The future for follow-up of gynaecological cancer in Europe. Summary of available data and overview of ongoing trials.

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Condensation

- Follow-up for gynaecological cancer is not supported by good quality evidence.
- Current relevant research in Europe is reviewed.
- Strategies using best evidence are discussed.

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ABSTRACT

After completing treatment, most patients follow a pre-determined schedule of regular hospital outpatient appointments, which includes clinical examinations, consultations and routine tests. After several years of surveillance, patients are transferred back to primary care. However, there is limited evidence to support the effectiveness and efficiency of this approach.

This paper examines the current rationale and evidence base for hospital based follow-up after treatment for gynaecological cancer. We investigate what alternative models of care have been formally evaluated and what research is currently in progress in Europe, in order to make tentative recommendations for a model of follow-up.

The evidence base for traditional hospital based follow-up is limited. Alternative models have been reported for other cancer types but there are few evaluations of alternative approaches for gynaecological cancers. We identified five ongoing European studies; four were focused on endometrial cancer patients and one feasibility study included all gynaecological cancers. Only one study had reached the reporting stage. Alternative models included nurse-led telephone follow-up and comparisons of more intensive versus less intensive regimes. Outcomes included survival, quality of life, psychological morbidity, patient satisfaction and cost effectiveness of service.

More work is needed on alternative strategies for all gynaecological cancer types. New models will likely include risk stratification with early discharge from secondary care for early stage disease with fast track access to specialist services for suspected cancer recurrence or other problems.

Key words

neoplasm; female continuity of patient care/standards; survivorship; neoplasm recurrence.

Introduction

Each year there are approximately 250,000 new diagnoses of gynaecological cancer in in Europe [1], many of whom would require follow after completing their treatment. This represents an enormous investment of clinical resource in providing ongoing care with surprisingly little quality evidence to suggest that cancer follow-up makes a difference in either improving survival or quality of life. A survey of European practice concluded that gynaecological oncologists rate the evidence base to guide practice for follow-up as 'low' or 'very low' [2]. If improved survival is not a realistic goal of scheduled hospital based surveillance then models of delivery of care should arguably be more flexible to meet the individual needs of patients. While benefits of follow-up might be questionable, patients often experience long-term side effects following their treatment and may experience psychological or psychosexual issues [3,4]. In addition, patients often experience anxiety prior to their appointments for cancer follow-up [5-8] and brief consultations may not provide opportunities for discussion of emotional problems and concerns. This paper seeks to examine the current rationale and evidence for hospital based follow-up for women who have completed treatment for gynaecological cancer. We investigate what alternative models of care have been evaluated and what research is currently in progress across Europe. The aim is to provide recommendations for follow-up care pathways which are flexible to the needs of patients with different gynaecological tumours and in different healthcare settings.

Routine follow-up in oncology practice

Following treatment for cancer, patients usually have a series of hospital-based medical-led follow-up appointments with a prescribed schedule of visits for several years. The most common duration of routine follow-up is for at least five years [2,9]. The reported aim of regular follow-up is to allow detection of recurrent disease before symptoms develop, allowing earlier

treatment with a possible improved outcome, as well as providing an opportunity to provide information and signal early and late consequences of treatment. For follow-up to be effective in this context, the management of recurrence must be amenable to an intervention which itself leads to an improved survival [10]. However, for many cancers, recurrences are not commonly identified in asymptomatic patients at follow-up consultations and most recurrences are reported as interval events [11]. There is limited evidence that hospital based follow-up impacts on survival, indicating that other outcomes such as psychological morbidity and quality of life should be a priority for any follow-up regime. Prioritising these outcomes can be justified as patients consistently report problems associated with cancer and its treatment, including physical problems, impaired quality of life, psychological distress, sexual problems, relationship problems and financial concerns [12].

Alternatives to traditional doctor-led hospital-based follow-up have been evaluated for different cancer types. A systematic review on follow-up of cancer in primary versus secondary care reported weak evidence that primary care follow-up was effective [4]. Patients treated for breast and colorectal cancer have reported high levels of satisfaction with nurse-led telephone follow-up [13-15]. In the United Kingdom (UK), the National Cancer Survivorship Initiative (NCSI) and the more recent Living With and Beyond Cancer (LWBC) programme both advocated an individualised approach to follow-up based on risk stratification, concentrating care for those perceived to be at a greater risk of recurrent disease and for other issues that arise as a consequence of diagnosis or treatment [16].

Follow-up in gynaecological oncology

For gynaecological cancers, follow-up is mainly delivered by doctors in secondary care [9] and there is very little quality evidence to inform guideline developers in relation to gynaecological oncology follow-up [17]. Eighty per cent of all gynaecological cancer recurrences generally occur

in the first two years after treatment [18] and follow-up visits are more frequent during this time. An appointment usually consists of a consultation, a physical examination and consideration for routine tests such as a serum CA125 for ovarian cancer patients or cervical or vaginal cytology for cervical cancer patients [19-22]. Few routine tests are recommended in gynaecological practice for cancer follow-up and are usually requested only if they are clinically indicated.

Endometrial cancer recurs in less than 20% of cases of which 15% is located only in the vagina and amenable to re-cure [23-29]. Recurrence of endometrial cancer is often symptomatic although reported to vary from 40-91% (23-25,27,28,30-32]. Most recurrences (70-95 %) occur within three years of initial treatment [31,33]. Symptomatic recurrences of endometrial cancer may have a worse prognosis than asymptomatic recurrences, as reported from recent studies carried out in Italy and Japan [34,35], although evidence is conflicting as other studies showed no such differences [23,36,37]. There is no consensus on what tests should be offered for endometrial cancer follow-up [31]. The Society for Gynecologic Oncology recommends a pelvic examination at each visit but suggests that routine CA125 testing, chest radiography and vaginal cytology is controversial and that there is no randomised data to guide practice [38]. The European Society for Medical Oncology recommends clinical examination only [33].

To date only one randomised controlled trial (RCT) on endometrial cancer follow-up has been reported [39]. The ENDCAT trial recruited 259 patients, randomised to nurse-led telephone follow-up or standard hospital based follow-up, in a non-inferiority trial for all stage one endometrial cancers. Patients were recruited at five centres across the North West of England. The primary outcomes were psychological morbidity and satisfaction with information. Secondary outcomes included satisfaction with the follow-up service, quality of life, cost effectiveness and time to detection of recurrence. Nurse-led telephone follow-up was not inferior to hospital-based follow-up in terms of psychological morbidity, patient satisfaction and

quality of life. There were no differences between groups in time to detection of recurrent disease.

About 70% of patients with ovarian cancer are diagnosed in advanced stage and about 70% of these will relapse [40]. The tumour marker CA125 is superior to all other tumour markers in the detection of early recurrence in ovarian cancer. The National Cancer Institute consensus statement for follow-up has recommended that asymptomatic patients should include a CA125 assay as part of each routine visit. Pre-clinical elevation of CA125 is seen several months prior to clinical recurrence [41]. A review by Piovano *et al* (2014) looking at HE4 currently has no recommendation regarding its incorporation into clinical practice [42] although elevated levels may be more sensitive at detecting relapse then serum CA125 [43]. The use of other tumour markers such as CEA and routine imaging have not been recommended for asymptomatic women from a Cochrane review of ovarian cancer follow-up [44]. Furthermore, this systematic review reported on only one RCT. This was a study by Rustin *et al* (2010), which reported data on immediate treatment for ovarian cancer recurrence following a rise in serum CA125 levels versus delaying treatment until symptoms developed. There was no survival advantage for routine surveillance with CA125 testing, and those having CA125 measurements had more chemotherapy and more complications from more treatments. Quality of life was impaired in the group who had chemotherapy based on a rise in CA125 only. However, this study may not accurately reflect current follow-up practice as it included taxane based chemotherapy in just 54% of cases and surgery was not included in the management algorithm for recurrence. The results of a further RCT, DESKTOP 3 are awaited and will clarify the value of secondary cytoreductive surgery in this context [45]. A further RCT of 112 patients with ovarian cancer treated with surgery or surgery and chemotherapy by Lanceley *et al* (2017) comparing 'individualised nurse-led follow-up' to standard medical based hospital follow-up reported no difference in quality of life despite a later time of detection of recurrence in the intervention

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group [46]. Recurrent ovarian cancer is usually treated when symptomatic as there are no interventions for women after completion of treatment which has proved to be sufficiently effective to improve survival. Correspondingly, the value of routine follow-up for ovarian cancer regarding survival is questioned [47]. Therefore, clinical assessment is ideal for patients reporting symptoms with prompt investigation with imaging and tumour markers as indicated.

For cervical cancer, the majority of relapses are symptomatic which would merit early review even in the absence of a routine follow-up schedule [19,48-50]. An audit of 291 post-surgical patients with cervical cancer from Wales showed that seven out of 47 patients with recurrence were detected at routine follow-up and only two of those were asymptomatic [51]. Median survival in this study was worse for those who presented at the routine appointment rather than those who self-presented (but the result was non-significant due to small numbers). Cervical cytology is recommended during follow-up after loop conisation for early stage cervical cancer by many countries. However, cytology following radiotherapy as a high false positive rate and so should not be recommended [2,52]. A systematic review of seventeen retrospective studies noted that there is little evidence to suggest that vaginal vault cytology after hysterectomy is useful in detecting early disease recurrence and that the routine use of various radiological or other investigations in asymptomatic patients is not recommended [53]. Routine use of positron emission tomography–computed tomography scanning has not proved cost-effective in the follow-up of neither early nor advanced stage cervical cancer [54]. Human papillomavirus (HPV) testing may have a future role for follow-up and again studies of HPV testing are required in the cervical cancer follow-up setting. A recent Cochrane review of follow-up after treatment for cervical cancer found that there was no evidence from RCT's to support different follow-up protocols and future well designed prospective research was advised [55].

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Overall, the use of routine tests to assist follow-up for endometrial, ovarian and cervical cancer has not proved valuable regarding recurrence detection and concurrent survival benefit. It

remains controversial what is the optimal surveillance programme following treatment for gynaecological cancer.

Randomised controlled trials currently recruiting in Europe

A number of studies focusing on follow-up care for women with gynaecological cancer are in differing stages of development in several European countries. Most of the studies are specifically for endometrial cancer patients. The ENDCAT and the Lanceley *et al* ovarian cancer trials have reached completion and have been described [39, 46]. Details on the status of further studies in progress are presented below.

ENSURE is a trial of a reduced hospital-based follow-up regime of four visits in three years compared to standard follow-up of 10 to 13 visits in five years for women with low risk endometrial cancer. Patients receive a document explaining signs of recurrence and contact information. The majority of cancer centres in the Netherlands are involved to recruit 282 patients. Recruitment is to continue until 2017 with completion of three-year follow-up in 2020. The primary outcomes are patient satisfaction with follow-up care and cost effectiveness between groups. Secondary outcomes include satisfaction with information, worry, health care use, and illness perceptions (Trial number: NCT02413606).

OPAL is a study based in Denmark recruiting from four cancer centres. Women diagnosed with stage one low to intermediate risk endometrial cancer are randomized between patient-initiated follow-up and standard follow-up with approximately eight outpatient visits in three years. For the patient-initiated follow-up group, women do not attend scheduled follow-up visits, but are instructed in 'alarm symptoms' that require examination by a physician. Furthermore, they are provided with a contact person whom they can contact in case of symptoms or worries. The primary outcome is fear of recurrence. Secondary outcomes include

quality of life, unmet needs and cost-utility. Recruitment has closed with a total of 211 patients, with completion of three-years follow-up in 2019 (Trial number: NCT01853865). A feasibility study of the OPAL-trial in Norway has commenced in 2015 and is expected to run for one year.

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TOPCAT-G is a Welsh feasibility study planned for 50 patients. Recruitment was over nine months and commenced in 2015 (Trial number: ISRCTN45565436). All gynaecological cancers are included except for pelvic sarcomas, trophoblastic and ovarian borderline tumours. The primary outcome of the feasibility study is patient recruitment and attrition and for the subsequent main study quality of life. Recruitment is from a single site to determine difference in patient experience with reduced regime of nurse-led telephone follow-up.

TOTEM is a prospective randomised study that is being carried out in Italy and France. It includes all endometrial cancer patients (Trial number: NCT00916708). This study compares the value of more intense follow-up to a standard protocol. Several centres are recruiting to schedule toward a target of 2300 patients. The primary outcome is overall and progression-free survival and quality of life.

Only TOTEM has an active arm for more intense follow-up and is uniquely powered to compare survival. TOTEM compares differences in overall survival, but requires a large sample size due to the small number of anticipated recurrences. It is also the only study comparing a more intensive surveillance regime compared to standard care. TOPCAT-G includes non-endometrial gynaecological cancers but excludes sarcomas and trophoblastic tumours.
ENSURE had a reduced schedule of follow-up appointments and OPAL is comparing patient-initiated follow-up compared to standard care. All but TOTEM and TOPCAT-G restricted recruitment to low and intermediate risk endometrial cancer. These studies are using differing

patient-reported outcome measures (PROMs) as their primary outcome, but all include the generic questionnaire EORTC QLQ-C30 to assess health-related quality of life so that it will be possible to compare results on EORTC QLQ-C30 across studies. ENSURE reports on satisfaction with follow-up care, OPAL on fear of recurrence, and TOPCAT-G quality of life. ENSURE, OPAL and TOPCAT-G also include an economic evaluation. Data from current and planned European studies will help to clarify if routine surveillance is useful for the follow-up of gynaecological cancer patients. The studies described will collect information on the use and benefit of the use of PROMs in the follow-up and whether less intense and non-medical led regimes of follow-up are suitable for patients with endometrial and possibly for other gynaecological cancers.

Economic evaluation of oncology follow-up

Seventy per cent of all tumour related expenditure is spent on follow-up [31]. This means that a large amount of clinical time and costs are targeted to care after treatment rather than treatment itself. This is likely to represent an inefficient use of finite healthcare resource and an important consideration to derive a workable algorithm for follow-up. A cost effective form of surveillance following treatment for gynaecological cancer is important due to the large number of female cancer survivors [52].

There are few economic evaluations of alternative strategies for the follow-up of cancer patients. Beaver *et al* (2009) reported that nurse-led telephone follow-up for breast cancer patients represented savings for patients in terms of time and money but was more costly to the UK's National Health Service (NHS) as telephone calls were longer than hospital appointments and were made by senior nurses [56]. However, Kimman *et al* (2011) carried out an economic evaluation of four follow-up strategies after curative treatment for breast cancer in the Netherlands and concluded that nurse-led telephone follow-up was a cost effective alternative to hospital follow-up for breast cancer patients during their first year after treatment

[57]. The economic evaluation conducted as part of the ENDCAT trial indicated that nurse-led telephone follow-up was cost neutral for the UK's NHS and patients saved time and money [58]. Lanceley *et al* (2017) reported a cost saving for nurse-led individualised follow-up compared to standard care for ovarian cancer patients [46]. More prospective trials are needed to explore the economic impact of different follow-up regimes. Lajer *et al* (2010) stated that follow-up should have a clearly defined evidence based purpose and, if survival is not an appropriate end point, then cost effectiveness, quality of life and toxicity should be evaluated [59].

What questions remain

Although trials with different approaches to follow-up are ongoing, there is a need for consensus on the most appropriate outcomes, to enable meaningful comparisons and to meet the individual needs of patients. The current suite of trials is focused primarily on early stage endometrial cancer but there is a need to explore the follow-up care needs of other gynaecological cancers and patients at high risk of recurrence. Supported self-management approaches are being advocated for low risk patients but we do not know if patients will feel able to self-manage based on the information they have been given. If patients are discharged earlier from secondary care following treatment, as part of a self-management approach, we do not know if primary care practitioners will be able to provide the support that patients may need if they have concerns or experience long term effects of treatment. There are also financial considerations in transferring follow-up from secondary to primary care.

There is a need for effective communication to facilitate timely access to various care professionals so that patients requiring specialist evaluation can be referred as required and relevant investigations performed promptly. This team approach could be enhanced by care co-ordinators as part of the cancer multidisciplinary team relaying management decisions by phone, letter, fax or secure email.

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Algorithms for gynaecological cancer follow-up would be informed if researchers were able to determine optimal formats for follow-up from the ongoing prospective studies in Europe. There is a need to find out if there is a difference in PROMs such as illness perceptions, information provision or management of treatment side effects between types of follow-up and if there is a difference in outcome for patients failing to attend follow-up for gynaecological cancer. Furthermore, there is a need to determine what if any routine serum, cytological or imaging investigations are worthwhile for providing useful information for follow-up of healthy women at pre-determined times that may indicate possible recurrence, which in turn, may be treatable. It is possible that different follow-up algorithms could be appropriate for different cancer sites, stages and possible different tumour types (such as for type one and two endometrial or ovarian cancer). Finally, various follow-up strategies (such as nurse-led or patient-initiated follow-up) could be included in other clinical cancer studies evaluating treatment interventions to report alongside with standard quality of life measures.

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Conclusions

Follow-up after treatment offers opportunities to deliver support from clinical teams to their patients. Evidence based guidelines for follow-up will inform the variety of professions involved in follow-up. Such guidelines may be drawn from the suite of listed completed and ongoing studies. Until the required information becomes available, patients should be made aware of what options there are for effective provision of cancer follow-up as well as the lack of evidence that supports the current longstanding medical model for regular doctor-led hospital based visits. Regardless of healthcare resources, future cancer follow-up should be about how a service is delivered that ensures patients can access the support they need when they need it. Also by decreasing unnecessary follow-up of healthy patients, more time would be available to address potential problems.

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