

FOLLOW-UP IN GYNAECOLOGICAL CANCER PATIENTS

– a Health Technology assessment
Summary

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**Follow-up in Gynaecological Cancer Patients
– a Health Technology; Summary**
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Summary

Introduction

About 1100 women develop endometrial or ovarian cancer annually in Denmark. These are the most frequent forms of gynaecologic cancers among women. According to the Danish Gynaecological Cancer Database, the five-year survival rates are 77 % for endometrial cancer and 30–40 % for ovarian cancer.

After completing treatment for endometrial or ovarian cancer, patients are offered standard follow-up. The purpose of this follow-up is to diagnose any relapse at an early stage to increase the likelihood of success in treating the relapse. Further, the follow-up aims to monitor the effects and side effects of treatment and ensure that patients feel secure.

Both clinical and administrative personnel want to assess the need for follow-up to investigate whether the benefits of this care justify the resources used.

Clinically, it is relevant to assess the extent to which follow-up can detect remission and whether follow-up benefits patients compared with self-care: the patient being instructed on how to detect symptoms of relapse and whom to consult if these symptoms appear.

From the patient's perspective, it is relevant to assess whether follow-up makes patients feel secure as they emerge from a period of illness or whether follow-up creates unnecessary insecurity and anxiety at every consultation. Investigating patients' experience and expectations in relation to follow-up is therefore relevant.

The hospital department at which the patient completed treatment usually provides follow-up. Thus, women who have completed treatment for endometrial or ovarian cancer receive follow-up at one of the ten departments of oncology or 29 departments of gynaecology in Denmark. Assessing the differences and similarities between these departments would be relevant for optimizing patient care. Another relevant angle is determining the medical devices and personnel required and thereby determining which specialist levels of the health care system can provide follow-up.

Information on what operating resources these departments use as well as economic analysis are therefore relevant to ensure that resources are appropriately allocated in Denmark's health care system.

Based on these considerations, a relevant assessment of health technology would investigate the aspects related to patients, organization and economic in addition to assessing the clinical effects of follow-up after the completion of treatment for endometrial or ovarian cancer.

Purpose

The purpose of the project is to assess the follow-up provided for women who have completed treatment for endometrial or ovarian cancer in order to:

- to assess the effects of follow-up and
- to improve the follow-up

Follow-up usually comprises clinical examinations, sometimes with other tests, with the aim of detecting relapses after cancer treatment as early as possible. This HTA-report make up scientific guidance to assess the complete documentation of follow-up for cancer patients after treatment for endometrial or ovarian cancer. The report contributes to the continuation of the work with health planning in the National Board of Health. The conclusions of the report are not official recommendations from the National Board of Health.

Target group

The target group for this health technology assessment includes the Cancer Steering Committee under the National Board of Health, Denmark's Task Force on Patient Pathways for Cancer and Heart Disease, the Health Planning Division and Patient Pathway Division of the National Board of Health and administrative and clinical decision-makers in Denmark's health care system. Other stakeholders are Denmark's Ministry of Health and Prevention, the Government of Denmark, the Folketing (Parliament), Denmark's five administrative regions, representatives of patients' organizations and the general public.

Scope

This health technology assessment covers women with cancer after they complete a course of treatment for endometrial or ovarian cancer. The advantages of selecting endometrial and ovarian cancer for this health technology assessment are:

- a significant number of patients;
- the ability to study follow-up with (ovarian cancer) and without (endometrial cancer) postoperative oncological treatment. In addition to the clinical aspects, the organizational differences are substantial;
- the opportunity to assess follow-up in two different diseases where the prognosis for the primary diagnosis is relatively good (endometrial) versus relatively poor (ovarian);
- the opportunity to assess follow-up in two groups where relapse is frequent (ovarian) and infrequent (endometrial); and
- patients can sometimes identify the symptoms of relapse themselves (self-care).

Uterine cancer may originate in the endometrium (lining), the connective tissue of the endometrium or the endometrial muscle. Ovarian cancer may originate in the surface epithelial cells, germ cells or stromal cells of the ovary. This health technology assessment covers endometrial cancer, which comprises about 97 % of the cases of endometrial cancer, and ovarian epithelial cell tumours, which comprise more than 90 % of the cases of ovarian cancer.

Investigating whether follow-up for patients with cancer influences their rehabilitation would be important. This health technology assessment focused on the key clinical content of the follow-up, since assessing rehabilitation is too complex and comprehensive to include given the limited resources and tight time schedule of the project. A separate working group under the auspices of the National Board of Health will cover the rehabilitation of patients with cancer.

Methods

Systematic literature searches were conducted on all aspects of this assessment to investigate the questions related to assessing health technology in this report. The literature

found in the searches was critically assessed, and studies considered to be of sufficiently high quality are included as a basis for the conclusions.

The quality of the literature was assessed overall in relation to each question related to assessing health technology. The studies included are graded for their value as evidence in tables based on the Levels of Evidence and Grades of Recommendation of the Centre for Evidence-Based Medicine in Oxford (Annex 1), which grades the studies according to their design.

The annexes outline the specific search strategies for each chapter (annexes 3c, 3d, 4b, 6b), assess the overall quality of the literature for each question related to assessing health technology and provide evidence tables with the literature included in the assessment.

Further data were collected to supplement the literature searches. Focus group interviews were conducted as part of analysing the patients, and the organizational analysis included performing a questionnaire survey among relevant hospital departments and interviewing key people. The economic analysis is based on the primary data collection and registry analysis.

The individual chapters and annexes describe the methods used in detail.

Technology

Assessment of evidence

The evidence presented in the chapter on technology was graded in accordance with the Levels of Evidence and Grades of Recommendation of the Centre for Evidence-Based Medicine in Oxford. The authors of this report emphasize that assigning a study a high grade of evidence based on assessing the design does not necessarily mean that the study is of high quality. This is outlined in the detailed assessment of the studies that describes any reservations about the quality of the studies.

Endometrial cancer

Based on the literature found, the current follow-up does not seem to improve survival in the overall group of women with endometrial cancer. Most (80–90 %) of the relapses arise within three years after completion of treatment, and three years is generally considered to be the optimal follow-up interval in Denmark if follow-up is to be provided. Smear should not be performed routinely. Symptoms appear in about 70 % of relapses. The women with relapses who do not have symptoms comprise a special problem, especially those for whom the relapse is in the top of the vagina and is thereby potentially curable. Gynaecological examination appears to be the best method of diagnosing these women. Radiological examinations do not seem to have any value as routine follow-up after treatment of endometrial cancer. Given the options available for treating relapses, most women do not benefit from follow-up after treatment for endometrial cancer measured solely as improved survival. Categorizing the patients into two risk groups can thus illustrate the effects of follow-up, given current knowledge on the risk of relapse, the proportion of patients with symptoms and the fact that only patients with localized relapses have a chance of becoming cured. Thus, only two of 1000 women with low risk would potentially benefit from follow-up. This increases to seven of 1000 women with high risk. Many follow-up consultations therefore need to be provided to detect a very small number of patients who relapse, especially among

the women with low risk. Nevertheless, a supposedly low risk for relapse does not mean that relapse does not occur.

Ovarian cancer

No evidence indicates that the current intensive, hospital-based follow-up improves survival or the quality of life of women treated for a primary diagnosis of ovarian cancer. This is based on the fact that there are virtually no studies on this topic. It cannot therefore be excluded that such follow-up would have an effect. Evidence contraindicates routinely use of diagnostic imaging in follow-up. Evidence indicates that measuring the serum concentration of cancer antigen 125 (CA-125) is effective in demonstrating relapse among a large group of women, but no evidence indicates that the earlier diagnosis benefits the women in terms of improving survival. No study has investigated how follow-up affects the women's quality of life. It is assumed that follow-up among women without primary elevation of CA-125 would have limited effect.

Patients

Reviews from 2004 and 2007 mainly concluded that knowledge is severely lacking on how follow-up affects these women's quality of life. Such studies are few and generally suffer from serious methodological problems, especially selection bias and very small populations that are difficult to describe statistically. Further, since the conclusions are often ambiguous or even contradictory, the level of evidence must generally be considered low. To the extent that the literature can be summarized in meaningful conclusions, they must therefore be weighted with great caution in relation to the other parts of the health technology assessment.

The most consistent message in the existing literature is clearly that patients with cancer find that follow-up promotes a feeling of security. Follow-up consultations, especially in the first few months after treatment ends and in case of unexpected symptoms, meet a need to confirm that treatment has succeeded and that new disease has not developed. Reassurance is the most important benefit of follow-up consultations even after several years of follow-up. A gynaecological examination and assurance by a physician that relapse is unlikely provides a feeling of security, but many women express special faith in more "technology" such as blood tests and diagnostic imaging, typically severely overestimating their effectiveness. Many patients with cancer feel somewhat nervous in the days before a follow-up consultation and the consultation can cause uncertainty among women who otherwise consider themselves healthy. Nevertheless, most women think that the advantages outweigh the discomfort.

In contrast to the convincing evidence that women perceive psychosocial benefit in follow-up, the literature review did not clearly determine whether follow-up affects women's quality of life as measured using quantitative, standardized scales for anxiety, depression and health-related quality of life. No study has compared patients with cancer receiving regular follow-up with patients who are not offered follow-up at all. The studies that are most similar compare with women carrying out self-care: being instructed on how to detect symptoms of relapse and whom to consult if these symptoms appear. These studies found no positive or negative association between the quality of life and regular follow-up.

Continuity and consistency are very important in determining how patients with cancer feel about follow-up consultations. Changes in examinations and tests between consultations may promote insecurity. The literature implies that being treated by and

receiving follow-up from the same physician improves the personal interaction and increases the patients' faith in the physicians' professional competence.

Patients with cancer consider detecting relapse to be the most important purpose of follow-up. Nevertheless, both the literature and the focus groups pay considerable attention to communication and the more psychological dimensions of consultations. An especially widespread complaint seems to be that follow-up consultations focus on pure physiology and ignore the psychosocial aspects related directly to cancer. The literature indicates that more holistically oriented health check-ups are not allocated time or attention.

Women with cancer in the genital organs generally prefer to receive follow-up at specialized hospital departments, which they consider to be more competent and secure. Some parts of Denmark's health care system, however, have experimented with courses of follow-up in which regular follow-up consultations are delegated to general practitioners or are eliminated and replaced by self-care systems led by experienced nurses specializing in oncology. Women in such courses of follow-up have the same user satisfaction as women in traditional follow-up, and studies have found no measurable effects on the quality of life. Nevertheless, the results should be interpreted very cautiously. One factor is that user satisfaction measures the level of services provided, which should not be confused with, for example, the feeling of security, which many people may consider more important. Further, the data are weakened by severe selection bias: in one study, half the women selected in the sample declined to participate in the self-care system.

A few studies have attempted to identify demographic, clinical or other types of patterns among patients who especially express a desire for regular follow-up consultations. This need seems to be weakly correlated with the women's general anxiety level. However, the literature reviewed does not clearly indicate what type of follow-up patients with cancer prefer as a group. This is a heterogeneous population, and one standardized type of follow-up definitely cannot fulfil their individual needs and preferences.

Finally, once again the literature provides limited and inadequate answers to all the questions related to assessing health technology. To put it simply, we know very little, and what we do know, we do not know with much certainty.

Organization

Women treated for endometrial or ovarian cancer generally receive follow-up in the hospital department that was responsible for completing the treatment. The follow-up consultations are typically outpatient and provided by a senior hospital physician, specialist physician or sometimes another hospital physician, assisted by a nurse.

Departments vary somewhat in the frequency of follow-up consultations. Nevertheless, most patients typically receive follow-up every 3–4 months the first year, every 4–6 months the second year, every 6–12 months the third year and every 12 months in the fourth and fifth years. Then follow-up is no longer offered. Follow-up consultations for endometrial cancer are generally less frequent than those for ovarian cancer.

The examinations and tests used in follow-up after the completion of treatment for endometrial and ovarian cancer typically include clinical examination (both types of

cancer), blood tests (ovarian cancer) and sometimes ultrasound imaging (for both types of cancer, but especially ovarian cancer). More comprehensive diagnostic imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET)/CT are not used unless relapse is suspected.

The scientific background for organizing follow-up for patients with endometrial and ovarian cancer includes scientific evidence, scientific assessment and professional traditions. Hospital departments in Denmark largely organize follow-up based on clinical guidelines, including guidelines from the Danish Gynaecological Cancer Group, local guidelines and guidelines from the National Board of Health.

The assessment provides no final answer as to the human resources and medical devices required for follow-up after treatment is completed for endometrial and ovarian cancer. However, based on guidelines, practice and interviews, the human resources required include a specialist physician (or other hospital physician) in gynaecology and/or oncology and a nurse. The medical devices required for normal examinations and tests include devices for analysing blood tests (for ovarian cancer) and perhaps devices for ultrasound imaging. Advanced diagnostic imaging devices are used if relapse is suspected.

The motivation to provide follow-up to patients who have completed treatment for endometrial or ovarian cancer includes scientific and patient-oriented incentives and incentives related to education and research.

The current organization of follow-up does not include transitions between departments, and it is generally attempted to assign the patients a regular contact person in the hospital department that provides the follow-up.

Economics

The operating costs for providing follow-up for patients who have completed treatment for endometrial and ovarian cancer were calculated based on the direct variable costs of follow-up consultations at hospital departments. The costs were calculated based on a standard course of follow-up in which the costs of each activity included in a follow-up consultation at a hospital are determined and totalled to arrive at the operating costs. Indirect costs and the direct costs for patients are not included, and the costs of patient transport are excluded.

For patients who have had endometrial cancer, the calculated operating costs of a standard follow-up consultation are €98 in a department of gynaecology and €141 in a department of oncology.

For patients who have had ovarian cancer, the calculated operating costs of a standard follow-up consultation are €184 in a department of gynaecology and €260 in a department of oncology.

The corresponding DAGS (Danish Ambulatory Grouping System) rates are €277 if ultrasound imaging is performed and €305 if the lungs are X-rayed. If a practising specialist physician provides the follow-up, the corresponding rates would be €88 for the first consultation and €56 for each subsequent consultation, including ultrasound imaging.

The total annual operating costs of follow-up at hospitals are an estimated €497,000 for patients who have had endometrial cancer and €966,000 for patients who have had ovarian cancer.

The individual hospital departments vary in how they organize and provide follow-up for patients who have had the two types of cancer, including the frequency and number of consultations and the examinations and tests provided in follow-up consultations. Sensitivity analysis has been carried out that adjusted the standard course of follow-up and some of the assumptions behind the calculation of the operating costs to investigate how these changes would affect the operating costs. The sensitivity analysis showed that these adjustments greatly affect the operating costs. For example, if the number of consultations in follow-up is reduced such that it more closely matches the recommendations by the Danish Gynaecological Cancer Group, the annual operating costs would decline by about €416,000. If the examinations and tests offered were reduced to solely include gynaecological examinations of patients with endometrial or ovarian cancer and measuring the serum concentration of CA-125 among patients with ovarian cancer, the annual operating costs would decline by about €591,000.

The literature on the costs of follow-up for patients with these two types of cancer is generally modest, and no studies from Denmark have been found. The results from the studies outside Denmark are based on retrospective calculations. These results cannot directly be transferred to the situation in Denmark because of differences in the organization of examinations and tests and the ones provided by the health care system, since the studies outside Denmark generally found more consultations and more types of examinations and tests per consultation than those that take place in Denmark.

Synthesis

Most people who have cancer are offered one or more types of treatment in the form of surgery, chemotherapy or radiation therapy at some point in their course of illness. All these types of intervention affect the person physically, and the treatment probably also influences the person mentally and socially. A person with cancer must provide informed consent for treatment based on careful, evidence-based information from health care personnel on the purpose, the intervention itself, the effects, the side effects and the potential complications. The information provided is often based on national guidelines. Based on the results of this report, follow-up after treatment should be considered to be a type of intervention that is similar to treatment, and the follow-up should be evidence-based with a clearly defined purpose. This includes harmonizing the expectations of the patient and the health care personnel on the options for treatment in case of relapse, the purpose of follow-up, the length of follow-up, the frequency of consultations and which technology is used.

One purpose of follow-up for patients with endometrial and ovarian cancer is to improve survival. The potential beneficial effect of follow-up on survival is based on the assumption that diagnosing relapse early and thereby initiating treatment early are useful. This assessment found that existing scientific literature does not support this assumption, since no evidence shows that follow-up for women with endometrial and ovarian cancer has any substantial positive effect on survival. Asking whether follow-up for patients with endometrial and ovarian cancer may have other positive effects is therefore appropriate. Receiving follow-up from a specialist physician may make many women feel secure, and this positive effect seems to outweigh the anxiety that emerges before the follow-up consultation. The feeling of security is mainly based on the com-

munication from the physician that there is no relapse and, if there is a relapse, it will be diagnosed as early as possible. This feeling of security should be weighed against the fact that endometrial and ovarian cancer become chronic diseases upon relapse and that there is no effective, life-extending treatment in most cases. Thus, the patients' needs for feeling security seem to need to be harmonized with the evidence-based benefit of follow-up in extending survival.

Patients with cancer seek continuity in follow-up and seek more holistically oriented consultations that also consider the sequelae of treatment and psychosocial reactions to cancer. The patients thus express the key words: feeling secure, continuity and holistic orientation. The current organization of follow-up does not seem to optimally meet the expectations of patients with cancer towards this care. It is therefore appropriate to question whether specialized oncologists in hospitals always have to provide follow-up in accordance with current practice or whether other health care personnel, such as specially trained nurses, can meet patients' needs. Patients should definitely have direct access to the services of specialist physicians when needed, but it is not certain that the primary contact person at all follow-up consultations must be a specialist physician.

Surgery cures the vast majority of women with endometrial cancer, whereas about 90 % of women with ovarian cancer experience relapse. Women with these two types of cancer thus differ greatly in the proportion experiencing relapse. It is generally inappropriate to frequently shift between, for example, primary care or regional hospitals and highly specialized hospitals. It therefore seems optimal to organize the future follow-up for women with ovarian cancer at the highly specialized departments of oncology that treat the cancer initially and upon relapse. Based on the concept of offering the least specialized care while ensuring adequate professional competence, future follow-up for patients with endometrial cancer could be provided outside the highly specialized hospital departments, since the great majority of women do not need further treatment at these departments. Nevertheless, some women with advanced stages of endometrial cancer have a high risk of relapse. A department of oncology normally treats these women, and having oncologists provide follow-up for these women may be appropriate. Similarly, women with localized ovarian cancer who do not need further treatment after surgery have a low risk of relapse and little need for follow-up at a highly specialized hospital department.

The future organization of follow-up must naturally ensure that the necessary competence and technology are available. This report's results clearly indicate that follow-up for women with endometrial and ovarian cancer is low technology: that is, gynaecological examinations supplemented with ultrasound imaging and blood tests for women with ovarian cancer. Low technology may require excellent professional expertise, and this report does not indicate whether such physicians as general practitioners or practising gynaecologists are competent to provide follow-up for patients with endometrial cancer that solely includes gynaecological examination.

For women with endometrial cancer who have a low risk of relapse, one option is to replace the present, formalized follow-up with self-care: being instructed on how to detect symptoms of relapse and whom to consult if these symptoms appear. This would require thoroughly instructing these women on the warning signs of relapse and ensuring the opportunity for subacute examination by a physician. Self-care focuses on these women being most likely cured of cancer. The responsibility for follow-up is largely placed on the women, which breaks with the cultural attitude that the health care system is responsible for all follow-up. This type of self-care may work for some

patients but probably requires substantial consideration of each patient's individual desires and opportunities.

The report's chapter on economics found a relatively high average cost of follow-up for patients with endometrial and ovarian cancer. Follow-up for patients with these two types of cancer alone in Denmark requires €1.46 million annually. This expenditure could be reduced by phasing out the follow-up from highly specialized departments and phasing in care at less specialized departments and/or specially trained nurses, practising gynaecologists and general practitioners. Further, doctors with specialized competences in these areas are presently lacking and are projected to be in short supply for many years to come. Using these specialized personnel where they generate the most benefits is therefore important.

Endometrial and ovarian cancer is just two of the many types of cancer. Cancer may develop in organs or in the blood and at different stages of life. Cancer may thus differ vastly in location in the body, the stage and whether it has metastasized, treatment and survival. Cancer is thereby not one disease, and the report's conclusions cannot uncritically be transferred to other types of cancer. Nevertheless, this report can serve as the basis for a model that can inspire similar considerations for other types of cancer. Planning future follow-up for patients with all types of cancer in Denmark it will be appropriate to perform health technology assessment on the evidence-based utility of follow-up.

Based on the results of this report, it is appropriate to question whether follow-up has become a natural extension of treatment: that is, part of the course of cancer that has become a tradition and an established part of the treatment culture in Denmark. However, this does not change the viewpoint that follow-up is an intervention and that health care interventions must be evidence-based to be justified, even though follow-up is used to identify suitable patients for scientific studies.

In a system with limited resources, debate on priorities is a positive sign. This report focuses objectively on follow-up for women with endometrial and ovarian cancer, and it is hoped that the report can support a scientific debate on priorities that leads to the benefits of follow-up for patients with cancer outweighing the efforts necessary to provide this care.

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