All Wales Guideline for the Management of Cancer of the Cervix

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Contents

List of Tables

Foreword

Cervical cancer is an uncommon condition that affects around 150 women in Wales each year. Women of any age can be affected with the peak incidence in the 25-29 year old age group. The treatment for cervical cancer is complex and can involve surgery, radiotherapy and systemic anticancer therapy. Women with cervical cancer are often of child-bearing potential and they may require specific counselling on fertility sparing options. Patients need timely expert help and support to navigate through their cancer diagnosis, treatment and after-effects. 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 fo treatment for women with cervical cancer in Wales.

Scope of this document

This document covers the diagnosis and treatment of cancer of the cervix. It also considers support of patients and consequences of cancer treatment. Screening and prevention of cervical cancer is addressed by Cervical Screening Wales in their guidelines and policies (Cervical Screening Wales Quality Manual and Laboratory Handbook
http://howis.wales.nhs.uk/screeningprofessionals/quality-manual

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1 Background

1.1 Incidence, age and mortality

1.1.1 Incidence

Cervical cancer is the 13th most common cancer in females in the UK (CRUK, 2017). In 2014 there were 164 cases of cervical cancer in Wales, giving a European age-standardised rate of 10.7 per 100,000 and a lifetime risk of around 1 in 135 women in the UK. Cervical cancer accounts for less than 1% of all cancer cases in the UK. The incidence peaked around 1985-1987, but decreased by around a quarter from the 1990s, as a result of the cancer screening programme, but has remained fairly constant since 2000. It is anticipated the national programme to vaccinate girls and boys against human papilloma virus (HPV) will reduce the incidence further.

1.1.2 Age

Over half of all cases of cervical cancer occur in women under the age of 45. The peak age group affected by cervical cancer is the 25 to 29 year old age group. In contrast, the majority of deaths from cervical cancer occur in women aged 45 and over.

1.1.3 Mortality

In 2014 there were 52 deaths in Wales from cervical cancer (CRUK, 2017). The highest mortality is in over 85 year olds. Since the 1970s, cervical cancer mortality rates have decreased by almost three quarters in the UK.

1.2 Aetiology

The main risk factor for cervical carcinoma is HPV infection. Most women are exposed to HPV, but it is persistent infection that leads to malignant change. Genital tract HPV is considered fairly ubiquitous, and it is estimated that the vast majority of sexually active adults will acquire the infection before the age of 50 (Manhart *et al.,* 2006). The majority of individuals however will clear genital tract HPV infection, but some develop persistent infection leading to progression of a clone of epithelial cells which may develop into pre-cancer and ultimately to cancer. Not all pre-cancerous lesions develop into cancer; regression and clearance may occur. HPV types 16 and 18 confer the highest risk, and are found in over 70% of cervical cancers. There are now over a dozen identified high risk types, including types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 (Castellsague, *et al.,* 2006; Muñoz *et al,* 2003). The viral proteins E6 and E7 are responsible for malignant transformation and herpes simplex virus type 2 may act as a co-factor (Smith *et al.*, 2002).
Other risk factors are:

- Early onset of sexual activity
- Early age at first pregnancy
- Multiparity
- Multiple sexual partners
- Partner who has had multiple sexual partners
- Use of oral contraceptive pill (Moreno *et al.*, 2002)
- Cigarette smoking
- Increased deprivation (WCISU, 2011)
- Immunocompromise (AIDS defining illness)
- Diethylstilboestrol exposure *in utero* (clear cell carcinoma, as in vagina)

2 Screening and prevention

2.1 Screening

Cervical screening prevents cancer by detecting the presence of HPV and if positive, by additionally detecting dyskaryotic cells in a sample taken from the cervix using a soft brush, to allow subsequent treatment of the abnormality.

Cervical screening in Wales is overseen by Cervical Screening Wales using a call and recall system. Women aged from 25-49 are invited every three years and women aged 50-64 are invited every five years.

Screening coverage exceeds 76% in all Health Boards in Wales, and at 31 March 2015, 78% of women in the target age group had been screened with an adequate result at least once in the last five years (CSW, 2015).

From September 2018, Wales converted over to a HPV-based primary screening system, which detects 13 high risk HPV strains. This is more sensitive than cytology-based screening (Arbyn M, 2009; Anttila A, 2010; Katki HA, 2011). The clinical pathways for managing HPV results are outlined on the CSW intranet page for professionals (http://howis.wales.nhs.uk/screeningprofessionals)

2.2 Prevention

2.2.1 UK HPV vaccination programme

The UK national HPV immunisation programme was introduced in 2008. From 2012, the vaccine Gardasil® has been made available on the national programme, which is designed to prevent infection by HPV types 6, 11, 16 and 18 and therefore offers some protection against genital warts. In Wales, vaccine is offered to girls from age 12. The vaccine is normally offered through schools but is also available from GPs. Uptake of one dose of HP vaccine in girls turning 14 years of age during the School Year 9 was 90% in Wales (Public Health Wales, 2016). Human Papillomavirus (HPV) vaccine uptake in girls turning 14 years of age during the 2017/18 school year was 87% for the first dose. Uptake of the complete two-dose course in girls turning 15 years of age was 83% (Wales).

2.2.2 Reduction of risk factors

Smoking cessation should be encouraged, because smoking is a risk factor for squamous cervical cancer (Foseca-Moutinho, 2011).

There is some evidence that the use of safe sex methods such as using a condom can reduce the chance of HPV infection (Winer *et al.,* 2006).

3 Pathology

3.1 Types of tumour

The following types of malignant tumours occur in the cervix (WHO, 2014).

- Epithelial tumours
    - Squamous cell carcinoma, NOS
        - Keratinizing
        - Non-keratinizing
        - Papillary
        - Basaloid
        - Warty
        - Verrucous
        - Squamotransitional
        - Lymphoepithelioma-like
    - Adenocarcinoma
        - Endocervical adenocarcinoma, usual type
        - Mucinous carcinoma, NOS
            - Gastric type
            - Intestinal type
            - Signet-ring cell type
        - Villoglandular carcinoma
        - Endometrioid carcinoma
        - Clear cell carcinoma
        - Serous carcinoma
        - Mesonephric carcinoma
        - Adenocarcinoma admixed with neuroendocrine carcinoma
    - Other epithelial tumours
        - Adenosquamous carcinoma
            - Glassy cell carcinoma
        - Adenoid basal carcinoma
        - Adenoid cystic carcinoma
        - Undifferentiated carcinoma
    - Neuroendocrine tumours
        - Low-grade neuroendocrine tumour
            - Carcinoid tumour
            - Atypical carcinoid tumour
        - High grade neuroendocrine carcinoma
            - Small cell neuroendocrine carcinoma
            - Large cell neuroendocrine carcinoma
- Mesenchymal tumours
    - Leiomyosarcoma
    - Rhabdomyosarcoma
    - Alveolar soft-part sarcoma
    - Angiosarcoma

    - Malignant peripheral nerve sheath tumour
    - Other sarcomas
- Mixed epithelial and mesenchymal tumours
    - Adenosarcoma
    - Carcinosarcoma
- Melanocytic tumours
    - Malignant melanoma
- Germ cell tumours
    - Yolk sac tumour
- Lymphoid and myeloid tumours
    - Lymphomas
    - Myeloid neoplasms

The cervix can also be a site of spread for metastatic cancers.

3.2 Grade

The Royal College of Pathologists currently recommends that squamous carcinomas are graded according to a modified version of Broders as well-differentiated (keratinising), moderately or poorly differentiated (Stock *et al.,* 1994). Grading is based on the degree of keratinisation, cytonuclear atypia and mitotic activity. It may not be possible or relevant to grade very early, minimally invasive carcinomas of squamous or glandular type and in such situations it is recommended that tumours are graded as GX (grade cannot be assessed). There is no agreed grading system for cervical adenocarcinoma. It has, however, been recommended that these tumours be graded according to the FIGO system for endometrial adenocarcinoma (NHSCSP Publication No 10, 1999), but in cervical adenocarcinoma the nuclear grade may be more significant (Nola et al., 2005). Grading of adenosquamous carcinomas as well, moderately or poorly differentiated according to the degree of differentiation of the squamous and glandular components is suggested by the Working Group (NHSCSP Publication No 10, 1999). Neuroendocrine carcinomas are not graded. The carcinomas are, by definition, high-grade, aggressive tumours - Royal College of Pathologists dataset for reporting cervical neoplasia (Hirschowitz *et al.,* 2011).

3.3 Dataset

Pathology reports should be compiled in accordance with the Royal College of Pathologists core dataset for reporting of cervical cancer (Hirschowitz *et al.,* 2011):

3.3.1 Reporting for cervical cancer in excisional cervical biopsies

- Description of specimen and core macroscopic details
- Core microscopic items
    - Type of cancer
    - Differentiation/grade
    - Distribution of invasive component
    - Tumour size
    - Whether invasive foci are present in three or more sequential slices of tissue
    - Excision status

    - If complete excision, distance to closest resection margin and which margin is closest
    - Other features
        - Cervical intra-epithelial neoplasia (CIN) and grade
        - Cervical glandular intra-epithelial neoplasia (CGIN) and grade
        - Stratified mucin-producing intra-epithelial lesion (SMILE)
        - Whether specified excision margins are clear or involved with CIN, CGIN or SMILE
    - Lymphovascular space invasion
- Provisional FIGO stage; SNOMED codes

3.3.2 Reporting for cervical cancer in hysterectomy specimens

- Description of specimen and core macroscopic items
    - Vaginal cuff presence, length and diameter
    - Dimensions of uterus
    - Adnexa presence and whether normal or abnormal
    - Whether cervical tumour seen and maximum dimensions of tumour
    - Position of cervical tumour
    - Macroscopic involvement of vagina, parametria or paracervical tissues
- Core microscopic items
    - Histological type
    - Differentiation/grade
    - Tumour size
    - Minimum thickness of uninvolved cervical stroma and position
    - Closest radial resection margin and position
    - Vaginal involvement and position
    - Paracervical and parametrial involvement
    - Lymphovascular invasion
    - Presence of CIN and grade, CGIN and grade or SMILE
    - Pelvic nodes, right/left, number and number involved
        - Extranodal spread
    - Para-aortic nodes, total number and number involved
        - Extranodal spread
- Other tissues or organs; endometrium, myometrium, right and left adnexa and whether abnormal
- Provisional pathological FIGO stage and SNOMED codes

4 Staging

The FIGO and the TNM staging systems have been designed to correspond with each other, but there are important differences in the assessments allowed for each system.

For TNM staging, the regional lymph nodes are the pelvic nodes. The new 2018 FIGO staging system states that lymphatic spread is to regional lymph nodes, namely obturator, external iliac and internal iliac, and then to the common iliac and para-aortic nodes (Bhatla, 2018).

4.1 FIGO staging

The 2009 FIGO staging of cervical cancer is a clinical stage, based on clinical evaluation. This requires careful clinical examination, preferably by an experienced examiner. The FIGO clinical staging rules only allow the following tests to be permitted: palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, X-ray examination of the lungs and skeleton, and conisation or amputation of the cervix (Benedet *et al.,* 2000). Although the current (2009) staging system states that any other investigations may be used in planning treatment, but they must not change the clinical staging,

The new FIGO staging system (2018) notes that clinical assessment is the first step in allocation of staging and now also allows for imaging and pathology to be taken into consideration. Imaging modalities include ultrasound, CT, MRI and positron emission tomography (PET). MRI is the best radiological method to assess tumours greater than 10 mm. The modality of imaging used should be noted.

We have inserted both staging systems here but the UK will formally adopt the FIGO 2018 system in 2020 to allow for changes to the cancer registries. The FIGO staging also states that when in doubt, the lower staging should be assigned (Bhatla 2018)

Table 1 The FIGO staging system for cervical cancer(adapted from Pecorelli, 2009)

FIGO stage	Description
Stage I	Carcinoma confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≤7 mm
IA1	Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm
IA2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm
IB	Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA
IB1	Clinically visible lesion ≤4.0 cm in greatest dimension
IB2	Clinically visible lesion >4.0 cm in greatest dimension
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
IIA	Without parametrial invasion
IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension
IIA2	Clinically visible lesion >4 cm in greatest dimension
IIB	With obvious parametrial invasion
Stage III	The tumour extends to the pelvic wall and / or involves the lower third of the vagina and / or causes hydronephrosis or non-functioning kidney
IIIA	Tumour involves lower third of the vagina, with no extension to the pelvic wall

IIIB	Extension to the pelvic wall and / or hydronephrosis or non-functioning kidney
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

FIGO 2014

Table 2 The FIGO staging system for cervical cancer (adapted from Bhatla *et al.,* 2018)	
FIGO stage	Description
Stage I	Carcinoma confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma which can be diagnosed only by microscopy, with maximum depth of invasion ≤5 mm [1]
IA1	Measured stromal invasion of ≤3.0 mm in depth
IA2	Measured stromal invasion of ≥3.0 mm and not >5.0 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5.0mm (greater than Stage 1A), lesion limited to the cervix uteri
IB1	Invasive carcinoma ≥5mm of stromal invasion and <2cm in greatest dimension
IB2	Invasive carcinoma ≥ 2cm depth of stromal invasion and <4cm in greatest dimension
IB3	Invasive carcinoma ≥4cm in greatest dimension
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
IIA	Involvement limited to the upper 2/3 of the vagina without parametrial involvement
IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension
IIA2	Clinically visible lesion ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
Stage III	The tumour extends to the pelvic wall and / or involves the lower third of the vagina and / or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or para-aortic lymph nodes
IIIA	Tumour involves lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and / or hydronephrosis or non-functioning kidney (unless previous known cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes[2]

[1] The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered

[2] Adding notation of R (imaging) and p (pathology) to indicate the findings that are used to allocate the cases to Stage IIIC

IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lynph node metastasis
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

FIGO 2018

4.2 TNM staging

In contrast to the FIGO 2009 staging system, the TNM system encourages the use of diagnostic imaging techniques. Other investigations such as examination under anaesthesia, cystoscopy, sigmoidoscopy, intravenous pyelography are optional and no longer considered mandatory in the TNM staging system.

Table 3 The TNM staging system for cervical cancer (adapted from UICC, 2009)	
TNM stage	Description
T stages	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ* (preinvasive carcinoma)
T1	Tumour confined to the cervix (extension to corpus should be disregarded)
T1a1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread of 7.0 mm or less
T1b	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a
T1b1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	Tumour invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	Tumour without parametrial invasion
T2a1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	Tumour with parametrial invasion
T3	Tumour extends to pelvic wall, involves lower third of vagina, causes hydronephrosis or non-functioning kidney
T3a	Tumour involves lower third of vagina
T3b	Tumour extends to pelvic wall, causes hydronephrosis or non-functioning kidney
T4	Tumour invades mucosa of the bladder or rectum, or extends beyond true pelvis
N stages	

NX	Regional lymph nodes cannot be assessed
N0	No regional node metastasis
N1	Regional lymph node metastasis*
M stages	
M0	No distant metastasis
M1	Distant metastasis (includes inguinal lymph nodes and intraperitoneal disease except metastasis to pelvic serosa). It excludes metastasis to vagina, pelvic serosa and adnexa
*Regional lymph nodes are the paracervical, parametrial, hypogastric (internal iliac, obturator), common and external iliac, presacral and lateral sacral nodes. Para-aortic nodes are not regional.	

4.2.1 TNM stage groups

The TNM stage groups are slightly different from the FIGO stage groups.

Table 4 The TNM stage groups (adapted from UICC, 2009)

T / N / M stages	N0	N1	M1
Tis	Stage 0	Stage IIIB	Stage IVB
T1	Stage I	Stage IIIB	Stage IVB
T1a	Stage IA	Stage IIIB	Stage IVB
T1a1	Stage IA1	Stage IIIB	Stage IVB
T1a2	Stage IA2	Stage IIIB	Stage IVB
T1b	Stage IB	Stage IIIB	Stage IVB
T1b1	Stage IB1	Stage IIIB	Stage IVB
T1b2	Stage IB2	Stage IIIB	Stage IVB
T2	Stage II	Stage IIIB	Stage IVB
T2a	Stage IIA	Stage IIIB	Stage IVB
T2a1	Stage IIA1	Stage IIIB	Stage IVB
T2a2	Stage IIA2	Stage IIIB	Stage IVB
T3	Stage III	Stage IIIB	Stage IVB
T3a	Stage IIIA	Stage IIIB	Stage IVB
T3b	Stage IIIB	Stage IIIB	Stage IVB
T4	Stage IVA	Stage IVA	Stage IVB

5 Indications for referral

5.1 Symptomatic patients

Patients with locally advanced disease may present with symptoms such as post-coital bleeding, dyspareunia, vaginal discharge, pelvic pain, back pain, abnormal vaginal bleeding or menorrhagia. For symptomatic patients, a referral via a suspected cancer pathway (two week wait) should be considered if the appearance of the cervix is consistent with cervical cancer (NICE, 2015). Clinical examination in primary care including abdominal, vaginal and speculum examination is therefore of paramount importance in diagnosing cervical cancer, as NICE guidance is based on the appearance of the cervix.

For GPs: if cancer of the cervix is suspected then referral should be to the Cancer Unit lead clinician or to the Cancer Centre team. The patient should be seen within 10 working days of the initial referral from the GP.

For non-oncological gynaecologists: if the patient is referred to a gynaecologist, then referral should be at the earliest opportunity to the lead clinician in gynaecological oncology in the Cancer Unit or the Cancer Centre team. If the woman presents with advanced disease such as renal failure from ureteric obstruction or bowel complications, she may be seen initially by the urologists or the general surgeons. Thence, patients should be referred to the lead clinician in gynaecological oncology in the Cancer Unit or the Cancer Centre team for consideration of further management.

5.2 Asymptomatic patients

Patients with asymptomatic early stage disease who are detected via the cervical screening programme are referred urgently to gynaecology.

6 Diagnostic and treatment pathways

Timely diagnosis and treatment is of paramount importance in cervical cancer. Local pathways should be agreed.

7 The role of the multi-disciplinary team (MDT)

All cases of cervical cancer should be reviewed by a gynaecological cancer centre MDT. The role of the MDT is to agree the clinical facts through multidisciplinary specialist review, bringing together all clinical and diagnostic information and advise the clinical team delivering the care on evidence based treatment options and clinical trials. Whilst strong individual and consensus views should be recorded, it is the individual consultant and his/her team that has direct clinical responsibility for the care of the patient (Jones and Allan, 2014).

It is likely that the patient will be discussed in two different MDTs, within the Cancer Unit and the Cancer Centre. The Unit and Centre MDTs must work together to ensure that processes and pathways are developed to ensure efficiency and timeliness of referrals *(Level 5).*

8 Clinical assessment and investigation

Formal assessment should include an assessment of disease extent and spread, and tissue is required for histological diagnosis. Colposcopic assessment is required for microinvasive (FIGO Ia) disease.

Diagnosis depends on a suitably-sized biopsy (loop, cone, wedge biopsy or punch biopsy for macroscopic tumours). A biopsy sufficient to establish a diagnosis is required. A loop (LLETZ, NETZ or laser excision) or knife cone biopsy for suspected microinvasive disease and multiple punch biopsies from the edge of a macroscopic lesion are recommended.

A biopsy can often be performed in an out-patient clinic. If the patient cannot tolerate an outpatient procedure then examination under anaesthetic should be performed.

9 Staging investigations and pre-treatment work-up

9.1 Staging

For a FIGO stage to be assigned, careful clinical examination should be performed in all cases. The FIGO guidelines state that examination under anaesthetic is preferable although not mandatory (Benedet *et al.,* 2000).

Staging should be undertaken by a suitably trained individual or under their direct supervision. Staging should include assessment of the size of the tumour, extension to the vagina, the pelvic side wall and the mobility of any mass. Rectal examination assesses parametrial involvement and spread of the tumour towards the pelvic side wall. In clinically visible disease, consideration should be given to an examination under anaesthetic (EUA), cystoscopy and sigmoidoscopy. However, cystoscopy and sigmoidoscopy should not be routinely performed for staging purposes for all cancers, and should be considered only if patients are clinically symptomatic (Bhatla 2018)(*grade B recommendation).*
Examination under anaesthesia requires a vaginal examination to determine the degree of encroachment of tumour into the vagina, to the pelvic side wall and the mobility of any mass. Rectal examination allows assessment of parametrial involvement and spread of tumour toward the pelvic sidewall. Simultaneous rectal and vaginal examination may provide improved assessment of the uterosacral ligaments and pelvic sidewall compared to rectal examination. Clinical staging may underestimate the extent of tumour due to difficulties in assessing parametrial, pelvic sidewall, rectal and bladder invasion as well the presence or absence of metastatic disease.

Increasingly with the widespread availability and use of cross sectional imaging, sufficient information can be gained to direct treatment without the use of EUA. EUA can add an extra step to the diagnostic pathway that could increase the time to treatment. If it is felt that enough information has been gained by other means to direct treatment appropriately then EUA can be omitted. *(Level 5)* Documentation of examination findings that are available to all members of the MDT is essential, e.g. in the same format as an EUA operation note if an EUA is not performed.

9.2 Imaging

9.2.1 General principles

1. All imaging request forms for a patient on a cancer pathway target (e.g. 31 days for USC) must be appropriately marked with this information and with the priority box ticked Urgent.
2. All imaging requests for cancer investigation should adhere to the Cancer Network referral protocols and any other specific requirements set out under each cancer site-specific set of standards.
3. All urgent requests must be delivered and/or otherwise communicated to the appropriate Radiology Dept within 1 working day of signature by the referrer in strict accordance with the agreed referral route as indicated by the Radiology Department in their written referral guidelines.
4. In order to avoid unnecessary travel, imaging should always be arranged as close to the patient's home as is possible without detriment to quality and safety. This is a core commitment of Welsh Government as outlined in the NHS Wales Delivery plan: "Together against Cancer". Arrangements should be in place at the patient's local hospital to accept appropriate referrals for imaging from approved clinicians across the network.

Standard: Imaging departments should provide clear, written information to MDTs on the range of investigations provided and their availability. Where availability is limited or intermittent, particularly for complex investigations, there should be written alternative referral pathways agreed with the Cancer Network.

Standard: All Departments of Clinical Radiology should have written policies on the referral and imaging investigations of patients with cancer or suspected cancer by cancer site. These should reflect the latest advice from the Royal College of Radiologists which includes recommendations on imaging protocols (Rockall *et al.,* 2014).

9.2.2 MRI scan

MRI scan abdomen/ pelvis for: primary tumour size, presence of lymphadenopathy (>1cm diameter), ureteric involvement and parametrial spread. This should be arranged locally with the aim that this is performed within 2 weeks of request. The scan needs to include upper abdominal imaging for para-aortic lymph nodes. Cervical biopsy/loop/cone will cause some artefact and MRI should either be performed prior to this or ideally after at least 1 week. IV gadolinium is not routinely required. IV buscopan may reduce artefact from bowel peristalsis if problematic. Parametrial spread is best assessed on high resolution small FOV T2 axial oblique imaging (i.e. perpendicular to the cervix). The following Royal College of Radiologists recommendations (2014) are considered the minimum standard (Rockall *et al.,* 2014):

Table 4 Protocol for imaging of carcinoma of the cervix

Sequence	**Plane**	**Slice thickness**	**Field of view**	**Principle observations**
T1W	Axial	5/6 ± 0.5/1 mm	Large From renal vessels to symphysis pubis	To identify para-aortic and pelvic lymph nodes and rule out hydronephrosis
T2W	Axial	5/6 ± 0.5/1 mm	Whole pelvis	
T2W	Sagittal	5/6 ± 0.5/1 mm	Small	To assess size and position of tumour in relation to internal os and adjacent tissues
T2W Perpendicular to cervix	Oblique*	3 ± 1 mm	Small	To assess parametrial spread and measure size

T2W**	Coronal or axial	6/7 ± 1 mm	Large	Abdominal lymph nodes and kidneys
T1W + fat sat +gad	Axial	5 ± 1 mm		Optional sequence: to identify enhancing soft tissue nodules
* Perpendicular to plane of endocervical canal ** Choice of axial or coronal upper abdominal images can be according to local preference				

9.2.3 Other imaging

The Royal College of Radiologists recommends staging imaging in all patients presenting with histologically proven cervical cancer (Rockall *et al.,* 2014). MRI is the modality of choice for local disease stage, but CT is also a valuable technique for staging abdominal and pelvic disease, as well as the chest in locally advanced disease (Rockall *et al.,* 2014).

The chest should be imaged to look for metastatic disease. Chest X-ray (CXR) or CT thorax (+/- abdomen and pelvis as required) are undertaken.

9.2.4 PET-CT

PET scanning in cervical cancer is currently commissioned in Wales for the following indications (WHSSC, 2016), which are based on the FIGO 2009 staging:

a) Staging or restaging of patients with carcinoma of the uterine cervix being considered for exenterative surgery.
b) Staging of patients with carcinoma of the uterine cervix FIGO stage <IB2 with suspicious pelvic nodes on MRI or FIGO stage IB2-IVB with the exception of those patients with stage IVB who have disease outside of a radically-treatable radiotherapy field. PET scan should be requested at the earliest opportunity as aforementioned.
c) Suspected recurrence of cervical cancer where other imaging is equivocal and where there is a potential radical treatment option such as para-aortic radiotherapy or stereotactic radiotherapy for in-field lymph node recurrences.

9.3 Other tests

FBC, renal, liver and bone profiles.

10 Referral to the cancer centre

Women with cervical cancer should be referred to the cancer centre for treatment with the exception of patients with stage IA1 cancer who may be treated with local excision in the colposcopy unit. The principle is that referral should be done as soon as possible. In general, the biopsy and staging investigations should be done in the cancer unit to decrease the waiting time, including request for PET-CT scan in women with locally advanced cancer, as soon as lymph nodes are suspected of being involved or clinically the cancer is greater than 4 cm or locally advanced. Cancer units and cancer centres should discuss and agree local protocols for referral to ensure that patients' treatments are not delayed. This may include referring patients before all staging investigations are complete, if it is clear that a referral to the cancer centre is indicated.

11 Treatment of cervical cancer

11.1 Treatment of stage IA1 cervical cancer

Stage IA1 cancer means there is microinvasive disease. Treatment of stage IA1 cervical cancer will depend on whether there is LVSI and whether the patient wishes to retain her fertility.

11.1.1 Stage IA1 cervical cancer with no LVSI

The risk of lymph node metastases is so low in stage IA1 disease that, unless there are signs of lymphovascular invasion, the lymph nodes do not need to be removed (Sevin *et al.,* 1992). *(Level 4)* The excision margins should be free of both CIN and microinvasive disease, and the gynaecological centre pathologist and MDT should review the histology.

11.1.2 Fertility sparing options

For women who wish to retain their fertility, loop or cone biopsy is suitable treatment for stage IA1 disease ≤3 mm stromal invasion, non-confluence, no lymphovascular space invasion and where excision is complete (Johnson *et al.,* 1992). A suitably planned loop or cone biopsy may be both diagnostic and therapeutic. The entire invasive component must be included in the pathological specimen.

If the resection margins are positive, options are repeat loop or cone, trachelectomy or hysterectomy.

11.1.3 Non fertility sparing options

For women who do not wish to retain their fertility, simple hysterectomy is sufficient treatment in stage IA1 cervical cancer. Peri- and postmenopausal women are also recommended to have bilateral salpingo-oophorectomy.

11.1.4 Stage IA1 cervical cancer with LVSI

Treatment for women with stage IA1 cervical cancer with LVSI should include lymph node dissection whether or not a hysterectomy is performed.

11.2 Treatment of stage IA2, IB1 and IIA1 cervical cancer

The advantages of surgery over primary radiotherapy in early stage cancer include the ability to preserve ovarian function, less early morbidity and the lack of late effects of radiotherapy, including second malignancy.

A retrospective SEER study also suggested a survival advantage to surgery, although this was a non-randomised study that did not account for bias that might have impacted on treatment selection (Bansal *et al.,* 2009).

For patients with non-bulky cervical cancer measuring ≤4 cm and without parametrial involvement, surgery is the preferred treatment option. *(Level 3)*

In surgically treated patients with stage IA2, IB1 and IIA1 pelvic lymph node dissection should be undertaken because of the risk of lymph node spread. Recommended treatment of the primary is radical hysterectomy with the exception of patients with stage IA2 disease in whom cone biopsy or simple hysterectomy may be sufficient if negative margins can be achieved.

Primary radiotherapy is reserved for patients who are not suitable for surgery because of medical comorbidity or who decline surgery.

11.2.1 Radical hysterectomy

Radical hysterectomy is the standard surgical treatment for women with stage IB1 and IIA1 cancer. Radical hysterectomy for cervical cancer should be undertaken by appropriately trained doctors in the context of full support services. *(Level 4)*

The operation involves a radical hysterectomy, removing parametrium, the upper third of the vagina and a formal bilateral pelvic lymphadenectomy removing the common iliac, internal and external iliac and obturator lymph nodes.

The ovaries are removed if there is coincident ovarian pathology or if the patient is approaching or beyond the menopause.

The procedure requires close dissection to and mobilisation of the ureters, and women should be informed of the possibility of damage to ureters. Complications can be limited by careful surgical technique, five days of continuous bladder drainage, and antibiotics. Drainage of the lateral pelvic sidewalls is not routinely indicated.

Thromboprophylaxis is required and blood transfusion may be needed.
Radical hysterectomy has traditionally been undertaken via the abdominal route, but laparoscopic, vaginal routes and robotic surgery can also be considered by appropriately trained Gynae-oncologists. Controversially, the recently published Laparoscopic Approach to Carcinoma of the Cervix (LACC) study showed improved survival with open radical hysterectomy for cervical cancer compared to a minimally invasive approach (Ramirez *et al,* 2018). The LACC study was a randomized controlled study powered to 90% to show non-inferiority for minimal access radical hysterectomy at 4.5 years. Although the data are not fully mature and several shortcomings have been identified, the results cannot be completely ignored. Therefore, patients should be informed of the concerns regarding minimal access surgery for cervical cancer. However, the study did not advocate open radical surgery for low risk, small tumours. Patients with tumours which are 2-4cm in diameter should be offered open surgery. Patients with smaller tumours should be offered laparoscopic radical surgery. Therefore, the outcomes of all surgically managed cervical cancer cases should be monitored going forward.

11.2.2 Fertility sparing options

Radical trachelectomy

A radical trachelectomy may be considered as a fertility sparing treatment for women who have a strong desire to preserve fertility. *(Level 4)*

A case-control study reported that for selected patients with stage IB1 cancer, fertility-sparing radical trachelectomy appears to have similar oncological outcomes to radical hysterectomy (Diaz *et al.,* 2008). A recent study of 55 patients reported that 32.7% attempted to conceive after laparoscopic radical trachelectomy. Fourteen pregnancies occurred in 10 patients, and 9/10 patients gave birth to 10 healthy babies. The spontaneous abortion rate and live birth rate were 28.6% and 71.4 % respectively. The preterm birth rate was 60%. The operation involves removing a 1 to 2 cm

cuff of vaginal mucosa around the cervix. The cervix is removed with a margin and care is taken to preserve the ureters. The vagina is then attached to the lower part of the remaining uterus and a cerclage can be placed, alternatively the cerclage can be omitted and placed in pregnancy. The procedure can be performed via either the vaginal/abdominal or laparoscopic routes.
Criteria for trachelectomy include:

- Woman of reproductive age (usually up to 40 years old, but occasionally up to age 45 is acceptable).
- Squamous carcinoma or adenocarcinoma (no high risk pathologies such as neuroendocrine cancer).
- Tumour ≤2 cm with limited endocervical extension.
- No evidence of lymph node metastases.
- Treatment in a centre where there is sufficient expertise to undertake the procedure.

11.3 Adjuvant treatment after surgery for cervical cancer

Patients who have undergone surgery for cervical cancer may have histological findings that indicate further treatment with postoperative radiotherapy should be offered. If patients are fit enough, concurrent cisplatin chemotherapy should be added to radiotherapy (Peters *et al.,* 2000). A meta-analysis of clinical trials looking at the effect of adding cisplatin based chemotherapy to radiotherapy suggested the greater benefit is in patients with high-risk early-stage disease (RR = 0.56; 95% CI 0.41-0.77) (Lukka *et al.,* 2002) *(Level 1)*
Postoperative chemoradiotherapy is indicated in the following situations *(Level 2)*:

- Positive pelvic lymph nodes
- Parametrial invasion
- Positive resection margin

Close resection margins are also a risk factor for recurrence and case series suggest that adjuvant treatment may improve outcomes (Estape *et al.,* 1998), although there are no randomised trials to direct what resection margin should trigger a decision to offer adjuvant treatment. Postoperative chemoradiotherapy should be considered for patients with resection margins of less than 3 mm *(Level 5)*.

11.4 Definitive radiotherapy for cervical cancer

For radical radiotherapy for cervical cancer good practice is for treatment to start within 2 weeks, with 4 weeks as a maximum acceptable wait (Joint Council for Clinical Oncology, 1993).

11.5 Definitive radiotherapy in stage IA, IB1 and IIA1 cervical cancer

Radiotherapy may be preferable to surgery in patients with early stage disease (IA, IB1, IIA1) where a patient is unfit for surgery or in cases where nodal involvement has been detected on pre-operative staging. Very rarely, patients may decline surgery.

11.6 Treatment of stages IB2 and IIB to IVA

Chemoradiotherapy is the first line standard treatment for patients with bulky and locally advanced cervical cancer. Five randomised clinical trials of concurrent platinum-based chemoradiotherapy showed an overall survival benefit to adding chemotherapy to radiotherapy in locally advanced and high-risk early stage disease (Keys *et al.,* 1999; Morris *et al.,* 1999; Rose *et al.,* 1999; Whitney *et al.,* 1999; Peters *et al.,* 2000). The effect was confirmed by meta-analysis (Green *et al.,* 2001). A further

systematic review and meta-analysis of eight randomised trials demonstrated the relative risk of death for the whole group was 0.74 (95% CI 0.64-0.86) in favour of concurrent cisplatin based chemotherapy (Lukka *et al.,* 2002). For patients with locally advanced disease the RR was 0.78 (95% CI 0.67-0.86). *(Level 1)*

All patients with stage IB2 or IIB to IVA cervical cancer should be considered for radical chemoradiotherapy. The presence of para-aortic lymph node metastases does not change the FIGO stage unless they are detectable clinically. With TNM staging, para-aortic nodal disease is classed as M1 disease (stage IVB). These patients should also be considered for radical chemoradiotherapy if the disease is encompassable within a radical radiotherapy treatment volume.

A dose of at least 45 Gy in 25 fractions should be delivered to the primary treatment and nodal disease of up to 57-60Gy in 28 fractions over 5.5 weeks (Royal College of Radiologists, 2019), with consideration of a boost to areas of gross nodal disease. Cisplatin 40 mg/m^2 is administered weekly for five weeks during the external beam therapy. PET-CT fusion can aid the radiotherapy planning process. This should be followed by intracavitary brachytherapy using image guided brachytherapy (IGBT). Use of MRI images for planning is standard treatment unless the patient is unable to tolerate the procedure.

The overall treatment time should not exceed 56 days (RCR, 2019).

In patients of poor performance status or with significant comorbidity, radical radiotherapy alone may be offered.

Radical radiotherapy and radical chemoradiotherapy for cervical cancer should be undertaken by an oncologist with a site-specialist interest in gynaecological cancer. *(Level 5)*

11.7 Treatment of stage IVB cervical cancer

Patients with metastatic disease (other than those whose disease is confined to para-aortic lymph nodes) require palliative treatments aimed at improving quality of life. Options include systemic anticancer therapy (SACT), radiotherapy and surgery (e.g. stoma formation to relieve symptomatic fistulae). Neoadjuvant treatment is currently the subject of clinical trials, however it could be considered after full discussion with patients with very bulky disease where radiotherapy fields would be very large.

12 Special clinical situations

12.1 Cervical cancer in pregnancy

Cervical cancer in pregnancy is rare, with an incidence of approximately 0.05% of all patients with cervical cancer. Stage for stage, the survival is the same as for non-pregnant women (Hopkins *et al*., 1992; Lee *et al*., 2008; Stensheim *et al*., 2009). It is now believed that the route of delivery of the child does not affect the overall five-year survival.
Most women present with abnormal bleeding, although 20% of women are asymptomatic.

Women with cervical cancer in pregnancy should be referred to the Cancer Centre. Treatment is individualised and depends on the gestational age of the fetus, the clinical stage of the cancer and the patient's wishes. It is co-ordinated with obstetric and paediatric specialties.

For women who do not desire the continuation of their pregnancy, the management is similar to that of non-pregnant women.

For women who wish to continue their pregnancy, delivery should be as soon as possible after 35 weeks. Radiotherapy to the pelvis during pregnancy is contraindicated because of the effect of ionising radiation on the foetus. Similarly, the use of ionising radiation for diagnostic purposes (e.g. CT scan, plain X-ray) should be avoided. Patients with very early stage disease can be monitored during pregnancy while for those with more advanced disease, chemotherapy in the second or third trimesters could be considered, although there is a lack of data on long-term effects upon the fetus.

12.2 Cervical stump cancer

Patients with cervical stump cancer should be referred to the cancer centre. Treatment is with surgery (radical trachelectomy), radiotherapy or chemoradiotherapy.

12.3 Unsuspected cervical cancer after simple hysterectomy

On occasion, a cervical cancer is detected on histological examination following simple hysterectomy. The stage of the primary tumour should be assessed carefully and further treatment arranged as required by the stage of the cancer. Treatment is individualised and may include further surgery (radical parametrectomy), radiotherapy or chemoradiotherapy.

12.4 Neoadjuvant chemotherapy for FIGO stage IB2 or other bulky cervical carcinomas

Neoadjuvant chemotherapy prior to planned surgery for locally advanced disease (such as for FIGO stage IB2) is not recommended as standard treatment at present in Wales although case reports and small series show benefit. Similarly, neoadjuvant chemotherapy could be considered for bulky tumours before planned chemoradiation. INTERLACE is currently recruiting for patients having chemoradiation in a randomised setting.

12.5 Small cell cancer

Small cell carcinoma of the cervix is a rare and aggressive tumour. Information on treatment comes mainly from reported case series. Most patients receive chemotherapy (platinum and etoposide) similar to small cell lung cancer, with the addition of pelvic radiotherapy in patients with localised disease. Surgery may be suitable for the few patients with small-volume, early-stage disease. Although the incidence of brain metastases appears to be less than for patients with small cell lung cancer and whole brain radiotherapy is not routinely indicated (Viswanathan *et al.,* 2004), staging should include a CT scan of head, thorax, abdomen and pelvis (level 5)

12.6 Rare types of cervical cancer

Rarely, histological types of cancer other than carcinoma can occur in the cervix, such as lymphoma, sarcoma and melanoma or metastases from other primary tumours. Treatment is individualised and should be undertaken in conjunction with the relevant oncology team.

13 Management of recurrent cervical carcinoma

13.1 Radical treatments

Occasionally, patients with localised recurrences are suitable for radical treatment. In patients who have received surgery, radical chemo- radiotherapy may be an option. In patients who have received radical radiotherapy, exenterative surgery may be an option in patients with central recurrences. Patients with isolated lymph node metastases may be suitable for stereotactic radiotherapy. Exceptionally, laterally extended endopelvic resection (LEER) should be considered in patients with recurrent carcinoma <5cm diameter involving the sidewall of an irradiated pelvic tumour.

13.1.1 PET scanning

PET scanning in recurrent cervical cancer is commissioned as described previously (WHSSC, 2016).

13.1.2 Pelvic exenteration

For patients with an isolated central pelvic relapse who have previously received radical radiotherapy to the pelvis, or those in whom radiotherapy is contraindicated, pelvic exenteration should be considered. Pelvic exenteration is a major surgical procedure with a significant risk of short- and long-term morbidity affecting the bowel, urinary system and sexual function. Pelvic exenteration should be considered in women for whom a complete resection is considered feasible, who are physically able to tolerate the procedure and who are prepared to accept the significant functional changes. PET-CT scanning is recommended prior to the procedure, and pre-operative counselling is required.

13.2 Palliative treatments

Agents such as cisplatin, carboplatin, paclitaxel, topotecan, gemcitabine may produce useful responses in around 30% of patients.

The decision on which treatment to use is agreed by the patient and oncologist, taking into such as performance status, co-morbidity and patient preferences. In patients who are well and are able to tolerate potential hair loss, carboplatin and paclitaxel is generally used first line with a response rate of 60% (Kitagawa *et al.,* 2015).

The GOG-0179 trial was a phase III randomised controlled trial that reported increased median overall survival for topotecan plus cisplatin compared with cisplatin alone; 9.4 versus 6.5 months, respectively (p = 0.017) (Long *et al.,* 2005). NICE guidance recommends that topotecan in combination with cisplatin is recommended as a possible treatment for women with recurrent or stage IVB cervical cancer only if they have not received cisplatin before (NICE, 2009).

Final results of the GOG-240 study found that bevacizumab in combination with chemotherapy is associated with a significantly improved overall survival (16.6 months versus 13.3 months; p = 0.0068) versus chemotherapy alone (Tewari *et al.,* 2014). Toxicities include gastrointestinal perforation and fistula, and thrombo-embolic events. At the time of writing, bevacizumab has currently not been approved by NICE and is only available in Wales for patients with exceptional clinical circumstances by the Individual Patient Funding Request (IPFR) system.

Palliative procedures may be indicated in patients with localised problems who are of good performance status and in the absence of rapidly progressive disease. Obstructive uropathy may be relieved by ureteric stents or nephrostomies. Fistulae may be bypassed by formation of stomas.

14 Follow up

There is a lack of evidence to suggest what follow up patients should receive following treatment for cervical cancer. Aims of follow up include: to detect potentially curable recurrences, to detect and treat consequences of cancer treatment, and to provide psychological support. Clinical assessment should include enquiry for symptoms relating to late effects of cancer treatment or recurrence and clinical examination including vaginal and speculum examination. Patients with symptoms following pelvic radiotherapy should have access to specialist gastrointestinal, urological and psychosexual support. Cervical HPV testing is recommended for the follow up of early stage cervical cancer if the cervix is conserved (Luesley and Leeson, 2010). The role of vault smears in patients following hysterectomy is less clear, and there is no evidence that it adds more than direct visualisation (Elit *et al.,* 2010).

A suggested scheme is as follows:

- Three-monthly for the first year
- Six-monthly for the second year
- Annually until five years
- Discharge at five years if all well

14.1 Follow up after trachelectomy

There are no specific guidelines on follow up of patients following trachelectomy, but it is agreed that close surveillance is required to detect local recurrences at a time when they are potentially radically treatable. Direct visualisation of the upper vagina and remaining isthmus of the uterus is recommended, which can be facilitated by colposcopy. Clinical examination, MRI scanning and smears should be carried out as directed by the treating oncology centre.

15 Complications of treatment

Treatment for cervical cancer can result in significant morbidity.

15.1 Lymphoedema

All women who develop lower-limb lymphoedema should have access to the four cornerstones of lymphoedema care:

- skin care to maintain a good tissue condition and reduce the risk of infection
- external compression in the form of elastic compression garments that help reduce new lymph formation and encourage lymph drainage by improving the efficiency of muscle pump
- a programme of exercise and movement to promote lymph drainage without over exertion
- simple lymphatic drainage: a method of lymph drainage that can be carried out by the patient or carer and involves a series of simple hand movements.

The aims of this regimen are to rehabilitate the cancer patient, to reduce any disability as far as possible, to help the patient to achieve an independent lifestyle and to give the patient the skills to manage their own condition (British Lymphology Society, 2009). This advice should be provided by a locally accessible lymphoedema service.

15.2 Complications following pelvic radiotherapy

Late radiation changes as a result of pelvic radiotherapy can be associated with bowel, bladder and psychosexual problems, in addition to lymphoedema. Follow up strategies should be designed to detect such changes. The use of screening tools such as the ALERT-B questionnaire (see Appendix 3) for gastrointestinal symptoms can aid detection of chronic symptoms related to pelvic radiotherapy (Taylor *et al.,* 2016).

Patients who develop troublesome gastrointestinal symptoms should be investigated using an algorithm-based approach (Benton *et al.,* 2011; Andreyev *et al.,* 2013).

Patients with troublesome urinary symptoms should be considered for pelvic floor exercises or Urological referral.

Patients with psychosexual problems should have access to appropriate counselling.

Minor bowel or urinary symptoms can be managed by the gynae-oncology team (e.g. hyoscine for abdominal cramps or antimuscarinics for frequency of micturition).

15.3 Early menopause

Patients who experience an early menopause should be offered hormone replacement therapy.

16 The role of the Clinical Nurse Specialist (CNS)

All women with a diagnosis of gynaecological cancer should be offered the support of, and have access to, a CNS, in order to facilitate the women's needs throughout the cancer journey, including those of her partner or carer.

Within an MDT, the CNS is in an ideal position, frequently as the key worker, to be able to address the often complex and sensitive issues identified and experienced by the patient (NICE, 2004). Access to self help, support groups and charitable organisations may also be of significant benefit, allowing women to share experiences and seek support from other women diagnosed and treated for the same condition.

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Appendix 1: Methodology

These guidelines were written in accordance with the Cancer NSAG Guidance for Clinical Guideline Development including:
Literature review by Library and Knowledge Management Service, Public Health Wales
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 of document in response to comments
Circulating to wider network for consultation

Apendix 2: Levels of evidence

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

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Apendix 3 ALERT tool

Assessment of Late Effects of RadioTherapy-Bowel

ALERT-B Screening Tool

Date:

Your specialist has asked you to complete this screening tool to pick up any bowel or tummy problems you may have developed following radiotherapy treatment.

Please answer Yes or No to the following questions:

1. Do you have difficulty in controlling your bowels (having a poo), such as:

   - Having to get up at night to poo — Yes ☐ No ☐

   - Having accidents, such as soiling or a sensation of wetness ("wet wind") — Yes ☐ No ☐

2. Have you noticed any blood from your bottom recently? (any amount or frequency) — Yes ☐ No ☐

3. Do you have any bowel or tummy problems that affect your mood, social life, relationships or any other aspect of your daily life? — Yes ☐ No ☐

   (e.g., do you avoid any activities or situations- travel, work, social life or hobbies? Do you take continence supplies or spare clothing with you when you go out? Have you made any dietary changes? Do you need to allow for frequency or urgency of needing the toilet?)

If you have any other problems your doctor will be happy to discuss this with you.