

A Review of Patients with High-risk Carcinoma of the Cervix Treated with Combined Surgery and Postoperative Radiotherapy

H S Khoo Tan,*^{MBBS, FRCR}, K M Lee,**^{MBBS, FFRCSI, FRCR}, V K Sethi,***^{FAMS, MBBS, DMRT}, E J Chua,****^{FAMS, MD, DMRT}

Abstract

From May 1992 to October 1995, 57 patients with early stage cervical carcinoma were treated with hysterectomy and postoperative pelvic radiotherapy because of the presence of adverse histopathologic features. On prospective follow-up and analysis, the clinical outcome for 50 of these patients showed a pelvic disease control rate of 90.9%, a disease-free survival of 80.6% and an overall survival of 86.3%. Of the 8 relapses, half occurred in the pelvis i.e. 2 in the vaginal vault and 2 in the pelvic side walls. No severe complications were observed, but there was a 20% long-term Radiation Therapy and Oncology Group (RTOG) grade 1 to 2 urinary bladder dysfunctional problem and 28% incidence of suprapubic and/or leg oedema.

Ann Acad Med Singapore 1998; 27:618-21

Key words: Complications, Disease control, Hysterectomy, Radiation therapy

Introduction

It is generally accepted that early stage invasive carcinoma of the cervix, stage I to stage IIA disease, can be treated with equal effectiveness with either radical hysterectomy or radical radiotherapy.¹⁻³ However a proportion of patients treated with surgery may be classified as having a significant risk of relapse based on both clinical and histopathologic features. Between half to two-thirds of these relapses occur in the pelvis and therefore local disease control is an important end point in assessing the benefits of therapy. Hence many of these high-risk patients are given postoperative radiation therapy to enhance pelvic disease control. There are a number of predictive clinical and pathological risk factors used for assessing the probability of relapse. These include tumour size at presentation, nodal involvement, presence of lymph-vascular emboli, inadequate surgery or involved surgical margins and deep cervical stromal invasion.³⁻⁷ This paper is a report on a series of such a group of patients treated with hysterectomy and postoperative radiotherapy, prospectively followed up for a minimum period of two and a half years.

Patients and Methods

From May 1992 to October 1995 a total of 57 patients were referred to the Department of Therapeutic Radiol-

ogy, Singapore General Hospital, following hysterectomy for a newly diagnosed early stage carcinoma of the cervix. These included patients of International Federation of Obstetrics and Gynaecology (FIGO) stages I to IIB disease treated with either Wertheim's hysterectomy or a simple hysterectomy and were regarded as having a significant risk of relapse. The risk factors considered are listed in Table I. Ten patients with only a simple hysterectomy done were included in this group as they were deemed inadequately treated and furthermore the risk of nodal metastasis would be significant.

All the patients initially received external beam radiation therapy using a 10 MeV energy photon beam from a linear accelerator. For the radiotherapy technique, either a 4-field treatment arrangement was used, treating alternate opposing fields daily with the dose prescribed to the axial isocentre or a 2-field parallel opposed anterior-posterior technique was used with the dose prescribed to the mid-plane. The external beam treatment was delivered once daily in a 5-day per week schedule. A total dose of either 5000 to 5040 cGy was given in 25 to 28 fractions with dose per fraction of either 200 or 180 cGy. Following the completion of the external beam therapy, a vaginal vault boost was given using the high dose rate intracavitary brachytherapy technique. This was done 5 days after the last external beam frac-

* Consultant

** Senior Registrar

*** Senior Consultant

**** Senior Consultant and Head

Department of Therapeutic Radiology

National Cancer Centre

Address for Reprints: Dr H S Khoo Tan, Department of Therapeutic Radiology, National Cancer Centre, Singapore 169608.

tion. A total of 2 applications were used giving 500 cGy to a distance of 5 mm from the surface of the applicators. Applicators used were either a pair of vaginal ovoids or a vaginal cylinder. The duration between each applicators was 4 days. There were only 2 patients among the 50 who received a course of adjuvant chemotherapy after their surgery but prior to delivery of pelvic radiation therapy.

At the end of the treatment, the patients were followed up, initially at 4 weeks after the last brachytherapy insertion and then thereafter 3 monthly. At each post treatment review a clinical examination was done which included a digital pelvic examination. Any suspicious lesion detected on examination was sent for biopsy and histologic confirmation of relapse. Imaging with plain X-rays, ultrasound and / or computer tomographic (CT) scans were ordered when clinically indicated. Complications arising from therapy were documented and treated according to the discretion of the oncologist. The median follow-up for the 50 patients was 34 months, with a range of 6 to 65 months.

Results

A total of 57 patients were accrued in this prospective study of which 5 were foreigners who did not return for follow up after treatment. Another 2 patients defaulted follow-up after the first 3-monthly assessment and could not be contacted. This left 50 patients in the study eligible for evaluation. The median age of this cohort of patients was 47 years, with a range of 27 to 69 years. At the time

of the analysis, there were 6 deaths in this cohort.

The racial distribution showed the majority of cases to be Chinese, 44 (88%), followed by 2 (4%) Malays and 1 (2%) Indian. The remaining patients were foreigners. The major portion of the cases were squamous cell carcinoma with 35 cases (70%), followed by adenocarcinoma with 12 cases (24%), 1 case of adenosquamous carcinoma and 2 cases of small cell carcinoma (Table II). The grade and description of the tumour are listed in Table III. It showed that large portion of histologic grades fell in the moderate and poorly differentiated subtypes. In 6 cases the histologic grades were not available.

Most of the patients were either in stage IB or IIA (FIGO classification), with only 2 staged as early non-bulky IIB disease, both had Wertheim's hysterectomy (Table IV). The total number of relapses at last follow-up stands at 8, with 2 patients showing relapse in the vaginal vault, 2 in the pelvic side wall and another 4 relapsing with distant metastasis. The distributions of these relapse cases according to histologic type, grade and stage are represented in the corresponding tables.

TABLE I: POOR PROGNOSTIC FEATURES

Poor prognostic factor	Number of patients (%)
Nodal positive	13 (26)
Lymph-vascular space emboli	30 (60)
Unclear margins	10 (20)
Deep stromal invasion	34 (68)
Bulky tumours >4 cm size	17 (34)
Residual CIN /VAIN	11 (22)
Paracervical extension	14 (28)
Simple or vaginal hysterectomy only	10 (20)

TABLE II: DISTRIBUTION OF HISTOLOGIC TYPES

Histology	Numbers (%)	Site of disease failure		
		Local	Regional	Distal
Squamous cell carcinoma	35 (70)	1	1	4
Adenocarcinoma	12 (24)	1	1	0
Small cell carcinoma	2 (4)	0	0	0
Adenosquamous carcinoma	1 (2)	0	0	0
Total	50(100)	2	2	4

TABLE III: HISTOLOGICAL GRADING

Differentiation	Numbers (%)
Well	6 (12)
Moderate	21 (42)
Poor	16 (32)
Not specified	6 (12)
Neuroendocrine	1 (2)
Total	50 (100)

TABLE IV: DISTRIBUTION ACCORDING TO FIGO STAGE AND RELAPSE PATTERN

Stage	Numbers (%)	Site of disease failure		
		Local	Regional	Distal
IB	31 (62)	1	1	3
IIA	17 (34)	1	0	1
IIB	2 (4)	0	1	0
Total	50 (100)	2	2	4

TABLE V: COMPLICATIONS OF TREATMENT

Complication	Number of patients (%)
Vaginal adhesions	1 (2)
Vaginal stenosis	6 (12)
Proctitis	6 (12)
Urinary difficulties	10 (20)
Suprapubic oedema	5 (10)
Pedal oedema	8 (16)
Both suprapubic and pedal oedema	1 (2)

All relapses occurred by the second year of follow-up with one exception which occurred at 25 months. The actuarial disease-free survival in this cohort of patients treated with combined surgery and radiotherapy was found to be 80.6% at 4 years with a local pelvic control rate of 90.9% (Fig. 1). The actuarial overall survival was 86.3% at 4 years (Fig. 2).

A number of complications associated with treatment were observed and shown in Table V. The most commonly seen complications were related to bladder function (10 patients), and oedema (8 involving the legs, 5 the suprapubic region, and 1 patient had oedema on both sites). The bladder problems included urinary incontinence (8 patients), urinary frequency (3), persistent nocturia (2), and sense of incomplete micturition (1). Other less common complications included vaginal narrowing and proctitis. However all the complications were mild, classified as RTOG grade 1 to 2 and either resolved

spontaneously or controlled with simple conservative measures. There were no treatment-related deaths.

Discussion

With increasing public education and awareness and more widespread acceptance of Pap smear screening programme, the incidence of early stage carcinoma of the cervix has been increasing. There are two equally effective treatment modalities be it surgery or radiotherapy for this malignancy. Certainly in the good prognostic group the likelihood of long-term tumour control and survival is of the order of more than 80% to 90%.³⁻⁶ However, there is a subset of patients with early stage disease of cervical carcinoma who have a higher likelihood of developing recurrence. The more commonly accepted factors which predict such an increase risk include inadequate surgery, nodal metastasis, bulky tumour, lymph-vascular invasion, high tumour grade and poor histologic subtypes like adenocarcinoma and small cell tumours.^{8,9} In such situation, there is a need for postoperative radiotherapy as it has been shown to reduce the incidence of pelvic recurrence.⁷ The role of adjuvant chemotherapy in improving the results for such high-risk patients remains to be proven.¹⁰⁻¹⁴

In our present review of high-risk patients following hysterectomy and postoperative radiotherapy for carcinoma of the cervix, we observed a favourable degree of local pelvic disease control i.e. 2 vault recurrences and 2 pelvic side wall relapses only. The other relapses were metastatic disease, the incidence of which is unlikely to be influenced by the use of loco-regional treatment modalities of surgery and radiation therapy. This gave a relapse rate of 19.4% and an overall actuarial survival rate of 86%. This is comparable with a recent reported 5-year review of early stage disease by Tay et al,⁴ which showed a 13.1% recurrence rate and an overall survival of 85%. In their study, 81% of patients had radical hysterectomy alone and only 14% had combined surgery and radiotherapy. Similarly, the 5-year actuarial survival in Landoni's et al randomised trial³ in early

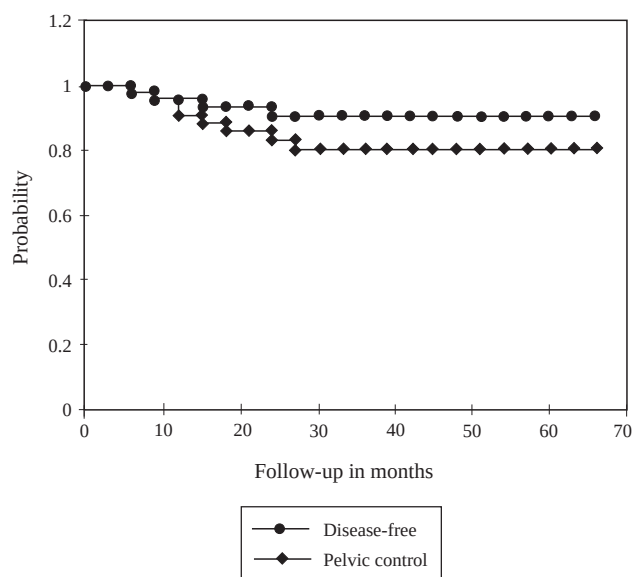


Fig. 1. Disease-free and pelvic control probability.

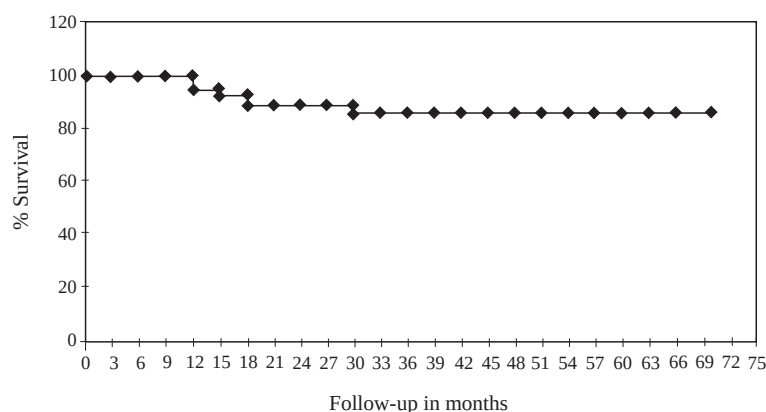


Fig. 2. Overall survival.

stage cervical cancer was 83%, whether surgery or radical radiotherapy as the primary treatment. However, it must be noted that 54% of their post-Wertheim's group received adjuvant radiation therapy for a variety of poor risk factors. This group showed a 5-year actuarial survival of 80%, a figure very much the same as our series. The pattern of relapses was also similar to those observed in other series, where the majority of failures appeared by 2 years and about half of the relapses occurred in the pelvis.^{3,4} An analysis of the risk factors which may predict for pelvic recurrence in this cohort of patient was not conclusive in view of the small number of patients in this series.

However, it was observed that a number of patients experienced complications related to the combined therapy. Some 22 patients were found to have some long-term complications, the most common being urinary bladder dysfunction (20%) and oedema affecting the legs and suprapubis (28%). Though these were not severe, they were of concern as many of these patients are expected to survive long term and that some radiation therapy induced complications may develop many years later.¹⁵ Landoni et al,³ in a recently published randomised trial showed that patients who received combined treatment had a higher complication rate (29%) compared to either surgery (24%) or radiation therapy alone (16%). This is probably explained by the fact that those with combined modality treatment will suffer the additive risk of both surgical and radiotherapy morbidity.

In conclusion, our prospective review of 50 patients with early stage but poor risk cervical carcinoma revealed a good local control rate and an overall survival of 86.3%. However because of the potential risk of increased morbidity with combined surgery and radiation therapy, selection of patients with early stage disease for surgery should be done with more care. This would avoid or minimise the need for postoperative radiation therapy in these patients without compromising the disease control rate and cure. In addition, selective irradiation of the pelvic lymphatic channels can be considered whereby patients who have undergone a complete pelvic lymphadenectomy and shown to have no nodal involvement need not receive radiotherapy to these sites. We have commenced this selective nodal irradiation in post-Wertheim's patients in our management policy and will review their outcome in due time.

Acknowledgements

The authors would like to thank Drs E T Chua, T L Yang, K W Fong, J Wee, K S Lee, and T Tan for their support in putting their patients into this prospective study. We also acknowledge the integral contribution of the physicists, nurses, radiographers and clerical staff in this programme.

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