Costs and benefits of routine follow-up after curative treatment for endometrial cancer

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Abstract

Objective: To examine the costs of routine outpatient follow-up after curative treatment of endometrial cancer, and to determine whether this leads to early detection of recurrence or survival. The impact of specific disease characteristics on survival is examined.

Design: Retrospective chart review, and calculation of costs.

Setting: Ottawa Regional Cancer Centre-Civic Division (ORCC-C).

Patients: All 432 patients referred to the ORCC-C with endometrial cancer between 1982 and 1991 who received treatment with curative intent and who continued with routine follow-up.

Results: Cancer recurred in 50 patients (11.57%). There was no statistically significant difference in overall survival between patients with symptomatic and asymptomatic recurrences, or between those with recurrences detected during routine follow-up visits or in the interval between routine visits. Of 4830 Papanicolaou (Pap) smears performed routinely, cancer was detected in 6 cases. The mean cost of the routine follow-up procedures for each patient with a recurrence was $19 200.

Conclusion: Intensive follow-up of women with endometrial cancer does not result in improved survival. A prospective randomized study is warranted to evaluate other potential benefits of follow-up, such as improved quality of life or decreased morbidity. There is no economic or clinical justification for the routine use of the Pap smear in the follow-up of patients with endometrial cancer. The potential benefits of routine follow-up in endometrial cancer and other types of cancer with favourable prognoses warrant critical evaluation.

Résumé

Objectif : Examiner les coûts des suivis de routine en clinique externe de patientes qui ont reçu un traitement curatif pour un cancer de l'endomètre afin de déterminer s'ils permettent de détecter rapidement une récurrence ou s'ils ont une incidence sur la survie. On examine l'impact de certaines caractéristiques de la maladie sur la survie.

Conception : Examen rétrospectif des dossiers et calcul des coûts.

Contexte : Centre régional d'oncologie d'Ottawa - Division Civic (CROO-C).

Patientes : Les 432 patientes envoyées au CROO-C et atteintes d'un cancer de l'endomètre entre 1982 et 1991, qui ont reçu des traitements visant à les guérir et qui ont continué à participer à des suivis de routine.

Résultats : Le cancer est réapparu chez 50 patientes (11,57 %). Il n'y avait pas de différence significative sur le plan statistique quant à la survie générale entre les patientes qui ont été victimes de récurrences symptomatiques et asymptomatiques, ou entre celles dont la récurrence a été détectée au cours d'un suivi de routine, ou entre les visites de routine. Sur 4830 tests de Papanicolaou de routine, on a décelé un cancer dans six cas. Le suivi de routine chez chaque patiente victime d'une récurrence a coûté en moyenne 19 200 $.

Conclusion : Le suivi rapproché de femmes victimes d'un cancer de l'endomètre

Evidence

Études

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n'améliore pas la survie. Une étude randomisée prospective s'impose si l'on veut évaluer d'autres avantages éventuels du suivi, comme une amélioration de la qualité de vie ou une baisse de la morbidité. Aucune raison financière ou clinique ne justifie l'utilisation de routine du test de Papanicolaou pour assurer le suivi des patientes atteintes d'un cancer de l'endomètre. Les avantages éventuels d'un suivi de routine des cas de cancer de l'endomètre et d'autres types de cancer qui présentent un pronostic favorable justifient une évaluation critique.

For patients with cancer, long-term, close surveillance has traditionally been the *sine qua non* of post-treatment care. In the past, these patients have usually been treated within the context of a clinical trial in which close follow-up protocols were used to evaluate the results. Since prognoses were generally poor, close monitoring was felt to be necessary. Furthermore, it was hoped that early detection of a recurrence would result in decreased morbidity and mortality.

In this era of health services research, this tradition of close surveillance (follow-up after treatment) is being challenged and evaluated.[1–3] Both its clinical effectiveness and cost-effectiveness are now being exposed to greater scrutiny because of the high costs to patients, cancer clinics and the overall health care system.[4]

A number of studies have documented a large variation in surveillance practices[5–7] and an associated large variation in costs.[8–11] However, studies consistently show that, despite close follow-up, most recurrences are detected in the interval between routine follow-up visits, when patients present because of signs or symptoms of disease.[12–16] Research also reveals that close surveillance protocols do not result in improved survival.[17–19]

Most research on the effectiveness of follow-up has focused on patients with breast and colorectal cancer. However, endometrial cancer is also a subject of close long-term surveillance practices. The most common type of gynecologic cancer in North America, endometrial cancer affects 31 000 women annually in the US[20] and 3000 in Canada.[21] Of these, 70%–80% are diagnosed with limited disease and have an excellent prognosis,[22,23] as indicated by the low incidence-to-death ratio of 0.20.[20] The vast majority of these women are followed closely in outpatient cancer clinics. However, few studies have been conducted to evaluate the practice of routine outpatient follow-up after curative treatment for endometrial cancer.[24] The objective of this study was to examine the costs of routine follow-up of patients with endometrial cancer, and to determine whether there was a difference in survival between patients with recurrences detected during routine visits versus "interval" visits (between routine visits), or between patients who were symptomatic versus asymptomatic when their recurrences were detected.

Setting

The Ottawa Regional Cancer Centre-Civic Division (ORCC-C) is a tertiary care cancer clinic serving a population of 1.5 million in eastern Ontario. Patients were referred to the ORCC-C after surgery consisting of total abdominal hysterectomy and bilateral salpingo-oophorectomy in 94% of cases. At the ORCC-C they received adjuvant radiation treatment if the stage of the carcinoma was more advanced than stage I, the histologic grade was greater than 2, or myometrial invasion was greater than half its thickness. Patients in whom a local recurrence developed were treated with radiation therapy if they had not previously undergone such therapy. Patients with a distant recurrence or those who had previously undergone radiation therapy were treated systemically with chemotherapy, hormonal therapy or both.

After completing primary treatment, all patients were followed at the ORCC-C according to a uniform protocol. They were seen in an outpatient clinic every 3 months in the first year, every 4 months in the second year, every 6 months in the third to fifth years and annually thereafter. At each visit patients had a pelvic examination and Papanicolaou (Pap) smear from the vaginal vault. A chest radiograph was taken annually. When clinically indicated, abdominal ultrasonograms, computed tomographic (CT) scans of the pelvis and abdomen, and biopsies were performed. Suspected vaginal recurrences were confirmed by biopsy during examination under anesthesia (EUA). Recurrences at other sites were confirmed by fine-needle aspiration (FNA) or laparotomy, except when the patient was not healthy enough for such a procedure or multiple metastatic disease was present.

This protocol was adhered to in more than 90% of the patients followed up at the ORCC-C.

Methods

We conducted a retrospective chart review of all patients referred to the ORCC-C between 1982 and 1991 with a diagnosis of cancer of the uterine body. Permission to conduct the chart review was granted by the Ethics and Research Committee of the ORCC-C. Patients were included if they had stages I to III endometrial carcinoma

(FIGO classification), that was treated with curative intent and subsequently followed up at the ORCC-C.

Patients with a recurrence were identified in 1992; additional recurrences and survival were ascertained in 1995. A total of 618 charts were reviewed, of which 432 were suitable for analysis. Of the 186 patients not included in this analysis, 44 had sarcoma, 1 had choriocarcinoma, 13 had an active second tumour, 52 were not treated with curative intent, 44 were treated elsewhere and 32 were lost to follow-up.

The number of clinic visits, Pap smears and chest radiographic examinations performed were calculated for each patient from the time of diagnosis to death or to September 1992, when the records were reviewed. In the analysis, recurrences in the vault of the vagina and the pelvis were classified as local and other sites as distant. Visits were classifed as routine or "interval" (nonroutine), which may have been initiated by the patient or her family physician.

Statistical analysis

The data were analysed using the BMDP statistical package and the Graphpad Prism software for generation of survival curves and log rank tests. Survival analysis was performed using the Kaplan–Meier product limit method.[25] Information on patients who were alive at the last follow-up was treated as censored data. (A statistical term, "censored" here describes data about patients who were still alive at the time of analysis; survival analysis is designed to accommodate these kinds of data.) The difference between survival curves was evaluated using the log rank test.[26] The effect of age, stage and grade of disease, and depth of myometrial invasion were assessed in univariate and multivariate analyses using the Cox proportional hazard model.[27] The same model was used to test the differences in the disease characteristics between the patients with recurrent disease diagnosed during an interval or a routine visit to the ORCC-C.

Cost analysis

The objective of the cost analysis was not solely to estimate the absolute costs of routine follow-up, but also to provide estimates of the incremental costs of providing routine Pap smears and chest radiographic examinations in addition to ambulatory care, and to estimate the costs of surveillance in patients in whom recurrence occurred. This was done by adding up the costs of routine follow-up visits, Pap smears and chest radiographic examinations.

The unit cost of a routine visit can be broken down into the costs of the physician's time (fee), nursing time (salary plus benefits), and administration and overhead costs. Nursing time associated with a routine visit was estimated to be 15 minutes, with salary and benefits based on the grade of nursing staff generally used at the Ottawa Cancer Centre for such visits. Administration costs for routine ambulatory care visits were obtained directly from the Ottawa Cancer Centre.

The Ottawa General Hospital Case Costing Project provided estimates of the unit costs of a Pap smear and a chest radiographic examination. This project allows the measurement of departmental workload, identification of patient-specific resource use and calculation of unit costs for individual resource items. In accordance with national guidelines, the direct costs of treatment (e.g. staff, materials used to obtain Pap smears) are allocated directly to the treatments received; indirect costs (e.g. overhead expenses) are also allocated to treatments. All costs except physician costs were specific to the Ottawa Cancer Centre and may differ at other centres. However, only substantial variation in unit costs would significantly alter the specific results of the study.

Results

Recurrence and survival

Of the 432 cases analysed in 1992 (Table 1), the median follow-up was 54.5 months (range 3 to 138 months). Follow-up was more than 80 months in 25% of cases. Fifty patients had a recurrence. The records of this group with a recurrence were reviewed to the end of 1995, at which time 25% had been followed for 42 months after recurrence, (median of 9.5 months, range 1 to 147 months). For all 432 patients, the overall survival rate from the time of diagnosis of endometrial cancer was 86.3% at 5 years and 73.0% at 10 years. For the patients who had a recurrence, the survival rate was 44% at 5 years and 22% at 10 years.

Of the recurrent cases, 19 (38%) were local and 31 (62%) were distant. The median time to recurrence was 18.5 months (range 3 to 194 months), and 80% of recurrences occurred by 36 months. Thirty-five of the patients with a recurrence (75%) had died by the time of analysis: 30 from cancer and 5 from other causes. The median survival after a recurrence was 9.5 months (range 1 to 103 months).

A total of 5254 visits were made to the clinic by all of the patients, an average of 12 visits per patient. Twenty-five of the 50 recurrences (50%) were identified during these routine visits; 23 recurrences (46%) were diagnosed during an interval visit when the patient had symptoms; in 2 cases (4%) it was impossible to determine whether the diagnosis was made at a routine or an interval visit. Twenty-one recurrences (42%) were detected by physical examination (7 at interval visits, 13 at routine visits and 1 unknown); 9 recurrences were detected by a chest radi-

ographic examination (2 at interval visits and 7 at routine visits); and 2 recurrences were detected by a Pap smear taken during a routine visit.

Of the 50 recurrences, 20 (40%) were detected in asymptomatic patients (10 local recurrence and 10 distant), and 30 (60%) were detected when the patients had symptoms (9 local and 21 distant). The median duration of symptoms was 3 weeks (range 1 to 20 weeks) before confirmation of the recurrence; 75% were confirmed by 8.5 weeks. The most common symptoms, occurring in 70% of patients, were vaginal bleeding or abdominal pain. Patients with a distant recurrence were more likely to have symptoms at the time of diagnosis of the recurrence (21/31 [67.7%]) than were patients with a local recurrence (9/19 [47.4%]). Similarly, patients with a distant recurrence were more likely to be diagnosed at an interval visit (16/31 [51.6%]) than were patients with a local recurrence (7/19 [36.8%]). Most symptomatic recurrences were detected at interval visits (23/30 [76.7%]), whereas all 20 asymptomatic recurrences were detected at routine visits.

There was no statistically significant difference in overall survival (i.e., from the time of initial diagnosis) between symptomatic patients (median 42 months, range 11 to 147 months) versus asymptomatic patients (median 47 months, range 12 to 134 months) (p = 0.33, Fig. 1) and between patients in whom a recurrence was diagnosed at

Table 1: Age, disease characteristics and survival of patients with endometrial cancer

Age, disease characteristic or survival	No. (and %) of patients except where indicated				
	All *n = 432*	With recurrence *n = 50*	With recurrence diagnosed at interval visit *n = 23*	With recurrence diagnosed at routine visit *n = 25*	With recurrence, type of visit unknown *n = 2*
Initial cancer					
Median age, yr	64.8	67.5	67.1	68.0	67.7
Stage of disease					
I	343 (79)	28 (56)	16 (70)	12 (48)	
II	63 (15)	14 (28)	5 (22)	8 (32)	1 (50)
III	21 (5)	7 (14)	1 (4)	5 (20)	1 (50)
Unknown	5 (1)	1 (2)	1 (4)		
Depth of myometrial invasion					
None	78 (18)	4 (8)	3 (13)	1 (4)	
Inner third	168 (39)	17 (34)	7 (30)	9 (36)	1 (50)
Middle third	95 (22)	6 (12)	4 (17)	2 (8)	
Outer third	76 (18)	20 (40)	7 (30)	13 (52)	
Unknown	15 (3)	3 (6)	2 (9)		1 (50)
Grade of disease					
1	255 (59)	14 (28)	7 (31)	7 (28)	
2	121 (28)	22 (44)	9 (39)	12 (48)	1 (50)
3	48 (11)	12 (24)	6 (26)	6 (24)	
Anaplastic	1	1 (2)	1 (4)		
Unknown	7 (2)	1 (2)			1 (50)
Recurrent cancer					
Status of symptoms when recurrence detected					
Symptomatic		30 (60)	23 (100)	5 (20)	2 (100)
Asymptomatic		20 (40)	0	20 (80)	0
Site of recurrence					
Local		19 (38)	7 (30)	11 (44)	1 (50)
Distant		31 (62)	16 (70)	14 (56)	1 (50)
Patient status at end of study					
Alive		15 (30)	6 (26)	9 (36)	0
Dead		35 (70)	17 (74)	16 (64)	2 (100)
Survival, median no. of mo (and range)					
After recurrence		9.5 (1–103)	7.0 (1–89)	24.0 (1–103)	1.5 (1–2)
Overall		44.5 (11–103)	45.0 (11–134)	44.0 (12–134)	26.5 (11–42)
Duration between initial treatment and recurrence, median no. of mo (and range)		18.5 (3–194)	18.0 (4–118)	22.0 (3–194)	21.0 (9–33)

a routine visit (median 44 months, range 12 to 134 months) versus an interval visit (median 45 months, range 11 to 134 months) (p = 0.97, Fig. 2). Also, there was no statistically significant difference in survival after detection of the recurrence in symptomatic patients (median 7 months, range 1 to 103 months) versus asymptomatic patients (median 31 months, range 1 to 96 months) (p = 0.135) and between patients diagnosed with a recurrence at routine visits (median 24 months; range 1 to 103 months) versus interval visits (median 7 months; range 1 to 89 months) (p = 0.25). In patients with a local recurrence, there was a trend toward both longer overall survival (from the time of diagnosis) and longer survival after recurrence than those with a distant recurrence, but these differences were not statistically significant (Figs. 3 and 4). The median overall survival from the time of initial diagnosis was 65 months for patients with local recurrence and 38 months for those with distant recurrence (p = 0.24); median survival after recurrence was 38 and 7 months respectively (p = 0.10).

Detection of recurrences

Twenty-five recurrences (50%) were detected at routine visits: 13 (26%) by physical examination alone, 7 (14%) by routine chest radiographic examination, 2 (4%) by routine Pap smear and 3 (6%) by clinically indicated tests (e.g. CT scan and ultrasonogram following suspi-

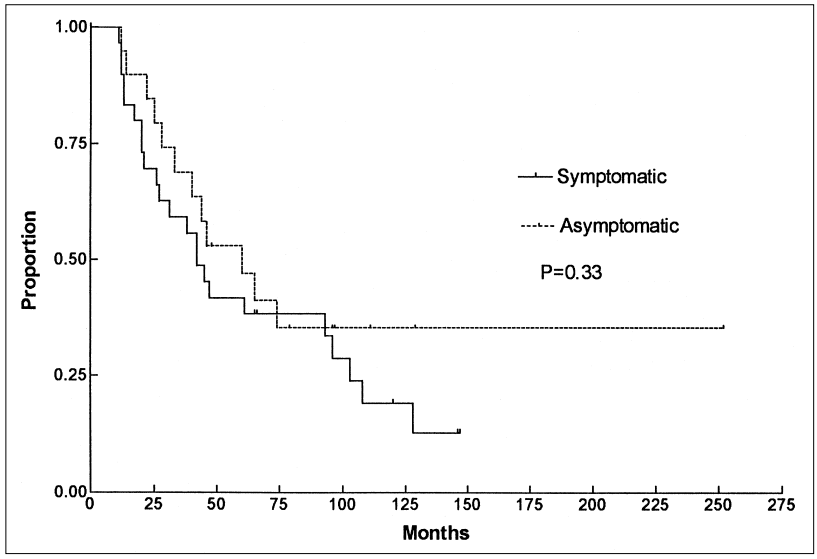

Fig. 1: Overall survival rates (from time of initial diagnosis) of patients who were symptomatic and asymptomatic at time of diagnosis of recurrent endometrial cancer.

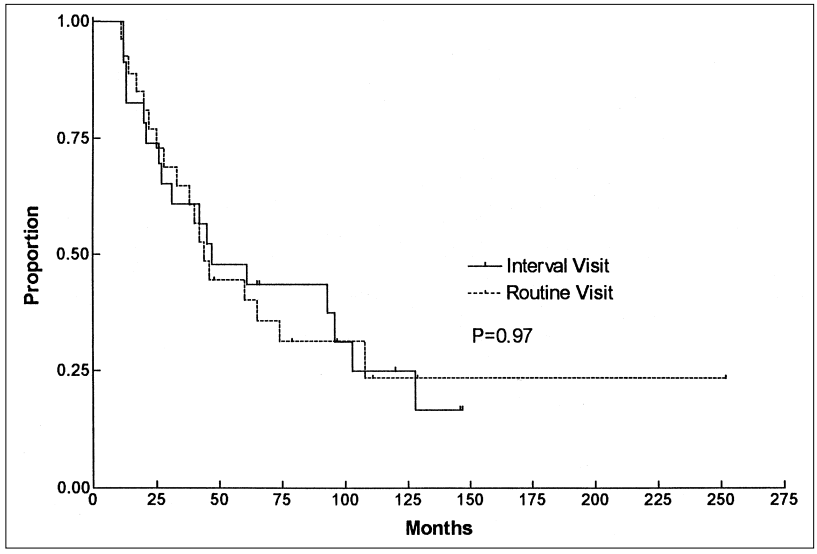

Fig. 2: Overall survival rates of patients in whom recurrence of cancer was diagnosed at interval visits or at routine visits.

cion of recurrence). There were 7 chest radiographic examinations with positive results from a total of 2057 performed routinely (0.34%). Pap smears were performed routinely on 410 (95%) of the patients. There were 7 Pap smears with positive results from a total of 4830: 4 patients had clinically evident disease when the Pap smear was taken, 2 had clinically evident disease within 3 months of the smear being taken and 1 patient continued to be free of disease 3 years later. Thus, 6 recurrences were identified from the 4830 Pap smears performed.

Costs

The average cost of a routine visit was estimated to be $58.55, including $25.00 administration costs, $27.55 physician costs and $6.00 for the cost of nursing time. On the basis of the Ottawa General Hospital's case-costing system, the cost of a Pap smear was estimated at $11.21 and that of a chest radiographic examination at $57.32. The total costs of follow-up for the 432 patients were $480 000: 64% for routine visits, 11% for Pap smears and 25% for chest radiographic examinations.

The 5254 routine visits cost a total of $308 000 (Table 2). Sixteen recurrences were detected during these routine visits by a combination of physical examination and clinically indicated tests, resulting in a cost per recurrence detected of $19 200. There were 2057 annual routine chest radiographs taken, at a total cost of $118 000. These rou-

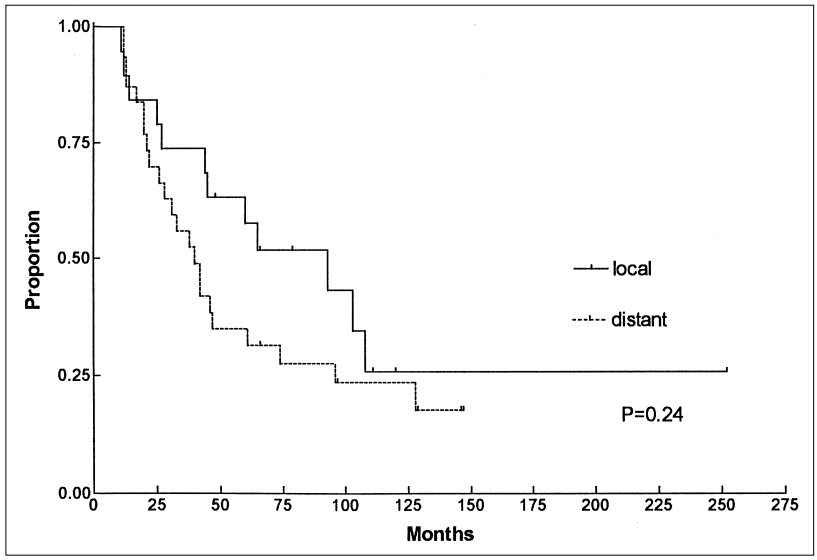

Fig. 3: Overall survival rates of patients in whom local or distant recurrent cancer was diagnosed.

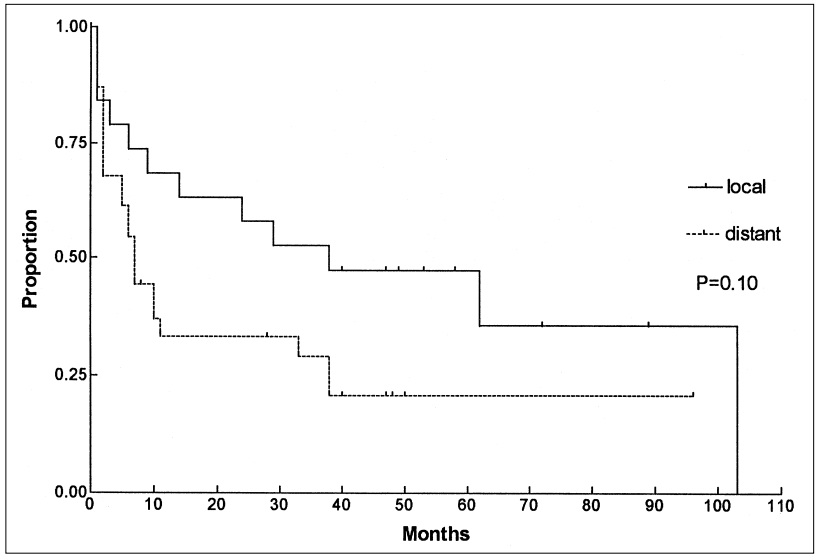

Fig 4: Survival of patients with local or distant recurrent cancer from recurrence to death or last follow-up date.

tine radiographic examinations led to an additional 7 recurrences being detected, at an incremental cost of $16 900 per case.

A total of 4830 routine Pap smears were conducted at a total cost of $54 000. These led to an additional 2 recurrences being detected, at an incremental cost of $27 000 per case (Table 2).

Discussion

Detection of recurrence and survival

The overall 5-year survival rate for patients who had a recurrence was 84.3%. This is consistent with other published data which show survival rates ranging from 76.3% to 98% for stage 1 disease and 5% to 30% for stage 3 disease.[28] The finding, albeit nonsignificant, in our study that patients with a distant recurrence have a worse prognosis than patients with local recurrence is consistent with the results of other studies.[24,29–31] Similarly, the recurrence rate of 11% noted in this study is consistent with other published results concerning endometrial cancer.[23,29]

Univariate and multivariate analyses showed that overall survival is not influenced by age at diagnosis, stage of disease, depth of myometrial invasion or local or distant recurrence of disease. Only the grade of disease showed a trend toward statistical significance ($p = 0.08$) in both univariate and multivariate analyses. However, after recurrence, survival was influenced by the grade of the disease ($p = 0.05$ in both univariate and multivariate analyses). Higher grade of disease was associated with increased risk of dying from cancer after recurrence, by a risk ratio of 1.56 (95% confidence interval 0.69 to 2.44).

Comparison of the disease characteristics at presentation of the patients with a recurrence detected at an interval visit or at a routine visit showed a statistically significant difference in the stage of disease ($p = 0.03$) in favour of the patients with a recurrence detected at a routine visit. However, a log rank test of difference between these groups in terms of overall survival and survival after recurrence did not achieve statistical significance. This result could be due to the small number of patients in the study and the lack of statistical power to detect small differences in length of survival.

Follow-up procedure

Patients with cancer are routinely followed after curative treatment in order to detect and treat recurrence promptly and thus to achieve lower morbidity and improved survival. Our findings in this study with respect to endometrial cancer do not support this notion. Irrespective of whether the patient has symptoms, or the recurrence is diagnosed at a routine or interval visit, overall survival or survival after recurrence is not significantly different. Other authors have reached the same conclusion that intensive surveillance does not improve survival of patients with endometrial cancer.[24,29] Our finding that routine chest radiographic examinations or Pap smears at each scheduled visit do not contribute significantly to early detection of recurrent disease also supports the results of other investigators.[24,29,30]

Costs of follow-up

From an economic perspective, 25 of the 5254 routine visits resulted in the detection of a recurrence. Of these 25 cases, 16 were detected by physical examination and clinically indicated tests, 7 by chest radiographic examinations and 2 by Pap smears for a total cost per recurrence detected of $19 200. However, routine follow-up, excluding the use of routine chest radiographic examination and Pap smears, would also generate a cost per recurrence detected of $19 200. Since these 2 figures are the same, an initial interpretation may be that routine follow-up, including a chest radiographic examination and Pap smear is as cost-

Table 2: Cost per recurrence of endometrial cancer detected by various combinations of routine follow-up procedures (n = 432)

Variable	(1) Routine physical examination and clinically indicated tests only	(1) plus routine chest radiograph	(1) plus routine chest radiograph plus routine Pap smear	(1) excluding nursing costs	(1) plus routine chest radiograph, excluding nursing costs
Total cost, $	308 000	426 000	480 000	276 000	394 000
No. of cases detected	16	23	25	16	23
Cost per case detected, $	19 200	18 500	19 200	17 300	17 100
Incremental cost, $		118 000	54 000		118 000
Incremental no. of cases detected		7	2		7
Incremental cost per case detected, $		16 900	27 000		16 900

effective as follow-up excluding these tests. However, after considering the incremental cost per recurrence detected, the cost-effectiveness of including a routine Pap smear becomes less clear. This is because the incremental cost per recurrence detected of including routine annual chest radiographic examinations is $16 900 compared with $27 000 when including routine Pap smears.

An additional issue is the cost of nursing time associated with routine follow-up. Nursing coverage is supplied routinely because of the sensitive nature of the physical examination for endometrial cancer. It could be argued that such coverage need not be provided by highly trained nursing staff and could be provided by auxiliaries or volunteers, especially if routine Pap smears were not considered cost-effective. Nursing staff costs make up 10.2% of the costs of the routine physical examination. If these costs could be saved, the cost per case detected of routine physical examinations alone could be reduced to $17 300, and the cost per case detected of physical examinations plus routine chest radiographic examinations would be reduced to $17 100.

Conclusions

The follow-up protocol for endometrial cancer evaluated in this study is standard practice in the US and Canada.[32] The findings of this study led us to the following conclusions.

1. No difference in survival related to the routine follow-up visit was found. However, there may be other potential benefits of follow-up, such as psychosocial support or more effective control of symptoms after recurrence, which should be addressed in a prospective randomized study designed to evaluate these aspects.
2. Since 80% of all recurrences occur by the third year, follow-up beyond 5 years is not warranted.
3. The continuation of routine chest radiographic examinations as part of follow-up may be supportable on economic grounds, since the incremental cost per case detected is small. However, it has yet to be proven that early detection of pulmonary metastases leads to improvements in morbidity.
4. There is no economic or clinical justification for routine Pap smears in the follow-up of endometrial cancer.

At a time of dwindling resources for medical care, the potential benefit of routine follow-up in endometrial cancer and other types of cancer with favourable prognoses warrants critical evaluation. Considerable resources could be saved and diverted to other areas of need in the health care system.

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