All Wales Guideline for Gynaecological Cancer Follow-up

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Foreword

Patients need timely expert help and support to navigate through their cancer diagnosis, treatment and after-effects. Cancer and its treatment can have a considerable long term impact on everyday life. Multidisciplinary team-working is of paramount importance.
In preparing this guideline, specialists from around Wales have come together to form a consensus document which can be used by those who plan and deliver gynaecological cancer services. The aim of the guideline is to help improve and coordinate care and bring about uniformity for the follow-up after treatment for women with gynaecological cancer in Wales based on the best available evidence. Sources of information are drawn from regional cancer guidance documents as well as the published cancer guidelines from the British Gynaecological Cancer Society (BGCS).

Scope of this document

This document covers the follow-up for gynaecological cancer patients. Management of differing cancer types are managed in separate site specific guideline documents.

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1. Background

There are approximately 21,000 new cases of gynaecological cancers each year in the UK and one in five female cancer patients have a gynaecological cancer (CRUK, 2014). In Wales, over 1,000 women are diagnosed with gynaecological cancers each year (WCISU, 2019). 70% of all tumour related expenditure is required for follow-up (Sartori et al, 2010). A large amount of clinical time is targeted to care after treatment rather than treatment itself. A cost effective form of surveillance must be available following treatment for gynaecological cancer (Salani et al, 2011).

Follow-up currently provided after treatment for gynaecological cancer is underpinned by a largely retrospective evidence-base. Furthermore, there are no guidelines from the National Institute for Health and Care Excellence (NICE) as to what form or frequency of follow-up is appropriate in relation to either effective recurrence detection or holistic wellbeing.

Traditionally, patients who have had treatment for are kept on regular review in hospital outpatient clinics for years (Kew and Cruickshank, 2006).
Aims may be:

- to detect recurrence of tumour
- to monitor and manage the late effects of treatment
- to collect data
- to provide support and referral to other specialties as needed
- and to offer patients an opportunity to raise concerns or anxieties arising from their cancer (Kerr-Wilson and McCrum, 1995; Kew et al, 2007; Kew et al, 2011).

The most common practice is for clinicians to review patients on a regular basis, in a hospital-based, outpatient clinic over a number of years (Leeson et al, 2013) with the aim of checking for local recurrence or distant metastases (National Cancer Institute, 2019). However, there is no prospective evidence that the traditional method of follow-up identifies recurrences earlier or improves overall survival. Most cervical cancer recurrences are symptomatic (Kunkler et al, 1991; Gerdin et al, 1994; Ansink et al, 1996; Lim et al, 2004). Follow-up of women with gynaecological cancer may be accomplished using patient-reported outcome measures (Nama et al, 2013). For many cancers, recurrences are not commonly identified in asymptomatic patients at follow-up consultations and most recurrences are reported as interval events (Jefford et al, 2013). The majority of patients relapse with symptoms that would prompt reassessment even if the patient was not on routine review. There is also a worry that patients may wait for their next routine appointment to disclose symptoms (Olaitan et al, 2001) thus possibly delaying detection and appropriate symptom management. This problem may be minimised with advice to patients at the end of their treatment regarding symptoms and signs that may be suggestive of recurrence.

As a guide, 80% of all gynaecological cancer recurrences generally occur in first two years after treatment (Kerr-Wilson and McCrum, 1995) and follow-up visits generally are more frequent during this time. However, the current practice of seeing all women at short term regular intervals several times per year and then reducing to annual visits seems illogical when different cancers have different recurrence risks and times to recurrence. Follow-up intervals should depend on the threshold for detection, the incidence of any abnormal

findings and the benefit derived from early detection. Rapid access to oncological assessment at recurrence may be more important than offering frequent routine appointments (Shumsky et al, 1994; Gulliford et al, 1997). Knowing that different schedules of follow-up do not impact upon survival, delegation of routine follow-up could be to carers other than gynaecologists or oncologists (Vistad et al, 2012).

In terms of psychological morbidity there is evidence that routine appointments can lead to high levels of anxiety during follow-up (Kew et al, 2009), suggesting that patients' psychosocial needs are not being met. Within the population of cancer patients, women have significantly higher levels of anxiety and depression than men (Polidoro et al, 2014) and furthermore, one study reported that 29% of gynaecological cancer patients report depressive symptoms (Hartung et al, 2017). Studies have identified that the least met needs of cancer outpatients typically include wanting more information on genetic issues, lifestyle changes, worries regarding spread or recurrences and parking near the treatment centres (Morrison et al, 2012). Access to mainstream psychological treatments are important (especially via primary care as well as cancer specific psychological services). These are available across Wales as part of the Mental Health Measure (Mental Health Wales, 2010).

2. Options for the delivery of cancer follow-up care

Some patients may prefer alternative models for follow-up (Lydon et al, 2009).
Follow up may be:

- in primary care
- at hospital based nurse-led clinic
- by telephone or videoconference
- at request of patient; i.e. patient initiated follow-up (PIFU).

Patients should be made aware of available options for effective follow-up. Individualised follow-up strategies should be prescribed by the multidisciplinary team once treatment is complete. These should stratify patients by anticipated risks of recurrence, side effects of treatment and take into account patient or local factors. A patient leaflet explaining the follow-up process would be helpful and in particular explaining why a prudent approach to follow-up is beneficial (both in terms of managing patient anxiety and cost to the NHS), and essentially promote to the patient that this is not a 'lesser service' due to cost. At the first follow-up appointment a card with contact details should be given to the patient. This may provide a source of security especially in the presence of symptoms. Alternatively, the contact card could be designed in the same way as a credit or bank card, i.e. in plastic with contact numbers on one side and a list of relevant complications to be aware of on the other. An educational programme should be available for all patients following treatment. Although education on the consequences of treatment needs to start prior to treatment, all patients need to know what to look for regarding recurrence and metastatic disease and how to access help for other issues.

For many women attendance at hospital may be difficult. Many parts of Wales are quite rural and for some the journey can take hours. There is also the issue of parking at the hospital and home arrangements for child care, after school pick-ups or making alternative arrangements for dependents, this in itself can be quite stressful. As a consequence of the COVID 19 pandemic, telephone and video consultations are being used more widely.

Consideration should be given to videoconference platforms (e.g. Attend Anywhere and AccuRx) which can be used to enable remote consultations including follow-up appointments and transfer of documentation. Video consultation technology is funded by the Welsh Government. Telephone or videoconference appointments would aid patients who live in rural areas or by patient choice to avoid travelling to cancer centres and waiting for in busy outpatient clinics.

Patients should be informed of access to talking therapies and psychological therapies during the follow-up years given that this is likely to be a time when patients are most concerned of recurrence and associated anxiety. This need not always be with face-to-face interventions. The Welsh Government has funded a self-referral service for computerised cognitive behavioural therapy (CBT). Powys is hosting this for the rest of Wales and CBT-led interventions within this include anxiety, depression, long term conditions, sleep and money worries as examples (https://www.silvercloudhealth.com/uk).

Patients considered for PIFU should have a Holistic Needs Assessment (HNA) within three months of completion of treatment. Patients planning to transfer to PIFU at a later time point should have an informal assessment and if considered unsuitable for self-managing care then alternative follow-up is advised.

A careful history, assessment of new and potentially tumour-related symptoms is essential at follow-up visits. Models of delivery of care should be more flexible to meet individual needs of patients if improved survival not a realistic goal of scheduled hospital-based surveillance. Follow-up should focus on detecting potentially curable recurrences, such as central pelvic recurrence for cervical or endometrial cancer for those who could tolerate salvage radiotherapy or exenterative surgery or isolated vulval recurrence of vulval cancer. Follow-up can also manage treatable relapsed disease for ovarian, fallopian tube or primary peritoneal cancers. Furthermore, the organisation of clinics should include continuity of care, address survivorship issues and prescribe in advance the frequency and purpose of follow-up. Timely and targeted referral to Allied Health Professionals (AHPs including physiotherapy, occupational therapy and dietitians) is required to support patients fully with survivorship. AHP interventions from rehabilitation to the palliative stage will support the person-centered care focus and support workload of the clinical nurse specialists (CNSs) and doctors. This will allow patents to achieve maximum quality of life. Cancer teams should hold details of support services for patients (via CNS networks) in their own communities and particularly for patients who live in rural areas or some distance from their local hospital. This could be usefully included as part of a package of information at the end of treatment.

Routine follow-up to detect recurrence can be discontinued in women not considered fit for any further treatment after discussion with the patient and appropriate links with community palliative support established where needed.

In summary, an individualised approach to follow-up is likely to be important to concentrate care for those at greater risk of recurrent disease or other issues of survivorship. This may permit risk stratification where effective interventions for physical, psychological and social

issues are evaluated with patient centred needs assessments as defined by National Cancer Survivorship Initiative (Watson et al, 2012).
By decreasing unnecessary follow-up of healthy patients, more time is available to address potential problems. However, more frequent review is appropriate for patients with an anticipated high risk of replapse or other cancer related isssues. Regardless of healthcare resources, future cancer follow-up should be about how service is delivered that ensures patient access to support they need when they need it. Studies show that:

- various options for follow-up are available which if used appropriately would not adversely affect outcome
- communication and access is important
- CA125 may be useful for subset of ovarian cancer patients who may be suitable for surgery at relapse/ cervical testing after loop or cone (see ovary and cervix follow-up sections)
- and ideal duration of follow-up unclear.

3. Role of the clinical nurse specialist (CNS)

All patients should have a named key worker to co-ordinate treatment and their care pathway. For the vast majority of patients this will be the clinical nurse specialist.
The key worker can be an information gatherer, patient advocate and often, the first point of contact (Williamson et al, 2018). Following treatment, there is also an opportunity to seek support and care from the CNS to provide psychosexual counselling and advice. An end of treatment summary is provided. HNAs can form part of the end of treatment summary and can be performed at any time in the patient care pathway. More information about the HNA can be found at www.macmillan/org.uk/recoverypackage. Patients should have the contact details of their key worker so that they access an early review for unexpected symptoms. Generic contact details must be available which should also be available on health board websites.

An increase in telephone or videoconference consultations would take up much of the work of the CNS and the extra work may not always be appropriate. These consultations could be provided by another person, such as a band 5 nurse or health care assistant, as long as they are knowledgeable about follow-up care and can guarantee a prompt appointment or response to be reviewed by the gynaecological consultant or CNS.

4. Follow-up practice for individual tumour types

4.1. Cervix

All patients must be encouraged to report any symptoms suggestive of recurrent disease immediately by contacting their CNS or key worker rather than wait until their next outpatient appointment. Women should receive information on symptoms that should prompt medical attention such as, for example vaginal bleeding and discharge.

The best evidence comes from a Canadian systematic review, a Cochrane review in 2011 and a consensus ESGO State of the Art conference in 2014 but most is low certainty evidence (Lanceley et al, 2013; Elit et al, 2009, Zola et al, 2015).

Following surgery without any added radiation, follow-up has been in the gynaecological oncology clinic supervised by specialist teams. If any uncertainty a biopsy will be organised. There is no proven benefit for imaging of asymptomatic patients, but imaging will be directed by symptoms. Traditionally, most recurrences were thought to occur within the first two years of follow-up following definitive treatment, but recent evidence suggests that this may be delayed when chemotherapy is incorporated in the treatment. Patients receiving concomitant cisplatin-based chemotherapy have a better outcome than those treated by radiation alone and recurrences are more frequently documented after the second year. This has significant implications as historically follow-up was more closely observed in the first two years, but now patients may need to be seen more frequently for longer. Women treated by LLETZ or cone biopsy should have HPV testing at six and 12 months following treatment, then annually to 10 years. If HPV negative at 10 years, they can return to routine recall (Cervical Screening Wales Quality Manual & Laboratory Handbook, 2019). Vault cytology is not helpful following simple or radical hysterectomy and is not recommended if the patient has had radiotherapy. As the risk of recurrence is less than 10% in women having surgery with no adjuvant treatment (Elit et al, 2009) then patient initiated follow-up is an option for patients having recovered from the acute morbidity of surgery. For the remainder hospital-based follow-up including a clinical examination may be reasonable (see figures 1 and 2).

If women have not had radiotherapy, the following should be assessed; sexual function, fatigue, body image, pain, urinary function, vaginal bleeding, leg swelling, menopause symptoms, work, finances and anxieties about recurrence. These can be elicited using a semi-structured clinical enquiry or a formal written assessment tool, according to local practice. Women who have also had external beam radiotherapy to the pelvis should have additional regular enquiries about defecation frequency, bleeding from the rectum, stools that float, weight loss, diarrhoea, rectal urgency and incontinence, haematuria, bladder urgency and capacity, vaginal dryness and dyspareunia. These problems can be reviewed within a late effects clinic using validated assessment tools. Women who have received radiotherapy should have a vaginal examination and dilation therapy advised if they are clinically at risk of vaginal stenosis, or if they have an intention in the future of having penetrative sex.

Although randomised data is lacking, oestrogen replacement therapy appears safe for premenopausal women with squamous cell carcinoma having had bilateral oophorectomy or have menopausal symptoms after their hysterectomy. More caution is advised for adenocarcinomas although evidence of risk is lacking. Patients with menopausal symptoms after primary radiotherapy or chemoradiation should be treated with a continuous combined preparation (Richardson *et al,* 2019).

Apart from the PIFU patients who would not need a follow-up appointment schedule after two years, a suggested scheme is as follows:

- three-monthly for the first and second years
- six-monthly for the third year
- annually until five years
- discharge at five years if all well (see figures 1 and 2).

4.2. Endometrium

All patients must be encouraged to report any symptoms suggestive of recurrent disease immediately by contacting their CNS or key worker rather than wait until their next outpatient appointment. Women should receive information on symptoms that should prompt medical attention such as, for example vaginal bleeding and discharge.

There is currently no evidence to support the use of routine imaging or biochemical testing in follow-up for endometrial cancer. One randomized controlled trial (RCT) comparing hospital and telephone follow-up for women treated for endometrial cancer (ENDCAT: Endometrial Cancer Telephone follow-up trial) showed that telephone follow-up was not inferior to hospital follow-up in terms of psychological morbidity (Beaver et al, 2017). Alternative modes of follow-up such as telephone follow-up do not appear to be inferior to hospital follow-up, in terms of quality of life for stage I endometrial cancer.

Although counterintuitive, there is no evidence that early detection of recurrent disease improves survival (Tjalma et al, 2004, Kew et al, 2005; Baekelandt et al, 2009). A systematic review designed to inform the Canadian healthcare system on optimum follow-up strategies for endometrial cancer reviewed 16 non comparative observational studies (Fung-Kee-Fung et al, 2006). Survival graphs show that most of the deaths from high grade disease occur within the first two years but well differentiated tumours and adjuvant radiotherapy are associated with much longer remission intervals. This implies that follow-up appointments should be most frequent in the first two years for high grade tumours and much less frequent in other cases. It also implies that there may be some cases where the risk of recurrence falls below the threshold for any follow-up.

There is no evidence to suggest that general practitioners, hospital consultants or CNSs have better outcomes. Continuity of care may be associated with greater satisfaction and this is why the CNS or key worker should be involved in all follow-up programmes.

Follow-up should aim to identify isolated pelvic recurrence or vaginal vault recurrence. For women with low risk endometrioid endometrial cancers as defined by ESGO with grade 1-2 endometrioid tumours confined to the inner half of the myometrium with no lymphovascular space invasion (Colombo et al, 2015), it is reasonable to offer an alternative schedule for follow-up such as to discharge to PIFU. Such patients should receive written instructions on when to seek medical input and re-referral. Their GP should be informed of this. For women with high risk endometrial cancers, it is reasonable to use a more rigorous follow-up schedule, with more frequent visits in the first two years, either in the clinic setting or by telephone and then follow-up by any modality for up to five years (see figures 1 and 2). The data is not robust enough to allow us to calculate the utility of follow-up with precision but women with low risk endometrial cancer should be reassured that failure to attend at a follow-up clinic is extremely unlikely to be detrimental to their survival prospects.

If women have not had radiotherapy, the following should be assessed; sexual function, fatigue, body image, pain, urinary function, vaginal bleeding, leg swelling, menopause symptoms, work, finances and anxieties about recurrence. These can be elicited using a semi-structured clinical enquiry or an HNA, according to local practice. Women who have

also had pelvic radiotherapy should have additional regular enquiries about defecation frequency, bleeding from the rectum, stools that float, weight loss, diarrhoea, rectal urgency and incontinence, haematuria, bladder urgency and capacity, vaginal dryness and dyspareunia. These problems can be reviewed within a late effects clinic using validated assessment tools. Women who have received radiotherapy should have a vaginal examination and dilation therapy advised if they are clinically at risk of vaginal stenosis, or if they have an intention in the future of having penetrative sex.

4.2.1. HRT use and endometrial cancer risk

Hormone replacement therapy (HRT) does not appear to alter disease free survival (Barakat et al, 2006) and continuous combined therapy may be theoretically most appropriate for post-operative patients with persistent climacteric symptoms using a low dose progestin. Use of HRT post-surgery is confined usually to young patients who may have preferred to have had their ovaries removed. For the remainder, non-hormonal management is preferred. Cases should be managed on an individual basis and patients should be given a comprehensive explanation balancing any potential risks with benefits.

Patients will need genetic counselling if other family members have had endometrial or other relevant cancers. Weight reduction is advised for those with a high BMI as 60% of deaths from one RCT were from intercurrent disease (Nout *et al,* 2010).

Apart from the PIFU patients who would not need a follow-up appointment schedule, a suggested scheme is as follows:

- three-monthly for the first and second years
- six-monthly for the third year
- annually until five years
- discharge at five years if all well (see figures 1 and 2).

4.2.2. Follow-up for endometrial sarcomas

There is no evidence on the optimal follow-up strategy for patient with uterine sarcoma (leiomyosarcoma and high grade endometrial stromal sarcoma). As early detection of recurrence with the aim of complete surgical resection is the only effective way of managing recurrent sarcoma, most soft-tissue sarcoma guidelines recommend regular CT scans and physical examinations (ESMO/European Sarcoma Network Working Group, 2014). Imaging of the chest should be also part of follow-up.

4.3. Ovary, fallopian tube and primary peritoneum

All patients must be encouraged to report any symptoms suggestive of recurrent disease immediately by contacting their CNS or key worker rather than wait until their next outpatient appointment. Women should receive information on symptoms that should prompt medical attention such as, for example abdominal bloating or pain, persistent altered bowel habit, frequency of micturition, shortness of breath and weight loss.

BRCA testing is now standard for all non-mucinous epithelial high grade carcinomas, regardless of family history, to plan suitability for PARP inhibitor maintenance therapy for

stage III+ patients after completion of first-line chemotherapy or further in the treatment pathway. Homologous recombination deficiency (HRD) testing is recommended in patients with high grade epithelial cancers to plan suitability for olaparib and bevacizumab maintenance treatment. BRCA testing does not affect treatment options for stage I and II patients but does allow referral to cancer genetics to identify high risk families.

An RCT did not reveal a benefit for routine CA125 testing and treatment of relapse at asymptomatic elevation in comparison to treatment at onset of symptoms (Rustin and van der Burg, 2009; Rustin et al, 2010). Patients with an asymptomatic elevated CA125 (two times above normal) were treated five months earlier and were re-treated for second relapse five months earlier for 1442 women having had debulking surgery and first line chemotherapy with a normal CA125 at the end of treatment. Overall survival and quality of life was equivalent in both groups.

DESKTOP III was a prospective randomized study of 407 women with first relapse, with at least partial platinum sensitivity and a positive AGO score (du Bois et al, 2020). A positive AGO score was defined as a performance status of 0, ascites no more than 500ml and complete resection at initial surgery. Median overall survival (OS) was 7.7 months better in the surgical group ($p=0.02$) and an OS benefit of 15.9 months for those having surgery with complete debulking (141 of 207 of the surgical group) versus those not having surgery ($p<0.001$). These results may potentially change current follow up recommendations for the subset of patients with compete resection at initial surgery, if secondary debulking surgery is accepted as a standard of care.

PARAGON was a pooled series of phase 2 trials and reported the role of anastrazole in 52 postmenopausal women with estrogen positive and/or progesterone positive recurrent ovarian cancer, who were asymptomatic and had CA125 progression after response to first line chemotherapy, where chemotherapy was not clinically indicated. Patients received anastrozole 1 mg daily until progression or unacceptable toxicity. Clinical benefit at three months (primary endpoint) was observed in 18 patients (34.6%; 95% confidence interval [CI] 23-48%). Median progression-free survival was 2.7 months but the median duration of clinical benefit was 6.5 months (95% CI 2.8-11.7). Most patients progressed within six months of starting anastrozole but 12 (22%) continued treatment for longer than six months. Anastrozole was well tolerated. Despite the methodological limitations of this small study, anastrozole may delay symptomatic progression and the time to subsequent chemotherapy and this subset of patients may also benefit from regular CA125 estimations (Kok et al, 2019).

Currently, CA125 measurement is not recommended for follow-up for AGO negative women following treatment for ovarian cancer without symptoms. Imaging for ovarian cancer is suggested to monitor response to chemotherapy or for suspected relapse only and is not recommended routinely. Despite this, some patients may wish to know what might lie ahead and for these CA125 testing is reasonable. CA125 testing may also include patients with estrogen and/ or progesterone receptor positive postmenopausal ovarian cancer after first line treatment. For AGO positive patients a rise in CA125 might indicate surgically resectable disease recurrence, while for others it may trigger imaging that will determine timing and value of further treatment (Hall and Rustin, 2011).

Because most patients with stage III disease recur after completion of treatment and most patients initially present with stage III/IV disease then follow-up should be in clinic for the first three years when recurrence is most likely.

The risk of recurrence is less than 10% for a subgroup of patients with stage Ia/b disease after complete surgical staging with pelvic and para-aortic lymphadenectomy. This small group of patients could be offered patient initiated follow-up (Colombo et al, 2019).

4.3.1. HRT use and ovarian cancer risk

A prospective questionnaire study of 948,576 women and subsequent meta-analysis showed that with a mean of 5.3 years follow up, current use of HRT for women without ovarian cancer at enrolment was associated with an increased incidence and death from ovarian cancer. The effect was seen in serous histology only and included borderline tumours. A non-significant increased risk was seen with increased duration of use. Previous use of the combined pill did not attenuate this effect. Also past users of HRT were not at increased risk. This effect was such that over five years one extra ovarian cancer was seen in 2500 users and one extra cancer death per 3300 users (Million Women Study Collaborators, 2007). A 33% increased relative risk was seen for serous and endometrioid cancer in women using HRT for more than five years from a US study of 169,391 women and follow-up for 9.8 years including 849 cases (Yang et al, 2012). These findings were confirmed in a meta-analysis of 12,110 women where the estimated increased risk of ovarian cancer was 1 extra case per 1000 users after five years of use (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2015). The effect was the same with oestrogen and eostrogen/ progesterone therapy and was confined to serous and endometrioid histological sub-types only. However, three studies showed no increased risk of recurrence in women taking HRT for ovarian cancer patients. One was a prospective controlled study of 150 women and two were meta-analyses, one of 1448 women and the other a meta-analysis of 1521 women (Eeles et al, 2015; Li et al, 2015; Pergialiotis et al, 2016). Although the data is conflicting between population and case studies, HRT should, in general, not be offered to women with serous or endometrioid carcinoma but women with serous borderline tumours should be fore-warned of a slight increased risk of recurrence of borderline disease should they choose to use HRT. This advice will depend of the wishes of each woman and the severity of the menopausal symptoms needing treatment.

Patients will need genetic counselling if other family members have had ovarian or other relevant cancers.

Apart from the PIFU patients who would not need a follow-up appointment schedule, a suggested scheme is as follows:

- three-monthly for the first and second years
- six-monthly for the third year
- annually until five years
- discharge at five years if all well (see figures 1 and 2).

A CA125 test may be appropriate for AGO positive women and women with estrogen and/ or progesterone receptor positive postmenopausal ovarian cancer after first line treatment.

This can be offered remotely for those having telephone follow-up after three years (see figures 1 and 2).

4.3.2. Follow-up for granulosa cell tumours and germ cell tumours

Patients having had treatment for granulosa cell tumours should have a serum inhibin test at each visit and follow-up should be for at least 10 years in view of known later recurrences between four to six years but can occasionally be much later (Colombo *et al,* 2012). Hospital follow-up is recommended. Similarly, germ cell tumours are restricted to hospital follow-up. Tumour markers with beta-HCG, CA125, alpha-fetoprotein should be taken at each follow-up visit.

4.3.3. Borderline ovarian or fallopian tube tumours

Patients with FIGO stage I-II borderline ovarian or fallopian tube tumours with complete surgical staging can be discharged from follow-up. More advanced cases may require lifelong follow-up but evidence to guide care is lacking.

4.4. Vulva

All patients must be encouraged to report any symptoms suggestive of recurrent disease immediately by contacting their CNS or key worker rather than wait until their next outpatient appointment. Women should receive information on symptoms that should prompt medical attention such as, for example the development of a new lesion on the vulva or vulval irritation.

Follow up should include clinical examination of the vulva and groins with assessment for physical and psychological sequelae of treatment. Evidence to inform the optimal follow-up regime in vulval cancer is lacking. Loco-regional recurrence rates are highest in the first two years and follow-up regimes should reflect this. Patients planning or having had a groin node dissection should have a lymphoedema clinic outpatient appointment to discuss skin care, compression stockings and limb elevation. Further review with the lymphoedema team, in addition to outpatient surgical follow-up will be at the discretion of the lymphoedema team.

As patients who relapse locally with vulval carcinoma have a good chance of cure and prolonged remission with prompt re-treatment, the patient should be followed up in an environment where trained personnel are available to recognise the earliest signs or symptoms of recurrence at the cancer centre or unit. In one retrospective review overall vulval squamous cell carcinoma (VSCC) recurrence rate was 22.6%, although the local recurrence rate is proportional to the duration of follow-up, with an annual rate of approximately 4%. The odds ratio (OR) of having a recurrence of VSCC associated with differentiated vulval intraepithelial neoplasia (dVIN) alone was 3.85 (95% CI 0.52, 28.24) and higher when dVIN is in combination with lichen sclerosus or lichen planus (OR 4.3; 95% CI 0.84 to 21.92). The risk of VSCC recurrence on a background of usual-type VIN (uVIN) was much less (OR 1.35; 95% CI 0.20, 9.01). Even in early stage disease, local recurrences can occur a long time after primary treatment, leading some to advocate life-long follow-up after a diagnosis of vulval cancer (Te Grootenhuis et al, 2018). However, those with unifocal, HPV-related disease are at lower risk and the in absence of new areas of uVIN developing

during follow-up, discharge from follow-up, with emphasis on the need for rapid re-referral in the event of developing a new lesion, may be considered after five years.

A recent study suggested that three-monthly ultrasound of the groins for two years following negative sentinel node dissection was cost effective in the detection of lymph node metastasis (Pouwer et al, 2018).

There is no proven regimen for follow-up of VSCC. However, recurrence rates and new foci are common, especially on a background of lichen sclerosus. Those with no recurrence of VSCC or uVIN could be discharged with access to rapid re-referral after five years. Those with recurrent disease and multi-focal disease may need life-long follow-up. All patients should be told to report new lesions and be seen urgently since interval cancers are common and should be treated promptly.

4.4.1. Follow-up of Basal cell carcinoma of the vulva

Patients with basal cell carcinoma, if margins are clear following surgery, are unlikely to have recurrent disease and long term follow-up is not indicated. Patients with Gorlin's syndrome are at risk of basal cell carcinoma across skin sites and so long-term follow-up with a specialist dermatology team is more appropriate.

4.4.2. Follow-up of Vulval Paget's Disease

The risk of recurrence or development of invasive disease is high and, with lack of data to guide recommendations, long-term follow-up in a specialist gynaecological cancer clinic is suggested (RCOG, 2014).

4.4.3. Follow-up of malignant melanoma of the vulva

Recurrence is common and early with these tumours and follow-up should be hospital-based.

A suggested scheme for VSCC is as follows:

- three-monthly for the first and second years
- six-monthly for the third year
- annually thereafter.

4.5. Other tumours

Juvenile tumours
Soft tissue sarcomas (excluding uterine leiomyosarcoma and endometrial stromal sarcoma)
Stromal tumour of uncertain malignant potential (STUMP)

Due to the low incidence and lack of data regarding outcomes of differing modes of follow-up, all juvenile tumors and soft tissue sarcoma (including STUMP) patients should be seen at regular intervals in the gynaecological oncology or sarcoma clinics for their follow-up.

5. Recommendation for care

The BGCS has issued a comprehensive paper about the value of patient initiated follow-up in gynaecological cancers, that supports the approach of the all-Wales guideline in patients with early disease who have not experienced any relapse (Newton et al, 2020). Please see follow-up algorithm below.

Figure 1

	Endometrium	Cervix	Ovarian	Vulva/vaginal
PIFU for 5yrs from treatment	**Low risk** (<10% risk of recurrence ROR) from end of treatment HNA by 3/12. **Intermediate risk** (10-20% ROR) offer from end of treatment or 2yrs for all; **High risk** (>20% ROR) offer from 2yrs from end of treatment.	Excluding fertility sparing surgery/LLETZ; **Low risk** from 2yrs. HNA by 3/12.	Excluding fertility sparing surgery; **Low risk** (stage 1a/b fully staged) from end of treatment. HNA by 3/12.	
Remote/telephone +/- bloods	**Intermediate risk** up to 2yrs and **high risk** up to 5yrs in place of clinic based FU.		**All others**: option of remote for yrs 4&5 post first-line treatment (clinic based FU 1-3yrs). CA125 if AGO +ve. BRCA testing.	
Clinic based FU (shared with surgical, clinical or medical oncology if multimodality treatment)	**Intermediate risk** up to 2yrs and **high risk** up to 5yrs in place of remote FU.	**Intermediate** and **high risk**: 1-5yrs post completion of treatment.	**All others**: 1-3yrs if suitable & elects remote FU for years 4&5; 1-5yrs if not suitable or declines remote FU for yrs 4&5. CA125 if AGO +ve. BRCA testing.	FU including clinical inspection for at least 5yrs from last treatment. Include lymphoedema clinic.

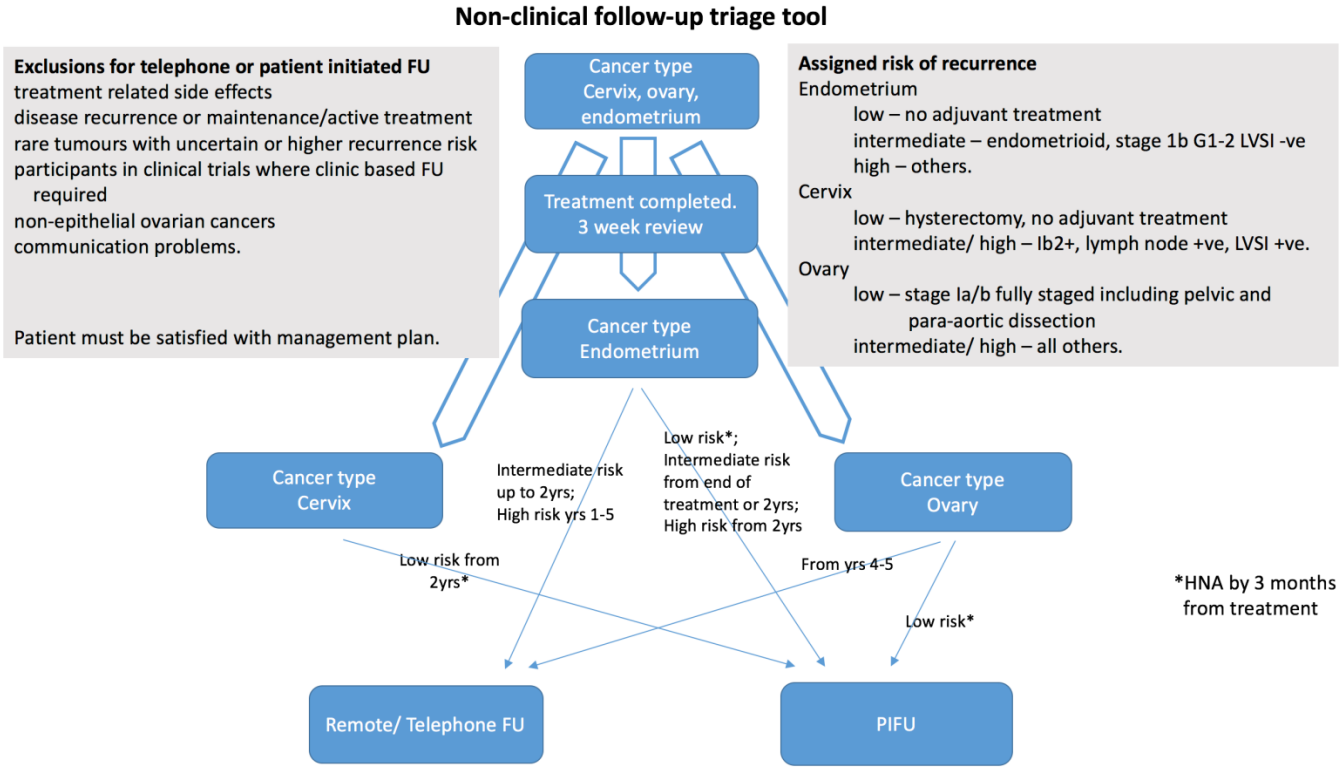
Assigned risk of recurrence (ROR: low <10%; intermediate 10-20%; high >20%)

- Endometrium
  - low – no adjuvant treatment
  - intermediate – endometrioid, stage 1b G1-2 LVSI –ve
  - high – others.
- Cervix
  - low – hysterectomy, no adjuvant treatment
  - intermediate/ high – Ib2+, LN +ve, LVSI +ve.
- Ovary
  - low – stage Ia/b fully staged including pelvic and PAN dissection
  - intermediate/ high – all others.

For ovarian cancer patients: CA125 testing recommended for AGO positive women for remote or clinic-based follow-up. Other subsets (as described in section iii) may have CA125 testing.

Non-clinic based follow-up options can be interpreted with the following algorithm:

Figure 2



6. Implications for service

Clinic templates must have capacity for patients to be seen at short notice who request or need review from PIFU or remote follow-up. This will be up to local teams to organise. Case management must be reviewed by regular audit, for example, to ensure that HNAs are completed prior to patients starting PIFU or remote follow-up; timeliness for review patients once returned to clinic and waiting room waiting times for all follow-up patients in hospital based clinics.

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Appendix : Methodology

These guidelines were written in accordance with the Wales Cancer Network Guidance for Clinical Guideline Development

- Email to members of the Wales Cancer Networks asking for expressions of interest in contributing to guideline development
- Initial meeting
- Circulating of draft document to those who had expressed an interest
- Modification in response to comments
- Circulating to wider network for consultation
- Comments reviewed by group prior to submission on 19.02.21.