invasion where 8 patients had lymph node metastasis without stromal invasion (Table 2). But patients with risk factors (LVSI and stromal invasion) have significant node positivity which was the aim of our study and so the management varied accordingly. According to Sartori E et al, post-operative radiotherapy is controversial in node-negative pathologic stage IB cervical cancer. Radical surgery alone has low morbidity, enables more accurate prediction of prognosis and may be the sufficient therapy in the majority of patients with lymph node-negative early stage cervical cancer[27]

Our patients with lymph node positivity, positive vaginal margins, parametrial positivity (1 out of 3 high risk factors) received chemo-radiation. Patients with lesion size more than 4 cm, Lymphovascular Space Invasion(LVSI), Deep stromal invasion (2 out of 3 intermediate risk factors) received radiation only. The post-operative hospital stay was 8-12 days with a mean of 11 days. Except for one individual who developed urinary incontinence, none of the other cases had major complication. Superficial wound infection was noted in three cases.

CONCLUSIONS:

To conclude, the incidence of lymph node metastasis in cancer cervix patients is significant and is mostly found in stage IB2 and IIA2 which is evident in this study. This is due to large volume of tumor with early metastasis to lymphovascular channels then to nearby pelvic nodes. Wertheim's hysterectomy with its various modifications with bilateral pelvic lymphadenectomy is the most safe and cost effective mode of treatment in patient with early stage Cervical cancer. In most of cases radical surgery is sufficient without any addition of adjuvant therapy. In other early cases it helps in risk stratification as per post operative histopathological parameters to decide the need of adjuvant therapy in form of radiation or chemo radiation for the better survival of patients.

REFERENCES

1. Kaarthigeyan, K. "Cervical Cancer in India and HPV Vaccination." *Indian Journal of Medical and Paediatric Oncology : Official Journal of Indian Society of Medical & Paediatric Oncology* 33.1 (2012): 7–12. PMC. Web. 2 Mar. 2016.
2. Li X, Yin Y, Sheng X, et al. Distribution pattern of lymph node metastases and its implication in individualized radiotherapeutic clinical target volume delineation of regional lymph nodes in patients with stage IA to IIA cervical cancer. *Radiation Oncology (London, England)*. 2015;10:40. doi:10.1186/s13014-015-0352-5.
3. Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. *Int J Gynaecol Obstet*. 2009 May. 105(2):107-8.
4. Berek JS, Novak E. 2012 *Berek & Novak's Gynecology*. Wolters Kluwer Health/Lippincott Williams & Wilkins: Philadelphia
5. Therapeutic role of lymphadenectomy for cervical cancer. *Shah M, Lewin SN, Deutsch I, Burke WM, Sun X, Herzog TJ, Wright JD. Cancer*. 2011 Jan 15; 117(2):310-7.
6. Sartori E, Tisi G, Chiudinelli F, La Face B, Franzini R, Pecorelli S. Early stage cervical cancer: adjuvant treatment in negative lymph node cases. *Gynecol Oncol* 2007; 107:S170-4.
7. Terada KY, Morley GW, Roberts JA. Stage IB carcinoma of the cervix with lymph node metastases. *Gynecol Oncol* 1988; 31:389-95.
8. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. *Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, Favini G, Ferri L, Mangioni C. Lancet*. 1997 Aug 23; 350(9077):535-40

9. Sreedevi A, Javed R, Dinesh A. Epidemiology of cervical cancer with special focus on India. *International Journal of Women's Health*. 2015;7:405-414. doi:10.2147/IJWH.S50001.
10. Ware RA, van Nagell JR. Radical hysterectomy with pelvic lymphadenectomy: indications, technique, and complications. *Obstet Gynecol Int* 2010; 2010 :1-9. pii: 587610. doi:10.1155/2010/587610. Epub 2010 Sep 1.
11. Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. *Obstet Gynecol* 1974; 44:265-72
12. Endo D, Todo Y, Okamoto K, Minobe S, Kato H, Nishiyama N. Prognostic factors for patients with cervical cancer treated with concurrent chemoradiotherapy: a retrospective analysis in a Japanese cohort. *Journal of Gynecologic Oncology*. 2015;26(1):12-18. doi:10.3802/jgo.2015.26.1.12.
13. Ho CM, Chien TY, Huang SH, Wu CJ, Shih BY, Chang SC. Multivariate analysis of the prognostic factors and outcomes in early cervical cancer patients undergoing radical hysterectomy. *Gynecol Oncol* 2004; 93:458-64
14. Ayhan A, Al RA, Baykal C, Demirtas E, Ayhan A, Yüce K. Prognostic factors in FIGO stage IB cervical cancer without lymph node metastasis and the role of adjuvant radiotherapy after radical hysterectomy. *Int J Med Health Sci*. Oct 2013, Vol-2; Issue-4 390 hysterectomy. *Int J Gynecol Cancer* 2004; 14:286- 92.
15. Landoni F, Maneo A, Cormio G, Perego P, Milani R, Caruso O, et al. Class II versus class III radical hysterectomy in stage IB-IIA cervical cancer: a prospective randomized study. *Gynecol Oncol* 2001; 80:3-12.
16. Tsai CS, Lai CH, Wang CC, Chang JT, Chang TC, Tseng CJ, et al. The prognostic factors for patients with early cervical cancer treated by radical hysterectomy and postoperative radiotherapy. *Gynecol Oncol* 1999; 75:328-33.
17. Michalas S, Rodolakis A, Voulgaris Z, Vlachos G, Giannakoulis N, Diakomanolis E. Management of early-stage cervical carcinoma by modified (Type II) radical hysterectomy. *Gynecol Oncol* 2002; 85:415-22.
18. Zheng M, Huang L, Liu JH, Xiong Y, Li JD, Huang X, et al. Type II radical hysterectomy and adjuvant therapy for pelvic lymph node metastasis with stage IB-IIIB cervical carcinoma: a retrospective study of 288 patients. *J Surg Oncol* 2011; 104:480-5
19. Brockbank E, Kokka F, Bryant A, Pomel C, Reynolds K. Pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer. *The Cochrane database of systematic reviews*. 2011;(4):CD008217. doi:10.1002/14651858.CD008217.pub2
20. Srisomboon J, Kietpeerakool C, Suprasert P, Manopanya M, Siriaree S, Charoenkwan K, et al. Survival and prognostic factors comparing stage IB 1 versus stage IB 2 cervical cancer treated with primary radical hysterectomy. *Asian Pac J Cancer Prev* 2011; 12:1753-6.
21. Ungár L, Pálfalvi L, Tarnai L, Horányi D, Novák Z. Surgical treatment of lymph node metastases in stage IB cervical cancer. The laterally extended parametrectomy (LEP) procedure: experience with a 5 year follow-up. *Gynecol Oncol* 2011; 123:337- 41.

22. Sakuragi N, Satoh C, Takeda N, Hareyama H, Takeda M, Yamamoto R, et al. Incidence and distribution pattern of pelvic and paraaortic lymph node metastasis in patients with Stages IB, IIA, and IIB cervical carcinoma treated with radical hysterectomy. *Cancer* 1999; 85:1547-54.
23. Cai HB, Chen HZ, Zhou YF, Lie DM, Hou HY. Class II radical hysterectomy in low-risk IB squamous cell carcinoma of cervix: a safe and effective option. *Int J Gynecol Cancer* 2009; 19:46-9.
24. Schorge JO, Molpus KL, Koelliker D, Nikrui N, Goodman A and Fuller AF (1997) Stage IB and IIA cervical cancer with negative lymph nodes: the role of adjuvant radiotherapy after radical hysterectomy *Gynecol Oncol* 66 31–5 DOI: [10.1006/gyno.1997.4691](https://doi.org/10.1006/gyno.1997.4691) PMID: [9234917](https://pubmed.ncbi.nlm.nih.gov/9234917/)
25. Amitabh Jena, Rashmi Patnayak, Siva kumar Reddy, B.Manilal, Kausik Hari, A Ramesh. Cancer Cervix and Pelvic Lymph Nodal Metastasis – Our Experience from A Tertiary Health Care Center in South India. *Int J Med Health Sci.* Oct 2013, Vol-2; Issue-4.
26. Kundargi RS, Guruprasad B, Rathod PS, Shakuntala PN, Shobha K, Pallavi VR, Umadevi K and Bafna UD (2013) Risk strata-based therapy and outcome in stage Ib–IIa carcinoma cervix: single-centre ten-year experience *ecancer* 7 341.
27. Sartori E, Tisi G, Chiudinelli F, La Face B, Franzini R, Pecorelli S. Early stage cervical cancer: adjuvant treatment in negative lymph node cases. *Gynecol Oncol* 2007; 107:S170-4.