

Adjuvant Chemotherapy in “High Risk” Patients after Wertheim Hysterectomy—10-year Survivals

V Sivanesaratnam,**FAMM, FRCOG, FACS*

Abstract

Although the primary operative mortality following radical hysterectomy for stage IB and early stage IIA cervical carcinoma is less than 1%, survival is poor in those patients with histological evidence of “risk” features—lymph node metastases, lymphatic vascular tumour permeation and clinically undetected parametrial metastases. In the 7-year period 1983 to 1989, 239 patients with stage IB and early IIA disease had radical hysterectomy and pelvic lymphadenectomy. One hundred and eight patients (45.2%) had various poor prognostic histological features and received adjuvant chemotherapy—70 had cisplatin, vinblastine, bleomycin (PVB), 16 had mitomycin C (MMC) and 22 others received mitomycin C + 5-fluorouracil (5-FU). Although not randomised, the risk factors present in each group were identical. These patients have now been followed up for periods ranging from 8 to 14 years. All recurrences, except one, occurred within 23 months of surgery; in the remaining this occurred 8 years later. This suggests that very close long-term follow-up is needed. Recurrences were markedly higher in the group who refused adjuvant chemotherapy (31.6%).

The 10-year survival in patients without risk factors was 97.2%. In those patients with risk factors refusing adjuvant therapy it was 73.7%. The adjuvant chemotherapy group had a better survival of 86.1% (P = 0.001). The 10-year survivals in patients with positive nodes were similar—66.7% in the MMC group and 71.4% in the PVB group.

The 10-year survival in patients with squamous cell carcinoma was significantly better (90.3%) in the mitomycin C (and MMC + 5-FU) group compared to the PVB group (80.1%) (P = 0.005).

The 10-year survival in patients with adenocarcinoma and adenosquamous carcinoma was significantly better (96.3%) in the PVB group compared to those receiving MMC (and MMC + 5-FU) (57.1%) (P = 0.01).

It would, thus, appear that the adjuvant chemotherapy of choice for patients with squamous cell carcinoma would be MMC (and MMC + 5-FU) and for those with adenocarcinoma, the PVB regime.

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Introduction

Wertheim radical hysterectomy has today become an accepted method of management of stage IB and early stage IIA cervical carcinoma, particularly in young patients in whom preservation of ovarian and coital function cannot be achieved if they were subjected to radiotherapy instead. However, a group of patients undergoing radical surgery is at “high risk” of developing not only local recurrences but also extra pelvic metastases. These “high risk” patients include those with large bulky cervical lesions,^{1,2} clinically undetected parametrial tumour extension,³ lymphatic/vascular permeation in the cervical stroma,^{4,5} and pelvic node metastases.^{6,7}

For many years adjuvant pelvic irradiation was advo-

cated in such patients; although its use will help reduce the risk of local pelvic recurrence, the development of distant metastases is not prevented and thus, the overall survival is not improved.

We had previously reported our preliminary results using adjuvant cisplatin, vinblastine and bleomycin (PVB) regime in “high risk” cases following radical hysterectomy for early invasive cancer of the cervix and obtained a disease-free survival of 86.4% at medium follow-up of 23 months;⁸ with mitomycin C (MMC) a disease-free survival of 87.5% was seen at a median follow-up of 29 months.⁹

We present here the long-term results of adjuvant chemotherapy following Wertheim radical hysterectomy.

* Professor, Head and Senior Consultant

Department of Obstetrics and Gynaecology

Faculty of Medicine, University of Malaya, KL

Address for Reprints: Professor V Sivanesaratnam, Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.

Materials and Methods

Two hundred thirty-nine patients with early invasive cancer of the cervix (stage IB and early stage IIA) had a type 3 radical hysterectomy and pelvic lymphadenectomy in the 7-year period 1 January 1983 to 31 December 1989. The operative specimens were carefully evaluated. Of these 135 patients (56.4%) who had poor prognostic histological features, 19 refused adjuvant therapy (either chemotherapy or radiotherapy) and 8 others received adjuvant pelvic irradiation.

Adjuvant Chemotherapy

The remaining 108 patients (45.2%) received adjuvant chemotherapy; 70 patients were given 3 cycles of PVB regime (Day 1—cisplatin 60 mgm/m², vinblastine 4 mgm/m², bleomycin 10 mgm/m²; Day 2—vinblastine 4 mgm/m²; Days 7 and 15—bleomycin 10 mgm/m²).

Sixteen patients received 5 cycles of mitomycin C (15 mgm/m²) as a single agent; 22 others received 3 cycles of mitomycin C + 5-fluorouracil (Day 1—mitomycin C 10 mgm/m², 5-FU 500 mgm/m²; Days 2 and 3—5-FU 500 mgm/m²). The interval between each cycles was 3 weeks.

Although these patient were not randomised, the risk factors present were similar in each group and are evaluable.

Patients were followed up closely at 3 monthly intervals for the first 2 years, then 6 monthly for the next 3 years and yearly thereafter. Survival was assessed using the life table method described by Kaplan and Meier.¹⁰

Results

The histopathological risk factors present in each of the groups are shown in Table I. Full thickness invasion of the cervix, lymphatic/vascular permeation, and positive pelvic nodes were the more common risk factors noted.

Two drug-related deaths occurred in the Mitomycin C group. One patient who completed 5 cycles of single

agent mitomycin C died from cardiotoxicity 6 months after the surgery, the other developed severe mucositis and septicaemia and succumbed.

The median duration of follow-up was 118 months for the PVB group (range 86 to 168 months), 101 months for the MMC (with or without 5-FU) group (range 86 to 148 months), and 117 months (range 89 to 170 months) in the group without risk factors and in whom no adjuvant therapy was given. For purposes of this analysis MMC (with or without 5-FU) has been grouped together.

Survival

The 10-year survival in patients without risk factors was 97.2%. The overall 10-year survival in patients receiving adjuvant chemotherapy was 86.1%. However, in those patients with risk factors who refused adjuvant therapy a significantly poorer survival of 73.7% was observed (Fig. 1) (*P* = 0.001).

In patients with positive nodes, although a significantly lower survival was observed compared to those without any risk factors, the survival rates in the PVB and mitomycin C groups were similar (Fig. 2), 71.4% and 66.7% respectively at 10 years.

The 10-year survival rates in patients with squamous cell carcinoma with risk factors were significantly better in the MMC group (90.3%) compared to the PVB group (80.1%) (*P* = 0.01, Fig. 3).

The survival in patients with adeno- and adenosquamous carcinoma with risk factors was significantly better in the PVB group (96.3%) compared to the MMC group (57.1%) (*P* = 0.001, Fig. 4).

In the presence of lymphatic/vascular permeation, the 10-year survival in those receiving chemotherapy was similar in the 2 groups—97.4% in the PVB group and 96.4% in the MMC group, which was almost the same in the group without any risk factors; the survival in the group with this risk factor but who refused adjuvant chemotherapy was 87.5% (Fig. 5).

TABLE I: HISTOPATHOLOGICAL RISK FACTORS - WERTHEIM RADICAL HYSTERECTOMY (1983 TO 1989)

Adverse factor	Chemotherapy group			
	PVB (n = 70)	MMC (n = 16)	MMC + 5-FU (n = 22)	No Adjuvant (n = 19)
Full thickness invasion of the cervix	46 (65.7%)	11 (68.7%)	18 (81.8%)	5 (26.3%)
Lymphatic/vascular permeation	62 (88.6%)	16 (100%)	20 (90.9%)	16 (84.2%)
Positive nodes	28 (40%)	3 (18.6%)	4 (18.2%)	3 (15.8%)
Parametrial extension	6 (8.6%)	3 (18.6%)	2 (9.1%)	-
Positive peritoneal washings	2 (2.8%)	-	1 (4.5%)	2 (10.5%)
Intestinal metastases	-	-	1 (4.5%)	-

PVB : cisplatin, vinblastine, bleomycin
 MMC: mitomycin C
 5-FU : 5-fluorouracil

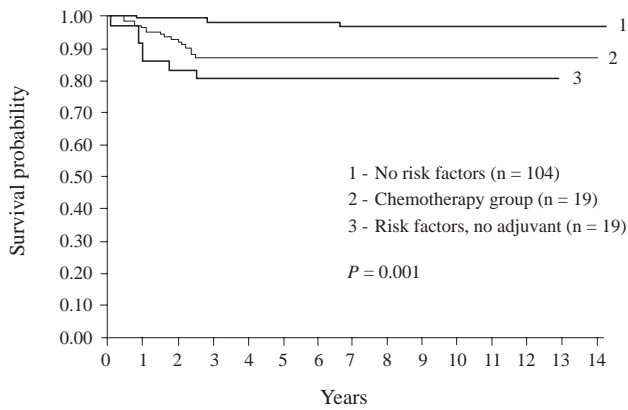


Fig. 1. Survival curves in patients with risk factors receiving chemotherapy compared to those without risk factors.

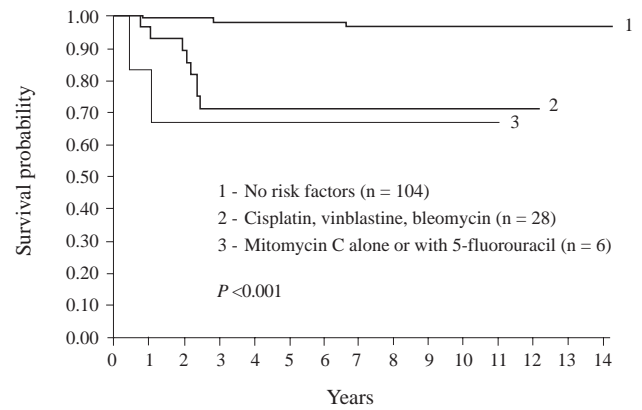


Fig. 2. Survival curves in patients with positive nodes.

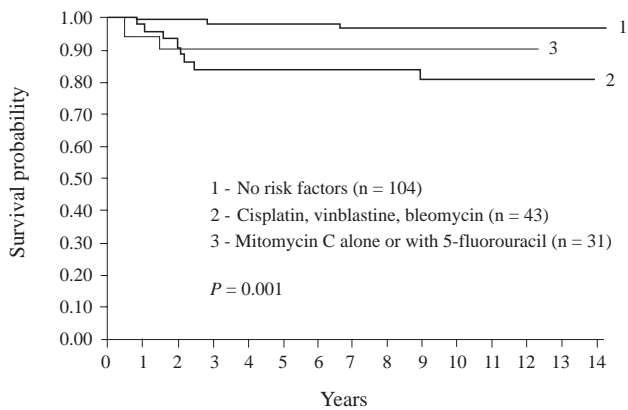


Fig. 3. Survival curves in patients with squamous cell carcinoma with risk factors.

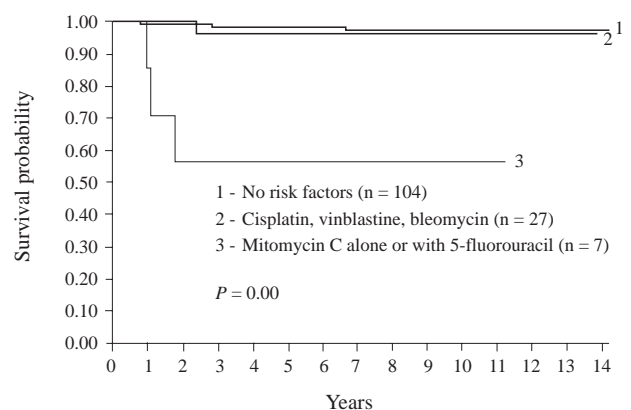


Fig. 4. Survival curves in patients with adenocarcinoma (including adenosquamous) with risk factors.

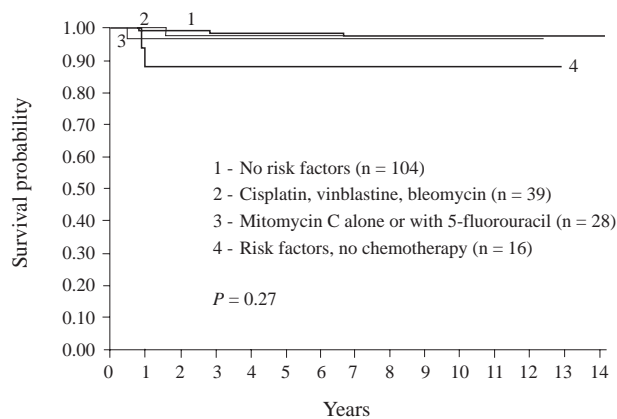


Fig. 5. Survival in patients with lymphatic/vascular permeation receiving chemotherapy compared with those without risk factors.

Recurrences

Table II shows the frequency of recurrences in the various groups. The number of recurrences was higher (31.6%) in those patients with risk factors who declined adjuvant therapy. In all cases, recurrences occurred within the first 28 months, except in one who had a

pelvic recurrence 8 years later. Both pelvic as well as extra pelvic sites of recurrences were noted in all groups.

Of the 14 cases in the PVB group who had recurrences, 5 survived. Three who developed pelvic recurrence responded to pelvic irradiation. One patient developed a solitary lung metastases 20 months after surgery; this was excised at thoracotomy and she remained well 12 years after surgery. Another developed a solitary metastasis in the right lung 4 months after surgery; after right lower lobectomy she remained well for 9 years.

In the MMC group, of the 5 recurrences, 1 has survived after irradiation for pelvic recurrence.

Discussion

Survival in patients undergoing Wertheim radical hysterectomy and pelvic lymphadenectomy is influenced by several “poor prognostic factors”. These include a large primary growth,^{1,2} undetected parametrial extension,³ presence of lymphatic/vascular tumour permeation^{4,5} and positive pelvic nodes.^{6,7} The presence of tumour associated tissue eosinophilia has an adverse

TABLE II: RECURRENCE AFTER ADJUVANT CHEMOTHERAPY

	Total number	Number recurred (%)	Number dead (%)	Number alive (%)
Chemotherapy group				
PVB	70	14 (20)	9 (12.9)	61 (87.1)
MMC and MMC + 5-FU	38	5 (13.2)	6 [†] (15.8)	32 (84.2)
Risk factors present (no adjuvant)				
Risk factors present (no adjuvant)	19	6 (31.6)	5 [‡] (26.3)	14 (73.7)*
No risk factors				
No risk factors	104	8 (7.7)	3 (2.8)	101 (97.2)

[†] one patient died from mitomycin C cardiotoxicity and another from severe mucositis and septicaemia

[‡] one died from clostridium difficile enterocolitis

* $\chi^2 = 14.06, P = 0.001$

PVB : cisplatin, vinblastine, bleomycin

MMC : mitomycin C

5-FU : 5-fluorouracil

TABLE III: SITES OF RECURRENCE

Site	Chemotherapy		Risk factors present (no adjuvant) (n = 6)	No risk factors (n = 8)
	PVB (n = 14)	MMC and MMC + 5-FU (n = 5)		
Pelvis	11	4	2	7
Extrapelvic				
Lungs	3	2	3	1
Liver	1	-	-	1
Skeletal	3	-	-	-
Other	2	1	2	3

PVB : cisplatin, vinblastine, bleomycin

MMC: mitomycin C

5-FU : 5-fluorouracil

effect on prognosis;¹¹ this was associated with a higher recurrence rate of 36.4%.

When metastases to the pelvic nodes are present, survival drops to 48.5% if 1 to 4 nodes are positive, and to 19% if more than 4 nodes are involved.¹² Where undetected parametrial extension occurs, the 5-year survival is only 50%.³ The presence of lymphatic/vascular permeation reduced survival rates to 60-70%;^{4,5} even with postoperative irradiation in these cases, many cancers have been reported to recur.¹³

It is obvious that surgery alone is insufficient when these adverse factors are present. Whilst adjuvant pelvic irradiation might decrease the incidence of local pelvic recurrences, the development of distant metastases is not prevented, resulting in no improvement in overall survival.^{14,15} The addition of whole pelvic irradiation to radical hysterectomy also carried an increased risk of morbidity and mortality.¹⁶

The presence of tumour within vascular spaces in the cervical stroma in some patients would suggest that haematogenous spread is likely; patients with poor prog-

nostic features listed above can thus be regarded as having a systemic disease which requires systemic measures as micrometastases may occur not only in the pelvis but at extra-pelvic sites as well. It is for this reason that we advocate adjuvant chemotherapy in these “high risk” cases. Our earlier preliminary studies^{8,9} showed the usefulness of such an approach.

In the long-term study presented above, we have evaluated the results of adjuvant chemotherapy using the PVB regime and mitomycin C (with or without 5-FU). In the initial part of the study we used only MMC at a higher dose of 15 mgm/m² for 5 courses, the preliminary results of which were published earlier.⁹ One of the patients succumbed from MMC-related cardiotoxicity.¹⁷ As mitomycin C has a cumulative affect, clinicians should take note that such cardiac toxicity can be a late phenomenon. We therefore, reduced the dose of MMC to 10 mgm/m², and combined it with 5-FU.

The histological risk factors were similar in all 3 groups. A group of 19 patients with similar risk factors and who refused adjuvant therapy served as controls. The study clearly shows that patients who did not receive chemotherapy had a significantly higher recurrence rate of 31.6% compared to 20% and 13.2% for the PVB and MMC (with or without 5-FU) groups.

Lai et al¹⁸ using the PVB regime alone as adjuvant reported 5-year survival of 81.5% in their “high risk” early stage cervical cancer patients, compared to 66% and 67% in those patients treated with adjuvant pelvic irradiation or no adjuvant therapy respectively. Our study shows a similar benefit of adjuvant chemotherapy. Markedly improved 10-year survival of 86.1% was observed in the long-term in those receiving chemotherapy, compared to the significantly poorer survival (73.7%) in the high risk group who did not receive adjuvant therapy. In those without risk factor the survival was 97.1%. Our study shows that the survival in patients with squamous cell carcinoma was significantly better (90.3%) in those receiving mitomycin C (and mitomycin C + 5-FU) compared to PVB (80.1%) ($P = 0.005$). The 10-year survival in patients with adenocarcinoma and adenosquamous carcinoma was significantly better in the PVB group (97.1%)

compared to those receiving MMC (and MMC + 5-FU) (57.1%). These findings would suggest that chemotherapy regimes used for adjuvant therapy in cervical carcinoma should be selected according to histological type. It appears that whilst cisplatin-based combinations are effective in adenocarcinoma, they do not appear to be the drugs of choice in squamous cell carcinoma, which is better treated with mitomycin C + 5-FU. Nevertheless, the overall markedly improved survival with adjuvant chemotherapy suggests an important role this treatment modality has in high risk patients; further it has the added advantage of preserving coital function which may be compromised if adjuvant pelvic irradiation were used. When recurrences occur, a good number can still be salvaged. Pelvic radiotherapy has a role when recurrences occur locally in the pelvis; 4 of our patients have been successfully treated. Solitary lung metastases can be excised as was done in 2 of our patients.

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