Radiotherapy as Local Adjuvant Treatment for Endometrial Carcinoma—A Review of 45 Patients

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Abstract

Forty-five patients with endometrial carcinoma were treated with local postoperative adjuvant radiotherapy during the period 1992 to 1995. Radiotherapy technique comprised both external beam irradiation as well as high-dose-rate vaginal vault brachytherapy. The 5-year overall survival and relapse-free survival rates were 74% and 73%, respectively and poorly differentiated histology grade was associated with poorer prognosis. Only 1 patient developed an isolated vaginal vault recurrence and another 9 patients relapsed mainly at the distal anatomical sites. The main radiotherapy-related complications were vaginal adhesion and stenosis. Radiotherapy is therefore effective as local adjuvant treatment in reducing risk of local-regional relapse in endometrial carcinoma.

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Key words: Brachytherapy, Histology grade, Local control, Retrospective, Survival

Introduction

Radiotherapy as an adjunct to surgery has long been used in the management of endometrial carcinoma with the intent to improve local tumour control as well as to achieve excellent survival rates.[1,2] Over the years, however, the specific role and relative benefit of postoperative radiotherapy for this particular cancer has been the subject of interest and even contention among clinicians and investigators alike. As more data emerged regarding the natural history, patterns of relapse and prognostic factors for endometrial carcinoma, it became possible then to better understand both the efficacy and limitation of radiotherapy in influencing treatment outcome for this condition.

In this paper, we present a small retrospective review of our local experience in postoperative radiotherapy for 45 patients as local adjuvant treatment for endometrial carcinoma. Of note is the routine application of remote after-loading high-dose-rate (HDR) brachytherapy with the gammamed machine which uses an Iridium-192 source.

Materials and Methods

Forty-six patients with endometrial carcinoma were treated with postoperative HDR brachytherapy to the vaginal vault at the Department of Therapeutic Radiology, Singapore General Hospital, between 1992 and 1995. One of them defaulted follow-up on completion of treatment and this retrospective study is based on the individual medical records of the remaining 45 patients who were followed up for durations of 3 to 68 months with a median follow-up period of 32 months for the entire series.

The 45 patients were analysed with respect to age, race, International Federation of Gynaecology and Obstetrics (FIGO) stage of tumour, histological type and grade, treatment, relapse patterns, survival and radiotherapy long-term side-effects. Actuarial survival rates were derived using statistical life-table methods and represented by Kaplan-Meier plots.

Results

The patients' age ranged from 36 to 78 years with a mean age of 56 years old. The majority of the patients were Chinese (81%) followed by Malays (11%), Indians (4%) and other races (4%). All the patients were referred for radiotherapy after undergoing surgery, comprising a total hysterectomy and bilateral salpingo-oophorectomy (THBSO); one of the patients had a Wertheim's procedure as the tumour was initially thought to arise

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from the uterine cervix, and the only patient staged as FIGO IVB on the basis of inguinal lymphadenopathy underwent inguinal lymphadenectomy as well. All the patients were surgically stage prior to radiotherapy.

Tumour stage and histological characteristics are illustrated in Tables I to III. There was a preponderance of FIGO stages IIIA (32%) and IB (22%) in this series of patients referred for radiotherapy. The predominant histological type was endometroid adenocarcinoma (71%), followed by papillary-serous carcinoma (UPSC) (11%), adenosquamous carcinoma (9%) and clear-cell carcinoma (9%). Histological grading divided the tumours into well-differentiated (18%), moderately differentiated (38%) and poorly differentiated (38%) grades. The histological grade was not specified for 3 patients (2 clear-cell carcinomas and 1 adenosquamous carcinoma) and these were included as poorly differentiated tumours in the survival analysis.

All patients underwent HDR brachytherapy to the vaginal vault with insertions using either a pair of fixed ovoids (73%) or a cylindrical applicator (27%). The reference point for dose-prescription was 0.5 cm from the surface of the applicators and total brachytherapy doses ranged from 4 to 10 Gy delivered via 1 or 2 insertions for most patients (Table IV). Of the 45 patients, 43 (96%) were also treated with postoperative external beam radiotherapy (EBRT) using 10 MV photons targeted to the whole pelvis delivering a dose of 45 to 50.4 Gy via conventional fractionation over a period of 5 to 5.5 weeks. Four patients (9%) were also treated with adjuvant cisplatinum-based chemotherapy including 3 who had UPSC histological types.

With a maximum follow-up duration of 68 months, the 5-year overall (Fig. 1) and relapse-free survival (Fig. 2) rates of this retrospective series of patients were 74% and 73%, respectively. When overall survival was analysed according to histological grade (Fig. 3), patients with poorly differentiated (Grade 3) histology had the worst prognosis with a 5-year overall survival rate of 56%. When analysed according to FIGO stage, 5-year overall survival rates for stages I, II and III / IV were 72%, 63% and 78%, respectively (Fig. 4). The predominant cause of death was endometroid carcinoma which accounted for 80% of those who died. Out of the 45 patients in the study, 10 (22%) had relapsed and the median time to relapse was 7.4 months with the latest occurring at 37 months of follow-up. Most of the relapses were due to distal metastases at various anatomical sites (Table V) although 1 patient (2%) also had a recurrence in the ischio-rectal region at the same time she developed disseminated disease. Isolated vaginal vault recurrence was seen in only 1 patient (2%). Of the 4 patients

TABLE I: STAGE DISTRIBUTION

FIGO Stage	No. (%)
IA	2 (4)
IB	10 (22)
ICC	5 (11)
II	8 (18)
III	19 (43)
IV	1 (2)
Total	45 (100)

TABLE II: HISTOLOGICAL TYPE DISTRIBUTION

Histological type	No. (%)
Adenocarcinoma	32 (71)
Adenosquamous carcinoma	4 (9)
Uterine papillary serous carcinoma	5 (11)
Clear cell carcinoma	4 (9)
Total	45 (100)

TABLE III: HISTOLOGICAL GRADE DISTRIBUTION

Histological grade	No. (%)
Well differentiated (Grade 1)	8 (18)
Moderately differentiated (Grade 2)	17 (38)
Poorly differentiated (Grade 3)	17 (38)
Not otherwise specified	3 (7)
Total	45 (100)

TABLE IV: BRACHYTHERAPY TECHNIQUE

Applicator /Source	No. (%)	Dose/Fractions	No. (%)
Vaginal ovoids	33 (73)	4-7 Gy / 1	18 (40)
Cylindrical/Linear	12 (27)	8-10 Gy / 2	25 (46)
		22 Gy / 4	2 (4)
Total	45 (100)		45 (100)

TABLE V: SITE OF RELAPSE

Site		Occurrence
Distal		
Bone		3
Abdominal wall		2
Liver		2
Peritoneum		2
Cutaneous		2
Leptomeningeal		1
Lymph node		5
Para-aortic	2	
Supraclavicular	2	
Inguinal	1	
Local-regional		
Ischio-rectal		1
Vaginal vault		1

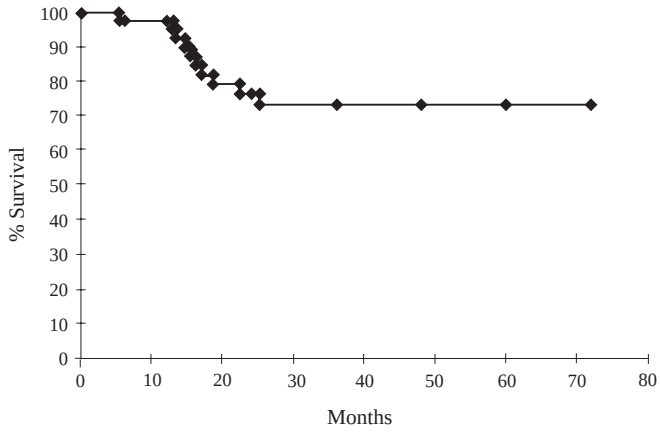

Fig. 1. Overall survival of 45 patients.

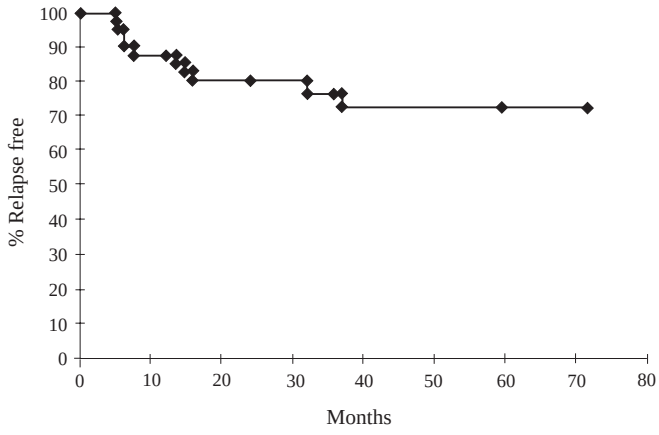

Fig. 2. Relapse-free survival of 45 patients.

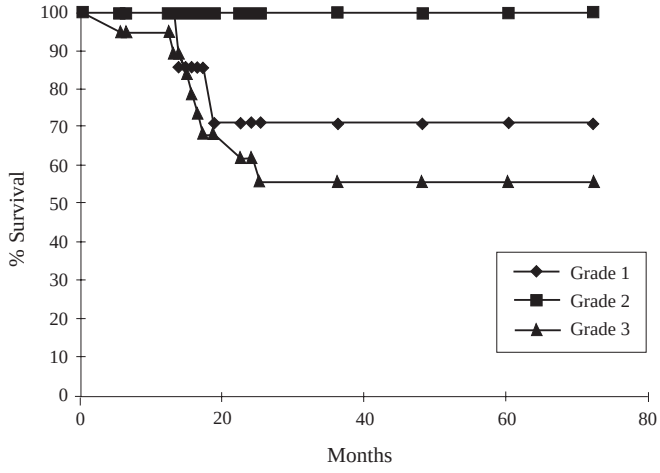

Fig. 3. Overall survival and histology grade.

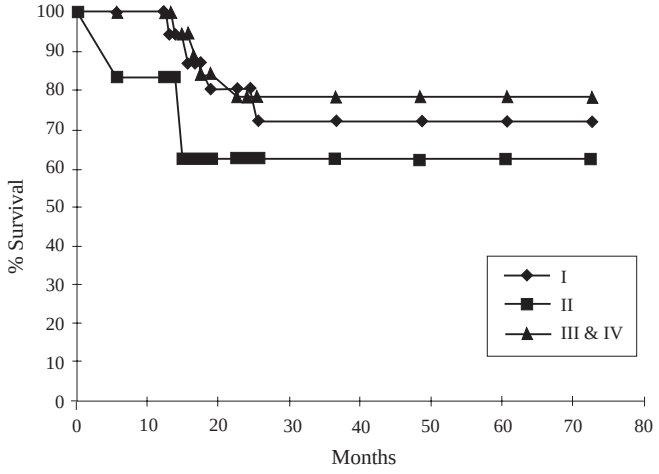

Fig. 4. Overall survival and FIGO stage.

who were also treated with adjuvant chemotherapy only 1 relapsed and died subsequently from disseminated disease.

Vaginal adhesions and stenosis were the main long-term complications related to radiotherapy occurring in 3 patients (6%). The other complications seen were chronic lower-limb lymphoedema (2%) and bowel perforation (2%). One other patient developed aplastic anaemia but this was found to relate more to the parvovirus strain isolated from the patient.

Discussion

The increasing incidence of endometrial carcinoma in the West has led to much renewed interest in the study and treatment of this tumour over the last two decades. Issues which attracted much attention and yet still not fully resolved include the pattern of spread and relapse of disease, prognostic factors, relative effectiveness of adjuvant treatment and optimization of radiotherapy techniques. This retrospective study of 45 patients was carried out to review our own experience in treating endometrial carcinoma in the light of data available from other studies reported in the literature.

The prognosis of patients with endometrial carcinoma is well known to be related to histology grade and stage of tumour. Thus it is not surprising to find that even in a small study as this, patients with poorly-differentiated (Grade 3) tumours have a poorer treatment outcome with a 5-year overall survival rate of 56%. Indeed much bigger series such as that reported by the Gynaecological Oncology Group (GOG)[3,4] and other groups[5-7] have identified major prognostic factors for survival and local failure rate to include age, histological grade, depth of myometrial invasion, adnexal spread, vascular space invasion, cervix / isthmus involvement, positive peritoneal cytology and gross peritoneal disease. The expected influence of FIGO stage on survival is not as well demonstrated in this series in that the stage III / IV patients had a better 5-year overall survival rate than the earlier stages. This is partly accounted for by the occurrence of 2 non-cancer-related deaths among the stage I patients as well as the relatively smaller number of stage II

patients in the study (Table I).

While the primary treatment for localized endometrial carcinoma has always been THBSO, the role of postoperative radiotherapy as an adjunct to surgery has not been as clearly defined. Only two early studies have reported a survival advantage[1,2] but the evidence for improvement in local control with adjuvant radiotherapy is much stronger.[1-4,8] It has also been suggested that postoperative radiotherapy influences the pattern of relapse resulting in higher proportion of distal relapses.[9,10] The low local-regional recurrence rate (4%) in this series coupled with the high proportion of distal relapses appear to be consistent with the findings of other studies. However, it remains to be seen from the results of ongoing studies, such as the GOG study no. 156, whether systemic adjuvant therapy with chemotherapy dose indeed reduce the rate of distal relapse rates and improve overall survival for endometrial carcinoma.

The mode of adjuvant radiotherapy that should be given has also been an issue of debate in that both EBRT and vaginal vault brachytherapy have been used as single-modality or in combination. Conflicting results have emerged from a number of mostly small studies seeking to resolve the issue. Some investigators have come out in favour of EBRT,[11] while others favour vault brachytherapy[12,13] and still others endorsing both EBRT and brachytherapy in combination.[14] So far, there has been only one large prospective randomized trial[14] published in 1980 which showed a local-control advantage with combined EBRT and brachytherapy over brachytherapy alone. The issue is more pertinent today with the shift in surgical practice to perform pelvic lymphadenectomy in addition to THBSO for completion of surgical staging. This has led to a re-think on the value of EBRT to the whole pelvis in patients who have undergone surgical lymph node sampling and / or pelvic lymphadenectomy. In our department, the choice of what radiotherapy to offer is dependent on the FIGO stage of tumour and the extent of surgery performed.

Remote after-loading HDR treatment is a relatively new technique in brachytherapy with the advantages of shortened treatment duration and ambulatory service in comparison with previously used low-dose-rate (LDR) techniques. However, optimal dose modifications have to be made and fractionation schedules worked out in order to achieve as good tumour control rates as those with LDR protocols, yet keeping radiation-related complications to a minimum. To this end, the complication rate and toxicity profile reported above suggest that our HDR brachytherapy technique is reasonably well-tolerated with acceptable side-effects.

In conclusion, this review of 45 patients is certainly not spared of the attendant limitations of any small retrospective study. Nevertheless, it does suggest that adjuvant radiotherapy continues to have a place in the treatment of endometrial carcinoma in minimizing the risk of local-regional recurrence.

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