

A 5-Year Review of FIGO Stage Ib Cervical Cancer in an Asian Population

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ABSTRACT

Objective: We studied the clinical patterns and outcome of patients with FIGO (1985) Stage Ib cervical cancer. In particular, looking at the clinico-pathological characteristics in relation with disease recurrence.

Patients & methods: Ninety-nine Asian patients were managed at (the former) K K Hospital, Singapore, from 1987 to 1991. The mean and median follow-up periods were 67 and 60 months respectively. This study was performed in 1995.

Results: The majority of the patients (81%) was treated by radical hysterectomy with or without adjuvant radiotherapy/chemotherapy while 15% were treated by radical pelvic radiotherapy alone and 4% of patients had pelvic radiotherapy following the diagnosis of cervical cancer after a simple hysterectomy. Thirteen patients developed tumour recurrence (13.1%). In these patients, there was a greater proportion of adenocarcinomas (31% vs 13%, $p=0.1065$), lymph node metastases (45% vs 20%, $p=0.09$) and surgical margins involvement (45% vs 7%) 7%, $p=0.004$) while there seemed to be no difference in histological sub-types, vascular space involvement and cytological grading. The relative risks of developing tumour recurrence in patients with adenocarcinoma was 2.5 times (95% CI: 0.88 - 7.05), lymph-node metastasis: 2.3 times (95% CI: 0.96 - 4.93) and involved surgical margins; 5.9 times (95% CI: 2.27 - 15.5). The mean time to recurrence were 21.7 months with all of them detected within 36 months following primary therapy. All of them had abnormal physical findings while routine follow-up Pap smear was positive in only one patient (8%). In general, the outcome of salvage treatment was poor.

Conclusions: In our group of patients with FIGO Stage Ib cervix cancer, majority had radical surgery performed initially. Thirteen percent had disease recurrence, in which there were greater proportions of patients with adenocarcinoma, lymph-node metastasis and involved surgical margins. The mean time-to-recurrence was 21.7 months with all detected by 36 months. Routine follow-up Pap smear seemed to be a poor indicator of disease status.

Keywords: cervix, cancer, Asian, FIGO Stage Ib

INTRODUCTION

The overall 5-year survival outcome of patients with FIGO Stage Ib cervical cancer undergoing radical

hysterectomy or radiotherapy is an optimistic 85%. However, there remained amongst these patients with such a clinically early stage cancer, a proportion of them who are at an increased risk of developing tumour recurrence, with a dismal 5-year reported survival rate of 5%⁽²⁾ or less. The clinicopathologic factors which predict a poorer outcome for these patients have been extensively studied⁽²⁻⁶⁾ and the results translated into recommendations for adjuvant therapy, with the aim of reducing the risk of tumour recurrence⁽³⁾. The risk factors that have been identified include: non-squamous histological type; high cytological grade; lymph-vascular space invasion; pelvic lymph node metastases; large tumour and deep cervical tumour invasion⁽³⁾.

We conducted a study on 99 patients with FIGO Stage Ib (1985) cervical cancer who were managed at (the former) K K Hospital, Singapore. The clinical patterns and the various known risk factors were studied in patients who remained disease-free and those who developed tumour recurrences. The clinical courses and outcomes of the latter group of patients were also surveyed and presented.

MATERIALS AND METHODS

A retrospective cohort study of our local patients with FIGO (1988) Stage Ib cervical cancer who were managed at (the former) K K Hospital, Singapore, from 1987 to 1991 was conducted. Three hundred and seventy-four medical case records belonging to patients with cervical cancer were reviewed. One hundred and two patients had Stage Ib cervical cancer, of which, 3 patients sought treatment elsewhere following their diagnoses. A total of 99 medical records were analysed. The follow-up notes were examined and every attempt was made to trace the outcome of all patients including those who had defaulted later management or had continued their follow-up care with private gynaecologists. The following information were obtained: patient profile; histopathological type; cytological grade; tumour size; tumour extension; lymph node metastases; lymph-vascular space invasion; treatment modalities; tumour recurrence and outcome.

The time to recurrence is taken from the first day of therapy to the date of first tumour recurrence as defined by the recommendations of WHO Standardisation of Reporting Results of Cancer Treatment⁽⁹⁾. The frequency of tumour recurrence, the

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Table I - Patients and tumour characteristics

Characteristics	Overall n=99	Disease-free n=86	Tumour recurrence n=13
Age at diagnosis (years)			
Mean	43.2	42.6	46.8
Median	43	40	46
Range	27 - 76	27 - 76	40 - 56
Race			
Chinese	96	84	12
Malay	3	2	1
Histology			
Squamous cell carcinoma	82	73 (85%)	9 (69%)
Adenocarcinoma	12	9 (10%)	3 (23%)
Adenosquamous	4	3 (4%)	1 (8%)
Others	1	1 (1%)	0
Cytological grade			
1	6	5	1
2	52	45	7
3	27	22 (31%)	5 (38%)
* ungraded	*14	*14	*0
Lymph node metastases (n)			
positive	(82) 19	(70) 14 (20%)	(12) 5 (42%)
negative	63	56 (80%)	7 (58%)
Lymph-vascular space			
#reported	#86	#75	#11
positive	32	28 (37%)	4 (36%)
negative	54	47 (63%)	7 (64%)
Surgical margins (n)			
positive	(81) 9	(70) 4 (6%)	(11) 5 (45%)
negative	72	66 (94%)	6 (55%)

Table II - Relative risks of developing tumour recurrence

Characteristics	Relative risk	95% CI
Presence of adeno-component	2.5 times	0.88 - 7.05
Cytological grade (G2&G3 vs G1)	0.9 times	0.84 - 1.17
Lymph node metastases	2.3 times	0.96 - 4.93
Positive surgical margin	5.9 times	2.27 - 15.5

CI: Confidence interval

mode of detection, their treatments and outcomes were analysed. The prognostic significance of the histopathological and clinical variables were studied and expressed in relative risks of developing tumour recurrence. The survival curves were presented using the method of Kaplan and Meier⁽⁸⁾.

RESULTS

General

Out of the 374 cases reviewed, there were 102 patients (27.3 %) with FIGO Stage Ib cervical cancers. Three patients sought treatment elsewhere following their diagnoses and a total of 99 cases were analysed. The mean follow-up period was 67 months with a median of 60 months. Thirteen patients developed tumour recurrence (13.1%). The patients' general and tumour characteristics are presented in Table I. The mean age for the population studied was 43.2 years, with a range of 27 to 76. The median age was 43. The population comprised entirely of Asians, with 96 Chinese and 3 Malays.

Primary treatment

Fourteen (15%) patients were treated by radiotherapy alone, comprising pelvic irradiation by standard external beam irradiation and intracavitary irradiation. Eighty-one (81%) patients had radical hysterectomy and pelvic lymphadenectomy employing the Okabayashi variant of the Wertheim's radical hysterectomy⁽¹⁾, of which 22 needed adjuvant radiotherapy and 1 needed adjuvant chemotherapy. The indications for adjuvant radiotherapy included: lymph node metastases; parametrial invasion; surgical margin involvement and lymph-vascular space invasion. There were 4 (4%) patients who had standard hysterectomy for benign conditions with incidental finding of early cervical cancer. No prior Pap smears were performed in three of them and the remaining one had a negative Pap smear just prior to surgery. They were all given pelvic irradiation. The median age of patients who were treated by surgery and radiotherapy primarily were 43 and 57 years old respectively.

Histologic characteristics

The majority of the cancer was squamous cell carcinoma (83%) while adenocarcinoma accounted for 12%. Four percent were adenosquamous and there was one case of small cell carcinoma. The histological grading of 86% of the tumour were reported, of which, the great majority (92%) were grades 2 or 3. There were 82 pelvic lymphadenectomy performed, including one patient who was laparotomised but radical hysterectomy was abandoned because of gross nodal disease, of which 23% were positive for metastatic tumour. Nine out of the 81 (11%) surgical specimens showed positive tumour cells at the surgical margins.

Patients with tumour recurrence have a greater proportion of adenocarcinomas and adenosquamous tumours (31% vs 14%, $p=0.1065$), involvement of the surgical margin (45% vs 6%, $p=0.004$) and pelvic lymph node metastases (42% vs 20%, $p=0.09$). Proportions of patients with the various histological sub-types, lymph-vascular space invasion and cytological grading were similar between the two groups of patients (Table I). The relative risks of developing tumour recurrence in the presence of the various risk factors are presented in Table II.

Tumour recurrence

Thirteen patients developed tumour recurrence (13%). The median time interval to recurrence was 21.7 months (7-36 months). Sixty-two percent recurred within 24 months and 100% of tumour recurrences were detected in 36 months following primary therapy. Pap smear was only positive in one patient (8%). Sixty-seven percent of the patients were symptomatic and all of them had abnormal physical findings which led to the discovery of tumour recurrence. Sixty-two percent of the tumour recurrence were in the pelvis and 38% were distant metastases. Treatments for tumour recurrence were individualised and heterogenous. Majority of the patients fared poorly regardless of the mode of treatment (Table III) with only one patient surviving 5 years.

Table III - Patients with tumour recurrence

Primary treatment	Site of recurrence	Treatment	Survival
Patients who had conservative management			
(1) RT	P central, Dist	Nil	12 mths
(2) RH+Adj.RT	P Sidewall	Nil	25 mths
(3) RH	Dist	Nil	3 mths
Patients who had salvage chemotherapy			
(4) RT	P central	Chemo + RT	16 mths
(5) RH + Adj RT	P, Vagina, Bone	Chemo + RT	41 mths
(6) RH + Adj RT	P sidewall, Dist	Chemo	40 mths
Patients who had radiotherapy			
(7) RH	P sidewall, Dist	RT	30 mths
(8) RH + Adj RT	Bone	RT	16 mths
(9) RH	Dist	RT	4 mths
(10) RH	Dist	RT	60 mths
(11) RH + Adj RT	P sidewall	RT	35 mths
Patients who had exenteration			
(12) RH	P central	Anterior exenteration	15 mths

(Default =1)

RH: Radical hysterectomy, RT: Radiotherapy, Adj: Adjuvant, Chemo: Chemotherapy, P: pelvis, Dist: distant metastases

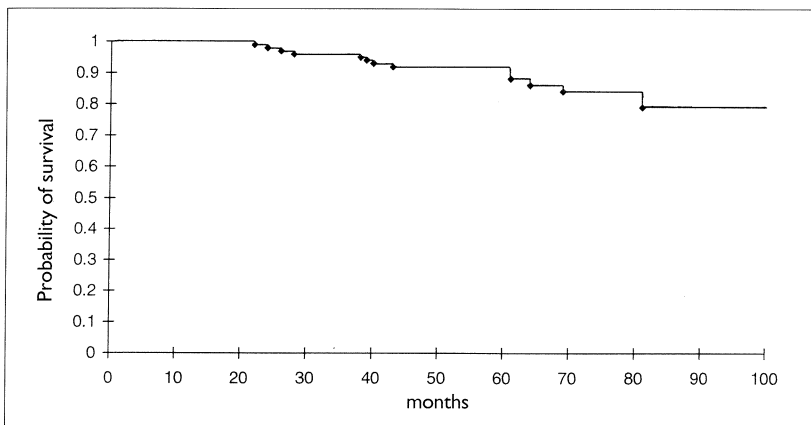


Fig 1 - Overall survival

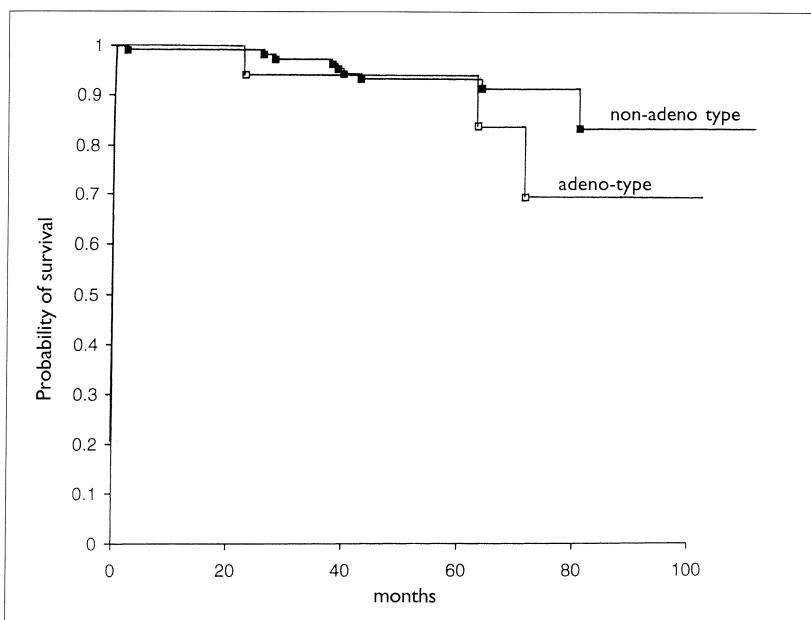


Fig 2 - Survival curves by histological types

Survival

Fig 1 shows the overall survival curve for this population of patients, with 13 tumour recurrences. The survival curves according to histological types, nodal status, surgical margin status and cytological grades are presented in Figs 2,3,4 and 5 respectively.

DISCUSSION

Various prognostic factors in early stage cervical cancer have been widely studied in many reports⁽²⁻⁶⁾, which evolved in an attempt to identify those who might benefit from adjunctive therapy. This report presents a review of Stage Ib (cervical cancer of our local population, of which 96% were Chinese and 4% were Malays. Majority of the patients were treated by radical surgery (89%), which consisted of at least a Type III radical hysterectomy (Piver et al) and bilateral pelvic lymphadenectomy. The Okabayashi variant of Wertheim's radical hysterectomy was largely employed⁽¹⁾, which has been recently reported to have good loco-regional control especially in patients with squamous cell carcinoma of the cervix⁽¹⁰⁾. The median age of patients who had surgery was expectedly lower (43 years) than those who were primarily treated by radiotherapy (57 years), presumably representing a physically fitter group of patients appropriate for surgical therapy.

In the univariate analysis of the various histological factors, the adenocarcinoma cell type, the presence of lymph node metastases and positive surgical margin carry the greatest prognostic significance with respect to increased tendency of developing tumour recurrence. The relative risk of tumour recurrence was 2.5 times in the presence of adenocarcinoma, 2.3 times for nodal metastases and almost 6 times of the surgical margins were positive. However, the 95% confidence interval for the former two variables spanned across 1.0, though marginal, probably due to the small sample size (Table II). Histological cellular grading and lymph-vascular space involvement were not demonstrated to be a useful prognostic indicator for tumour recurrence in this study. Stage for stage, the adenocarcinoma has a lower survival outcome as demonstrated by Hopkins and Morely⁽⁴⁾ which has prompted many clinicians leaning towards more aggressive surgical resection and adjuvant therapy. Patients with pelvic nodal disease had a higher therapeutic failure rate despite conventional adjuvant pelvic irradiation as it probably represents more extensive tumour spread, most likely beyond the pelvis, thus warranting a more aggressive adjuvant therapy. The benefits of resection of bulky nodal disease has been reported and advocated by Hacker⁽⁷⁾ and the role of routine use of extended field radiotherapy and multi-modal therapeutic approach favourably debated by Boronow⁽¹²⁾.

Lymph-vascular space invasion and degree of tumour differentiation though, have been reported to be significant in previous studies but controversies and disagreement arose partly because these observations are subjective and univariate analysis was employed⁽¹¹⁾. However, Delgado et al in the GOG

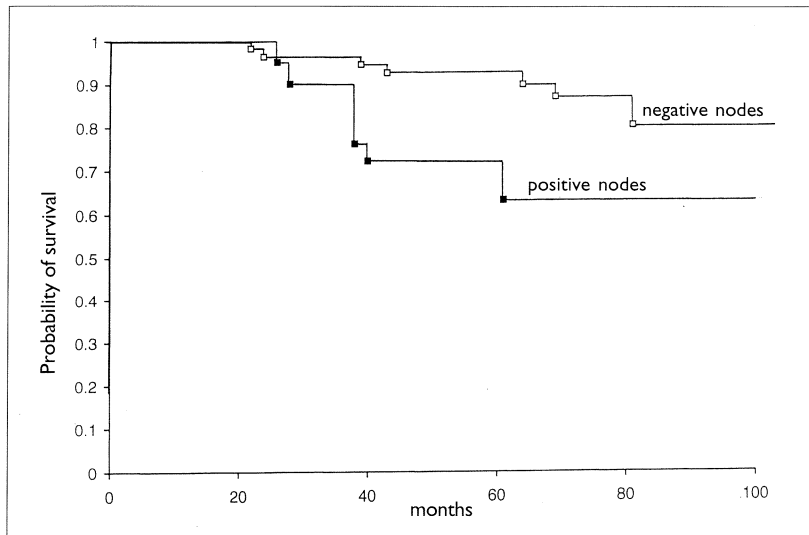


Fig 3 - Survival curves of nodal status

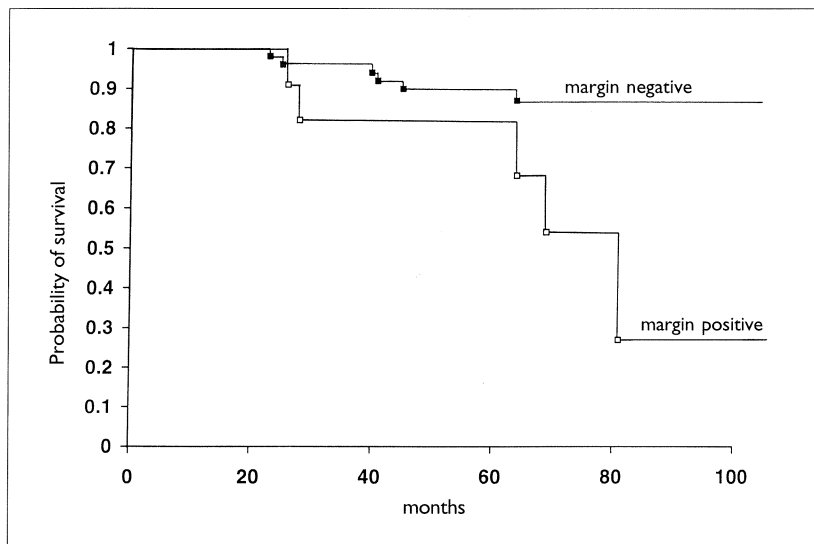


Fig 4 - Survival curves by surgical margin status

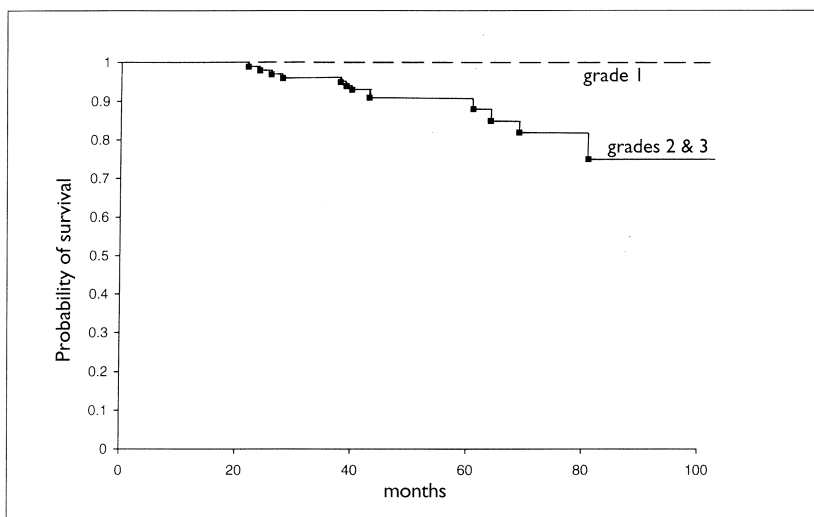


Fig 5 - Survival curves by cytological grades

study, had elegantly demonstrated by multivariate analyses, the importance of lymph-vascular space invasion, tumour size and depth of stromal invasion. Amongst the 3 factors, deep cervical stromal invasion is associated with the greatest relative risk of a reduced disease-free interval, a view that is strongly shared by Gauthier et al⁽⁵⁾. Using size of lesion and maximum depth (measured from the surface) of invasion, the latter identified the low, intermediate and high risk groups, showing that survival rate decreases with increasing risk.

The purpose of devising a scoring system, categorising patients into low and high risk groups, is to assist clinicians in planning further adjuvant therapy with the aim of prolonging the disease-free interval and improving survival rates, a potential benefit which remains to be fully established. The latter will also depend on the clinical management policy of individual oncology unit. The criteria as to who should be given adjuvant therapy is often arbitrary, and is often derived from balancing between the risk of redundant treatment versus potential benefit. It is generally agreeable that adjuvant therapy is not recommended for the low risk group but strongly recommended for the high risk group. However, for the controversial intermediate risk group, the potential benefit and risks should be routinely presented to the patients, making adjuvant therapy optional for them, because there is indeed an increased, though smaller, risk of treatment failure.

Thirteen patients (13%) developed tumour recurrence, which compared favourably with many other studies. However, by virtue that surgery was the main mode of therapy (81%) in this population probably reflect a healthier group of patients. The median age of 43 years was indeed lower compared with patients undergoing radiotherapy. The fact that the majority of tumour recurrence occurred within 2 years and all by 3 years following primary therapy, alert us to the need for increased vigilance during this initial period of follow-up, if early detection of recurrence is to be achieved. Although 62% of the tumour recurrence were in the pelvis, routine Pap smear was a poor indicator, which was only positive in one out of the 13 cases. Clinical symptoms and abnormal pelvic examinations were the key mode of detection, hence the importance of such simple and basic procedures. Generally, there is still little effective treatment for tumour recurrence, though a few patients in this study had a relatively long survival. In some of the latter cases, the recurrent tumours were well-localised and amenable to further therapy. The mode of therapy were highly individualised making it difficult to draw any trend indicative of superiority in any one of them.

The survival outcome of patients having nodal metastases and those without a tumour-free surgical margin were evidently poorer (Figs 3 & 4). Adjuvant pelvic radiotherapy given to these patients seemed to be insufficient treatment to improve their survival probability equal to that of their counterparts without such risk factors. There was also a tendency toward poorer survival outcome in tumours with

adenocarcinoma component and higher cytological grades, though less pronounced (Figs 2 & 5). This finding suggests that management of high-risk patients using adjuvant pelvic irradiation alone is not optimal. While the addition of a combination of extended-field radiotherapy with adjuvant chemotherapy seemed to be a logical way to manage patients with an increased risk of para-aortic nodal metastases or systemic spread, its survival benefits await confirmation.

In conclusion, the results of this study on an Asian population with FIGO Stage Ib cervical cancer concurred with many previous studies on non-Asian population. The presence of nodal metastases, adenocarcinoma cell type and positive surgical margin indicate an increased risk of tumour recurrence. There is a need for regular documentation and reporting of tumour size and depth of tumour invasion, which have been shown to be significant prognostic factors. Tumour recurrences occur mainly in the first two to three years of follow-up and routine Pap smears seemed to do little in aiding their detection. The adjuvant therapy used for the high-risk patients in this study was not optimal and may justify the need to explore the use of combination extended-field radiotherapy and chemotherapy. Salvage therapy for tumour recurrences were generally disappointing.

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