Late recurrence of cervical cancer: a report of 16 cases

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Summary

Purpose: To analyze the clinical characteristics and outcome of cervical cancer patients presenting late recurrence. *Materials and Methods:* The medical records of 16 patients who were treated between 1974 and 1999 at the Institution and whose cancer recurred after a five-year disease-free interval were reviewed. *Results:* Mean time from initial therapy to recurrence was 162.5 months (60 - 360 mean). Smear abnormalities, atypical genital bleeding, abdominal and lumbar pain, and respiratory findings were the most common symptoms and signs associated with late recurrence. Fourteen patients were diagnosed by physical examination. Three of the six patients with local recurrence who were re-irradiated developed a vesico-vaginal fistula. At a median follow-up time of 12.5 months (4-38 mean), 12 patients were alive and the median survival time was 30 months. *Conclusions:* Cervical cancer patients surviving free of disease after the fifth year post-treatment are still at risk for relapse and in most of them, the recurrence is suspected by clinical examination alone.

Key words: Cervical cancer; Late recurrences.

Introduction

Deaths resulting from cancer of the cervix occur most frequently during the first years after therapy; about half of all deaths occur during the first year, 25% occur during the second year, and 15% occur during the third year, for a total of approximately 90% by the end of the third year [1]. Paunier *et al*., [2] indicated that 92.5% of deaths resulting from carcinoma of the cervix occur during the first five years after diagnosis. Recurrent cervical cancer carries a dismal prognosis as most recurrences are not amenable to local curative therapies; hence, most patients receive palliative chemotherapy [3].

Currently, no prospective randomized studies have been carried out to demonstrate that post-treatment surveillance of invasive cervical cancer improve the prognosis, however, it seems clear that prognosis can be improved when patients are diagnosed with an asymptomatic recurrence compared to those who are symptomatic [4, 5], suggesting that sensitive and specific methods such as positron emission tomography-computed tomography (PET-CT) can increase probability of detecting asymptomatic recurrences [5, 6] and eventually could improve survival of recurrent cervical cancer patients.

Late recurrence after a disease-free interval of five or more years after the primary therapy is uncommon in cervical cancer. According to several reports, it has been estimated that late recurrences may occur at a rate of 0.4-7.5% [7-12]. Whether tumors recurring after such a long-term have a similar clinical and biological behavior as compared to tumors recurring within the first five years postherapy is still unknown, due to the scarcity of publications on the issue. The authors report the clinical characteristics and outcome of 16 patients with cervical cancer who developed recurrent disease five years after completing primary treatment.

Materials and Methods

The present study was a retrospective review of 16 patients with cervical cancer who were treated between 1974 and 1999 at the Institution and whose cancer recurred after a five-year disease-free interval. Their charts were revised to obtain their clinical and demographic characteristics, primary therapy, length of the disease-free interval, clinical findings of recurrence, site of recurrence, treatment for recurrence, and outcome.

Statistical analysis

All data are expressed in terms of mean and standard deviation from the mean. Survival was calculated from the date of recurrence to the date of death. Analyses were performed using the statistical software package (StatView, SAS Institute, NC).

Results

The characteristics of patients are summarized in Table 1. The age distribution was from 28 to 62 years (mean 42) at primary therapy and from 35 to 71 years (mean 55) at recurrence. The period from initial therapy to recurrence ranged from 60 to 360 months with a mean of 162.5 months. The disease-free interval was within five to ten years in eight patients (50%), between ten and 20 years in six cases (37.5%), and more than 20 years in two cases (12.5%) - 29 and 30 years after initial therapy. The staging distribution at initial diagnosis, according to the FIGO classification, was as follows: Stage IA, one

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Table 1. — *Clinical characteristics of patients*.

Characteristics	No.	(%)
Age at initial diagnosis (years)	28 - 62 (mean 42)	
Age at recurrence (years)	35 - 71 (mean 55)	
Disease-free interval (years)		
≥ 5 - < 10	8	50.0
≥ 10 - < 20	6	37.5
≥ 20	2	12.5
FIGO Stage		
IA	1	6.25
IB	4	25.0
IIA	2	12.5
IIB	1	6.25
IIIA	1	6.25
IIIB	4	25.0
Unknown	3	18.7
Histology		
Squamous cell carcinoma	15	93.7
Adenocarcinoma	1	6.25
Primary therapy		
Radiation	10	62.5
Surgery	3	18.7
Surgery → Radiation	2	12.5
NACT → Surgery → Radiation	1	6.25

NACT: Neoadjuvant chemotherapy.

Table 2. — *Clinical findings at presentation of recurrence*.

Clinical findings	No.	(%)
Smear abnormalities*	2	12.5
Genital bleeding	1	6.25
Genital bleeding, abdominal and lumbar pain	3	18.7
Abdominal and lumbar pain	4	25.0
Dyspnea and lumbar pain	1	6.25
Cough and weight loss	1	6.25
Chest pain and hemoptysis	1	6.25
Dysphonia and lymph node enlargement (SC)	1	6.25
Lymph node enlargement (SC)	1	6.25
Numbness and pain of inferior limb**	1	6.25

No.: number; * these two patients were asymptomatic; SC: supraclavicular; ** this patient underwent exploratory laparotomy for diagnosis.

(6.25%); Stage IB, four (25%); Stage IIA, two (12.5%); Stage IIB, one (6.25%); Stage IIIA, one (6.25%); Stage IIIB, four (25%). In three patients it was not possible to assign a stage as they came to the Institution after they received primary treatment. The histological subtypes included 15 squamous cell carcinomas (93.75%), and one adenocarcinoma.

Overall, ten patients (62.5%) received primary pelvic radiation, three (18.75%) surgery, two (12.5%) surgery and adjuvant radiation, and one neoadjuvant chemotherapy followed by surgery.

Table 2 shows the clinical findings at diagnosis of recurrence. Only two cases (12.5%) were asymptomatic and the diagnosis was suspected by an abnormal pap smear. The most common clinical findings that raised the suspicion of recurrence were abdominal and lumbar pain in four patients, followed by genital bleeding and pain in three, as well as respiratory symptoms alone or in combination with other signs or symptoms in other three patients. In all cases

Table 3. — *Pattern of relapse*.

Sites of recurrence	No.	(%)
Pelvic site only	6	37.5
Systemic visceral only		
lung	1	6.25
Systemic lymph nodes only	4	25.0
Supra-clavicular	1	
Supra-clavicular/para-aortic	1	
Mediastinal/para-aortic	1	
Inguinal/para-aortic	1	
Pelvic/systemic lymph nodes	1	6.25
Pelvis/mediastinal	–	–
Pelvic/systemic visceral	2	12.5
Pelvis/bone	1	
Pelvis/lung/pleura/mediastinal	1	
Systemic visceral/lymph nodes	2	12.5
Lung/pleura/mediastinal	1	
Lung/liver/para-aortic/mediastinal	1	

Table 4. — *Treatment of recurrences*.

Treatment at recurrence	(No.)	Site of relapse	Re-irradiation
Pelvic RT	(2)	local	yes (2)
Pelvic RT	(1)	local	no
Pelvic CTRT	(1)	local	no
Pelvic CTRT	(2)	local	yes (2)
Systemic CT + Pelvic RT	(1)	local/syst	yes (1)
Systemic CT + pelvic CTRT	(1)	local/syst	yes (1)
Systemic Chemotherapy	(7)	systemic	no
Untreated	(1)		no

RT: radiation therapy; CTRT: chemotherapy + radiation therapy.

with respiratory complaints, diagnosis was made by a chest-X-ray. In the two cases with supraclavicular disease, the diagnosis was established by a fine-needle aspiration. A patient complaining of pain and numbness of the right inferior limb, imaging studies, and gynecological exploration showed no disease, so she underwent an exploratory laparotomy to confirm diagnosis. Once diagnosed, patients were evaluated to determine the extent of disease with CT. Two patients underwent bone scanning.

Among the 16 recurrent patients, six recurred in the pelvis as the sole site of disease (37.5%), a single case had visceral disease only (lung); four (25%) had systemic lymph node disease only; one had pelvic and systemic nodal disease, two had systemic visceral and lymph node disease, and two patients had visceral and lymph-node disease (Table 3).

The treatment of recurrence is shown in Table 4. Half of patients (eight) received pelvic radiation (four concurrent with chemotherapy and four alone); six as the only form of treatment, and two cases following systemic chemotherapy. Of note, six of these eight patients had received primary radiation, and three of these six re-irradiated patients developed a vesico-vaginal fistula, and another presented a rectal stenosis. Systemic chemotherapy was delivered in seven patients (six with carboplatin and paclitaxel and one, single agent gemcitabine). One patient refused treatment. At a maximum follow-up time of 38 months, the median survival time was 30 months and the projected survival was 32% (Figure 1).

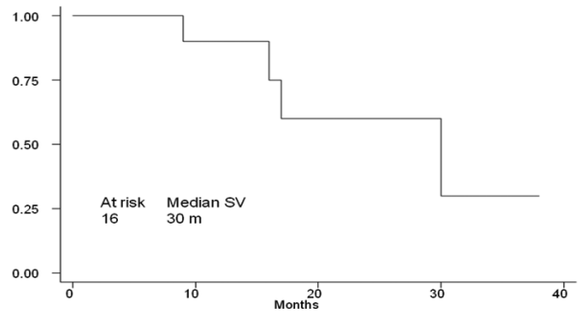

Figure 1. — At a maximum follow-up time of 38 months, the median survival time was 30 months and the projected survival was 32%.

Discussion

In this review of late recurrences of cervical cancer, which the authors considered as any recurrence beyond the fifth year post-treatment, it is shown that most occurred between five and ten years, followed by those presenting after ten years, and only two after 20 years. An unanswered question is whether in particular those recurrences after 20 years truly are recurrences or second primary tumors. Nevertheless, this kind of very late recurrences is less uncommon in neoplasias such as breast cancer, hence this may only indicate a very long period of tumor dormancy [13]. Nonetheless, it has been hypothesized that some of these tumors could be late radiation-induced cancers [11, 14, 15]. However, evidence in literature speaks of second primary tumors within radiation field (bladder, rectum) and out of the field, such as lung and leukemia [16, 17]. None of these were present in the patients studied, so it is unlikely that even those highly delayed "recurrences" are second malignancies.

Takehara *et al*., [1] found that the probability of late recurrence in patients with Stage II or III disease was significantly higher than in those with Stage I disease which is also seen in this study. This solely can be explained on the basis of less likelihood of control due to more advanced disease. All late recurrent cases, except one patient, were found to be squamous cell carcinoma in the present study. Other authors, such as Takehara and Van Herik [1, 11], also exclusively found this histology. In this report, all but one patient had squamous histology which suggests that there was an over-representation of squamous histology in patients with late relapse. Whether this is just random due to the small number of patients, or if is the reflection that adenocarcinoma and adenosquamous histologies tend to have a poorer prognosis and exhibit poorer responses to radiation [18-20] and consequently prone to earlier relapses, remains to be studied.

It is known that the site of metastases in breast cancer is related to the histopatological characteristics of patients. For instances, estrogen receptor (ER)-negative tumors recur more often in visceral and soft-tissue sites, while patients with ER-positive tumors are more likely to recur in bony sites [21]. The few reports on late recurrences of cervical cancer left unclear whether there is a common pattern of sites of relapse in this condition. Van Herik *et al*., [11] reported that the organs and tissues within the pelvis were most frequently involved in patients who had recurrence more than ten years after primary therapy. Others authors reported a predilection of bone in late relapses of cervical cancer [1, 22, 23]. The present study is remarkable because bone metastases were also observed in two patients (one as the sole site of disease), but also that four patients exclusively presented disease at lymph nodes, whereas another three had disease at lymph nodes and other organs such as lung, liver, and pleura. These data may suggests that cervical tumors destined to have late relapses are likely to have biological characteristics that preferentially drive tumor cells to lymph nodes, where they can remain dormant for longer times. This is supported by recent data in a breast cancer model of metastases where authors found that 12 out of 17 proteins overexpressed in metastases as compared to the primary tumors were found in lung metastases, as compared to only seven of these proteins in lymph node metastasis, and three in bone metastases [24].

Metastatic, recurrent, and persistent cervical cancer patients have a dismal prognosis. The most recent data of the GOG-204 study comparing four cisplatin-containing doublets indicate a median survival rate ranging from ten to 12.9 months depending on the doublet which is not statistically significant [25]. In addition, patients who failed to first-line chemotherapy have a dismal prognosis as no second- or third-line chemotherapy is considered standard with response rates below 15% [26]. In this selected population of late-relapsed patients, tailored treatment with radiation, chemoradiation, systemic chemotherapy or combination of these yielded a median survival of 30 months. At first sight this finding may suggest that late relapses may have a less aggressive course of the disease, however, this is only a suggestion. Finally, it should be stressed that despite re-irradiation can achieve a 60% of long-term control [15], the high complication rate found in the six re-irradiated patients merits a careful selection and dose planning to decrease the complication rate.

In summary, this report stresses that cervical cancer patients surviving free of disease after the fifth year post-treatment are at risk for recurrent disease. In addition, the clinical features of this population suggest that these tumors may have a different biological behavior and can be achieved better treatment results as compared to patients who relapse within the first five years post-treatment. This conclusion however, is not supported by the data here presented and should be viewed as hypothesis-driven.

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