Outcome of Early Cervical Carcinoma Treated by Wertheim Hysterectomy with Selective Postoperative Radiotherapy

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Abstract

Seventy-five consecutive patients with histologically confirmed FIGO stage IB-IIA cervical carcinoma who underwent Wertheim hysterectomy were studied retrospectively. Poor prognostic factors were found in 42 (56%) patients in whom postoperative adjuvant pelvic irradiation was given. The overall disease-free survival rate was 78% at 5 years and 75% at 9 years. The tumour recurrence rate was 12.1% in the low-risk patients and 35.7% in the high-risk patients. Tumour recurrences occurred significantly more frequently in patients with tumours with high grade squamous cell carcinomas and adenosquamous carcinoma. No recurrences occurred in patients with adenocarcinomas. After adjuvant radiotherapy, there was no statistically significant difference in the recurrence rates between lymph node positive and negative patients (26.7% and 19.6% respectively), however extrapelvic recurrences were more common in those with diseased lymph nodes. The recurrence rate was 40% in patients with involved resection margins compared to 16.7% of patients with clear margins. The recurrence rates were similar for patients with and without tumour embolisation of vascular/lymphatic channels.

Wertheim hysterectomy with postoperative pelvic irradiation for selected high-risk patients was an effective treatment for FIGO stage IB-IIA cervical carcinoma. Despite radiotherapy, the high-risk patients still experienced a high tumour recurrence rate.

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Key words: Adenocarcinoma, Adenosquamous carcinoma, Disease-free survival, Metastases, Tumour recurrence

Introduction

Cancer of the cervix is the fourth most common cancer in females in Singapore after breast, colorectal and lung cancers.[1] It forms 7.8% of all cancers in females for the period 1988 to 1992. It is also the third commonest female cancer for those in the age group of 35 to 65 years old, forming 11.1% of cancer cases. This rate is higher than that of European countries and the USA but lower than those in the developing world.

Early cancers can be treated by either radical hysterectomy and pelvic lymphadenectomy, or radical pelvic radiotherapy. There is a considerable geographical variation in the choice of modality of treatment. In one review of the available world data the results for patients treated by surgery alone or by surgery with radiotherapy are better than patients treated by radiotherapy alone.[2] The significantly higher mean age in the radiotherapy alone group in the study suggests that there may be considerable selection of cases to one mode of treatment or the other.

Of patients treated for stage IB-IIA cervical cancer by radical surgery, approximately 15% will suffer a recurrence of the disease within 5 years of diagnosis. Of these patients, 46% recurred within the first year, 73% by the end of the second year and overall 93% by the end of the fifth year. Factors associated with high risks for recurrences included positive surgical margin, positive lymph node metastases and tumour size.[3-5] Some have advocated adjuvant radiotherapy to these high-risk patients. Clinical experience on this approach has been controversial.[6,7]

We report here a retrospective analysis on patients with carcinoma of the cervix stage IB-IIA who underwent Wertheim radical hysterectomy in one institution. The aims of the study were:

1. to determine the incidence of tumour recurrence and the survival rate of patients with stage IB-IIA who underwent Wertheim radical hysterectomy,
2. to investigate the distribution of poor prognostic parameters among patients with recurrent tumours, and
3. to determine the impact of adjuvant radiotherapy to selected patients.

Patients and Methods

Patients who had undergone Wertheim's radical

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hysterectomy and who were seen at the Division of Gynaecological Oncology of the Department of Obstetrics and Gynaecology in one institution were studied.

These patients underwent radical hysterectomy between March 1988 and October 1995. All the patients received a standard preoperative evaluation. All surgeries were performed by gynaecologic oncologists. The surgical technique consisted of a Type III and IV radical hysterectomy as described by Piver and Rutledge and bilateral pelvic lymphadenectomy.[8] Patients with gross lymph nodes confirmed to be metastases on frozen section during surgery underwent lymph node resection. They were treated by primary radiotherapy.

Adjuvant Radiotherapy

Adjuvant radiotherapy was administered to patients who were at high risk of recurrence which was defined by either lymph node metastases, lymph-vascular space tumour embolisation, full thickness tumour invasion of the cervical stroma and tumour infiltration of surgical margins. These patients received a total dose of 45 to 50 Gray to the pelvis by external beam radiotherapy.

Follow-Up

Patients were followed up at the Cancer Clinic in the Division of Gynaecologic Oncology. They were seen one month after surgery and subsequently at three monthly intervals during the first two years. Subsequently, the patients were followed up six monthly. At every follow-up consultation, the patient's general condition was elicited with specific inquiry into micturition and bowel habits. Symptoms and signs that would suggest recurrence like cough, weight loss, haematuria and vaginal discharge and complications of radiotherapy were elicited. Positive symptoms were followed up with appropriate investigations; e.g. chest X-ray, computed tomographic scans and histopathological confirmation were obtained in all cases of disease recurrence.

Analysis

Patients were further subdivided into those who received radiotherapy and those who did not. Each of these groups were studied for disease recurrence both locally and in distant sites.

Results were analysed with respect to the following parameters: histological type, grade of tumour, lymph node metastases, involvement of resection margins, metastases to vascular and lymphatic channels, disease recurrence either locally (within pelvis) or at distant sites (remote from pelvis).

Chi-square test and Fisher's Exact test were used for statistical analysis for significance where appropriate. The survival rate and probability of recurrence-free survival were analysed using the Kaplan-Meier life-table analysis.

Results

A total of 87 patients were studied. Twelve patients were excluded because they were followed up in other countries. The median period of follow-up was 48 months. The mean age of the remaining 75 patients was 47 years with a range of 33 to 61 years. Sixty-four patients were Chinese (85.3%), 8 were Malays (10.7%), 2 were Indians (2.7%) and 1 Eurasian (1.3%). Fifty-eight patients were stage IB and 17 were stage IIA. In 42 (56%) patients at least one poor prognostic factor for recurrence of tumour was detected. Despite postoperative irradiation to the pelvis, tumour recurrence occurred in 15 (35.7%) patients. In contrast, only 4 (12.1%) patients in the low-risk group (without adjuvant radiotherapy) developed tumour recurrence (P <0.02). The sites of recurrence and the distribution of risk factors among these patients are shown in Tables I and II.

The overall disease-free survival rate was 78% at 5 years and 75% at 9 years. There were 12 deaths. Of these, 7 perished from local pelvic recurrences of the cancer, 2 had liver secondaries and 1 had lung metastases. Two patients died from unrelated causes, although one of them also had a pelvic recurrence (Fig. 1).

Recurrent cancer was detected in 19 patients (25.3%). Of these, 12 (63.2%) had local recurrences and 7 had distant recurrences. The distant recurrences included lung (n = 3), liver (n = 1), liver and femur (n = 1), supraclavicular lymph node (n = 1) and the sacral spine (n = 1). The recurrence rate was higher among patients with high-risk factors compared to patients without high-risk factors (Fig. 2).

TABLE I: SITE OF TUMOUR RECURRENCE IN RELATION TO ADJUVANT RADIOTHERAPY

	Number of patients		
Mode of treatment	n	Local recurrence	Distant recurrence
Surgery alone	33	2	2
Surgery and radiotherapy	42	10	5
Total	75	12	7

TABLE II: DISTRIBUTION OF POOR PROGNOSTIC FACTORS AMONG PATIENTS WHO DEVELOPED TUMOUR RECURRENCE

	Number of patients (%)	
Prognostic factor	Present	Absent
Lymph node metastases	15 (26.6)	41(73.4)
Lymphovascular channel emboli	16 (69.6)	7(30.4)
Tumour involving resection margins	9 (26.5)	25(73.5)
Poorly differentiated SCC	25 (33.3)	50(66.7)

SCC: squamous cell carcinoma

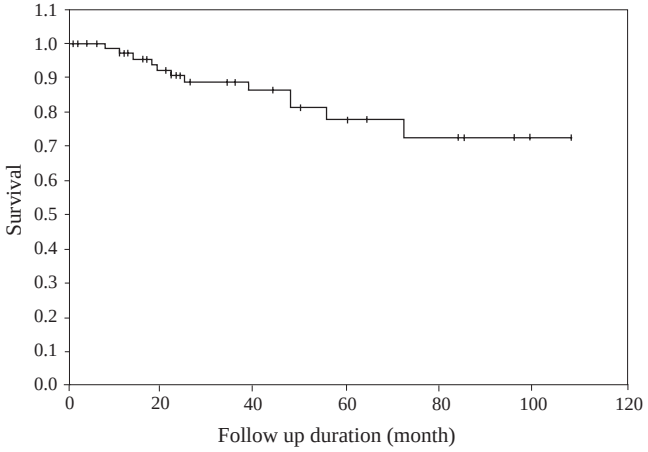

Fig. 1. Overall survival by life-table analysis.

The majority of recurrences occurred in histologically high grade tumour or adenosquamous tumour (Table III). Moreover, the frequency of distant metastases increased with higher grade squamous cell carcinoma and 2 out of 5 (40%) recurrences in patients with adenosquamous carcinoma were distant recurrences. Adjuvant radiotherapy did not reduce the incidence of tumour recurrence (Table IV).

Lymph node status was available for analysis in 66 patients. Of these, 15 (22.7%) patients had metastases of the tumour in pelvic lymph nodes at Wertheim's operation. Recurrences occurred in 4 (26.1%) out of these 15 patients with diseased lymph nodes compared with 10 (19.6%) patients among the remaining 51 patients who were negative for lymph node metastases. The difference between these 2 subgroups was not statistically significant. Distant metastases occurred in 3 out of 15 patients with metastatic lymph nodes and 4 out of 51 patients with negative nodes (P >0.05).

TABLE III: DISTRIBUTION OF ALL PATIENTS ACCORDING TO HISTOLOGICAL TYPE

Histological grade	n	Overall recurrence (%)	Local recurrence	Distant recurrence
G1SCC	12	0 (0)	0	0
G2SCC	24	2 (8.3)	1	1
G3SCC	25	12 (48.0)	7	5
Adenosquamous	8	5 (62.5)	3	2
Adenocarcinoma	6	0 (0)	0	0
Total	75	19 (25.3)	11	8

G1: grade 1; G2: grade 2; G3: grade 3; SCC: squamous cell carcinoma

TABLE IV: COMPARISON OF INCIDENCE OF TUMOUR RECURRENCE BETWEEN SURGERY ALONE AND SURGERY + ADJUVANT RADIOTHERAPY GROUPS OF PATIENTS

	Incidence of tumour recurrence (%)	
Histological grouping	Surgery alone	Surgery + Radiotherapy
G1SCC	0/7	0/5
G2SCC	0/10	2/14 (14.3)
G3SCC	3/11 (27.3)	9/14 (64.3)*
Adenosquamous	1/2 (50.0)	4/6 (66.7)
Adenocarcinoma	0/3	0/3
Overall	4/33 (12.1)	15/42 (35.7)

* P <0.001

Nine patients with high grade squamous cell carcinoma who received adjuvant radiotherapy were analysed for recurrence with respect to their lymph node status (Table V). Three out of 5 lymph node positive patients (60%) developed recurrence while 1 of the remaining 4 patients (25%) who were lymph node negative developed recurrence. The difference between these two subgroups was not statistically significant (P >0.2

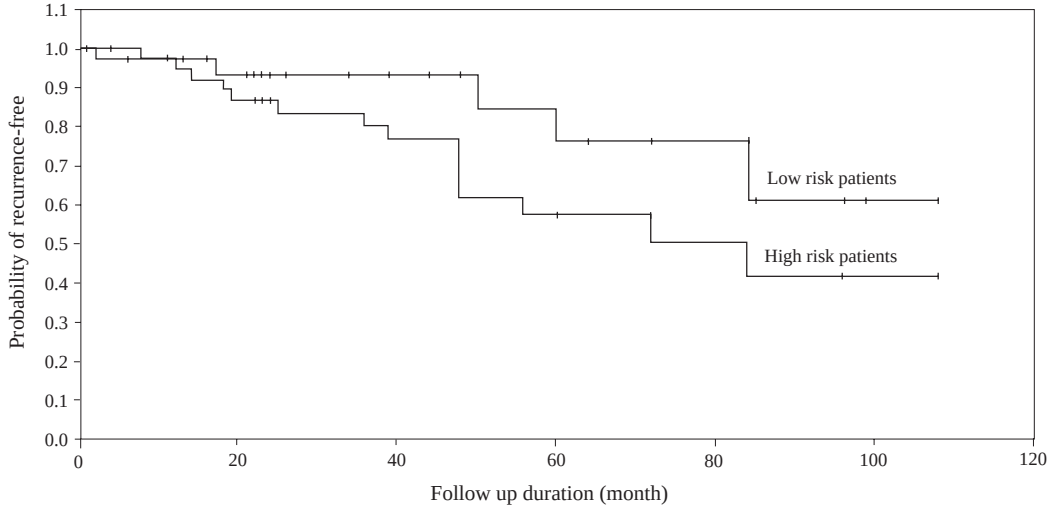

Fig. 2. Probability of recurrence-free in patients with and without radiotherapy.

TABLE V: TUMOUR RECURRENCE ACCORDING TO LYMPH NODE STATUS IN PATIENTS WITH GRADE 3 SQUAMOUS CELL CARCINOMA OF THE CERVIX RECEIVING ADJUVANT RADIOTHERAPY

G3	n	Overall recurrence	Local recurrence	Distant recurrence
		No. (%)		
Positive lymph nodes	5	3 (60)	1	2
Negative lymph nodes	4	1 (25)	0	1
Total	9	44.4	4	1 3

P >0.05(Fisher's Exact test)

(Fisher's Exact test). Again distant recurrences occurred in both subgroups, affecting 4 out of 51 (7.8%) lymph node negative patients and 3 out of 15 (20%) lymph node positive patients.

The status for resection margins of the surgical specimens were available for analysis in 64 patients. Of the 10 patients with positive margins, 4 (40%) developed tumour recurrence, whereas 9 out of 54 patients (16.7%) whose resection margins were clear had subsequent tumour recurrence (*P* >0.05). In the group that received adjuvant radiotherapy, 3 out of 9 (33.3%) with involved margins had distant recurrences in contrast to only 1 out of 25 (4%) patients with clear resection margins. The group that did not receive adjuvant radiotherapy were mainly patients with clear resection margins (29 of 30) who had an overall recurrence rate of 10% with 2 out of 29 lymph node positive patients (6.9%) having distant recurrences. This figure does not differ appreciably from the 4% in the equivalent group who received adjuvant radiotherapy.

The status of vascular / lymphatic channels was only available in 38 patients in whom 11 (28.9%) developed recurrence. In total, 6 out of 22 patients (27.3%) with tumour emboli positive vascular / lymphatic channels developed recurrence while this was seen in 5 of the remaining 16 patients (31.3%) whose vascular and lymphatic channels were negative for tumour emboli. Distant recurrences occurred in 4 out of 22 (18.2%) patients with involved vascular / lymphatic channels compared to 2 out of 16 (12.5%) patients whose channels were clear. When these patients were analysed according to whether adjuvant radiotherapy was administered, the recurrence rate for the adjuvant radiotherapy was higher than those who did not receive it for both patients with involved vascular / lymphatic channels (31.3% versus 16.7%) and for those with clear vascular / lymphatic channels (42.9% versus 22.2%).

Discussion

The overall disease-free survival rate of our patients was 78% at 5 years and 75% at 9 years. Of those with tumour recurrence, 63.2% were local recurrences while 36.8% were extrapelvic. These results are comparable to recent reports by Gadducci et al[9] with an overall recurrence rate of 18.7%, of which 60.7% were local recurrences, and by Pedulla et al[10] with an overall recurrence rate of 23%.

In this study, histological grade emerged as the most significant predictor of recurrent disease. In particular, high grade squamous cell carcinoma and adeno-squamous carcinoma had high recurrence rates of 47.8% and 62.5% respectively. The frequency of distant recurrences occurring in these subtypes was also high. Furthermore, the addition of adjuvant radiotherapy did not alter this trend. Our result concorded with that reported by Smiley et al.[11]

Interestingly, our patients with adenocarcinoma of the cervix appeared to have a good prognosis with none of the 9 patients developing tumour recurrences. This is in marked contrast to literature reports. Eifel et al[12] found a recurrence rate as high as 45% in their series of adenocarcinomas. Our results concurred with the conclusion of Steren et al[13] that radical surgery is an acceptable primary treatment for early stage adenocarcinoma of the cervix.

Our patients with adenosquamous carcinoma had the highest recurrence rate. This is consistent with the result of Costa et al.[14] The interpretation of our result should be cautioned because of the small number of patients in this category.

In our study, 19.6% of lymph node negative patients developed recurrences. Similar result (15%) was reported by Pedulla et al.[10] On the other hand, among the lymph node positive patients, tumour recurrence rate in our study (26.7%) was markedly lower than that reported by Pedulla et al (52%).[10] Our result may be a consequence of thorough lymphadenectomy and adjuvant radiotherapy which effectively eliminated micrometastases in the pelvic sidewalls. However, the pattern of recurrence among lymph node negative patients significantly differed from lymph node positive patients. In our study, distant metastases were detected in 7.8% of lymph node negative patients and 20% of lymph node positive patients. This is consistent with Gadducci's findings.[9]

Among our patients, tumour involvement of surgical margins and vascular / lymphatic spaces appeared to predispose recurrences at sites remote from the pelvis although the numbers in this study were too small for any statistical test to be applied.

Our "low-risk" non-irradiated group had a recurrence rate of 12.1%. This is comparable to the 11.5% quoted in Wilailak's series.[15] It is disappointing that adjuvant radiotherapy is not able to reduce the incidence of recurrence in the "high-risk" group to the level of the "low-risk" group.

Overall, 35.7% of the high-risk patients who underwent adjuvant radiotherapy subsequently developed recurrence which is comparable to the 45% recurrence rate that Stock et al[16] reported. Compared to a relapse rate of 78% in patients with Wertheim hysterectomy alone, they found that postoperative irradiation significantly improved pelvic control. There was also a significant improvement in disease-free interval and overall 5-year survival among the postoperatively irradiated patients.

In summary, the result of our study showed that the overall survival of stage IB-IIA cervical cancer was good. Our selection of patients for postoperative irradiation appeared to have a significant impact on the overall outcome of the treatment, particularly for those patients with metastatic pelvic lymph nodes.

Patients treated using our approach remained at high risk of tumour recurrence when the tumour had a high histological grade, had adenosquamous histological type or had involved surgical resection margins. For these high-risk patients, other modalities of treatment may be called for in order to improve the overall disease-free survival.

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