Original Article

Cervical Cancer: Outcome of Treatment and Causes of Failure

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Abstract

Objective: To summarize the data and look into the various treatments offered to cervical cancer patients at Institute of Nuclear Medicine and Oncology (INMOL) to highlight the most likely causes of treatment failure.

Methods: In this retrospective study, case files of all patients presenting with invasive carcinoma of uterine cervix during 1993-2002 were studied in respect to personal profile, disease related risk factors, pathological characteristics, treatment administered and outcome in the form of tumour response and survival.

Results: Early age at marriage, multiple marriages of self or spouse, multiparty, prolonged use of contraceptives and smoking were some of the risk factors for cervical cancer in this group of patients. Out of 618 patients presenting with invasive cervical cancer,65% presented in advanced stages II and III. Apart from advanced stage at presentation, anaemia, poor nutrition, and ignorance about self-hygiene and lack of follow-up were main causes of treatment failure. Outcome of treatment was improved when chemotherapy was added to radiation.

Conclusion: Advanced stage at diagnosis and lack of follow-up were main causes of treatment failure. Implementation of screening programs on national level for early detection is therefore recommended (JPMA 56:436;2006).

Introduction

Cancer of the cervix uteri is one of the most common cancers in women, worldwide.[1] In fact, it has been reported to be the second commonest malignancy that affects women, (after breast cancer).[2] Around the world, about 450,000 women are diagnosed with cervical cancer each year and the disease kills 200,000 annually.[3]

Almost 80% of these deaths occur in developing countries, (where Papanicolaou smear screening has been insufficiently implemented). Here cervical cancer is now the leading cause of cancer mortality in women.[4] In the United States, although screening practices have seen cervical cancer rate steadily declining since the 1940s, approximately 13,000 new cases and 4100 cervical cancer deaths are registered each year.[5] Despite falling incidence, cervical cancer remains the 10th leading cause of cancer death in the United States.[6] Overall survival rates of women with locally advanced cancer have held more or less steady for decades now. Since 1998, the mortality rate remains near 3.0 deaths per 100,000 women.[6]

No accurate figures exist for the prevalence and mortality of cancer in Pakistan. However, figures from neighbouring India estimate cervical cancer to be the second most common malignancy in females.[7] At the Institute of Nuclear Medicine and Oncology, Lahore (INMOL) (capital of the North-eastern province of Punjab, Pakistan), we manage approximately 65 new cases of

cervical cancer every year accounting for the 4th common female malignancy.

Massive Pap screening in the United States is credited for bringing cervical cancer to number 10 in the causes of cancer death from being the leading cause of cancer death in 1941. Reports from Europe claim that introducing screening programs to unscreened populations reduced cervical cancer rates by 60% to 90% within three years.[8] When cervical cancer trends in North America and Europe were correlated significant reductions in incidence of invasive cervical cancer and a 20% to 60% reduction in cervical cancer mortality was reported.[8]

Survival of cancer of the cervix uteri is predicted by the stage at diagnosis. According to an estimate although 95% of women will survive 5 years when the cancer is localized, only 13% will survive distant disease.[9,10] This means detection of cervical cancer in its earliest stages does save lives.

After establishing the diagnosis of invasive cervical cancer, histologically, the disease is staged clinically. This determines the direction further management will take.[6]

Treatment of the early stage Ia-IIa is surgery and/or radiotherapy. Stage Ia tumours have a low risk of nodal metastases, and hence the prognosis is good. Five-year survival exceeds 95 percent with appropriate treatment.[10] Surgical hysterectomy is the recommended option.[11]

Concurrent Chemo-Radio-Therapy (CCRT) is now the preferred treatment for more advanced stages of disease (Ib-II b, III, and IV a). Stage I and IIa tumours can be treated surgically or with radiotherapy, with a five-year survival rate of 80 to 90 percent.[12]

Bulky stage Ib tumours carry a poorer prognosis. A combination of radiotherapy and cisplatin, followed by adjuvant hysterectomy is reported to have halved the risk of disease progression and death.[11]

Radiation therapy provides five-year survival rates of 65, 40 and less than 20 percent for stages IIb, III and IV, respectively.[12] Stage IV b cancers are treated by chemo and radiotherapy for palliation. Patients with distant metastases (stage IVb) also require chemotherapy to control systemic disease. Research is being conducted to improve the rate of survival in advanced-stage disease.[6,13]

Tumour bulk and advanced stage at presentation is an understandable cause of treatment failure. However reports of patients with early disease showing poor control warrant investigation into the causes of such failures.[13]

The objective of this study was to summarise the data and look into the various treatments offered to cervical cancer patients at INMOL.

We also intended to find out some of the common risk factors prevalent in our patient population, to highlight the most likely causes of treatment failure apart from the advanced stage at presentation.

Materials and Methods

Case files of all patients presenting with invasive carcinoma of uterine cervix during 1991-2000 were studied in respect to personal profile, disease related risk factors, pathological characteristics, treatment administered and outcome in the form of tumour response and survival.

Most patients could not return for follow-up after initial treatment. We had to make telephonic contact or post letters wherever such contacts were available. This strategy resulted in improved information collection.

External Beam Radiotherapy (EBRT) was given to the whole pelvis using 4-field box or 2-field technique at 15MV linear accelerator or Cobalt therapy unit. Brachytherapy was given at Gamma Med III unit with three Cs-137 sources. Concomitant Chemo/Radio-therapy (CCRT) was given with Cisplatin, 5 Fluorouracil, and Mitomycin in different combinations according to a protocol.

Likelihood ratios and Spearman correlative test was applied using Statistical Package for the Social Sciences (SPSS) Software version 9.0.

Results

Approximately 65 new cases are registered annually at INMOL, rendering invasive cervical cancer 4th common female malignancy. Out of 618 patients presenting with invasive cervical cancer, large percentage (58%) presented in stage-III and IV (Table 1).

Most patients presented with one or more risk factors (Table 2) in addition to advanced stage at diagnosis.

Although appropriate treatment was offered to all the 618 patients, it was noticed that large numbers were lost to follow up making it impossible to assess overall survivals in cervical cancer (Table 2).

Follow-up at 5 years showed that, survival was directly proportional to the stage, and more so, on the bulk of tumour, percentage of mortality increasing with the stage (Table 3).

When different characteristics were compared in terms of mortality, interesting data showed up (Table 3). Mortality varied significantly depending on the stage at the diagnosis. When all the treatment modalities are considered together the difference among the mortality of different

Table 1. Outcome in evaluable patients n = 400 (65.5%).

FIGO Stage	Total	Completing Therapy		Number of patients died		Lost to Follow-up	
		Number	Percentage	At 2 years	At 5 years	Number	Percentage
I	81 (13)	63	77.8%	3 (5)	8 (13)	36	22.3%
II	179 (29)	109	69.5%	5 (5)	21 (18)	53	31.5%
III	204 (33)	176	80.2%	14 (8)	23 (13)	70	198.8%
IV	154 (25)	78	50.7%	65 (83)	78 (100)	36	49.4%
Total	618	426	68.9%	87 (20)	130 (31)	195	31.6%

Note: Percentage are calculated against the number completing therapy in each stage.

Table 2. Risk Factors Evaluation.

Reproductive Health Factors		
Age at Presentation		
Mean	42 years	
Range	33-82 years	
Age at onset of Sexual Activity		
Mean	18 years	
Range	13-28 years	
Age at first Childbirth		
mean	19 years	
Range	15-35 years	
Number of Marriages (Self or spouse) (n=618)	Frequency	Percentage
One	377	61%
More than one	241	39%
Number of Pregnancies		
Mean	4	
Range	4-14	
Contraceptive Use	Frequency	Percentage
Yes	136	22%
No	482	78%
Socio-economic Factors		
Tobacco Smoking	105	17%
Poor Socio-economic Status	574	93%
Anaemia (Hb<10 g/dl) & Poor General Health	513	83%

groups is not very significant. However, there is statistically significant difference showing better survivals for concomitant chemotherapy and radiotherapy compared with surgery or radiotherapy alone.

We could not find a significant difference in terms of statistical values between the different tumour grades if the mortality is considered, however this could be due to a large number belonging to the group whose tumour grade could not be determined.(Table 3). If the statistical analysis is performed among the known grades only, there is a significantly better outcome in favour of grades I and II. There is no significant difference in terms of statistical values between the different histopathology types if the mortality is considered. A significant difference is observed in the mortality rate among the different age groups, favouring better survival in the older age group (Table 3).

Table 3. Risk of death from Cervical Cancer in relation to clinical and Histopathological characteristics and treatment modility.

Characteristics	Patients n (%)	Number of deaths (%)		Odds Ratio	95% CI	Significance
		At 2 yrs	At 5 yrs			
FIGO Stage						
I	63 (15)	3 (5)	8 (13)	0.14	95±4.2	p < 0.02
II	109 (24)	5 (5)	21 (18)	0.09	95±4.7	
III	176 (41)	14 (8)	37 (21)	0.2	95±2.9	
IV	78 (18)	65 (83)	78 (100)	1	95±1.6	
Treatment Modalities						
Surgery	26 (6)	2 (8)	8 (31)	0.45	95±4.5	P < 0.1
Surgery/RT	48 (12)	3 (6)	9 (19)	0.23	95±4.7	
RT	143 (35)	37 (26)	74 (52)	0.21	95±3.3	P < 0.02
CCRT	189 (47)	12 (6)	26 (14)	1.01	95±1.4	
Tumour Grade						
1	89 (22)	13 (14)	33 (37)	0.59	95±2.3	
2	106 (26)	21 (20)	27 (25)	0.35	95±2.8	P < 0.02
3	42 (10)	7 (17)	32 (76)	0.29	95±1.6	
Unknown	163 (40)	18 (11)	84 (52)	1.01	95±1.4	P < 1.9 Not-Significant
Histopathology						
Large Cell	68 (17)	23 (34)	29 (43)	0.75	95±2.1	P < 2.01
Small Cell	36 (9)	11 (31)	18 (50)	1	95±2.1	Not-Significant
Adeno Ca	42 (10)	16 (38)	26 (62)	1.04	95±4.8	
Age (Years)						
< 50	308 (76)	24 (8)	56 (18)	0.2	95±3.1	
50-69	67 (17)	21 (31)	36 (54)	1.02	95±2.1	P < 0.1
> 70	31 97)	9 (26)	23 (74)	1.04	95±2.8	

Note: Percentage are calculated against the numbers in each characteristic..

Discussion

Reviewing the recently published data on cervical cancer treatment, it is noticed that a combination of external beam irradiation and intracavitary Brachytherapy achieves excellent loco regional disease control and survival for patients with early cervical cancer. Lowrey et al reported on their series of 701 Stage IB1 the 5-year disease-specific survival rate for this group was 95%[12] In the present study 87% evaluable patients survived for 5 years in stage I.

Eifel et al concluded that these results are achievable when the treatment is completed in 8 weeks or less, which is the time frame that is maximally efficacious and represents an acceptable treatment duration.[13] For Stage IIB disease, the 5-year survival rate ranges between 65% to 75%; for Stage IIIB it is 35%.[12,13]

Unfortunately in our study poor follow-up was observed leading to unnecessary delays in treatment thereby showing poor local control Referring to table 3 it is evident that the overall 5 year survival is 82% and 79% for stage II and III respectively. However, it should be noted that this improvement in survival is due to addition of cisplatin to radiation in these patients.

In 1999, five landmark papers reported significant improvement in survival for advanced cervical cancer patients through the concurrent administration of cisplatin-based chemotherapy with radiation therapy in women with locally-advanced disease.[14] These five studies demonstrated statistically improved disease free and overall survival with combination therapy in all disease stages.[10] All five of the trials included cisplatin in their chemotherapy regimen, and the National Cancer Institute issued a strong recommendation for inclusion of cisplatin-based chemotherapy for women who require radiotherapy in the treatment of cervical cancer.[10,14] Since then CCRT is the preferred mode of treatment for these patients at INMOL. The results indicate that 5year overall survival is improved from 48% to 86% just by adding weekly cisplatinum to the radiotherapy plan. This is comparable to the meta analysis of 5 studies by Im and Monk[10] and that of Rose et al[14] showing improvement of same magnitude (51% to 83%). It should be noted that most patients in CCRT group belonged to younger age.

Various risk factors were studied, only a small percentage of women in our study group admitted to smoking cigarettes (17%). We lack information on smoking patterns of patient's spouse which is also regarded as a significant risk factor.[15,16]

Although it was socially difficult to question about the number of sex partners, there is indirect evidence in that many women had been married more than once or were wives to men with multiple wives.[17] Workers in Japan have established an association between the HPV DNA genome and prognosis of cervical cancer.[18,19] This has started the quest for a possible vaccine against HPV that may ultimately help prevent the infection and hence cervical cancer.[20]

The role of HPV as a prognostic factor and in predicting response to chemo-radiotherapy is controversially reported in literature.[21] As a matter of fact the prevalence of HPV in our country remains un investigated. We at INMOL have initiated two inter related projects to identify the various genotypes of HPV in cervical cancer biopsies and general population to correlate its impact on response to chemo radiotherapy and overall survival.

Twenty two percent (22%) of our patients used oral contraceptives for 2 or more years. The role of oral contraceptives in lowering local resistance to HPV infection is under investigation and is quoted controversially by different investigators.[15,22]

Poor social status leading to anaemia is a common finding in cervical cancer patients and was evident in 83% of our patients. It has been shown that women who had a low Haemoglobin (Hb) at start of radiotherapy showed poor disease control, probably due to large hypoxic cell population in such tumours which has been associated with development of resistance to ionising radiation and some forms of chemotherapy leading to enhanced malignant progression and metastasis, potentially impacting long-term survival.[23]

Lack of follow-up is a major problem we faced when conducting this study, as 25% of the patients did not complete their treatment. In addition about the same number was lost to follow-up in subsequent years. Lack of follow-up can be a major contributing factor for treatment failure. Possible causes include poor patient education and shortage of resources to attend on time.

Conclusion

The present authors note with great concern that although cervical cancer seems quite prevalent in Pakistani women, we do not know the exact incidence or prevalence figures on the disease in our population. National cancer registry is the need of the hour.

As most patients presented in advanced stages, the need of the hour then is a patient education programme about sexual health. PAP smear is an inexpensive test that has been proven to save lives. A comprehensive screening programme is needed to save the countless lives of Pakistani women lost due to cervical cancer every year.

References

1. Elkas J, Farias-Eisner R. Cancer of the uterine cervix. Curr Opin Obstet Gynecol 1998;10:47-50.
2. Jemal A, Thomas A, Murray T, Thun M. Cancer statistics, 2002. CA Cancer J Clin. 2002;52:23-47.
3. Pisani P, Parkin DM, Bray F, Ferlay J. Estimates of the worldwide mortality from 25 cancers in 1990. Int J Cancer. 1999;83:18-29.
4. American Cancer Society. Cancer facts and figures, 2004. Atlanta: American Cancer Society, 2004. Accessed at: http://www.cancer.org/downloads/STT/CPED2004PWSecured.pdf on December 06, 2004.
5. Sasieni PD, Cuzick J, Lynch-Farmery E. Estimating the efficacy of screening by auditing smear histories of women with and without cervical cancer. The National Co-ordinating Network for Cervical Screening Working Group. Br J Cancer. 1996;73:1001-5.
6. Di Saia PJ, Creasman WT. Clinical gynecologic oncology. 5th ed. St. Louis: Mosby, 1997,
7. Desai PB. Cancer control efforts in the Indian subcontinent. Jpn J Clin Oncol. 2002;32 Suppl:S13-6.
8. Mather DB, Bastian L. Evaluation of Cervical Cytology: Evidence Report/Technology Assessment No. 5. (Prepared by Duke University under Contract No. 290-97-0014.) AHCPR Publication No. 99-E010. Rockville, MD: Agency for Health Care Policy and Research. February 1999. Available at: http://www.ncbi.nlm.nih.gov/books/bv.fcgirid=hstat1.chapter.6794. Accessed December 06, 2004).
9. Kolstad P. Follow-up study of 232 patients with stage Ia1 and 411 patients with stage Ia2 squamous cell carcinoma of the cervix (microinvasive carcinoma). Gynecol Oncol. 1989;33:265-72.
10. Im SS, Monk BJ. New developments in the treatment of invasive cervical cancer. Obstet Gynecol Clin North Am 2002;29:659-72.
11. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL 3rd, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 1999. 15;340:1154-61.
12. Lowrey GC, Mendenhall WM, Million RR. Stage IB or IIA-B carcinoma of the intact uterine cervix treated with irradiation: a multivariate analysis. Int J Radiat Oncol Biol Phys 1992;24:205-10.
13. Eifel PJ, Morris M, Wharton JT, Oswald NJ. The influence of tumor size and morphology on the outcome of patients with FIGO stage IB squamous cell carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 1994;29:9-16.
14. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999. 15;340:1144-53.
15. Daling JR, Madeleine MM, McKnight B, Carter JJ, Wipf GC, Ashley R. The relationship of human papillomavirus-related cervical tumors to cigarette smoking, oral contraceptive use, and prior herpes simplex virus type 2 infection. Cancer Epidemiol Biomarkers Prev 1996;5:541-8.
16. Tay SK, Tay KJ. Passive cigarette smoking is a risk factor in cervical neoplasia. Gynecol Oncol 2004;93:116-20.
17. Stoler MH. Human papillomaviruses and cervical neoplasia: a model for carcinogenesis. Int J Gynecol Pathol. 2000;19:16-28.
18. International Agency for Research on Cancer (IARC). Summaries and Evaluations: Human Papillomaviruses. Lyons: IARC; 1995;64. Available at: http://www.inchem.org/documents/iarc/vol64/hpv.html Accessed December 06, 2004.
19. Bosch FX, Manos MM, Munoz N, Sherman M, Jansen AM, Peto J. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. J Natl Cancer Inst 1995, 7;87:796-802.
20. Murakami M, Gurski KJ, Steller MA. Human papillomavirus vaccines for cervical cancer. J Immunother. 1999;22:212-8.
21. Harima Y, Sawada S, Nagata K, Sougawa M, Ohnishi T. Human papilloma virus (HPV) DNA associated with prognosis of cervical cancer after radiotherapy. Int J Radiat Oncol Biol Phys. 2002;52:1345-51.
22. Bosetti C, La Vecchia C. The risk of cervical cancer increases with increasing duration of oral contraceptive use-meta-analysis: Smith JS, Green J, Berrington de Gonzalez A, Appleby P, Peto J, Plummer M, Franceschi S, Beral V. Cervical cancer and use of hormonal contraceptives: a systematic review. Lancet 2003; 361:1159-1167.Evidence-based Obstet Gynecol 2003; 5:181-182.
23. Bachtiary B, Schindl M, Potter R, Dreier B, Knocke TH, Hainfellner JA. Overexpression of hypoxia-inducible factor 1alpha indicates diminished response to radiotherapy and unfavorable prognosis in patients receiving radical radiotherapy for cervical cancer. Clin Cancer Res. 2003; 9:2234-40.