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Value and cost evaluation of routine follow-up for patients with clinical stage I/II endometrial cancer

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Abstract

The aim of the study was to determine the value and the costs of routine follow-up for the detection of recurrences in patients treated for endometrial cancer. Between 1986 and 1995, 390 women with clinical stage I/II endometrial carcinoma were treated with combined surgery–radiation therapy. After treatment, follow-up was based on the clinical examination, a systematic Papanicolaou (Pap) smear and radiography (chest X-ray and abdomino-pelvic ultrasonography). 27 patients relapsed: 22 patients had symptoms and 5 were asymptomatic. None of the patients had recurrence detected on the routine Pap smear nor on the systematic chest X-ray. In conclusion, the follow-up of patients treated for endometrial cancer based on routine Pap smears and systematic radiography does not permit earlier detection of recurrences. Follow-up should simply include a clinical examination whose frequency should be based on prognostic factors. Approximately two-thirds of this cost was due to systematic examinations (Pap smears and radiography). Our results indicate that such expenditure could be avoided.

Keywords: Endometrial cancer; Follow-up; Recurrence; Pap smears

1. Introduction

Endometrial carcinoma is the most frequent gynecological cancer. In our institution, treatment of patients with early stage endometrial cancer is based on surgery combined, in most cases, with radiation therapy according to prognostic factors (brachytherapy with or without external radiation therapy) [1]. Routine follow-up has three objectives: to diagnose treatment complications, to detect recurrent disease after treatment and to screen for possible second cancers that epidemiological studies have associated with endometrial carcinoma (breast or colon cancer). The value of routine follow-up for the detection of recurrent disease has already been discussed in recent papers [2–5]. However, only one paper has studied the economic impact of routine follow-up [2]. The aim of this retrospective study, based on a large series of consecutive patients, was to evaluate the value of routine follow-up procedures for the detection of recurrent disease following treatment of endometrial cancer and particularly to evaluate their cost-effectiveness.

2. Patients and methods

From January 1986 to December 1995, 390 patients with stage I or II endometrial carcinoma (endometrioid carcinoma) according to the 1971 International Federation of Gynecology and Obstetrics (FIGO) classification of clinical criteria, were treated at the Institut Gustave-Roussy (France). Patients treated for other histological types of uterine tumours were excluded. Patients received combined radio-surgical treatment. Patients with clinically advanced disease (stage III or IV) were treated exclusively with radiation therapy and thus were

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excluded from this series. All patients underwent a preoperative evaluation with a clinical examination, laboratory studies and a chest radiography. During the first 5 years of this series, subjects were initially treated with preoperative vaginal brachytherapy at a dose of 60 Gy followed by surgery (216 patients; 55%). Since 1992, surgery has been the primary treatment with vaginal brachytherapy being performed after the surgical procedure. The surgical procedure consisted of peritoneal sampling for cytology and a total hysterectomy with bilateral salpingo-oophorectomy. A pelvic lymphadenectomy was also performed in patients with a good general status (299 patients; 77%). A vaginal hysterectomy was carried out in patients in a poor medical condition (23 patients; 6%). During the last 2 years of this study, a laparoscopy was performed in patients in whom a laparoscopic procedure was feasible. In these cases (7 patients; 2%), a hysterectomy with bilateral adnexectomy and pelvic lymphadenectomy were performed. Postoperative treatment (radiation therapy) was delivered according to the prognostic factors of the primary tumour determined at histological analysis (Table 1). 151 patients received external beam radiation therapy. Patients were reclassified in Table 1 with the 1988 FIGO classification [6] according to the results of the prognostic factor analysis after surgical staging.

21 patients had progressive disease at the end of the treatment and 18 patients were lost to follow-up. These patients were not included in the analysis of recurrence.

Table 1
Characteristics of 351 studied patients

	n (%)
Stage (FIGO 1988)	
I	250 (71)
II	70 (20)
III	29 (8)
IV	2 (0.6)
Myometrial invasion	
< 50%	263 (75)
> 50%	88 (25)
Nodal status	
Absence of lymphadenectomy	80
N−	260 (96)[a]
N+	11 (4)[a]
Peritoneal cytology	
Not performed (vaginal hysterectomy)	13
Negative	332 (98)[a]
Positive	6 (2)[a]
Grade	
1	132 (38)
2	192 (55)
3	27 (8)

[a] Per cent determined with the total of patients for whom a lymphadenectomy and/or a peritoneal cytology was performed.

Women with no residual tumour after the completion of treatment were followed-up according to our institutional protocol. A clinical examination consisting of a gynaecological examination and a Papanicolaou (Pap) smear was performed every 3 months during the first year, every 4 months during the second year, every 6 months during the third year and every year thereafter. A chest X-ray and abdomino-pelvic ultrasonography were performed annually.

Recurrence was defined, in this series, as confirmed endometrial cancer more than 3 months after the end of treatment. Each recurrence that developed in the 351 patients considered cured, was reviewed. The clinical examination, radiographical studies and the histological and cytological specimens were analysed. We also studied the duration of documented symptoms after the end of treatment, the topography and treatment of recurrences and survival.

2.1. Evaluation of costs

Economic analyses evaluated the annual cost of follow-up of all women treated for an endometrial carcinoma for the French National Health Scheme (Sécurité Sociale). The overall medical expensives of a patient treated for a cancer in France are covered and reimbursed by the French National Health Scheme and this corresponds to a unique fixed price. These costs are summarised in Table 2. We first estimated the cost of follow-up for the 351 cured patients treated in our institution.

As in France there is no National Cancer Registry, we considered data on the incidence of endometrial carcinoma in France [7] and on overall survival rates generally reported [8] in order to evaluate the number of patients treated for an endometrial carcinoma in our country. Thus, we estimated that each year 45 000 women were alive with a history of endometrial cancer, and that approximately 30 000 of them had been treated less than 10 years ago. These data are summarised in Table 3. Taking into account the mean age at diagnosis (65 years) and the mean duration of follow-up periods generally reported in the literature (5–10 years following the treatment) we based our economic analysis on a follow-up period of 10 years.

Table 2
Cost of each examination

Reimbursed cost (French francs — year 1999)	
Specialised consultation	150
Consultation with a general practitioner	115
Pap smear	108
Chest X-ray	151
Pelvic US	378

Pap smear, Papanicolaou smear; US, ultrasonography.

Table 3
Number of women living in France with a history of endometrial carcinoma

First year	4185
Second year	3718
Third year	3425
Fourth year	3192
Fifth year	3012
Sixth year	2870
Seventh year	2764
Eighth year	2661
Ninth year	2564
Tenth year	2474

Based on the follow-up protocols performed at the Institut Gustave Roussy and those reported by other teams [4,5,9–12], we considered the total number of clinical examinations, chest X-rays, pelvic ultrasound and Pap-smears systematically prescribed each year, and the annual cost of these different recommended schedules for follow-up examinations. We also evaluated the cost of various follow-up procedures, depending on the physician in charge (specialist in oncology or gynaecology, or a general practitioner). Costs are specified in millions (M) of Euros (€) and French francs (FF).

3. Results

Prognostic factors of patients studied are detailed in Table 1. 71 patients had stage I disease, grade 1 tumour, no nodal involvement, benign peritoneal cytology and myometrial invasion $<50\%$. Patients were followed-up for a median (range) duration of 42 months (12–137 months). 16 patients (5%) developed a second cancer (breast), while 27 developed a recurrent endometrial cancer (8%). The median time to the recurrence was 22 months (range 5–67 months) (standard deviation (S.D.) = 17). 85% (23/27) of these recurrences were detected within 36 months after the end of treatment. 7 patients had a local recurrence (5 vaginal and 2 pelvic), 19 patients had a distant recurrence and one patient had a local recurrence with metastases (Table 4).

Table 4
Characteristics of 27 patients with recurrence

Patient no.	Age (years)	Stage[a]	Grade	Myometrial invasion (%)	Nodal status	LSI[b]	Recurrences	
							Circumstances	Site
Asymptomatic								
1	61	Ib	2	<0	N−	No	Clinical examination	Vaginal
2	61	IIa	1	>50	N−	No	Clinical examination	Vaginal
3	68	Ib	2	<50	N−	No	Clinical examination	Vaginal
4	67	Ib	2	<50	N−	No	Surgery (cholecystectomy)	Peritoneal
5	60	IIIc	2	>50	N+	Yes	Routine ultrasonography	Para-aortic
Symptomatic							Symptoms	
6	53	IIa	2	>50	N−	No	Abdominal pains	Peritoneal
7	72	IIIa	2	>50	N−	No	Vaginal bleeding	Vaginal + chest
8	59	IIIa	2	>50	N−	No	Fever	Liver + chest
9	72	Ic	1	>50	N−	No	Abdominal pains	Liver + para-aortic
10	64	IIIc	2	<50	N+	No	Bowel obstruction	Peritoneal
11	64	IIa	2	<50	N−	No	Cardiac arrhytmia	Chest
12	66	IIb	3	>50	N−	Yes	Swelling of the legs	Chest
13	60	Ib	2	<50	N−	No	Vaginal bleeding	Pelvic
14	57	Ia	2	<50	N−	No	Abdominal pains	Peritoneal
15	65	IIIa	1	<50	N−	No	Lumbar pains	Para-aortic
16	74	IIIa	1	>50	N−	No	Pelvic pains	Vaginal
17	61	Ia	2	<50	N−	No	Abdominal pains	Liver
18	68	Ic	3	>50	N−	No	Hemianopsia	Brain
19	42	IIb	2	>50	NP[c]	Yes	Cough	Chest
20	59	Ib	2	<50	N−	Yes	Lumbar pains	Para-aortic
21	59	Ib	2	<50	N−	No	Pelvic pains	Vaginal
22	69	Ib	3	<50	N−	No	Headaches	Brain + chest
23	77	IIIc	3	>50	N+	No	Pelvic pains	Pelvic
24	58	IIIc	2	>50	N+	No	Abdominal pains	Para-aortic
25	77	IIa	3	>50	NP[c]	No	Bowel obstruction	Peritoneal
26	58	IIIa	2	>50	N−	Yes	Abdominal pains	Chest + para-aortic
27	56	IIIc	2	>50	N+	Yes	Crural pains	Bone

[a] According to the FIGO 1988 classification.
[b] Lymphovascular space involvement in the myometria.
[c] Lymphadenectomy not performed.

Table 4 indicates how recurrences were discovered: 22 patients had symptoms. 5 patients, however, were asymptomatic (Table 4, patients nos. 1–5): in 1 patient, peritoneal carcinomatosis was discovered during a surgical procedure for benign disease (cholecystectomy) and in another patient, para-aortic metastases were discovered at the systematic ultrasound examination. In the other 3 patients, the vagina had a suspicious appearance during the gynecological examination. The Pap smears were normal, but deep biopsies confirmed vaginal cuff recurrences.

Prognostic factors (the patient's age, tumour stage, tumour differentiation, myometrial invasion, nodal status and peritoneal cytology) concerning the 27 patients who developed a recurrence are detailed in Table 4. Treatment of recurrences consisted of: surgery (colpectomy in 3 patients), radiation therapy (7 patients), chemotherapy (13 patients) and hormonal therapy (8 patients). In 7 patients, several treatments were combined. In 2 patients ($\geqslant$75 years old age) whose medical condition was poor, no treatment was performed. Among the 27 recurrent patients one was lost to follow-up, 19 died at a median time of 12.2 months (range 2–70 months), 6 patients are alive with progressive disease and only the patient who had a vaginal recurrence treated by colpectomy is currently alive without persistent disease 5 years after treatment of this lesion.

In our study of 351 patients, the median duration of follow-up was 42 months. We estimated the total number of clinical and non-clinical examinations performed. At the beginning of the fourth year, we calculated that a quarter of the planned examinations had been performed. Thus, the total cost for these 351 patients was €238 500 French francs ((FF)1.55M). The cost for each patient was €680 (FF4416). The cost of the non-clinical examinations was €147 700 (FF960 000). This figure represented the cost for the diagnosis of the only asymptomatic recurrence using systematic non-clinical examinations (patient no. 5; Table 4). The annual cost of non-clinical examinations for each patient was €420 (FF2735). The cost of the clinical examinations of the 351 patients was €90 800 (FF59 000). 3 recurrent asymptomatic patients (with vaginal recurrence) had recurrent disease diagnosed during the clinical examination performed at the routine visit. Thus, the cost of clinical examination per recurrence detected at the routine visit was €30 250 (FF196 600).

In the literature, the recommended schedules for follow-up procedures varied according to the authors and countries. We only took into account the systematic procedures. In our institutional protocol, a clinical examination (with systematic Pap smear) was performed every 3 months during the first year, every 4 months during the second year, every 6 months during the third year and every year thereafter. A chest X-ray and abdomino-pelvic ultrasonography were performed annually. Podczaski and colleagues recommended four clinical examinations during the first year, two during the second year, and one the following years, two Pap smears and one chest X-ray during the first 2 years after the treatment [10]. Salvesen and coworkers recommended a similar clinical follow-up schedule, four Pap smears the first year, two the second year and one during subsequent years and one annual chest X-ray [5]. Berchuck recommended four clinical examinations during the first and second years, two during the third, fourth and fifth years, four Pap smears during the first 2 years, two during the third and fourth years and one the last year, and one annual chest X-ray during the 5 years [9]. No one prescribed systematic pelvic ultrasound. Some authors recommended that the follow-up period be reduced to 5 or 6 years [9,12].

The mean estimated annual cost of these different follow-up procedures applied to the French population of women with a history of endometrial carcinoma would be €1.6M (FF10M) to €4.65M (FF31.5M). Approximately one-third of this figure was due to clinical examinations (€0.46M (FF3M) to €1.4M (FF9.1M) and two thirds (€1.1M (FF7M) to €3.4M (FF22.3M)) to the non-clinical examinations procedures. When the 10-year follow-up is conducted by a general practitioner, the annual cost avoided does not exceed 0.3M (FF2M).

4. Discussion

The results of the present series indicate, as did other studies, that recurrent endometrial carcinomas are detected by routine surveillance after the end of the treatment in only a few patients [2,4,5,9]. Recurrence was detected in only 11% (3/27) of patients at the clinical examination. 22 patients exhibited symptoms and most of them had received medical advice before their routine follow-up visit following the onset of new symptoms (interval visit). Thus, the rate of symptomatic patients with recurrent disease was 81% (22/27). In the literature, this rate varies from 41 to 91% [5,10,11]. Furthermore, no difference was observed in the survival of symptomatic patients and asymptomatic patients with recurrent disease [2,4,5,11,12].

Most of the recurrences were detected within 36 months of the first scheduled follow-up visit [11,12]. Sites of recurrence were local (vagina/pelvis), distant (visceral metastases, peritoneal carcinomatosis, para-aortic lymph nodes) and both local and distant. In the present series, as in other studies, distant metastases were more frequent than local recurrences [13–15]. This may be due to good local control of the cancer in the pelvis by surgery combined with radiation therapy [13,14,16].

Recurrences of the vaginal vault were more frequently asymptomatic than metastases and were detected by clinical examination [17]. A vaginal recurrence can be treated by surgical resection and/or radiation therapy if the patients have not received radiation therapy for treatment of their primary tumour. In the present study, the only disease-free survivor is a patient who underwent colpectomy for an isolated vaginal recurrence. Early detection of local recurrence is therefore important and vaginal cytology could ideally lead to early diagnosis of recurrent lesions. However, as observed by Owen [4], Shumsky [12] and in our series, none of the recurrences was detected on the routine Pap smear. According to Owen, after treatment for endometrial cancer, the recurrent tumour invades the entire thickness of the vagina before cells can be sampled on a routine Pap smear, and at this stage of development, the recurrence becomes symptomatic [4]. Clearly, the routine Pap smear does not appear to be the most appropriate procedure for the detection of an early vaginal recurrence. In our study, all asymptomatic patients with vaginal recurrence suspected during the gynecological examination had a normal Pap smear and proof of recurrent disease was obtained at histological analysis of the deep biopsy specimen. Even in our series only 3 asymptomatic patients had vaginal recurrence diagnosed during the routine visit; gynaecological examination during the routine visit is fundamental in order to detect vaginal vault recurrence which is the only curable recurrent lesion. When a pelvic recurrence is diagnosed, a complete evaluation of local spread should be performed before deciding on the choice of treatment. During the study period, we used computer tomography (CT) scans, but during the last 3 years we preferred magnetic resonance imaging (MRI) that seems to provide a more accurate appraisal of abdomino-pelvic spread [18].

Until 1995, we performed a systematic abdomino-pelvic US and a chest X-ray in our institution to follow-up patients treated for endometrial cancer. Only 1 asymptomatic patient developed a recurrence (para-aortic nodes) that was diagnosed through these examinations. Patients with distant recurrences were more often seen during an interval visit than during a routine visit [2]. Systematic radiography did not permit early detection of metastases. Furthermore, according to Agboola, the survival of patients who develop a recurrence detected at the routine visit is not significantly different from that of patients in whom disease is diagnosed at the interval visit [2]. Thus, in our series as in the literature, carrying out systematic Pap smears, chest X-rays and abdomino-pelvic US does not improve survival. However, the economic impact of routine follow-up is far from negligible. Agboola estimated the mean cost of routine follow-up procedures to be $19 200 for each patient who had a recurrence (respectively, $16 900 to detect chest metastases on radiograms and $27 000 to detect a vaginal recurrence on Pap smears) [2]. The psychological impact of follow-up must also be taken into account. Follow-up with systematic examinations can be considered reassuring to some patients, while it may generate extreme stress and avoidance in others and, consequently, non-compliance with surveillance [12]. The psychological impact of follow-up cannot be easily quantitated [9].

Recent studies seem to suggest that serum CA 125 measurements could be useful for the diagnosis of recurrence [19,20]. This tumour marker may be elevated in patients treated for an endometrial carcinoma with a high-risk of recurrence [19,21]. Posttreatment follow-up of this marker could therefore be a predictor of recurrence. In the study by Rose and colleagues, 58% (19/33) of patients with recurrent disease had an elevated CA 125 level [19]. Only one recurrent patient was detected based on an elevated CA 125 level alone [19]. In fact, in the study of Rose and coworkers, the rate of recurrent patients detected by an elevated CA level is similar to the rate reported in the literature of patients with recurrent disease diagnosed through clinical examination and/or that of symptomatic patients [5,10,11]. However, in Lo's series, the median lead time between elevation of CA 125 and clinical evidence of recurrence was 6 months [20]. In this study, all recurrences diagnosed with elevated CA 125 were metastatic (lung, pleural and peritoneum) [20]. These recurrences were not usually curable and, as previously stated, early detection of these distant metastases is not associated with improved survival. Consequently, our team does not perform CA 125 measurements during follow-up of endometrial cancer.

In the literature, the recurrence rate correlates with prognostic factors of the primary tumour. These prognostic factors have been clearly identified in endometrial cancer [22,23]. In our series, none of the 71 patients with favourable prognostic factors developed recurrent disease. All recurrences were observed in patients with 1, 2 or more unfavourable histological prognostic factors (a stage > I and a grade 2 or 3 tumour, malignant peritoneal cytology, myometrial invasion > 50%, lympho-vascular space involvement, positive nodes — Table 4). Patients treated for an endometrial cancer can therefore be divided into two categories: subjects with good prognostic factors and patients with at least one unfavourable prognostic factor. The appropriate follow-up procedure must be commensurate with the requirements of each category. In all cases, follow-up should be based on the clinical examination, consisting of a gynaecological and a breast examination. For patients with favourable prognostic factors, follow-up visits could be less frequent (for example, every 6 months during the first year after initial treatment and every year thereafter). For patients with at least one unfavourable

prognostic factor, follow-up should be more frequent (for example, every 4 months the first year, every 6 months for 3 years and then annually. Patients should be advised to consult a doctor if new unusual symptoms appear (pain, bleeding, nausea, cough). Other examinations (Pap smear, biopsies, radiography) need not be performed routinely, but only when clinical abnormalities appear. We also recommend performing a systematic mammography to screen for possible second cancers in the breast. The frequency of the systematic mammography depends on the age and the previous history (personal and familial) of the patients.

In conclusion, clinical examinations seem to be sufficient for the follow-up of patients with endometrial carcinoma. The frequency of follow-up visits should be based on the prognostic factors of the primary tumour. Routine Pap smears and systematic radiography does not permit earlier detection of recurrences. Dispensing with these examinations in our country, (France), will allow us to economise between €2.8 M (FF18M) and €3.4 M (FF22.3M) depending on which non-clinical procedures are no longer performed and the duration of follow-up. A prospective study analysing survival, the recurrence rate, but also evaluating the economic and psychological impact, should be performed in order to assess the validity of this strategy for the follow-up of treated endometrial cancer patients.

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