Study protocol – TOTEM Study

- One amendment approved by the ethics committee on 14th Sept 2010:
In January 2010 the FIGO classification was changed. Patients who underwent surgery prior to 2009, classified as IAG3 according to previous FIGO classification, were shifted to high-risk group after this update and their follow-up program was updated consequently.

- Study protocol Vers. October 2010
Appropriateness evaluation of follow up procedures in Gynaecology Oncology
TOTEM Study: Multicentric randomized controlled clinical trial between two follow up regimens with different tests intensity in endometrial cancer treated patients

WRITING COMMITEE:
Giovanni Apolone – Istituto Mario Negri, Milano
Giovannino Ciccone – CPO Piemonte, Torino
Libero Ciuffreda – Ospedale S.Giovanni Battista –Le Molinette, Torino
Angiolo Gadducci – Azienda Ospedaliero Universitaria Pisana, Pisa
Luciano Galletto – ASL CN 1, Savigliano-Mondovì
Fabio Landoni – Istituto Europeo di Oncologia, Milano
Tiziano Maggino – Ospedale "Umberto I", Venezia-Mestre
Paola Mosconi – Istituto Mario Negri, Milano
Franca Ozzello – Ospedale Civile, Ivrea
Enrico Sartori – Spedali Civili, Brescia
Carlo Senore – CPO Piemonte, Torino
Alessandro Urgesi - Città della Salute e della Scienza di Torino, PO Sant'Anna, Torino
Paolo Zola – SSVD di Ginecologia Oncologica, Città della Salute e della Scienza di Torino, PO Sant'Anna, Torino (Principal Investigator)
SCIENTIFIC COMMITEE:
Annamaria Ferrero - Ospedale Mauriziano Umberto I, Torino
Simona Mazzola - Ospedale Mauriziano Umberto I, Torino
STUDY COORDINATORS:
Manuela Ceccarelli - CPO Piemonte,Torino
Roldano Fossati– Istituto Mario Negri, Milano
Luca Fuso - Ospedale Mauriziano Umberto I, Torino
Stefania Perotto - Ospedale Mauriziano Umberto I, Torino
Elisa Piovano - Città della Salute e della Scienza di Torino, PO Sant'Anna, Torino
Fabio Saccona – CPO Piemonte,Torino
Annalisa Rossi - Ospedale Mauriziano Umberto I, Torino
INDEPENDEND DATA MONITORING:
Istituto Mario Negri, Milano
COORDINATING CENTRE:
Ospedale Mauriziano Umberto I, Largo Filippo Turati, 62, 10128 Torino
Tel: 011/5082688
e-mail: paolo.zola@unito.it

INDEX

BACKGROUND

The term “follow-up”, in Oncology, refers to a group of pre-scheduled medical tests and procedures set to identify all disease relapses at a pre-clinical stage. This concept of long-term monitoring assumes that an early diagnosis may reduce patient’s morbidity and mortality.
The proper definition and realization of a programme of follow-up has to balance among the needs of clinicians, patients and Health Care System. The systematic controls schedule for the clinician has the aim to evaluate overall survival, disease control and performance status of the patient, to manage treatment complications and to detect early relapses.
At the same time the interest of the physician is focused on finding optimal time interval between controls, more effective diagnostic tests and most suitable programme of follow-up for each patient1-3. The patient wants to receive reassurances about her health status and about therapy which has been chosen, however an early diagnosis of disease recurrence3 remains a main issue.
The Health System Administrators are interested in assessing the effectiveness of diagnostic and therapeutic procedures, monitoring complications due to treatment and quality of services, limiting costs during a period of growing health care expenses linked to Oncology.
Nowadays in Gynaecologic Oncology the issue of follow up shows as a problem of Public Health because a gap between the “Observed” and the “Expected” exists: the “expected” identifies standardized policies of follow up which has to be reproducible, appropriate and based on scientifical evidence. The “observed” finds a considerable difference among the policies of surveillance adopted by different Institutions for patients treated for gynaecological cancers and a lack of scientifical information that could reduce the existing variability.
This uncertainty has been detected both internationally4 and in Italy through a retrospective multicentric study5. At present the data collected during the preliminary phase of current study by “Oncologic Piedmont and Valle d'Aosta net” are available too.

BACKGROUND: FOLLOW UP AND ENDOMETRIAL CARCINOMA

Worldwide endometrial cancer is the seventh most frequent malignant tumour and the most common cancer for women after breast cancer. The incidence varies according to geographic areas increasing by age group from 2 / 100000 in women younger than 40 years to 40-50/100000 after the sixth decade6. In Western Europe the endometrial cancer incidence is 24.7 / 100000 women and it is estimated that worldwide about 42000 women die from endometrial cancer each year7.
The age-incidence curve for endometrial cancer shows that in most cases the diagnosis occurs after menopause. The early appearance of symptoms explains why the majority of women who develop endometrial cancer have an early stage disease at diagnosis. For all stages taken together the overall 5-years survival rate is around 80%. About 80% of lesions may be classified

as endometrioid type (hormone-sensitive and low grade) and have a favourable prognosis; whereas different hystological lesions, such as special histotypes type 2, have a worse prognosis because of the higher tendency to recur and the higher rate of distant metastases even in early stages8.

Abnormal uterine bleeding is the most frequent symptom of endometrial cancer and in menopausal women the probability of a endometrial cancer diagnosis in association to bleeding is 5 up to 10%, although the percentage increases with age and risk factors (unopposed oestrogens, metabolic syndrome, nulliparity..)9-13

Until now there has been no screening program available concerning endometrial cancer because minimally invasive modalities (trans-vaginal ultrasound and cervical cytology) demonstrated to have limited accuracy in an asymptomatic general population. Usually the histological diagnosis of endometrial cancer is possible throughendometrial biopsies.

The cornerstone of endometrial cancer treatment is surgery (total hysterectomy including uterine cervix, bilateral salpingo-oophorectomy and peritoneal fluid cytologic assessment; in selected cases there is a place for omentectomy and retroperitoneal lymph-node dissection). Radiotherapy and chemotherapy are widely used in selected stages of the disease, alone or in combination. The choice of treatment is led by the aim to treat pelvic lymph-node regions that might contain microscopic disease as well as the central pelvic region including the upper vagina8.

In advanced-stage disease some studies which included both endometrioid and not endometrioid carcinomas showed that cisplatin and doxorubicin may be active agents14-16. Many other clinical trials investigating endometrial cancer treatment are still open.

A literature analysis conducted using Medline, Embase and Cochrane Library (EBM based) databases has shown that there is a critical lack of randomized perspective trials about follow up strategies for patients treated for gynaecological diseases (with the exception of breast). Concerning endometrial cancer follow-up we have found a Canadian systematical review conducted by Fung-kee-Fung et al. at Ontario University and by the Ottawa Regional Cancer Centre that included in its analysis 16 retrospective studies 17-32 and two systematics reviews33-34. Recently a retrospective study about the issue conducted has been published by Sartori et al 35.

From these studies it emerges that 13% of patients treated for endometrial cancer presents a recurrence diagnosed within the third year of follow-up in 68-100% of cases. The percentage of metastatic relapses is 61% in the systematic reviews and 55% in Sartori et al's article. In the systematic review 41-100% of recurrences are symptomatic, while in the Sartori et al.'s study the rate is about 52%.

An Italian retrospective multicentric study has been conducted in 2006, eight Italian Institutions considered as referral Centres for oncological gynaecology have been involved. Place and timing of recurrence have been investigated, but we focused our attention mostly on the description of follow-up policies adopted in Italy for patients with gynecological malignancies.

The data analyzed in the systematic review indicate that in one study22 there is a significant survival benefit for asymptomatic patients at the time of diagnosis of relapse compared with symptomatic patients; five studies18-20-21-26-33 do not show differences in survival rate between the two groups of patients while the remaining studies do not report data. The Italian multicentric study showed a median of survival in asymptomatic patients of 92.3 months and in symptomatic patients of 40.3 months (Log Rank p = 0.0003). These data are as well

confirmed by the study published by Sartori et al.35 Gadducci et al.20 demonstrated that survival rate after relapse does not appear linked to the stage, nor to the grade or the depth of invasion of miometrium. Survival rate is higher in patients whose recurrence was diagnosed after 17.5 months compared to those diagnosed earlier. Podczasky et al.27 collected patients with early relapse after primary treatment and reported how they had a prognosis worse than other patients. Berchuck et al 19 indicate as negative prognostic factor the grading and show that the survival rate increases for isolated vaginal recurrences than for any other site. For what concerns the timing of controls there is a major agreement among existing literature data and data collected in the Italian multicentric study or in the "Rete Oncologica" study: a clinical visit every 3-4 months for the first two years of follow-up, every 6 months until the fifth year starting from diagnosis and once a year later on.
The follow-up scheduling results from the steady fact that recurrences of endometrial cancer usually occur within the third year after primary treatment. The procedures adopted in different follow up policies, especially the frequency of their applications, remain strongly variable and comprise two main types of regimens : the first could be defined as "minimalist" (clinical examination associated with rare medical tests)18,22-24 and the second as "intensive" (clinical examination, imaging and markers)17-19-20. Nowadays there are no available data supported by an adequate level of evidence that a "intensive" programme of follow-up has a better impact on survival rate compared to a "minimalist" programme.

OBJECTIVES

General Objective

• Compare the effect of the two follow-up regimens on 5-years overall survival.

Secondary Objectives

• Quantify the intensive program possibility to advance the diagnosis comparing to minimalist program

• Evaluate the difference in terms of complications, recurrences of disease, second primary tumors and maybe other diseases

• Assessing the accuracy of the two schemes of follow-up as the ability to diagnose the relapse of disease in asymptomatic patients

• Describe the compliance to different follow-up programs

• Formally evaluate quality of life and patients satisfaction about the two strategies of follow-up

• Formally evaluate the cost-effectiveness and the cost-utility of the two regimens.

STUDY DESIGN

The study provides ,a univocal identifying number for each patient at randomization time. If elegibility criteria are satisfied and the written informed consensus is obtained, patients are stratified in the centre according to their risk level:

- Group 1 : patients at low risk of recurrence [stage IA G1 and stage IA G2];
- Group 2: patients at high-risk of recurrence [≥ stage IA G3].

NB: use new 2010 FIGO classification for endometrial cancer!!

Patients will be randomized in two regimens of follow up:

1. MINIMALIST (ARM 1)
2. INTENSIVE (ARM 2).

The procedure for centralized randomization, with blocks of variable length, will take place within each layer with 1:1 ratio and will be implemented within the centralized database, with sequences generated by dedicated software. The recruitment and randomization has to be registered on the website (www.epiclin.cpo.it) no later than 20 days after histological examination has been received. If patients do not need any kind of adjuvant therapy they will start follow-up program according to the regimen chosen for them at randomization, if adjuvant therapy is needed the patient at first will be registered and the randomization will be deferred at the end of treatment.
In presence of symptoms or signs detected during the clinical visit which may suppose a recurrence or in presence of abnormal tests, the clinician has to prescribe all medical tests and examinations required. The tests carried out in addition to follow-up scheduled program must be reported in the database. Nevertheless patients continue to be followed for the assessment of the performance status at 5 years, but the follow-up schedule is up to the clinician. An interim analysis is scheduled in 3.5 years starting from the beginning of recruitment (based on approximately 1 / 3 of the total expected events, when about 4 / 5 cases have already been enrolled). Patients will be stratified by recruitment Center, by level of risk (calculated according to the stage of the disease, the istotype and the grading) and by type of treatment performed.

CRITERIA of ELEGIBILITY

Inclusion criteria

- patients treated surgically for endometrial cancer, if in complete clinical remission confirmed by imaging stage FIGO I-IV
- not previous or concurrent neoplasia (with the exception of carcinoma in situ of the cervix and basalioma of the skin)
- other contemporaneous RCT may be allowed if there is not any restriction concerning follow up
- obtaining a written informed consensus before randomization
- age > 18 years

Minimal recruitment criteria

- chest x-ray
- complete abdomen CT executed within 20 days after the end of primary treatment (you can use the preoperative CT in case no locations of extrauterine disease are described. CT and MRI can be considered equivalent to randomization)
- histology report confirming the presence of endometrial malignancy without distinction of histotype.

Exclusion criteria

- presence of any psychological, familial, sociological or geographical condition that could potentially limit the compliance to the protocol and the follow-up planned: all these situations must be discussed with the patient before the randomization
- previous, concurrent or second malignancies
endometrial carcinoma in the context of a hereditary syndrome
- conditions which contraindicate medical tests scheduled according to follow-up regimen

DEFINITION OF FOLLOW-UP PROGRAMS

- The choice of medical examination scheduling is mainly based on indications suggested by experts and scientific associations with interest and experience in the field, but at the same time particular attention has been paid to the practicability of the choice in most hospitals.

- The timetable for the controls refers to the planned date of clinical visit. The patient should perform programmed diagnosis tests a few days before the appointment in order to allow their evaluation by the clinician during the follow up visit.

- The CA-125 marker dosage should be performed, as long as possible, at the same laboratory for the entire duration of the study.

- The patients who are allergic to the contrast medium used for CT can perform MRI instead.

- If CA-125 level is higher than normal, it is recommended to perform it again within 30 days in order to confirm the modification before prescribing further diagnostic investigations.

- Nowadays surgical treatments, adjuvant therapy and therapy of the relapses are not strictly standardized, so it is recommended to act following qualified guidelines. The treatments must be reported and described in protocol forms.

LOW RISK
(IA G1; IA G2)

Arm 1: minimalist follow up

- During first five years of follow-up since the end of primary treatment:
clinical visit* every 6 months.

Arm 2: intensive follow-up

- During first two years of follow-up since the end of primary treatment:
clinical visit* every 4 months;
Pap tests; chest, abdomen, pelvis CT every 12 months

- Since the third to the fifth year of surveillance:
clinical visit* every 6 months;
Pap test every 12 months.

Minimalist (ARM1) low risk

	Months since randomization														
PROCEDURES	0	4	6	8	12	16	18	20	24	30	36	42	48	54	60
Visit*	X		X		X		X		X	X	X	X	X	X	X
QoL Questionnaire **	X		X		X				X		X		X		X

Intensive (ARM 2) low risk

	Months since randomization														
PROCEDURES	0	4	6	8	12	16	18	20	24	30	36	42	48	54	60
Visit*	X	X		X	X	X		X	X	X	X	X	X	X	X
Pap Smear					X				X		X		X		X
CT chest, abdomen, pelvis					X				X						
QoL Questionnaire **	X	X			X				X		X		X		X

* Visit: clinical visit with gynecological visit
** Go to ENCLOSURE C: Protocol detailed Relational Studies Group (QoL)

HIGH RISK
(≥ IA G3)

Arm 1: minimalist follow up

- During first five years of follow-up since the end of primary treatment:
clinical visit* every 4 months;
chest, abdomen, pelvis CT every 12 months

- Since the third to the fifth year of surveillance:
clinical visit* every 6 months;

Arm 2: intensive follow-up

- During first three years of follow-up since the end of primary treatment:
clinical visit*, Ca125, trans-vaginal and abdominal ultrasound every 4 months (except in conjunction with TC)
Pap smear, abdomen, pelvis CT every 12 months

- In the fourth and fifth years of follow-up:
clinical visit*, Ca125, trans-vaginal and abdominal ultrasound every 6 months (except in conjunction with TC)
Pap smear; chest, abdomen, pelvis CT every 12 months

Minimalist (ARM 1) high risk

	Mesi dalla randomizzazione														
PROCEDURES	0	4	6	8	12	16	18	20	24	30	36	42	48	54	60
Visit*	X	X		X	X	X		X	X	X	X	X	X	X	X
CT chest, abdomen, pelvis					X				X						
QoL Questionnaire **	X	X			X				X		X		X		X

Intensive (ARM 2) high risk

	Mesi dalla randomizzazione														
PROCEDURES	0	4	6	8	12	16	20	24	28	32	36	42	48	54	60
Visit*	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Ca125		X		X	X	X	X	X	X	X	X	X	X	X	X
Abdomen & TV US		X		X		X	X		X	X		X		X	
Pap Smear					X			X			X		X		X
CT chest, abdomen, pelvis					X			X			X		X		X
QoL Questionnaire **	X	X			X			X			X		X		X

* Visit: clinical visit with gynecological visit
** Go to ENCLOSURE C: Protocol detailed Relational Studies Group (QoL)

STATISTICAL METHODS

Primary Endpoints
- Overall survival (OS): the percentage of patients in the study who are alive for the period of time from surgery to the death of the patient or the conclusion of the study.

Secondary endpoints

- Progression-free survival (PFS): the percentage of individuals in the study whose disease is likely to remain stable (and not show signs of progression) in the interval of time between the date of recruitment and the relapse or death for any reason.
- Proportion of complications, second cancers, co-morbidity.
- Proportion of asymptomatic patients with diagnosis of relapse.
- Proportion of subjects who complete the two different regimes follow up.

The proportion of patients with low risk of relapse is estimated to be 0.65, with a 5-year survival of 0.85. High risk patients show a 5-years survival rate of 0.65 (media pesata of 5 years survival: 0.78). The study has been planned in order to see if one of the two follow-up regimens may increase 5 years overall survival from 0.75 to 0.80, with a beta = 0.20 and an alpha error (two tails) of 0.05. A total number of approximately 2180 patients should be included in the final analysis considering a life expectancy for the recruitment of 48 months and a minimum follow-up of 36 months; an interim analysis will be conduced when about 30-35% of expected events have been reported (with a threshold value of "p" of logrank test of 0.0006, calculated with the design of O'Brien and Fleming). However assuming a rate of drop-out about 5%, it is estimated that it will be necessary to enrol in the study about 2300 patients (1150 in each arm).

Planned Analysis
The analysis of collected data will be carried out at the end of the study with a minimum follow up of three years. It is planned an interim analysis for any interruption provided by superiority when about 33% of total events will be reached (probably after 3 and 5 years since recruitment, when about 4 / 5 cases will have been enrolled already). The analysis will be made in accordance with the principle of the intention to treat.
The basic and demographic characteristics will be summarized in descriptive statistics for what concerns continue variables using tables, frequency will be used for discrete variables.
The time-dependent analysis will be performed using the method of Kaplan-Meier and differences between the groups will be evaluated with the log rank test. Live patients who show no event will be considered as "censored" on the date of the follow-up.
In order to correct any disproportion between the two groups comparisons using the Cox model will be performed, that choice will allow adjustments for prognostic factors which may be distributed in uneven manner and will consider possible differences between the centres.
If a low compliance to the study will be noticed as well as a contamination between the two groups, analyses will be carried on according to the protocol effectively enforced (analysis for protocol) too.

SCIENTIFIC COORDINATION

The organization of the study is based on a Scientific Committee (SC), a Coordination Center (CC) and an Independent Committee for Monitoring Data (CMD).
The Scientific Committee is constituted by gynaecologist surgeons, medical oncologists and radiotherapist representing the Promoter Committee of enrolling and participants centres. The

SC has decision-making functions and gives directives regarding the duration of the study, amendments to the Protocol and the results publication.
The Coordination Center is constituted by project managers, a biostatistician, a gynaecologist oncologist, a medical oncologist, a radiotherapist, a trial coordinator, a data manager and secretarial staff. The CC main tasks are randomization, protocol forms submission and on-line data base reporting quality control, periodic reports writing and data analysis. One more specific function of the CC is to help clinicians to solve medical-laboratory problems which may occur after randomization obtaining, if necessary, the advice of SC members. Finally the CC will write drafts of the publications which will be approved by SC.
Each participating Centre will nominate a person to monitor study progresses in his own centre and to answer questions coming from CC about quality and completeness of reported data.
The Independent Monitoring Committee Data is made up of members external to the study in order to verify all study progresses evaluating data collected by the CC. The CMD may decide, if there are consistent data, to suggest to modify or stop the study to the CS, which takes all final decisions. The CMD can ask for external data analysis for the planned interim analysis. If the results of these analysis did not require amendments to the Protocol, these will not be communicated in detail to the leaders of the clinical study.

PUBLICATIONS

The data belong to the study SC. The results will be published on behalf of the SC, the clinicians responsible for the participants Centres will be listed among the authors if they enrolled at least 10 cases per year with regular sending of all the requested data. An annual evaluation of the quality and appropriateness of the collected data is provided in order to certify the validity of each case.

COSTS CONSIDERATIONS

The proposed study is completely independent. The study is coordinated by the CC along with CPO Piemonte and monitored by the Laboratory for Clinical Oncology Research Institute of Pharmacological Research “Mario Negri”. The aim of the study is to assess the effectiveness of diagnostic programs in daily medical practice. Investigation proposals do not diverge significantly from those normally carried out in patients with endometrial cancer but, regarding minimalist regimen, should lead to a reduction in costs. The forms of the study will be provided by the Centre for Coordination.

ETHICAL ISSUES

Before enrolling patients into the study, clinicians should send the approval of the local Ethics Committee study protocol to the CC.
The consensus by the patient must be obtained after exhaustive explanation of all different options of the follow-up program and details concerning the study aims and structure. The right of the patient to refuse to participate in the study must always be respected. The clinician must feel free at any time to provide an alternative to what is scheduled in the Protocol if necessary for clinical issues, even if the patient has been enrolled in the trial. At the same time the patient must be free to leave the study at any time, without any influence on her future medical care.

QUALITY OF LIFE

The follow-up trial in endometrial cancer patients includes a formal assessment about the potential identification of different emotional impact on patients by different follow-up regimes, both in terms of quality of life and emotional behaviours.
Nowadays anxiety disorders are very common in patients with chronic diseases (such as diabetes mellitus, rheumatic diseases, cancer) and the prevalence of anxiety disorders in patients with cancer varies according to different studies by 0, 9% to 49% (with a range reduced to 10-30% in studies where standardized psychiatric criteria had been chosen); the problem of anxiety is not limited to the period of diagnosis or treatments, but more often occurs for long periods of time after primary treatment.
Patients need to liaise with clinicians even after primary treatment in order to control anxiety, if they maintain a link they instinctively feel much more protected against the disease and the fear of a relapse. The follow-up appointments have a double function: the first aim is to detect early relapses, the second is to maintain a relationship with patients during years in order to become a benchmark for all their health problems linked to the primary disease.
Often the periodic follow-up visit schedules many medical tests which signify many accesses to hospitals (maybe different from the one where therapies have been performed and follow-up visits are planned), much stress and time to perform all the examinations required. Setting out from the assumption that a patient feels more secure if many medical test have to be performed, while at the same time for others it means being stressed, the comparison between the two follow-up regimens has to be done assessing their impact in terms of anxiety using an objective and standardized tool. We can do it using specific questionnaires which will be distributed to patients during their periodic appointments.

The purposes of this section of the study are:
Assess the impact of the two different follow-up arms on patients wellbeing
Assess the impact of the two different follow-up arms on the emotional sphere of patients (anxiety, stress etc.).
What is the satisfaction reported by the patient in different follow-up arms

The questionnaires will be submitted at randomization time, during the first visit and after 12 months, after all the submission will continue with an annual administration of the questionnaire.

See Enclosure C.

INFORMATIVE BROCHURES

Enclosed to the main protocol of the study it is available an informative booklet for patients which has to be distributed to the patient at randomization time. The brochure (enclosure A), which is tailored on different arms of each risk level, talks about general information regarding the study and information on the particular regimen to which the patient has been assigned (type and timing of visits, examinations and questionnaires she has to fill).

Enclosed with the main protocol there is an informative letter which may be delivered to the General Practitioner in order to inform him/her about the protocol in general and his/her patient health situation (regimen assignment) as well (Enclosure B).

ECONOMIC ASSESSMENT PROJECT

The economic assessment is designed to compare the cost-effectiveness and cost-utility of the two post-operative follow-up programs. However, the main objective is to estimate the incremental ratio of cost-effectiveness of a protocol over the other. The study provides a cost evaluation starting from a "social" point of view or including all costs directly determined by programmes follow-up: i) costs rewarded by health care system for care given ii) the sanitary (visits, diagnostics, etc.) and not sanitary (transport costs etc.) costs directly sustained by the patient iii) the costs of non-productivity (working hours lost) of the patient and / or any accompanying person.

These assessments will be conducted during regular follow-up visits in disease free patients, in patients with a relapse and with progression disease. Differences in costs could also occur in a phase which is former the time of relapse diagnosis, if that event will be temporally different in the two follow-up regimens.
The methodology for collecting data needs the integration of different sources: the clinician responsible for the follow-up, the patient and, where possible, the archives of health data. The data about compliance to the planned follow-up will provide the main elements for the assessment of costs during the regular follow-up. The data of agreement to the Protocol will be integrated with information collected through specific questions addressed to patients. In particular, there are some questions available to assess the amount of time spent on visits and examinations scheduled by follow-up programs, the possible presence of accompanying people and costs added by the possible consultations of other doctors or other tests not

scheduled by the Protocol of the study which, especially in minimalist scheme, the patient may have asked to other clinicians.

If there is a relapse, the identification of the main assistance episodes will be done through a questionnaire addressed to patients and managed by the clinician, who considers just major healthcare resources (hospitalizations, chemotherapy treatments, radiotherapy, etc.). For what concerns Piedmont Region (and other places where this is possible as well) all information will be validated and supplemented through the use of individual linkage with the administrative records of current data. The collection of economic information will be done at the same time as the planned administration of questionnaires about quality of life. Regarding the evaluation of incremental ratio cost-effectiveness the outcomes which will be analysed (with a reference time horizon of five years) are: the diagnosis of a relapse, deaths, QALYs.
In order to estimate the QALYs we use the questionnaire EuroQoL EQ-5D 36, which is available in an official Italian translation and has a set of weights utility validated in all Europe. Alternatively we can use the questionnaire SF-6D, derived from SF-12: recently algorithms for estimating individual preferences are available 37. Eventually any cost-effectiveness evaluation at long-term will require the projection of the outcome over the lifetime of patients, through the elaboration of specific prediction models.

ENCLOSURES

- Enclosure A: Patient Brochure
- Enclosure B: GP Brochure
- Enclosure C: QoL Protocol
- Enclosure D: Informed consent
- Enclosure E: QoL Questionnaire

BIBLIOGRAPHY

[1] Morice P Value of routine follow up procedures for patients with stage I/II cervical cancer treated with combined surgery-radiation therapy. Annals of Oncology 2004;15:218-223.
[2] Von Georgy R, Schubert K, Grant P, Munstedt K. Post therapy survellance and after-care in ovarian cancer. Eur J Obstet Gynecol Reprod Biol 2004;114:228-33.
[3] David Sackett. Evidence-based medicine: what it is and what it isn't BMJ 1996;312:371-2.
[4] International survey on follow up. G.Favalli, dati non pubblicati, 2000
[5] 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 2007;107,Supplement:S150-S154.
[6] Podratz KC,Mariani A Webb MJ.Staging and therapeutic value of lymphadenectomy in endometrial cancer.Gynecol Oncol 1998;70(2):163-4.

[7] Smith RA,Cokkinides V,Eyre HJ.American Cancer Society guidelines for the early detection of cancer,2003.CA Cancer J Clin 2003; 53:27-43.
[8] Amant F, Moerman P,Neven P,Timmermann D, Van Limbergen E, Vergote I. Endometrial Cancer. Lancett 2005; 366:491-505.
[9] Potischman N,Hoover RN,Brinton LA et al.Case control study of endogenous steroid hormones and endometrial cancer.J Natl Cancer Inst 1996; 88:1127-35.
[10] Parslov M,Lidegaard O,Klintorp S, et al. Risk factors among young women with endometrial cancer: a Danish case-control study. Am J Obstet Gynecol 2000; 182:23-29
[11] Zeleniuch-Jacquotte A, Akhmedkhanov A, Kato I, et al. Postmenopausel endogenouls oestogens and risk of endometrial cancer: results of a prospective study. Br J Cancer 2001; 84: 975-81
[12] Kaaks R, Lukanova A, Kurzer MA. Obesity, endogenous hormones and endometrial cancer risk: A synthetic review. Cancer Epidemiol Biomark Prev 2002; 11:1531-43.
[13] Calle EE, Rodriguez C, Walker Thurmond K, Thun MJ. Overweight, obesity and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003; 348:1625-38.
[14] Morrow CP, Bundy BN, Homelsley HD, et al. Dopsorubicil as an ajuvant followin surgery and radiation therapy in patients with high risk endometrial carcinoma stage I and occult stage II: a Gynecologic Oncology Group Study. Gynecol Oncol 1990; 36:166-71.
[15] Lentz SS, Brady MF, Major FJ, Reid GC, Soper JT. High dose megestrol acetate in advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. J Clin Oncol 1996; 14:357-61.
[16] Tropè C, Johnsson J, Simonsen E, et al. Treatment of recurrent endometrial adenocarcinoma with a combination of doxorubicin and cisplatin. Am J Obset Gynecol 1984; 149:379-81.
[17] Morice P. Levy-Piedbois C, Ajaj S, et al. Value and cost evaluation of routin follow-up for patients with clinical stag I/II endometrial cancer. Eur J Cancer 2001;37:895-90.
[18] Owen P,Duncan ID.Is it any value in the long term follow up of women treated for endometrial cancer?BR J Obstet Gynecol 1996;103:710-3.
[19] Berchuck A,Anspach C, Evans AC,Soper JT,Rodriguez GC, Dodge R et al.Postsurgical surveillance of patients with FIGO stage I-II endometrial adenocarcinoma.Gynecol Oncol 1995;59:20-4.
[20] Gadducci A,Cosio S, Fanucchi A,Cristofani R,Genazzani AR.An intensive follow up does not change survival of patients with clinical stage I endometrial cancer.anticancer Res 2000;20:1977-84.
[21] Agboola OO,Grunfeld E,Coyle D,Perry GA.Cost and benefits of routine follow up after curative treatment for endometrial cancer.CMAJ 1997;157:879-86.
[22] Gordon AF,Owen P,Chien PFW,Duncan ID.A critical evaluation of follow up of women treated for endometrial adenocarcinoma.J Obstet Gynecol 1997;17:386-9.
[23] Ng TY,Ngan HYS,Cheng DKL,Wong LC.Vaginal vault cytology in the routine follow up of patients treated for endometrial carcinoma:is it useful?Aust NZ J Obstet Gynecol 1997;37:104-6.
[24] Salvesen HB,Akslen LA,Irvesen T,Irvesen OE.Recurrence of endometrial carcinoma and the valueof routine follow up.Br J Obstet Gynecol 1997;104:1302-7.
[25] Reddoch JM,Burke TW,Morris M,Tornos C,Levenback C,Gersheson DM.Surveillance for recurrent endometrial carcinoma: developement of a follow up scheme.Gynecol Oncol 1995;59:221-5.

[26] Shumsky AG,Stuart GC,Brasher PM,Nation JG,Robertson DI,Sangkarat S.An evaluation of routine follow up of patients treated for endometrial carcinoma.Gynecol Oncol 1994;55:229-33.
[27] Podczasky E,Kaminsky P,Gurski K,MacNeill C,Stryker JA,Singapuri K et al.Detection and patterns of treatment failure in 300 consecutive cases of "early" endometrial cancer after primary surgery.Gynecol Oncol 1992;47:323-7.
[28] MacDonald JH,Kidd GM.An audit of endometrial carcinoma: the value of routine follow up.J Obstet Gynecol 1990;10:548-50.
[29] Patsner B,Orr Jr Jw,Mann Jr WJ.Use of serum CA125 measurement in post-treatment surveillance of early stage endometrial carcinoma.Am J Obstet Gynecol 1990;162:427-9.
[30] Rose PG,Sommers RM,Reale FR,Hunter RE,Fournier L,Nelson BE.Serial serum CA125 measurements for evaluation of recurrence in patients with endometrial carcinoma.Obstet Gynecol 1994;84:12-6.
[31] Lo SS,Khoo US,Cheng DK,Ng TY,Wong LC,Ngan HY.Role of serial tumor markers in the surveillance foe recurrence in endometrial cancer.Cancer Detect Prev 1999;23:397-00.
[32] Price FV,Chambers SK,Carcangiu ML,Kohorn EI;Schwartz PE,Chambers JT.CA125 may not reflect disease status in patients with uterine serous carcinoma.Cancer 1998;82:1720_5.
[33] Kew FM,Roberts AP, Cruickshank DJ.The role of routine follow up after gynecological malignancy.Int J Gynecol Cancer 2005;15:413-9.
[34] Tjalma WA,van Dam PA,Makar AP,Cruickshank DJ.The clinical value and cost-effectiveness of follow up in endometrial cancer patients.Int J Gynecol Cancer 2004;14:931-7.
[35] E.Sartori, B.Pasinetti L.Carrara, A.Gambino, F.Odicino, S.Pecorelli. Pattern of failure and value of follow up procdures in endometrial and cervical cancer patients.
[36] Kind P. The EuroQol instrument: an index of health-related quality of life. In Spiker B, editor. Quality of life and pharmacoeconomics in clinical trials. Philadelphia, PA: Lippincott-Raven; 1996.pp. 191–201.
[37] Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. Med Care. 2004 Sep;42(9):851-9.