Patterns Of Faliure In Cervical Carcinoma and Outcome Of Salvage Therapy : A Retrospective Study

S. Vasishta[1], A. Varghese[1], A. Ragheb[1] .

[1]Department Of Radiation Oncology,
Kuwait Cancer Control Centre, Kuwait.

Abstract

Objective

The objective of this study was to study the patterns of failure after definitive therapy in cervical cancer, the treatment given to patients after recurrence and the final outcome in these patients.

Materials and Methods

Case records of 105 patients of cervical cancer of clinical Stages I to IV treated with definitive radiation or surgery with or without post-operative radiotherapy at Kuwait Cancer Control Centre (KCCC), Kuwait from 1995 to 1999 were retrospectively analyzed. Patients who developed recurrence were studied for the pattern of their recurrences, the type of treatment received by them after their recurrence and the results of their salvage therapy.

Results

The sites of failure were classified as pelvic only (P), pelvic+ distant metastasis (P+DM), or distant metastasis only (DM). Out of the thirty patients in stage Ib, the sites of first failure were, P = 5 (16.6%), P+DM = 1 (3.2%), DM = 1 (3.2%); of the fourteen patients in stage IIa , P = 2 (14%), P+DM = 1 (7%), DM = 2 (14%); of the 36 patients in stage IIb, P = 3 (8%), P+DM = 6 (16.5%), DM = 5 (14%); of the 14 patients in stage IIIb, P = 5 (35.5%), P+DM = 1 (7%), DM =0 (0%); of the 5 patients in stage IVa, 3 patients absconded after treatment and the failure rate was, P =0 (0%), P+DM = 0 (0%), DM = 1 (50%). The therapy after failure was surgery, irradiation, chemotherapy or supportive care. The median survival was evaluated as a function of time to failure after initial treatment and was 6, 6, 9, and 30 months for those failing less than 6, 6-12, 13-24 & 25-36 months after initial treatment respectively. The cohort treated initially with surgery had a better outcome of salvage therapy at relapse.

Conclusions

Long term survival can be achieved in a small percentage of selected patients who fail treatment with definitive radiation or surgery for invasive carcinoma of the uterine cervix. The probability of survival is greater for those who fail more than 24 months after initial treatment than for those who fail before 24 months. The chance of survival is also related to the initial type of treatment, site of recurrence & type of salvage therapy. The complications of salvage treatment of recurrent disease should be minimized.

Key words

Cervical carcinoma, Kuwait, Recurrence, Salvage Therapy, Outcome.

Introduction

Curability of cervical cancer depends on many factors. It is seen that one-third of cervical cancer will develop recurrent disease which can present within or outside the previously irradiated or operated area as an isolated lesion or as generalised disease.

Most of the recurrences are within the first two years following treatment [1,2].

The salvage of failures after definitive treatment must be individualised [3,4,5]. The curative treatment for these cases may involve radical surgery or irradiation. Chemotherapy & re-irradiation can be used for palliation [6,7]. Combination of these modalities are occasionally

Correspondence to: Dr. Saroj Vasishta, MD.,
P.O.Box.: 709, Ardiya 92400, Kuwait.
Tel: 00- 965-4813724. 4813724. Fax: 00-965-4810007,
E-mail: s_vasishta @ yahoo.com

employed. Long term survival can be achieved in some patients with salvage treatment [3,8].

The purpose of this study is to review the patterns of failure, describe the type of salvage therapy & evaluate its outcome in all patients with recurrent cervical cancer treated initially with definitive irradiation or radical surgery at our institution.

Materials & Methods

Case records of 105 patients of cervical cancer of clinical Stages I to IV treated with definitive radiation or surgery with or without post-operative radiotherapy at Kuwait Cancer Control Centre (KCCC), Kuwait from 1995 to 1999 were retrospectively analyzed and is the basis of this study. Of these patients, 33 (31.5%) were found to have recurrent cancer after initial therapy.

After completion of definitive therapy, patients were closely followed up by the Gynaecology Oncology team at regular intervals as per guidelines for follow up. Most of the patient suspected of having recurrent cancer underwent full physical examination, pelvic examination under general anaesthesia, blood counts, blood chemistry, MRI, urinalysis, X-ray assessment appropriate for the site of disease, CT Scan, bone scan were done when indicated & tissue biopsies were optained.

Treatment

The treatment of recurrent disease was individualized. The therapy consisted of radiation, surgery, chemotherapy or supportive treatment. A combination of the above modalities was used in a few patients. Nine (27%) patients did not receive any treatment after relapse.

STAGE	NO. OF RECURRENCES								Total recur. in each Rx gp	Total recur. in each stage
	Pelvic	%	Pelvic +DM	%	Total Pelvic	%	DM	%		
I										
SURG	5	19%	1	4%	6	23%	1	4%	7/26	7/30=23%
XRT	0	0%	0	0%	0	0%	0	0%	0/4	
IIa										
SURG	2	22%	0	0%	2	22%	1	11%	3/9	5/14=36%
XRT	0	0%	1	20%	1	20%	1	20%	2/5	
IIb										
SURG	0	0%	2	25%	3	25%	2	25%	4/8	14/36=39%
XRT	3	10.7%	4	14%	7	24.7%	3	10.7%	10/28	
IIIb										
XRT	5	35.7%	1	7%	6	42.7%	0	0%	6/14	6/14=43%
IVa										
XRT	0	0%	0	0%	0	0%	1	50%	1/2	1/2=50%

SURG- initial Rx with surgery
XRT- initial Rx with radiotherapy

Table 1 : Cancer of the uterine cervix – Relapse according to initial treatment

Thirteen patients (39.4%) were treated with radiotherapy after relapse. Most were treated with external radiotherapy (84.6%). Combined external irradiation & brachytherapy was used in 2 patients (15.4%), both of these patients belonged to the group treated initially with definitive surgery. External radiotherapy was delivered to the pelvis & / or para-aortic region or to areas of

SITE OF FAILURE	TYPE OF SALVAGE THERAPY							TOTAL REC. IN EACH STAGE	% REC. IN EACH STAGE
	CT	XRT	CT+ RT	XRT+S	CT+XRT +S	NO THERAPY	TOTAL SITEWISE		
STAGE IB PELVIC PELVIC+DM DM	1 (S) 1 (S)	1 (S)	2 (S)		1 (S)	1 (S)	5 1 1	7/30	23%
STAGE IIa PELVIC PELVIC+DM DM		1 (S) 1(RT)	1 (S)		1 (S)	1 (RT)	2 1 2	5/14	36%
STAGE IIB PELVIC PELVIC+DM DM	2 (RT) 2 (RT) 1 (RT)	1(RT)	1 (S) 2 (S)	1(RT)		1(S), 1(RT)	3 6 5	14/36	39%
STAGE IIIB PELVIC PELVIC+DM DM	2 (RT)					3 (RT) 1 (RT)	5 1 0	6/14	43%
STAGE IVa DM						1 (RT)	1	1/2 (3 pts defaulted)	50%
TOTAL RT GP SURG GP	 7 2	 2 2	 6	 1	 2	 9 2	 19/56 = 34% 14/49 = 28.6%		
GRAND TOTAL	9	4	6	1	2	11	PELVIC = 15 PELVIC + DM = 9 DM = 9	33/105 = 31.4%	

(S) = initially treated with surgery.
(RT) = initially treated with radiotherapy
CT = chemotherapy, XRT = radiotherapy, S = surgery after recurrence
Both in surg & RT group, most failures were loco regional.
In surg group, distant metastasis was mainly in para- aortic lymphnode region. (64%)
Three pts in Stage IVa defaulted after t

Table 2 : Site of Failure & Type of Salvage Therapy.

metastatic disease e.g supraclavicular lympnode area or area of bone metastases.

A pelvic exenteration was attempted in 2 patients. At the time of exploration, one of these 2 patients was deemed inoperable so only colostomy was done. The 2nd patient underwent total pelvic exenteration with intra-operative radiotherapy in Lyon, France. Laminectomy for spinal metastases was done in 1 patient. Two patients had percutaneous nephrostomy & 2 underwent D.J.stenting for obstructive nephropathy.

Chemotherapy was administered to 17 patients (51.5%) at relapse. Chemotherapy alone was given to 10 patients, 1 of whom was in 2nd relapse. In 5 patients, chemotherapy followed radiation treatment. Two patients who were treated with radiotherapy on 1st relapse, received treatment with chemotherapy after surgery during the 2nd relapse, one patient received chemotherapy with carboplatin & 5 fluorouracil concomitant with radical radiotherapy to the para aortic region. The same chemotherapy was continued for 2 more courses after radiotherapy in this patient. Chemotherapy consisted of multiple agents. Combination of carboplatin & taxol was used in 8 (47%) of chemotherapy treated patients, combination of bleomycin, ifosphamide & cisplatin in 4 (23.5%), carboplatin & 5 fluorouracil combination in 3 (17.5%), single agent carboplatin in 1 patient & gemcitabine single agent in 1 patient.

Statistical Methods

Data analysis was performed using SPSS statistical software package. The survival time was calculated from the time of recurrence. The X^2 statistic was used for contingency table analysis.

Results

The sites of failure according to stage & initial type of treatment are summarized in Table 1.

Of the 33 patients that relapsed, fifteen (46.0%) did so loco–regionally, 9 (27%) developed distant metastasis only & another 9 (27%) patients relapsed in the pelvis with distant

No	Name	STAGE	INITIAL Ry	TIME TO RECUR.	SITE OF RECUR.	SALVAGE Rx & OUTCOME
1	S.A	IIa	W. HYS	12 m	Paraaortic LNs	Ext RT 50Gy/25 Fractions + concomittant CT – Carbo & 5Fu x2. Then CT after RT – same regime x2 • Nephrostomy, then D.J.Stent • 3m after Rx – good PR – stent removed. • At 12 months – only scar on CT scan. • Alive free of disease at 62
2	M.O	IIa	W. HYS	1st relapse 6m 2nd relapse 28m	Central Vault recurrence + rectal infiltration.	Radical pelvic RT- Ext + Brachy. Laparotomy- Exenteration abandoned, only colostomy done. Chemotherapy: Taxol 320mg/m^2 + CARBO AUC 8 -every month x 3 courses. F.U. CT scan -no disease. Alive free of disease at 82 months. RT complications +

Table 3 : Long Term Survivors after Salvage Therapy.

metastasis. Commonest distant metastatic failure site was para-aortic lymph node region – 64% of all distant metastatic failure site in surgery group & 36% in the radiotherapy group. Other sites of distant metastasis were bone, supraclavicular lymph node region, liver & lung.

The commonest symptom at relapse was pain either in the pelvic region, abdomen, bone pain or pain in legs with or without swelling of legs. Other symptoms were bleeding &/or discharge per vaginum, faecal or urinary incontinence & in 2 patients, the recurrence was discovered on investigations.

Analyzing the pretreatment tumour characteristics, it was seen that there was an increased incidence of failure with increasing primary clinical stage, increasing primary tumour size & grade of tumour. None of the grade 1 patients developed distant metastasis whereas 12/18 (67%) of distant failures with or without pelvic failure & 6/8 (75%) of distal failures were of grade 3 histology [$p < 0.02$].

Outcome Of Salvage Therapy

The type of initial treatment, site of failure & the type of salvage therapy given in each stage are summarized in Table 2.

Survival after the diagnosis of recurrence ranged from 1 month to 82 months, with median survival of 7 months. Median survival in the cohort treated initially with surgery was 18 months compared to 3 months in the radiotherapy group. Fifteen of 19 (79%) radiotherapy group patients survived less than 6 months after the diagnosis of their recurrence, all but one of these had survival times less than 15 months & one patient who developed pelvic recurrence & spinal metastasis is alive 26 months after treatment with pelvic radiotherapy, laminectomy and radiotherapy to spinal metastatic site.

The cohort treated initially with surgery had better outcome of salvage therapy at relapse with 2(14%) long term survivors. The details of these two patients are as summarized in Table 3.

Complications Of Salvage Treatment

The incidence of grade 3 & 4 late radiation sequalae (RTOG criteria) was 6% (2/33 patients). One of these patients, whose details are outlined in Table 3. Tzhe second case, developed bleeding through the colostomy and also per rectal bleeding during follow up. Colonoscopy revealed a tight stricture in the sigmoid region & severe hyperaemia at the ano-rectal region. This was attributed to the radiotherapy with brachytherapy that she received at first relapse. Another patient developed intermittent haematuria, recurrent urinary tract infections & bleeding per rectum which was attributed also to the radiotherapy treatment.

Discussion

Almost 35% of all patients with cervical cancer will have recurrent or persistent tumour. The cause of death in almost 60% of these patients is related to local failure [1].

Our data show an overall failure rate of 31.5%. Of those who failed, 69.5% had some part of their failure in the pelvis. The patterns of failure for our patients was similar in the groups treated initially by surgery or radiotherapy & demonstrate an increasing incidence of relapse with increasing stage.

Perez et al summarized the data from the literature [9]. In patients with Stage 1 disease treated by surgery, the pelvic recurrence rate averages 7% and distant metastatic rate 5%, although with long term follow up, this frequency rises to between 10 & 12%. In our

Time to Recurrence	No. of patients	%	Median Survival
< 6 months	11	33.3	6 months
7-12 months	11	33.3	6 months
13-24 months	8	24	9months
25-36 months	3	9.4	30 months
TOTAL	33	100%	

Table 4 : Time to Recurence V/S Median Survival after Failure. :

Stage 1 surgically treated group, total pelvic failure rate was 23% & 1 of 7 patients (4%) that failed, did so in a distant site. This figure for local failure is higher than that reported in the literature.

In the cohort treated with definitive radiation, there were only four patients in Stage 1 & none of them showed relapse. In other stages our total pelvic failure rates are similar to that reported in the literature but there were no distant failures alone in Stage III b, these figures being lower than that in the literature [2]. All Stage IIIb patients that failed, did so in loco-regional sites. It is evident that in this stage, inability to control the tumour in the pelvis is still of significant concern as discussed in the article by Brady et al [1] requiring re-design of treatment programmes.

Chronological appearance of failures

Many authors have noted that about 80% of failures occur within 2 years of initial therapy [10, 11]. Patients who fail more than 24 months after initial treatment have an extended survival compared to those who fail before 24 months [11].

Similar results were obtained in our study as summarized in Table 4.

The majority of failures, 22 out of 33 patients (66.6%) appeared within 12 months after initial therapy in all stages & their median survival was 6 months. Thirty of the 33 (90.6%) occurred within the first 2 years after therapy. Only 3 (9.4%) recurrences occurred after 2 years and their median survival was 30 months.

Treatment

In our study population, 27% patients with recurrent disease did not receive treatment & patients receiving therapy had an improved survival compared with those not receiving therapy.The mode of treatment for recurrent disease depends on many factors. Palliative radiation to sites of metastatic disease is a well accepted practice. In our patients, external radiotherapy was delivered to sites of metastatic bone disease in 3 patients, supraclavicular lymph node area in 1 patient & para-aortic region in 2 patients, to total doses of 30 to 50 Gray with good partial responses & one complete response & long term survivor.

Re-irradiation of the pelvis is possible in selected patients. Prasasvinichai et al [4] employed re-irradiation or combined radiation & surgery for pelvic recurrences subsequent to definitive radiotherapy & achieved a 17.6% 5 year survival in a selected population of 51 patients. Prempree et al [5] also obtained similar results. In our series re-irradiation of the pelvis for those failing in the pelvis was performed in two of our patients, one of them with pelvic exenteration, intra-operative radiotherapy & external radiotherapy. These patients had been initially treated with Wertheim hysterectomy & post-operative external radiotherapy and brachytherapy. They achieved good partial responses for 6 to 10 months.

Radiotherapy for recurrence after surgery is discussed by Deutch et al [12] who had 18.75% survivors in their series. Pelvic radiotherapy for recurrence after Wertheim hysterectomy was given in 5 of our patients, 2 of whom had also received post-operative radiotherapy previously & are discussed above. Of the other 3 patients, 1 received external radiotherapy & 2 external radiotherapy with brachytherapy to vaginal vault with or without chemotherapy, with one patient (20%) surviving at 82 months. Therefore cure is possible with radiotherapy for recurrence after surgery but best results are achieved in central recurrences treated with external radiotherapy & brachytherapy.

Chemotherapy is a treatment option in selected recurrent cervical cancer patients. Data from the literature are summarised in Principles and Practice of Gynaecologic Oncology [13]. Single agent responses are usually partial & relatively short. A total response rate of 20% to 25% has been documented for 5 Fluorouracil & cisplatin.

Rose et al [14] reported on a phase II study of paclitaxel & cisplatin every 21 days. There was 12.2% complete response rate & 34% partial response.

In our study, combination of paclitaxel & cisplatin or carboplatin was given to 8 patients, 4 of whom (50%) achieved partial response & 2 (25%) achieved complete response, one

of these is a long term survivor. Combination of 5 Fluorouracil & carboplatin concomittent with para-aortic radiotherapy & also following radiotherapy produced one complete response & long term survivor.

Complications

Complications can & do occur following treatment of recurrent disease. The overall complication rate in our patients (6%) was acceptable.

Conclusions

Long term survival can be achieved in a small percentage of selected patients who fail treatment with definitive radiation or surgery for invasive carcinoma of the uterine cervix. The probability of survival is greater for those who fail more than 24 months after initial treatment than for those who fail before 24 months. The chance of survival is also related to the initial type of treatment, site of recurrence & type of salvage therapy. The complications of salvage treatment of recurrent disease should be minimized.

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