Risk Factors and Clinical Aspects of Recurrent Invasive Cervical Carcinoma

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Abstract

Objectives Recurrence of cervical cancer is one of the important and plausible discussions in oncology especially in patients with advanced stages. The purpose of this study was to introduce probability invasive cervical carcinoma recurrence as well as determining characteristics and the prognostic factors of this entity.

Methods A retrospective study was designed to identify risk factors and pattern of uterine cervical carcinoma recurrence evaluating the outcome of 36 registered patients. Recurrence was defined based on clinical or para-clinical documentation over at least 6 months after complete remission following surgery or radiotherapy. Treatment consisted of a radiosurgical combination and exclusive radiotherapy.

Results Mean age in selected patients is 54.8 ± 12.0 years. The pathological reports of primary diagnosis are squamous cell carcinoma in 94.44 % and adenocarcinoma in remaining patients. Mean duration of recurrence among patients is 2.75 ± 1.5 years after the initial treatment. Metrorrhagia is

mostly revealing symptom which patients present in recurrent episode. Usually, the recurrence of cervical cancer is presented in pelvic cavity locally. Marginal involvement is documented in 50 % of cases and lymph node in 33.3 % of patients with recurrent episode being involved. Most important prognostic factors are improper treatment (16.66 % of cases) after initial diagnosis.

Conclusions Prognostic factors such as selection of appropriate method for treatment are an important point for reducing the rate of recurrence. Moreover, warning patients about symptoms and frequent episodes of follow up is necessary for early diagnosis of recurrence.

Keywords Uterine cervix · Recurrence · Risk factor

Introduction

Cervical cancer is characterized by a range of minor-to-severe neoplastic changes of the epithelium which typically advances locally and via the lymphatic route, sometimes recurrently [1, 2]. Patients with initial minor stage disease (stages IB–IIA), who undergo appropriate treatment, will develop recurrence with risk factor of 10–15 %—mostly isolated in pelvic cavity [3]. In contrast, patients with severe stage disease (II–III) are at higher risk (20–50 %) of local relapse [4].

By means of intensive screening programs, the incidence of invasive cervical cancer especially cervical squamous cell carcinoma (SCC) has decreased, whereas the frequency

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of adenocarcinoma has increased or remained steady. Furthermore, advances in therapeutic methods and diagnostic tools, cannot improve the overall prognosis of patients with recurrent cervical cancer, and optimal treatment for recurrent disease is still on debate [5].

Most recurrences in cervical carcinoma occur within 5 years after the initial therapy [6], and recurrence after more than 5 years after the initial radiation therapy has been described in a few reports [7, 8]. Only 13 % of the recurrent patients with IB–IIB disease and 11 % of the recurrent patients with IIIB disease were cured which demonstrate that patients with locally recurrent cervical carcinoma have a poor outcome [9]. The overall 5-year survival rate of the recurrent patients varied between approximately 20–60 % [10].

It has been recommended by a previous study that analysis of recurrent cases should be performed in each individual institute because of different methods of therapy and follow-up systems [11].

This study was undertaken over a 5-year period, as a result of intensive long-term follow up, to analyze prognostic and risk factors of recurrence in cervical cancer and the patterns of recurrence.

Methods

The medical documents of 36 patients with stage IA2–IVA cervical carcinoma, who were treated at the Gynecology Division of Mahdiyeh Hospital affiliated to Shahid Beheshti University of Medical Sciences, between 2005 and 2010 were reviewed. Tumors were staged according to the latest modifications of the International Federations of Gynecology and Obstetrics (FIGO) system. Histological typing was performed according to the criteria of the WHO International Histological Classification of Tumors undertaken punch biopsy specimens. All patients were commenced on standard treatment for primary invasive cervical carcinoma as follows. A retrospective analysis was performed to identify risk factors and pattern of uterine cervical carcinoma recurrence. Recurrence was defined based on clinical or para-clinical documentation over a period of at least 6 months after complete remission following surgery or radiotherapy (DFI > 6 months). Patients with previous history of invasive cervical cancer, DFI < 6 months and records for a history of other cancers or medical diseases were excluded from study. According to site of recurrence, patients were divided to four groups: group 1—patients who had recurrence symptoms in local site such as vaginal cuff or cervix; Group 2—patients having recurrence in pelvic site; and finally group 3—consisting of patients having recurrence symptoms due to metastases into distant organs.

Remaining patients who had complex recurrence symptoms (recurrence symptoms in local site, in pelvis, and who had metastases to far organs) were classified in group 4. Univariate analysis of prognostic factors was performed with the test of log rank. A probability value of <0.05 was considered statistically significant.

Results

Among 133 registered patients in hospital database, 36 patients (27 %) suffered from tumor recurrence. Mean age in 36 selected patients was 54.8 ± 12.0 (ranging 37–80) years, with a peak between 53 and 58 years. Other clinical characteristics of the patients are summarized in Table 1. The pathologic reports of primary diagnosis were SCC in 34 patients (94.44 %), and adenocarcinoma in remaining patients (two cases). Most of the patients had non-keratinizing large cell SCC. Other types of cells are shown in Table 3.

The patients were staged as follows according to the FIGO classification: one case (2.77 %) in stage IA2, nine cases (25 %) in stage IB1, one case (2.77 %) in stage IB2, eight cases (22.22 %) in stage IIA, 12 cases (33.33 %) in stage IIB, three cases (8.33 %) in stage IIIA, one case (2.77 %) in stage IIIB, and finally one case (2.77 %) in stage IV.

With a follow-up time that ranged from 1 to 145 months, the mean duration of recurrence among patients (DFI) is 2.75 ± 1.5 years after the initial treatment; the average values of DFI in different stages are shown in Table 2.

Based on our findings, 25 patients (69.44 %) had self-referred and 11 patients (30.55 %) had been diagnosed after the routine follow ups. However, 91.7 % of all patients had clinical symptoms at the time of recurrence especially vaginal bleeding which was found in 82.6 % of the patients, followed by leukorrheas, which was recorded in 13.2 % of the patients at recurrence episode.

Based on classification of recurrence location, among all patients, 63.9 % were located in the group 1, 11.1 % had criteria of group 2, 13.6 % had recurrence symptoms because of metastases to far organs (group 3), and 11.1 % had complex recurrence symptoms (group 4). Two patients had lung metastases, three patients had liver metastases, and one patient had both liver and lung metastases.

Surgery was performed in 16 patients (44.4 %), of whom 5 (31.2 %) subsequently received postoperative adjuvant radiotherapy. The remaining 20 patients (55.5 %) with stage IB disease received primary radiotherapy.

Out of 16 patients who underwent surgical procedure as primary treatment, four patients had parametrium involvement and also, eight patients had marginal vaginal involvement. Twelve of the 16 patients had pathologic reports of lymph node involvement. DFI in these

Table 1 Patients' characteristics

Stages	Number of patients	Mean age (±SD) year	Type of histology			Type of treatment						
			KSS (% in stage)	LNK SCC (% in stage)	SC SCC (% in stage)	NS SCC (% in stage)	Adenocarcinoma (% in stage)	RH (%)	Ex (%)	EX & IN (%)	IM(%)	Other (%)
IA1	1	45				1 (100)						1 (100)
IB1	9	55.3 (±12.6)	2 (22.2)	4 (44.4)		2 (22.2)	1 (11.1)	4 (44.4)	2 (22.2)		2 (22.2)	1 (11.1)
IB2	1	38.5		1 (100)								1 (100)
IIA	8	53.9 (±12.7)	1 (12.5)	4 (50)	1 (12.5)	2 (25)		1 (12.5)	2 (25)		3 (37.5)	2 (25)
IIB	12	55.0 (±14.7)	2 (16.7)	3 (25)		6 (50)	1 (8.3)	1 (8.3)	6 (50)	1 (8.3)	1 (8.3)	3 (25)
IIIA	3	58.1 (±4.9)		1 (33.3)	1 (33.3)	1 (33.3)				2 (66.7)		1 (33.3)
IIIB	1	51		1 (100)								1 (100)
IV	1	73		1 (100)					1 (100)			
Total	36	54.8 (±12.0)	5 (13.9)	15 (41.7)	2 (5.6)	12 (33.3)	2 (5.6)	6	13	1	6	10

KSSC keratinizing squamous cell carcinoma, LNK SCC large cell non-keratinizing squamous cell carcinoma, SC SCC small cell squamous cell carcinoma, NS SCC non-specified squamous cell carcinoma, RH radical hysterectomy, Ex external irradiation, EX & IN external irradiation and internal irradiation, IM improper

patients who had parametrium and marginal vaginal involvement is lower than others who had same stages (Table 3).

Except ten patients, all cases are diagnosed in higher stages after recurrence compared with initial stage of diagnosis.

Poor and inadequate treatment in relation to disease stage had been documented in six patients (16.66 %) for the reason of recurrence.

Discussion

Among all women over age 40, it has been estimated that ~2 % develop cervical cancer in Iran [12]. The most important factor determining prognosis of most types of cancer was reported during the initial stage at diagnosis. Therefore, primary evaluation and selection of appropriate therapeutic regimens relative to stage of disease is the most common strategy for reduction of recurrence inconsistent with the finding of our study.

Based on the results of current study, approximately more than 50 % of our patients had stage over IIB. Unfortunately, lack of diagnostic instruments and cultural problem in the third world countries such as our region led to delay in diagnosis of cervical cancer. It is confirmed that treatment in patients with low stages of cervical cancers cure rates is 90–100 %, but in Patients with advanced cervical cancer cure rate is 25–50 %. Consequently, Iranian patients at invasive stages have higher chance of recurrence. As found In our results, only one of patients was in stage IA1; this is supported by previous evidences that indicate low recurrence of mild stages (1–2 %) [13]. On the other hand, lower number of patients with higher stages (IV and IIIB) in our study can be due to cut-point selection for DFI >6 months since many patients in higher stages present their recurrence episode promptly after treatment.

DFI is one of the important prognostic factors in patients with cervical cancer. DFI average values were different in various reports. At Dyun et al. [14] study, DFI average among 47 patients in different stages was 18 months, which stands close to our findings.

At Lim et al. [13] study, among 53 patients, DFI average was 17.6 months. Also, Mahe et al. [15] reported average of DFI as 70 months among seventy patients.

As we mentioned in “Results” section, poor and inadequate treatment in relation to disease stages had been documented in six patients (16.6 %) for the reason of recurrence. Previous investigations reported that for determining the appropriate therapeutic modalities including surgery, radiation therapy, chemotherapy or a multi-modal therapeutic approach, and the expectant prognosis, one needs to have complete information plus clinical staging. Nowadays, standard hysterectomy has long been

Table 2 Recurrence characteristics based on stage of diseases

Stages	Number of patients	Mean DFI ($\pm$ SD) months	Group 1 (recurrence symptom in local site) (%)	Group 2 (pelvic recurrence site) (%)	Group 3 (metastases to far organs) (%)	Group 4 (complex recurrence) (%)	Major presenting symptoms (%)	Parametrium involvement	Lymph node involvement	Marginal vagina involvement
IA1	1	36	1 (100)				Abdominal pain (100)		1	
IB1	9	32.2 ($\pm$ 10.7)	6 (66.7)	2 (22.2)	1 (11.1)		Vaginal bleeding (55.6)	1		3
IB2	1	8	1 (100)				Vaginal bleeding (100)		1	
IIA	8	8.0 ($\pm$ 4.3)	5 (62.5)	1 (12.5)	1 (12.5)	1 (12.5)	Vaginal bleeding (100)		1	1
IIB	12	7.2 ($\pm$ 2.8)	8 (66.7)		2 (16.7)	2 (16.7)	Vaginal bleeding (58.3)	2	1	3
IIIA	3	33.4 ($\pm$ 11.6)	2 (66.7)		1 (33.3)		Vaginal bleeding, abdominal pain and weight loss (33.3)			
IIIB	1	13	1 (100)				Abdominal pain (100)	1		1
IV	1	12				1 (100)	Vaginal bleeding (100)			
Total	36	27.5 ($\pm$ 13.6)	23 (63.9)	4 (11.1)	5 (13.9)	4 (11.1)	Vaginal bleeding (52.8)	4	4	8

Table 3 Recurrence characteristics based on methods of treatment

Treatment	Number of patients	Mean DFI ($\pm$ SD) months	Group 1 (recurrence symptom in local site) (%)	Group 2 (pelvic recurrence site) (%)	Group 3 (metastases to far organs) (%)	Group 4 (complex recurrence) (%)	Major presenting symptoms (%)
RH	6	8.3 ($\pm$ 4.0)	6				Abdominal pain (100)
Ex	13	37.3 ($\pm$ 11.2)	10	1		2	Vaginal bleeding (84.6)
Ex & IN	1	42.6 ($\pm$ 14.2)				1	Edema (100)
IM	6	27.4 ($\pm$ 9.6)	4	1	1		Abdominal pain (100)
Others	10	20.4 ($\pm$ 10.7)	3	2	4	1	Vaginal bleeding (60)
Total	36	27.5 ($\pm$ 13.6)	23 (63.9)	4 (11.1)	5 (13.9)	4 (11.1)	Vaginal bleeding (52.8)

RH radical hysterectomy, *Ex* external irradiation, *Ex & IN* external irradiation and internal irradiation, *IM* improper

recognized to be insufficient, and many surgeons opt for limited use of radical hysterectomy to women with stage IB, IIA, and recurrent cervical cancer.

Interestingly, in our assessment, the incidence of recurrence in SCC and adenocarcinoma was similar to general initial incidence of invasive SCC (~80–85 %) and invasive adenocarcinoma (10–15 %) [3].

Although designing a standardized protocol for early detection of recurrence during routine follow up was the most common method for detecting cancer recurrence, clinical signs and symptoms may have more efficiency in cancer recurrence diagnosis. In one study, 32 % of patients were diagnosed according to routine follow up; but 87 % of patients in that research showed initial clinical symptoms of cancer recurrence [14].

In another case series, out of 53 patients with recurrent cancer, only seven patients indicated routine follow ups [13]. In the present study, 91.7 % of patients had clinical appearance and symptoms at initial diagnosis of recurrence, but 30.5 % of these patients had been detected after routine follow up or other para-clinical assessment.

There are many different approaches for local recurrence management in cervical carcinoma. Patients with recurrent disease arising in the previously irradiated pelvis received chemotherapy or palliative care, except for patients with central recurrence, who were candidates for pelvic exenteration. Furthermore, radiotherapy was used to treat recurrent disease in patients with no prior history of receiving radiotherapy. The anatomic locations of recurrence should be considered for appropriate therapeutic strategy; based on previous reports, recurrent tumor that is located centrally in the pelvis associated with better prognosis which only 11.1 % of our cases had this status.

Conclusion

Delayed initial diagnosis and inadequate treatment were seen in our cases, as a factor for determining prognosis on cervical cancer recurrence; therefore, mortality and morbidity rates of cervical cancer recurrence could be reduced by means of proper diagnostic and treating strategy.

Conflicts of interest None.

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