

# Variation in gynecological oncology follow-up practice: attributable to cancer centers or to patient characteristics? A Piedmont Regional Oncology Network Study

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## ABSTRACT

**Aims and background.** Although guidelines recommend minimalist follow-up, there is wide variability in gynecological oncology practice. The aims of this study were to describe between-center differences in the follow-up of endometrial, ovarian, and uterine cervical cancer; to identify the determinants of test prescription; to estimate the related costs; and to assess the weight of center habits and patient characteristics as sources of unexplained variability.

**Methods and study design.** The medical records of patients treated between August 2004 and July 2005 for gynecological malignancies and followed up for the detection of recurrent disease were retrospectively collected from 29 centers of the Piedmont Oncology Network. Multivariate multilevel analyses were performed to study the determinants of test prescription and costs.

**Results.** Analyses were performed on 351 patients (median follow-up: 578 days). The unexplained variability in computed tomography prescriptions (26%), ultrasound prescriptions (17%), and total cost of follow-up (15%) can be attributed to center habits, independent of the clinical characteristics of the patients.

**Conclusions.** Much of the unexplained variability in the follow-up for gynecological malignancies is attributable to different habits of centers belonging to a cancer network. These results prompted us to design a multicenter randomized controlled trial to compare minimalist *versus* intensive follow-up programs in endometrial cancer.

**Key words:** appropriateness, evidence-based medicine, follow-up, gynecological cancer.

**Acknowledgments:** We kindly thank Fabio Lampis for data management, Laura Baruffaldi for data nursing, Dr Oscar Bertetto, Coordinator of Interregional and Inter-company Department of the Piedmont and Valle d'Aosta Oncology Network, for support in the project, and all members within the participating network for their collaboration.

**Funding:** This work was supported by the Piedmont Oncology Network (grant number 699/3566/10/2006).

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Received January 28, 2011;  
accepted March 24, 2011.

## Introduction

Cancer treatment accounts for a considerable percentage of the total global healthcare disbursement<sup>1</sup>. A substantial amount of this cost is considered to be imputable to follow-up procedures, which are characterized by a set of visits and examinations conducted in a systematic manner, often for many years<sup>2</sup>. Follow-up care is designed for patients submitted to oncology treatment and judged to be disease free. The overall goal of follow-up is to timely identify disease recurrence amenable to treatment in a primarily asymptomatic patient<sup>2</sup>.

The reasons why gynecological oncology programs suggest periodic follow-up exams are commonly accepted, including the following: to evaluate the control of the illness, the survival of the patient, the performance status, the diagnosis and amendment of the possible complications encountered following primary treatment (often a combination of integrated modalities), the chance to diagnose recurrent disease in advance in order to plan possibly lifesaving therapy, and finally to provide support and counseling to patients and family<sup>3</sup>.

An essential question is whether a procedure exists that allows the diagnosis of a recurrence in a subclinical phase of the disease. In addition, the clinician is interested in knowing what are the most appropriate follow-up procedures and their timing. Another question is whether a patient with early-stage disease should be followed up more or less frequently compared to a patient with a major risk of recurrence. An additional concern is the psychological impact on patients of frequent tests added to the primary visit<sup>3</sup>.

During the last few years, evidence-based medicine (EBM) has gained increasing acknowledgment. Similarly, there has been constant growth in the need and expectations of an individual's health. Above all, EBM tries to address the rapid increase in problems related to hospital management and the containment of resource pressure<sup>4</sup>.

In the near future, medical decisions will need to be made in an explicit and clear way where decisional pathways will be widely available to everybody interested. In addition, physicians will need to produce and describe the scientific evidence that supports and drives their own decisions. In health science, as a consequence of an observed growth in the need for well-being care, there will be a transition from decisional processes mainly based on opinions to behaviors founded on sound evidence<sup>4</sup>.

If we consider common practice, a widespread impression is that variability exists in the approach to the follow-up care in oncology<sup>5-8</sup> and more so in patients with gynecological cancers<sup>9-14</sup>. Indeed, an inconsistent number of examinations are often prescribed, with the hope of identifying treatable recurrent diseases.

As a matter of fact, there are two opposing tendencies suggesting different follow-up modalities. One trend is

based on a poor "evidence-based" literature suggesting "minimalist" follow-up, while the other tendency suggests the introduction of new therapies and technologies in which the physician follows an "intensive approach" and prescribes several investigations and strict surveillance.

In order to achieve clinical governance, the Piedmont Region has been organized into a regional oncology network to achieve benefits in terms of consistency in treatment procedures performed.

The present study monitored whether differences in common practice between oncologists belonging to the Piedmont Region network exist in terms of monitoring gynecological malignancies (including endometrial, ovarian, and uterine cervix cancer). One of the aims of the present survey is to identify the determinants of an examination's prescription, including whether exams are prescribed on the basis of the cancer patient's characteristics or whether part of the variability in follow-up is not explained. Additionally, the current study was designed to determine whether this unexplained variability is imputable to habits of the different centers that are unsupported by scientific evidence. Furthermore, determinants of an examination's cost have also been assessed.

To address these aims, a retrospective evaluation of cases was performed among centers belonging to the Piedmont Regional Oncology Network. Furthermore, a literature search was updated to corroborate the scientific evidence underlying the follow-up procedures of the gynecological tumors focused on in this study.

## Materials and methods

The present study protocol consisted of a retrospective review of the medical records of new patients radically treated for endometrial, ovarian, or uterine cervical cancer between August 2004 and July 2005 and followed up for at least 3 months. Patients with synchronous tumors were excluded. Information about the date of diagnosis, type of neoplasm, stage of disease, date and type of treatment received, date of diagnosis of recurrence, and symptoms at recurrence (if any) were recorded using standardized items and a common database. All exams and the date of assessment during the follow-up time (through December 2006) were traced. Evaluations performed earlier than 3 months from treatment and after a relapse diagnosis were excluded from the analysis. The study protocol was in accordance with the ethical standards of the regional committee on human experimentation.

Considering all of the diagnostic tests performed during the examinations, the total costs were calculated for each visit using the outpatient tariffs rewarded to hospitals by the Regional Health Service. Costs were expressed as a value of the Euro in 2007.

## Statistical analysis

Statistical analyses were performed allowing for the hierarchical structuring of the data. For analyses, examinations constituted the first-level units, patients the second-level units, and centers the third-level units.

The analyses were first carried out separately based on the type of gynecological cancer (endometrial, ovarian, or uterine cervix). Determinants of abdominal/thoracic computed tomography (CT) and abdominal/pelvic ultrasound (US) prescriptions (yes/no) during the examinations were evaluated using a 3-level logistic random intercept model. The time (in days) elapsed from the previous visit (<90, 90-179, 180-269,  $\geq 270$ ) and the same diagnostic examination performed during the previous visit were considered as an examination-level variable. Age at first examination (<60, 60-69,  $\geq 70$  years), stage of disease (I-IV) and presence of relapse symptoms during the follow-up examination were considered as patient-level variables. The type of units (gynecology, radiation, oncology, collegial evaluation) and the number of patients treated by each center were considered center-level variables. Moreover, for each exam (CT and US), determinants of prescription were evaluated in the whole group of patients, including the gynecological cancer as a covariate in the models.

Due to positive skewness of cost data, factors influencing the cost of each visit were investigated using a 3-level general linear mixed model (GLMM), with a gamma distribution and a logarithmic link function on the whole group of patients. Effects of covariates on the cost of each visit were shown by calculating the exponential of coefficients ( $\exp(\beta)$ ) derived from the model, which represent the relative change in cost associated with unit change of the predictor variable.

The covariates included in the model were the same as those evaluated in the previous models. In each multilevel model, the proportion of variance that is accounted for by the cluster levels was evaluated by calculating the intraclass correlation coefficients<sup>15</sup> ( $\rho_p$  for patient level,  $\rho_C$  for center level).

## Results

A total of 505 patients were retrospectively collected by 29 centers belonging to the Piedmont Oncology Network (an organization of the National Health Service covering a population of about 4.3 million). Seventy-one patients were excluded from the study due to missing follow-up data, 29 patients were excluded because they were not treated during the study period (protocol breach), and 54 patients were excluded because a single follow-up visit was performed during the first 3 months after initial treatment. After the exclusions, 351 patients were available for analysis.

Table 1 shows the characteristics of the patients enrolled in the study. The median age at diagnosis was 65

years. Of these patients, 86 suffered from ovarian cancer, 201 from endometrial cancer, and 64 from carcinoma of the uterine cervix. As commonly observed, the distribution of the disease by stage shows a majority of patients with stage I and stage II uterine cervix cancer (84.4%) or endometrial cancer (80.6%) and with stage III and stage IV malignant epithelial ovarian cancers (69.8%). The patients were treated in accordance with standard procedures.

During the follow-up period, with a median length of 578 days, 62 patients (17.7%) experienced a recurrence of the disease. Of the patients with recurrent disease, 14.0%, 6.2% and 5.5% of ovarian, cervical and endometrial cancers, respectively, produced symptoms at the time. For all cancers, the majority of patients (60-65%) were followed up by gynecologists.

Patients underwent a total of 1193 visits (second part of Table 1). The frequency of tests prescribed during follow-up are reported by type of cancer. The time between 2 consecutive visits was also determined. As shown, visits were closer in patients with ovarian cancer than in patients with endometrial and cervical cancer.

### Abdominal/thoracic CT prescription

Table 2 shows the results of the multilevel logistic modeling. The probability of prescribing an abdominal/thoracic CT, adjusted for all the variables analyzed, was positively associated with the stage of the disease in patients suffering from endometrial or cervical cancer. In patients with ovarian cancer, the probability of a CT prescription was positively associated with age and the time elapsed from the previous visit. For endometrial and ovarian cancer, the intraclass correlation coefficients indicate that 33% ( $\rho_C = 0.329$ ) and 34% ( $\rho_C = 0.337$ ), respectively, of the variance can be attributed to the center-level variable. In the pooled analysis (Table 3), stage of disease was confirmed as a strong predictor of CT prescription. Considering the whole group of patients, 26% ( $\rho_C = 0.262$ ) of the unexplained variability in CT prescriptions can be attributed to center-level variation.

### Pelvic/abdominal US prescription

Table 2 shows that the probability of prescribing pelvic/abdominal US was higher when examinations were further apart in time. Comparing examinations done less than 90 days after the last one to examinations done between 180-269 days in patients with endometrial or ovarian cancer, the probability of prescription of US was significantly higher. Stage of disease was negatively associated with US prescription in patients with ovarian cancer (stage III-IV *versus* stage I). For endometrial cancer, the intraclass correlation coefficients indicate that 31% ( $\rho_C = 0.305$ ) of the variance can be attributed to the center level. In patients suffering from ovarian cancer, 20% of the variance can be attributed to the patient level ( $\rho_p = 0.199$ ). Pooled analysis (Table 3) confirmed a higher probability of US prescription during examinations

**Table 1 - Patient and examination characteristics in relation to type of gynecological cancer**

Patients	Endometrium (n = 201)	Ovary (n = 86)	Uterine cervix (n = 64)	Total (n = 351)
Mean age at first examination in years (IQR)	68.0 (59.0; 74.0)	64.0 (56.2; 72.0)	57.0 (45.8; 69.0)	65.0 (57.0; 72.0)
Age distribution at first examination				
<60	25.9% (52)	33.7% (29)	54.7% (35)	33.0% (116)
60-69	30.9% (62)	34.9% (30)	23.4% (15)	30.5% (107)
≥70	43.3% (87)	31.4% (27)	21.9% (14)	36.5% (128)
Stage of disease				
I	69.65% (140)	26.74% (23)	51.56% (33)	55.84% (196)
II	10.95% (22)	3.49% (3)	32.81% (21)	13.11% (46)
III	17.41% (35)	55.81% (48)	12.50% (8)	25.93% (91)
IV	1.99% (4)	13.95% (12)	3.12% (2)	5.13% (18)
Treatment				
Surgery only	42.29% (85)	12.79% (11)	32.81% (21)	33.33% (117)
Surgery and chemotherapy	1.99% (4)	72.09% (62)	6.25% (4)	19.94% (70)
Surgery and radiotherapy	44.78% (90)	0.00% (0)	29.69% (19)	31.05% (109)
Other	10.95% (22)	15.12% (13)	31.25% (20)	15.67% (55)
Relapse symptoms during follow-up (yes)	5.47% (11)	13.95% (12)	6.25% (4)	7.69% (27)
Relapse during follow-up (yes)	8.46% (17)	41.86% (36)	14.06% (9)	17.66% (62)
Patient examinations frequency during follow-up, median (IQR)	3.00 (2.00; 4.00)	3.00 (2.00; 5.00)	2.50 (1.75; 4.00)	3.00 (2.00; 4.00)
Specialist who monitored the patients				
Gynecologist	60.20% (121)	62.79% (54)	65.62% (42)	61.82% (217)
Radiotherapist	14.93% (30)	0.00% (0)	21.88% (14)	12.54% (44)
Oncologist	6.97% (14)	37.21% (32)	4.69% (3)	13.96% (49)
Collegial evaluation	17.91% (36)	0.00% (0)	7.81% (5)	11.68% (41)
Examinations	(n = 677)	(n = 339)	(n = 177)	(n = 1193)
Diagnostic tests				
CA 125	26.29% (178)	75.22% (255)	7.34% (13)	37.38% (446)
Vaginal cytology	44.90% (304)	8.55% (29)	42.37% (75)	34.20% (408)
Abdomen US	24.1% (163)	13.6% (46)	9.6% (17)	18.9% (226)
Pelvic US	10.93% (74)	5.60% (19)	3.95% (7)	8.38% (100)
Hematochemical evaluation	14.9% (101)	19.2% (65)	11.9% (21)	15.7% (187)
MRI	1.18% (8)	2.06% (7)	9.04% (16)	2.60% (31)
Thoracic x-ray	7.98% (54)	4.42% (15)	2.82% (5)	6.20% (74)
Abdomen CT	14.3% (97)	26.6% (90)	16.9% (30)	18.2% (217)
Chest CT	2.66% (18)	8.55% (29)	2.26% (4)	4.27% (51)
Colonoscopy	14.48% (98)	1.18% (4)	25.42% (45)	12.32% (147)
PET	0.74% (5)	4.13% (14)	1.69% (3)	1.84% (22)
Other marker	5.47% (37)	7.96% (27)	2.26% (4)	5.70% (68)
Mammography	1.77% (12)	0.00% (0)	0.00% (0)	1.01% (12)
Days between two subsequent examinations, median (IQR)	165 (117; 204)	112 (58; 172)	163 (126; 215)	145 (101; 203)

US, ultrasonography; MRI, magnetic resonance imaging; CT, computed tomography; PET, positron-emission tomography; IQR, interquartile range. Data are mean (SD) and % (n) for continuous and categorical variables, respectively, unless otherwise indicated.

more distanced in time. Considering the whole group of patients, 17% ( $\rho_C = 0.174$ ) of the unexplained variability in US prescriptions can be attributed to the center level.

#### Cost analysis

The total cost for each visit was described by median values according to the factor investigated in the GLMM (Table 4). The GLMM showed that disease stage was positively associated with higher costs (Table 5). As regards the type of gynecological cancer, the cost of visits for patients suffering from endometrial cancer was lower than that for ovarian cancer. Visits performed with a

collegial evaluation seemed to be less costly than visits performed by the gynecological specialist alone.

The intraclass correlation coefficient indicates that 15% ( $\rho_C = 0.148$ ) and 17% ( $\rho_P = 0.167$ ) of the unexplained variability in visit costs can be attributed to center level and patient level, respectively.

#### Discussion

To the best of our knowledge, this is the first study that analyzes the determinants of the prescription of follow-

**Table 2 - Association between examination, patient and center characteristics and diagnostic exam prescription related to type of gynecological cancer**

	Abdominal/thoracic CT			Abdominal/pelvic US		
	Endometrium	Ovary	Uterine cervix	Endometrium	Ovary	Uterine cervix
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Time elapsed from the previous visit (days)						
<90 (Ref.)	1	1	1	1	1	1
90-179	1.36 (0.57, 3.24)	1.02 (0.53, 1.97)	0.34 (0.1, 1.19)	1.86 (0.78, 4.45)	2.46 (1.15, 5.26)	0.8 (0.17, 3.89)
180-269	0.85 (0.31, 2.29)	1.84 (0.78, 4.34)	0.16 (0.04, 0.65)	3.45 (1.28, 9.3)	3.27 (1.34, 7.98)	2.3 (0.52, 10.22)
≥270	2.59 (0.79, 8.52)	3.84 (1.11, 13.26)	0.3 (0.05, 1.8)	1.65 (0.5, 5.41)	1.56 (0.37, 6.55)	1.18 (0.15, 9.35)
Same examination performed during the previous visit	0.25 (0.12, 0.55)	0.58 (0.29, 1.14)	0.29 (0.06, 1.32)	0.55 (0.25, 1.18)	1.4 (0.64, 3.05)	0.49 (0.11, 2.1)
Age at first examination (years)						
<60 (Ref.)	1	1	1	1	1	1
60-69	0.91 (0.44, 1.89)	1.74 (0.8, 3.78)	0.4 (0.12, 1.35)	1.71 (0.82, 3.54)	1.18 (0.56, 2.48)	0.59 (0.17, 1.98)
≥70	0.7 (0.33, 1.50)	2.21 (0.93, 5.26)	4.83 (1.17, 20)	1.51 (0.7, 3.22)	1.55 (0.67, 3.6)	0.08 (0.01, 1.04)
Stage of disease						
I (Ref.)	1	1	1	1	1	1
II	1.44 (0.53, 3.91)	1.28 (0.19, 8.72)	2.99 (1.06, 8.42)	1.52 (0.56, 4.12)	-	0.41 (0.12, 1.4)
III-IV	5.67 (2.85, 11.26)	2.06 (0.92, 4.6)	0.83 (0.15, 4.65)	0.79 (0.4, 1.56)	0.39 (0.2, 0.78)	1.19 (0.05, 27.86)
Relapse symptoms	0.83 (0.25, 2.77)	1.17 (0.46, 2.98)	0.88 (0.1, 7.87)	0.59 (0.18, 1.96)	1.27 (0.45, 3.6)	0.57 (0.01, 22.85)
Patients followed by center (any 10)	0.84 (0.66, 1.04)	0.96 (0.80, 1.19)	1.00 (0.92, 1.14)	1.04 (0.84, 1.29)	1.04 (0.92, 1.13)	1.19 (1.04, 1.34)
Specialist who monitors the patients						
Gynecologist (Ref.)	1	1	1	1	1	1
Radiotherapist	0.54 (0.08, 3.84)	-	2.47 (0.68, 8.92)	0.4 (0.06, 2.88)	-	4.02 (0.58, 27.78)
Oncologist	0.08 (0.01, 1.06)	1.66 (0.29, 9.53)	-	2.28 (0.18, 28.75)	1.17 (0.41, 3.37)	4.98 (0.16, 157.9)
Collegial evaluation	0.31 (0.05, 1.92)	-	-	0.67 (0.11, 4.14)	-	13 (0.99, 171.49)
Random effects						
Patient level: variance	0.332	<0.001	<0.001	<0.001	<0.001	0.009
Patient level: $\rho_p$	0.062	<0.001	<0.001	<0.001	<0.001	0.003
Center level: variance	1.775	1.670	<0.001	1.450	0.199	<0.001
Center level: $\rho_c$	0.329	0.337	<0.001	0.305	0.057	<0.001

OR, odds ratio; CI, confidence interval; Ref, reference value.

up procedures and of the related costs in gynecological cancers within a cancer network, and that tried to estimate the variability attributable to patient or center level, using appropriate multilevel statistical methods. The main findings of the study were a confirmation of some expected results, such as the high degree of variability in the follow-up strategies within the regional cancer network and the predictive role of a few clinical characteristics in the prescription of imaging tests. It also produced some original evidence, such as the estimate of the net contribution of the centers to the variability, even after the specialist responsible for the patients and the clinical variables had been accounted for.

We recently conducted a systematic literature review using the Medline database<sup>3</sup> with the keywords “endometrial neoplasms” (MeSH) or “uterine cervical neoplasms” (MeSH) or “ovarian neoplasms” (MeSH) and (“costs and cost analysis” [MeSH] or “cost savings” [MeSH] or “health care costs” [MeSH] and “follow-up”) from 1980 to 2007. EMBASE and EBM secondary liter-

ature (Clinical Evidence, Database of Abstracts of Reviews of Effectiveness, Cochrane Database of Systematic Reviews, and ACP Journal Club) were further checked for the same period of time. We found a few papers that described a cost-effectiveness analysis of follow-up strategies for patients with gynecological cancers, and a current update of the review (2008) did not add significant evidence (data not shown). Actually, only a few studies have compared the cost-utility or cost-effectiveness of alternative practice in terms of frequency and the kind of examinations prescribed to follow up the gynecological cancer patient’s disease-free status after curative treatment. These studies are mainly based on retrospective analysis of efficacy and have been reported to provide a low level of evidence (level 4-5)<sup>16</sup>.

Few randomized trials comparing the effectiveness of different strategies of follow-up are available also for other common cancers. A Cochrane systematic review on follow-up strategies in breast cancer found only 2 ran-

**Table 3 - Association between examination, patient and center characteristics and diagnostic exam prescription**

	Abdominal/thoracic CT	Abdominal/pelvic US
	OR (95% CI)	OR (95% CI)
Time elapsed from the previous visit (days)		
<90 (Ref.)	1	1
90-179	1.22 (0.76, 1.96)	2.09 (1.28, 3.42)
180-269	0.91 (0.52, 1.61)	3.62 (2.17, 6.04)
≥270	2.34 (1.15, 4.76)	1.87 (0.92, 3.8)
Same examination performed during the previous visit	0.4 (0.25, 0.65)	0.72 (0.49, 1.04)
Age at first examination (years)		
<60 (Ref.)	1	1
60-70	1.23 (0.78, 1.94)	1.27 (0.88, 1.84)
≥70	1.14 (0.71, 1.84)	1.17 (0.79, 1.74)
Gynecological cancer		
Ovary	1	1
Uterine cervix	1.5 (0.75, 3.03)	0.54 (0.29, 1.03)
Endometrium	0.76 (0.45, 1.27)	1.41 (0.92, 2.16)
Stage of disease		
I (Ref.)	1	1
II	1.72 (0.93, 3.19)	0.94 (0.54, 1.64)
III-IV	2.93 (1.85, 4.66)	0.64 (0.44, 0.95)
Relapse symptoms	1.13 (0.58, 2.21)	0.95 (0.47, 1.94)
Patients followed by center (any 10)	0.96 (0.84, 1.14)	1.04 (0.92, 1.19)
Specialist who monitors the patients		
Gynecologist (Ref.)	1	1
Radiotherapist	1.14 (0.25, 5.26)	0.5 (0.15, 1.74)
Oncologist	1.34 (0.34, 5.31)	1.18 (0.4, 3.43)
Collegial evaluation	0.36 (0.08, 1.61)	0.81 (0.28, 2.38)
Random effects		
Patient level: variance	0.264	0.052
Patient level: $\rho_p$	0.055	0.013
Center level: variance	1.26	0.705
Center-level: $\rho_c$	0.262	0.174

CT, computed tomography; US, ultrasonography; OR, odds ratio; CI, confidence interval; Ref., reference value.

domized controlled trials (n = 2563 women) that compared follow-up programs based on a regular physical exam and yearly mammogram *versus* more intensive schemes including radiological and laboratory tests<sup>17</sup>. No differences were found between these 2 strategies in overall survival (hazard ratio 0.96, 95% confidence interval 0.80 to 1.15), disease-free survival, and quality of life.

Several guidelines for the treatment of gynecological malignancies are available for consultation by physicians and some of these provide recommendations for patient follow-up. For endometrial cancer, the guidelines are generally in agreement, even though randomized controlled trials are lacking. Based on the interpretation of evidence from retrospective studies and expert

**Table 4 - Median costs (in euro) for each examination based on gynecological cancer**

	Ovary		Uterine cervix		Endometrium		Total	
	n	Median cost	n	Median cost	n	Median cost	n	Median cost
Days from last examination								
<90 (Ref.)	119	63.05	23	81.10	75	51.85	217	63.05
90-179	144	95.15	78	43.40	307	65.25	529	65.25
180-269	55	134.15	59	58.80	235	92.30	349	91.85
≥270	21	250.00	17	58.80	60	87.10	98	92.38
Age at first examination (years)								
60 (Ref.)	115	63.05	100	58.80	193	80.30	408	65.25
60-70	118	122.95	46	56.70	221	87.10	385	91.85
≥70	106	87.05	31	43.40	263	67.70	400	67.70
Stage of disease								
I	92	101.10	92	58.80	478	73.70	662	67.70
II	9	51.85	60	58.80	62	51.68	131	51.85
III-IV	238	87.05	25	101.10	137	101.10	400	101.10
Relapse symptoms								
No	305	89.55	166	58.80	648	73.70	1119	70.00
Yes	34	95.33	11	360.00	29	134.15	74	122.95
Specialist who monitors the patients								
Gynecologist (Ref.)	234	64.15	122	55.33	446	90.70	802	73.70
Radiotherapist	-	-	30	311.70	66	51.85	96	80.88
Oncologist	105	122.95	8	44.40	64	47.45	177	81.10
Collegial evaluation	-	-	17	30.00	101	51.85	118	43.40
Number of patients followed by center								
1-13	116	203.00	43	43.40	210	73.70	369	73.70
14-20	41	89.55	48	114.50	162	51.68	251	58.80
21-44	76	51.85	30	43.40	201	96.50	307	65.25
45-65	106	102.03	56	58.80	104	113.40	266	90.70
Total	339	89.55	177	58.80	677	76.10	1193	73.70

Ref., reference value.

consensus opinion (grade of recommendation C-D<sup>16</sup>), it is recommended that all patients receive counseling about the potential symptoms of recurrence of endometrial cancer because the majority of recurrences were symptomatic. The Ontario Cancer Care guidelines<sup>18</sup> assert that the most appropriate follow-up strategy is one based upon the risk of recurrence and an individual patient's preferences for more or less follow-up are taken into account. A general examination, including a complete history and a pelvic-rectal examination, is suggested from 3 months to annually (based on the risk of recurrence) for the first 3 years, and semi-annually to annually for the next 2 years. In general, it is recommended that all patients undergo a targeted in-

**Table 5 - Association between examination, patient and center characteristics and cost for each examination**

	Exp( $\beta$ )* (95% CI)
Time elapsed from the previous visit (days)	
<90 (Ref.)	1
90-179	1.02 (0.88, 1.18)
180-269	1.01 (0.86, 1.19)
$\geq 270$	1.23 (0.98, 1.54)
Age at first examination (years)	
<60 (Ref.)	1
60-69	0.93 (0.79, 1.09)
$\geq 70$	0.86 (0.73, 1.02)
Gynecological cancer	
Ovary (Ref.)	1
Uterine cervix	0.8 (0.62, 1.02)
Endometrium	0.72 (0.59, 0.87)
Stage of disease	
I (Ref.)	1
II	1.15 (0.93, 1.42)
III-IV	1.42 (1.2, 1.67)
Relapse symptoms	1.25 (0.96, 1.63)
Patients followed by center (any 10)	0.96 (0.85, 1.08)
Specialist who monitors the patients	
Gynecologist (Ref.)	1
Radiotherapist	1.41 (0.86, 2.31)
Oncologist	1.03 (0.66, 1.6)
Collegial evaluation	0.67 (0.43, 1.05)
Random effects	
Patient level: variance	0.140
Patient level: $\rho_p$	0.167
Center level: variance	0.124
Center level: $\rho_c$	0.148

\*Effects were shown using the exponential of coefficients derived from the model, which represent the relative change in cost associated with the predictor variable. Ref., reference value.

investigation to rule out recurrence if symptoms do occur. Some guidelines agree that there is insufficient evidence to prescribe the routine use of Pap smear, chest x-ray, abdominal US, CT scan or CA 125 testing to detect asymptomatic recurrences<sup>18</sup>.

With regard to ovarian cancer, the European Society of Medical Oncology (ESMO), in agreement with several other available guidelines, suggests to follow up ovarian cancer patients with physical examinations including pelvic examination every 3 months for 2 years, every 4 months during the third year, and every 6 months during year 4 and 5 or until progression is documented. These guidelines state that CA 125 can accurately predict tumor relapse (IA evidence) and should be measured at each follow-up visit. In addition, the guidelines suggest that CT scans be performed only if there is clinical or CA 125 evidence for progressive disease<sup>19</sup>.

Finally, in terms of cervical cancer, the Scottish Intercollegiate Guidelines Network (SIGN) affirms that evidence for the effectiveness of post-treatment surveillance is inconsistent. History taking and clinical examination should be carried out during follow-up examina-

tions to detect symptomatic and asymptomatic recurrence. According to these guidelines, cervical cytology or vault smear are not able to detect asymptomatic relapse of the disease (grade of recommendation D). As a result, magnetic resonance imaging (MRI) and CT scans should be considered to assess potential clinical recurrence in symptomatic patients (grade of recommendation C) and a positron emission tomography (PET) CT scan is suggested if pelvic exenteration or radiotherapy are being considered as salvage treatment (grade of recommendation B)<sup>20</sup>.

The feeling within the medical practice (not supported by studies) is that there is no uniformity of behavior between different centers in following patients suffering from gynecological malignancies during the follow-up period. In fact, the existing guidelines, including the ones mentioned above, are oriented towards a minimalist follow-up strategy, which, however, does not seem to convince clinicians that several monitoring tests are often unnecessary.

The sample studied, including patients attending a large proportion of centers of the Piedmont Oncology Network, is sufficiently representative of the current practice<sup>21</sup>. The proportions of patients with recurrent disease, and of symptomatic patients at the time of recurrence, are in agreement with retrospective published data<sup>22,23</sup>.

As expected, patients with advanced-stage disease were followed more intensively by prescription of more CT scans (cervix and endometrium) and the increasing time elapsed from the previous visit induced clinicians to prescribe imaging tests (CT and/or US) in addition to a clinical visit (ovarian cancer).

Interestingly, our results suggest a reduced likelihood for patients to undergo CT or US and a lower cost of follow-up for patients managed by multidisciplinary teams in comparison with those followed up by single specialists (gynecologists, radiotherapists or oncologists). Patients were followed, on average, every 4 months for the first year, and those who were followed less frequently tended to be followed by more instrumental examinations.

For endometrial and ovarian cancer, 33% and 34%, respectively, of the variability in the prescription of CT scans is attributable to different habits at the centers regardless of the determinants considered. This was not true for cervical cancer, where the variability was minimal. Taking into consideration all the diseases, this unexplained variability is in the order of 26% for CT scan and 17% for US prescriptions.

Cost analysis indicated that cancers at an advanced stage and ovarian cancers are the ones at higher costs. Furthermore, it confirmed an unexplained variability of 15% that was attributable to policies not shared among the different centers. This observed difference is not explained by the series of determinants considered and we suppose it is due to the lack of good evidence from the literature, and to the weak recommendations of existing guidelines.

To obtain evidence of the cost-efficacy and the impact on quality of life and patient satisfaction of different follow-up programs, in terms of exams prescribed and timing of visits (based on the cancer recurrence risk), we planned a multicenter randomized controlled trial within the Piedmont Oncology Network for endometrial cancer patients (ClinicalTrials.gov identifier: NCT00916708). Currently, this study has been extended to a national level and is recruiting patients<sup>24</sup>.

## Conclusions

The current study identifies the existence of a non-negligible variability in the prescription of examinations and costs of follow-up strategies for gynecological malignancies, regardless of important clinical predictors. This variability, not supported by scientific evidence, is largely attributable to differences among cancer centers in preference and attitudes between minimal or more intensive schemes of follow-up. In particular, 2 diagnostic tests (CT scan and US) are prescribed with great variability between centers for examination of endometrial and ovarian carcinomas. The management of patients by multidisciplinary teams tends to reduce the request for tests and the cost of follow-up.

In the light of these results, it has been considered a high priority to carry out a randomized controlled trial to compare different and well-defined programs of follow-up on the basis of clinical outcomes, such as overall survival, disease-free survival, quality of life and patient satisfaction.

## References

- Brown ML, Riley GE, Schussler N, Etzioni R: Estimating health care costs related to cancer treatment from SEER-Medicare data. *Med Care*, 40 (8 Suppl): IV-104-117, 2002.
- Grogan M, Rangan A, GebSKI V, Boyages J: The value of follow-up of patients with early breast cancer treated with conservative surgery and radiation therapy. *Breast*, 11: 163-169, 2002.
- Zola P, FusO L, Mazzola S, Gadducci A, Landoni F, Maggino T, Sartori E: Follow-up strategies in gynecological oncology: searching appropriateness. *Int J Gynecol Cancer*, 17: 1186-1193, 2007.
- Muir JA, Gray J: Evidence-based health care: how to make health policy and management decisions. Churchill Livingstone, London, 1999.
- Richert-Boe KE: Heterogeneity of cancer surveillance practices among medical oncologists in Washington and Oregon. *Cancer*, 75: 2605-2612, 1995.
- Loomer L, Brockschmidt JK, Muss HB, Saylor G: Postoperative follow-up of patients with early breast cancer. Patterns of care among clinical oncologists and a review of the literature. *Cancer*, 67: 55-60, 1991.
- Vernava A, Longo W, Virgo K, Coplin MA, Wade TP, Johnson FE: Current follow-up strategies after resection of colon cancer. Results of a survey of members of the American Society of Colon and Rectal Surgeons. *Dis Colon Rectum*, 37: 573-582, 1994.
- Foster MF, Hill J, Leaper DJ: Follow up after colorectal cancer: recurrent practice in Wales and southwest England. *Int J Colorectal Dis*, 2: 118-119, 1987.
- Morice P, Deyrolle C, Rey A, Atallah D, Pautier P, Camatte S, Thoury A, Lhomme C, Haie-Meder C, Castaigne D: Value of routine follow-up procedures for patients with stage I/II cervical cancer treated with combined surgery-radiation therapy. *Ann Oncol*, 15: 218-223, 2004.
- Bodurka-Bevers D, Morris M, Eifel PJ, Levenback C, Bevers MW, Lucas KR, Wharton JT: Posttherapy surveillance of women with cervical cancer: an outcomes analysis. *Gynecol Oncol*, 78: 187-193, 2000.
- Agboola OO, Grunfeld E, Coyle D, Perry GA: Costs and benefits of routine follow-up after curative treatment for endometrial cancer. *CMAJ*, 157: 879-886, 1997.
- Morice P, Levy-Piedbois C, Ajaj S, Pautier P, Haie-Meder C, Lhomme C, Duvillard P, Castaigne D: Value of cost evaluation of routine follow-up for patients with clinical stage I/II endometrial cancer. *Eur J Cancer*, 37: 985-990, 2001.
- Tjalma WA, van Dam PA, Makar AP, Cruickshank DJ: The clinical value and the cost-effectiveness of follow-up in endometrial cancer patients [review]. *Int J Gynecol Cancer*, 14: 931-937, 2004.
- Bristow RE, Purinton SC, Santillan A, Diaz-Montes TP, Gardner GJ, Giuntoli RL 2nd: Cost-effectiveness of routine vaginal cytology for endometrial cancer surveillance. *Gynecol Oncol*, 103: 709-713, 2006.
- Snijders T, Bosker R: Multilevel analysis. An introduction to basic and advanced multilevel modelling. Sage Publications, London, UK, 1999.
- Oxford Centre for Evidence-Based Medicine - Levels of evidence (March 2009). Available at <http://www.cebm.net/index.aspx?o=1025>
- Rojas MP, Telaro E, Moschetti I, Coe L, Fossati R, Liberati A, Rosselli Del Turco M: Follow-up strategies for women treated for early breast cancer. *Cochrane Database of Systematic Reviews*, 4: CD001768, 2000.
- Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T, Gynecology Cancer Disease Site Group: Follow-up after primary therapy for endometrial cancer. Toronto (ON): Cancer Care Ontario (CCO), Evidence-based series, 4-9, 2006.
- Epithelial ovarian carcinoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol*, 18 (Suppl 2): ii12-ii14, 2007.
- Scottish Intercollegiate Guidelines Network: Management of cervical cancer. Guideline n 99, January 2008. Available at <http://www.sign.ac.uk/pdf/sign99.pdf>
- Centro di Riferimento per l'Epidemiologia e la Prevenzione Oncologica in Piemonte, Dati oncologici. Available at <http://www.cpo.it/dationcologici/>
- Zola P, FusO L, Mazzola S, Piovano E, Perotto S, Gadducci A, Galletto L, Landoni F, Maggino T, Raspagliesi F, Sartori E, Scambia G: Could follow-up different modalities play a role in asymptomatic cervical cancer relapses diagnosis? An Italian multicenter retrospective analysis. *Gynecol Oncol*, 107 (Suppl 1): S150-154, 2007.
- Gadducci A, FusO L, Cosio S, Landoni F, Maggino T, Perotto S, Sartori E, Testa A, Galletto L, Zola P: Are surveillance procedures of clinical benefit for patients treated for ovarian cancer? A retrospective Italian multicentric study. *Int J Gynecol Cancer*, 19: 367-374, 2009.
- Studio TOTEM. Appropriateness evaluation of followup procedures in Gynaecology Oncology. A multicentric randomized controlled clinical trial between two followup regimens with different tests intensity in endometrial cancer treated patients. Available at <http://www.epiclin.cpo.it/totem>