British Gynaecological Cancer Society (BGCS) Cervical Cancer Guidelines: Recommendations for Practice

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The remit of this guideline is to collate and propose evidence-based guidelines for the diagnosis and management of adult patients with cervical cancer being treated in the United Kingdom.

Grades of recommendations

Recommendations are graded as per the Royal College of Obstetricians and Gynaecologists document. Clinical Governance Advice No. 1: Guidance for the Development of RCOG Green-top Guidelines, available on the RCOG website at:

https://www.rcog.org.uk/en/guidelines-research-services/guidelines/clinical-governance-advice-1a/

Evidence was searched in the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library 2014, Issue 12), MEDLINE and EMBASE up to April 2018, registers of clinical trials, abstracts of scientific meetings, reference lists of included studies and contacted experts in the field.

Guidelines development process

1) These guidelines are the property of the BGCS, and the Society reserves the right to amend/withdraw the guidelines.
2) The guideline development process is detailed below:

   a) Chair, officers, council and guidelines committee (GC) nominated a lead for each guideline topic;

   b) Lead then identified a team called the guideline team (GT) to develop the 1st draft;

   c) 1st draft was submitted to the GC;

   d) GC approved draft and recommended changes;

   e) Changes were accepted by the GT who produced the guidelines;

   f) 2nd draft was then submitted to council members and officers;

   g) Council and officers approved 2nd draft and recommended changes;

h) Changes were then accepted by GC and GT;

i) 3rd draft was sent to national and international peer review;

j) GC and GT then made changes based on peer review comments;

k) 4th draft was sent back to council for approval;

l) 4th draft was sent to BGCS members for feedback;

m) GC and GT then made changes based on members' feedback;

n) 5th draft was sent to public consultation including patient support groups;

o) GC and GT then made changes based on non-members' feedback;

p) Final draft approved by council and officers.

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1. Introduction

Despite the presence of well-organized cervical screening programmes in the UK and the introduction of HPV vaccination in 2008 for schoolgirls, the incidence of cervical cancer is not expected to significantly decrease over the next few years. Over the last decade, cervical cancer incidence rates have increased by around 4% in females in the UK, although higher rates have been witnessed in Northern Ireland. Incidence rates for cervical cancer are projected to rise by 43% in the UK between 2014 and 2035, to 17 cases per 100,000 females by 2035.

The present document ranges from screening and investigation through to management of early and advanced invasive cancer and on to metastatic disease. In addition, we have included survivorship and quality of life and we increasingly rely on nurse specialists to provide support to our patients throughout their cancer journey. The aspect of fertility preserving therapeutic approaches will also be addressed at the various aspects of management.

2. Presentation and referral: Presenting symptoms and diagnostic methods

2.1 Presenting symptoms

The reader is directed to the National Institute for Health and Care Excellence (NICE) guidance (NG12) on referrals for suspected cancer (1), the Scottish Intercollegiate Guidelines network Guidance on management of cervical cancer (2) and the NHS Cervical Screening Programme NHSCP20 document (3).

Cancer of the cervix often has no symptoms in its early stages and may be detected after an abnormal screening smear test. Symptoms can be subtle and attributed to benign gynaecological conditions or remain asymptomatic until the cancer has reached an advanced stage. When symptomatic, the most common symptoms are abnormal vaginal bleeding, intermenstrual (IMB), postcoital (PCB) or postmenopausal bleeding (PMB). Other symptoms of cervical cancer may include dyspareunia and abnormal vaginal discharge. Abnormal appearance of the cervix during examination should also raise suspicion and referral for further investigations (4). It is possible for women of all ages to develop cervical cancer, but traditionally the condition mainly affected sexually active women aged between 30 and 45 years of age, however, recent data from Cancer Research UK shows the peak age of incidence has reduced to 25-29 years of age. Cervical cancer is very rare in women under 25 years old (4) and may be more difficult to prevent in younger age women. (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/cervical-cancer#heading-Zero).

If there is extra cervical advanced stage disease with spread into surrounding tissue and organs, it can cause other symptoms, including haematuria, urinary incontinence, bone pain, lower limb oedema, flank or loin pain (due to hydroureter or hydronephrosis), changes to bladder and bowel habits, loss of appetite, weight loss and fatigue.

Many of the signs and symptoms suggestive of cervical cancer are common to genital Chlamydia trachomatis infection. Women who have symptoms of irregular or contact bleeding or have an inflamed or friable cervix should be tested for Chlamydia trachomatis and treated if appropriate (5). The point prevalence of PCB in women in the community is 0.7-9% (6), but only a small proportion of these women are seen in secondary care. The probability that a woman under the age of 25 with PCB has cervical cancer is very low (6). Two per cent of women attending secondary care with PCB are diagnosed with cervical cancer (6). The risk of having a cervical cancer is not related to the duration and extent of symptoms (7). Women referred with PCB, where cervical cancer is excluded, have no increased risk of cervical cancer in the future (8). A systematic review identified no evidence to support performing a smear when a woman presents with PCB outside of the scheduled screening intervals (6) unless it is opportunistic in someone who has failed to attend regular screening.

Although the risk is not entirely removed in a woman presenting with symptoms, a woman with a negative screening history has a greatly reduced risk of cervical cancer compared to a woman with positive cytology (6,9).

2.2 History and examination

Current guidance in the UK, recommendations for diagnosis and referral are based on guidance from NICE, SIGN, NHSCSP and BSCCP (1-3).

The clinician should obtain a detailed account of the presenting symptoms, a full history including smoking status, previous smears and any previous cervical treatment. Women presenting with abnormal vaginal bleeding should receive an abdominal, speculum and pelvic examination at their clinical assessment (8). Sample-takers must visualise the cervix when taking a sample. If they notice abnormalities suggesting possible malignancy, the patient should be urgently referred for a colposcopic examination within a two weeks referral pathway (3). Treatment for patients referred via the two week wait rule or following high grade cervical cytology abnormality should be commenced within 62 days of referral or within 28 days from the date of decision to treat as per the Cancer Waiting Times guidelines. (1) (Grade D)

Screen-detected cancers which are not directly visible will be referred to colposcopy clinic. For clinically visible cervix cancers, formal colposcopy may be omitted. However, biopsies are the recommended diagnostic investigations. Biopsy should be a punch biopsy, multiple punch biopsies are usually more reliable than a single one, or even an excisional biopsy, such as a LLETZ especially if referral screening test indicates high grade lesion (3).

Recommendations:

- Patients with suspected cervical cancer should be seen urgently, ideally in the colposcopy clinic to obtain directed biopsies to make a diagnosis. (Grade D)

3. Pathways for management of cervical cancer

Staging System

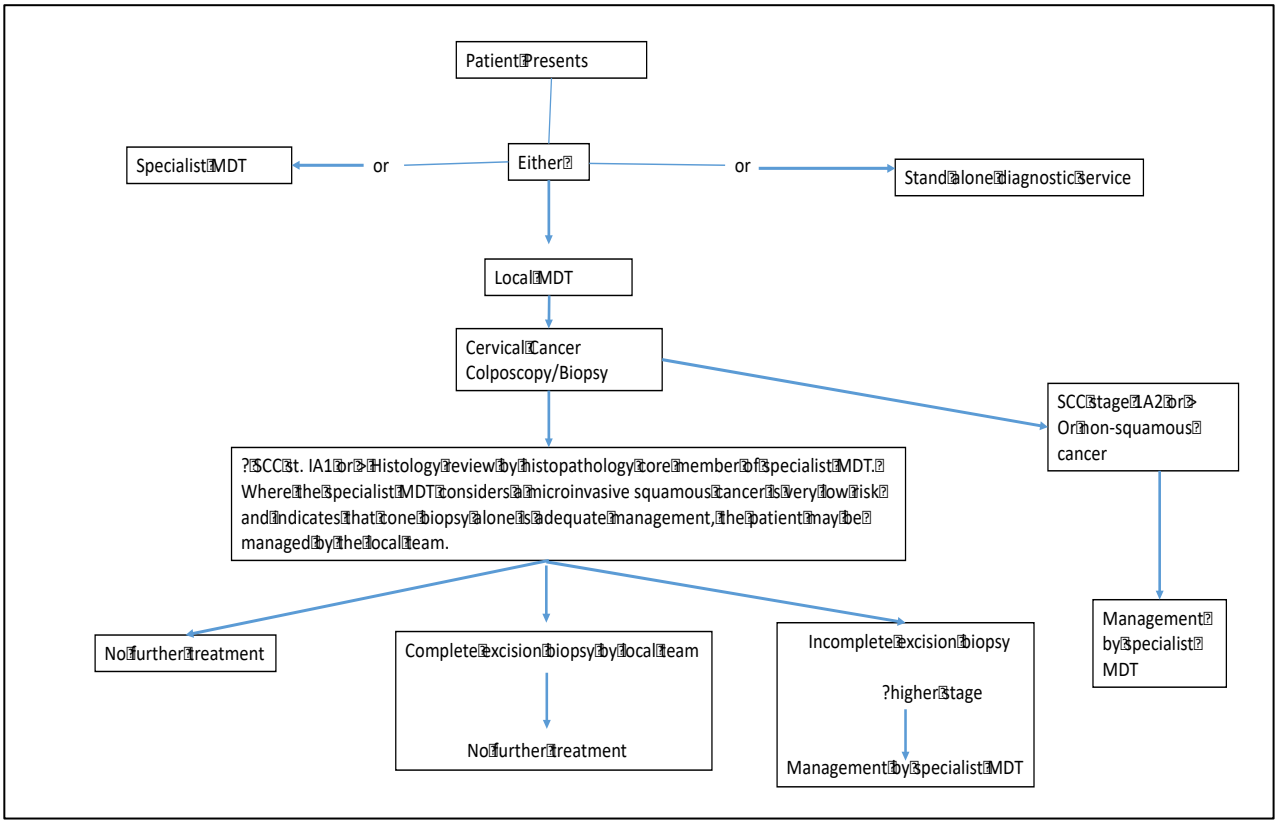
This document reflects the new FIGO staging 2018. Since this is a new system, all the presented supporting evidence reflects the earlier staging system, and this will be delineated and specified throughout these guidelines. The, previous and updated, FIGO classification systems are attached in the appendix of this document.

3.1 Patient care pathways associated with a local MDT

The National Cancer Intelligence Network report on routes to diagnosis revealed that in 2013 the majority of cervical cancers (61%) were diagnosed by the two week wait / direct outpatient referral from general practitioners (GPs), 17% were screen detected and 10% presented as emergency admissions. (12).

All women with a confirmed or suspected diagnosis of cervix cancer should be discussed at a specialist gynaecological cancer multidisciplinary team meeting. (SMDT) (Grade D). The SMDT should comprise a minimum of two surgical gynaecological oncologists, clinical oncologist (radiotherapy specialist), medical oncologist (chemotherapy specialist), radiologist, histopathologist, cytopathologist, clinical nurse specialist and a multi-disciplinary team co-ordinator. (13) (Grade D). Table one highlights the associated pathways with a local MDT.

Table One- Patient care pathways associated with a local MDT



Source: Manual for cancer services: Gynaecology measures 2014

3.2 Governance and failsafe

Failsafe mechanisms should be in place at each stage of the patient's journey, from referral to diagnostics and treatment. Healthcare providers should have systems in place to ensure that cervical smears suspicious of malignancy and cervical biopsies confirming malignancies are appropriately managed. Patients with recurrent 'red flag' symptoms such as intermenstrual and post coital bleeding should be encouraged to seek help, even if they have previously had normal findings following investigations.

The cancer centres should comply with requirements of submission of data items, including Cancer Outcomes and Services Dataset (COSD), to enable meaningful performance and outcomes assessments by the National Cancer Registration and Analysis Service (NCRAS).

Women <25 years of age should be managed in conjunction with the relevant teenage and young adult cancer network co-ordinating group (TYACNCG). The teenage and young adult (TYA), gynaecology cancer patient pathways provide additional guidance for initial management, treatment and follow up. (13,14). For women seeking fertility preserving options, please see section 10. Management of cancer in pregnancy will be found in section 12.

Recommendations:

- 'Red flag' symptoms include intermenstrual and post-coital bleeding should trigger referral for investigation in secondary care.
- All appropriate cases should be discussed at the Multi-disciplinary team meeting. (Grade D)

4. Preoperative assessment and imaging

All women with cervical cancer beyond stage IA1 should have a visual inspection of the cervix and vagina along with a bimanual vaginal examination to assess vaginal and parametrial extension. A rectal or rectovaginal examination is strongly recommended, especially when assessing larger tumours, or if there is uncertainty on bimanual vaginal examination or discordance between imaging and initial examination. (Grade D). However, this is usually carried out in the clinic before MRI scanning is undertaken. Examination under anaesthesia (EUA) may be required to gain tissue for diagnosis and to adequately assess for vaginal/parametrial extension in some cases, although the routine use of an EUA and cystoscopy for staging has been superseded by modern cross-sectional imaging techniques. However, the use of imaging does not negate the need for a thorough clinical examination. Discordance between initial clinical examination and cross-sectional imaging would be a further indication for EUA. Cross-sectional imaging does not have a role in staging IA1 tumours.

MRI is more accurate than CT in pre-treatment local staging of cervical cancers and thus patient selection for either surgery or primary chemoradiotherapy. In particular, candidates for fertility sparing surgery can be identified more accurately with specialised MRI techniques, compared to clinical examination alone (grade B). A systematic review of 57 studies comparing CT and MRI for staging of cervical cancer reported that MRI was more accurate than CT, particularly for parametrial involvement, bladder and rectal invasion (19). A systematic review of four studies with 366 patients with cervical cancer FIGO stage IIB or below reported a high level of accuracy of MRI in detecting involvement of the uterine internal os in cervical cancer (20). MRI should be performed to set protocols and interpreted by radiologists with expertise in gynaecological cancer. {RCR guidelines cervical cancer imaging 2014}. https://www.rcr.ac.uk/system/files/publication/field_publication_files/BFCR%2814%292_18_cervix.pdf} (Grade B).

Radiologists should be aware that post-biopsy changes can mimic malignancy and adversely affect the assessment of tumour volume particularly in small tumours (21). Staging MRI should be performed at least 7-10 days post biopsy to reduce post biopsy artefact, although there are no studies that evaluate the chronology of post-biopsy changes and they can be observed for longer.

Pre-operative chest radiology is part of staging and should be performed in all women with cervical cancer prior to surgery (Grade D). Plain chest X-ray is more cost-effective than CT in clinical early stage tumours as the risk of lung metastases is low.

Vaginal involvement can be seen on MRI by disruption of the low T2 vaginal wall by intermediate signal intensity tumour (22). Early involvement is best determined by clinical examination, as MRI may overestimate the degree of vaginal involvement especially at the fornices or when tumours are large or in cases of local inflammation (21,23).

With regard to parametrial assessment, MRI has been shown to outperform clinical examination (23,24). High resolution T2 axial oblique sequences tangential to the cervix are essential to evaluate the parametrium and when performed accurately achieve specificity of up to 97% and negative predictive value of 100% (25). When seen, the presence of an intact low T2 stromal ring has a high negative predictive value (22). Endorectal surface coil assessment of cervical cancer is more sensitive in the detection of parametrial invasion than standard body coil (26), but due to its more invasive nature is not used routinely. Due to the very high negative predictive value in the assessment of bladder and rectal involvement, MRI can safely obviate the need for invasive cystoscopic or endoscopic staging in the majority of patients, if imaging does not show any bowel or bladder involvement (27).

In relation to nodal involvement, cross sectional imaging is essential. Studies have investigated both CT and MRI and show that either can be used, although both may present limited sensitivity and specificity, depending on the study (19, 27). Some studies have shown that diffusion weighted imaging (DWI) MRI improves detection of nodal metastases but further studies with standardized protocols are required to provide conclusive evidence (28). If nodal disease is suspected, PET/CT has shown to be the most sensitive in locally advanced cervical cancer. The MAPPING study (Clin Trials Ident: NCT01836484) will present findings around the diagnostic accuracy of MRI, DWI MRI, FDG-PET/CT and FEC PET/CT in the detection of lymph node metastases in surgically staged endometrial and cervical carcinoma.

FDG PET/CT should be considered in patients staged>IB1 planned for radical chemoradiation therapy (grade B). A meta-analysis to compare the diagnostic performance of CT, MRI and PET or PET/CT for detection of metastatic nodes in cervical cancer reported PET or PET/CT had the highest pooled sensitivity (82%) and specificity (95%) whilst sensitivity and specificity for CT (50% and 92%) and MRI (56% and 91%) were less accurate (29). A systematic review and meta-analysis of diagnostic accuracy of tests for lymph node status in primary cervical cancer reported the greatest accuracy with sentinel node biopsy and that PET/CT was superior to MRI and CT (30). Surgical staging with lymphadenectomy remains the gold standard.

Recommendations:

- Visual inspection of the cervix is essential with thorough clinical staging
- MRI is the preferred imaging technique. DWI may increase the sensitivity
- FDG-PET scanning should be carried out in cases more advanced than stage IB2 (FIGO 2018) and in all cases planned for combined chemotherapy and radiation therapy (Grade B)
- For further reading and references, the reader is directed to the following (32-48).

5. Sentinel lymph node biopsy

The recent consensus statement on sentinel lymph node biopsy (SLNB) from the BGCS is accessible using the link below. This also includes recommendation on the pathological processing of sentinel lymph nodes (SLNs). https://bgcs.org.uk/news/sentinel-consensus-document-for-endometrial-and-cervical-cancer-bgcs.html

SLNB has a high sensitivity for detection of metastases in tumours <2 cm, but is less accurate for larger tumours, (Grade B). SLNB is a technique in which the first draining lymph nodes (known as sentinel lymph nodes) are removed and examined histologically in order to provide information about the status of the nodal basin (metastatic or non-metastatic) without the need for full lymphadenectomy. SLNB is now integrated into staging protocols for breast and vulval cancers and has been of increasing interest in the management of cervical cancer. The identification of positive nodes pre-operatively may allow the selection of women that would benefit from primary chemo-radiotherapy and can spare these women the additional morbidity associated with radical hysterectomy and pelvic lymphadenectomy. Taken overall, the results of studies to date indicate that the negative predictive value of an uninvolved sentinel node is high (95%) and is superior to all other imaging modalities, including PET/CT.

In one multi-centre prospective study, when combined with pre-operative lymphoscintigraphy, 17% of involved SLNs were identified in unexpected anatomical locations. In addition, in 39.1% of cases, histological ultra-staging and immunohistochemistry detected micro-metastases that would have been undetected by conventional histopathological assessment (49). Therefore, SLNB may be more reliable in determining lymph node status than conventional full lymphadenectomy.

Combined use of Technetium-99m colloid (99mTc) lymphoscintigraphy and blue dye currently appears to be the most reliable detection method for SLNB. (Grade A)

Of the three most commonly used detection methods for SLNB (Technetium-99m colloid, blue dye or a combination of the two), the combined method using Technetium-99m colloid (99mTc) and blue dye together is consistently shown to be the most reliable in high quality meta-analyses (50-53). The sensitivity of a combination of 99mTC and blue dye for detection of SLN metastasis in early cervix cancer is 88-92%. Bilateral detection rates are 92-97% for the combined method compared with 81-88% for blue dye alone and 88-90% for 99mTc alone. Near infrared (NIR) fluorescence imaging is a more recent technique which uses medical dyes that fluorescence in the NIR spectrum. Indocyanine green is the most commonly used dye and has gained interest with the increased use of robotic surgical platforms that are compatible with NIR detection. Because there is no requirement for the lengthy regulatory processes associated with the use of radioactive methods, NIR imaging is also seen as attractive method, due to its simplicity and ease of use. The formal evaluation of NIR fluorescence imaging for SLNB in cervix cancer compared with full pelvic lymphadenectomy is limited to a few studies with small patient numbers. These show promising results and indicate successful bilateral detection rate for SLNs in 60-89% of cases with a negative predictive value of 93-100% rate for SLNs in 60-89% of cases with a negative predictive value of 93-100% (54-56). Until these findings are confirmed in larger studies, directly comparing the use of NIR fluorescence imaging with combined radiocolloid and blue dye detection, or in high quality meta-analyses, results should be interpreted with caution.

Failure to identify a SLN in one hemi-pelvis, necessitates a full lymphadenectomy on that side. (Grade D). As a midline structure, the cervix drains to nodal basins on both sides of the pelvis. Therefore, where SLNB is used, sentinel nodes must be identified in both sides of the pelvis, as the histological status of the SLN in one hemi-pelvis does not predict the histological status of the nodes in the contralateral hemi-pelvis (57-58). Lymph node metastasis in one hemi-pelvis may prevent normal drainage to that side and lead to false negatives. This phenomenon is seen in other cancers where SLNB is used in management. Therefore, failure to identify a SLN in one hemi-pelvis mandates full pelvic lymphadenectomy on that side.

SLNs should be processed by serial sectioning and immunohistochemistry. (Grade B). Multiple studies have found that intra-operative frozen section is limited in its ability to identify small metastases and micro-metastatic disease with sensitivity as low as 21% reported (53-55). A high false negative is particularly associated with tumours of >20 cm^3 volume (56-58). More recent reports show improved outcome with lower recurrence rate. Histopathological ultra-staging of the lymph node with serial sectioning and immunohistochemistry is required. As such, intra-operative evaluation of non-enlarged nodes is limited, in terms of clinical utility. Therefore, until more accurate methods of intra-operative histopathological assessment have been developed, a two-stage procedure is required in which the SLNB biopsy is performed initially, followed by definitive surgery on another date, in the case of a histopathologically negative SLN.

Assessment of lymph node status with SLNB can be considered in centres with sufficient expertise and training in this technique (Grade B). Systematic reviews of SLNB in clinically staged, early cervix cancer show that it is a reliable method for detection of lymph node metastases in this setting, particularly for small tumours (<2cm) (59-61).

In a recent randomised prospective multicentre study of 206 women with stage IA-IIA1 cervical cancer (FIGO 2009 staging system), women with a negative intra-operative frozen section of SLNs were randomised to either no further nodal dissection (SLNB alone) versus SLN surgery plus complete pelvic lymphadenectomy. No false negatives were identified in the women undergoing SLN surgery plus complete lymphadenectomy. Morbidity was significantly reduced in the SLNB only group compared to those having complete lymphadenectomy (31.4% and 51.5% respectively, P=0.0046). Quality of life scores were better in the SLNB only group and lymphoedema rates were reduced. Two isolated lymph node recurrences were reported in the SLNB-only group, compared with none in the group having SLNB plus complete lymphadenectomy. The study did not have sufficient statistical power to assess survival

outcomes, although recurrence-free survival does not appear significantly different in the two groups at 3 years (62). Longer term outcomes following SLNB alone are awaited. The SENTIX trial, a prospective multicentre trial of sentinel lymph node surgery alone in SLN negative patients which commenced enrolment in June 2016, has recruited 340 patients and will report on 5-year oncological outcomes at the end of 2021. The SENTICOL III study, started accrual in 2018 and randomizes women with a negative SLN on intra-operative frozen section to SLN biopsy alone versus SLN and pelvic lymphadenectomy. The end points are 3-year disease-free survival and quality of life. There is currently not enough data on oncological outcomes and centres adopting this technique should maintain prospective data on patients.

Multiple protocols have been used for SLNB across different studies using different detection methods, timing of injections, numbers of injections, and volumes and sites of injection. To date there is no standard accepted protocol. There is also a learning curve associated with the technique of SLNB across all tumour sites. Improved detection rates are consistently seen with increased numbers of procedures performed. Therefore, surgeons performing SLNB are strongly advised to undertake this procedure as part of a full lymphadenectomy initially, in order to determine their false negative rate as a quality assurance process during their learning curve. Results of local practice should be audited. Women considering SLNB should be advised that the long-term survival outcomes following sentinel node surgery alone are not yet available. SLNB should be offered within the context of relevant clinical trials, such as SHAPE (63).

More recent studies offer alternative opinions, the lower sensitivity of SLN for pelvic LN staging had only been shown in early reports however more recent papers did not show this demonstrating a higher sensitivity (64, 65).

Recommendations:

- SLNB can be considered in the management of women with tumours of <2 cm in diameter in addition to formal PLND.
- Strict adherence to protocol is important and surgeons must perform side-specific nodal dissection in any cases of failed mapping.
- There should be an initial training period with high exposure to ensure quality.
- All suspicious or grossly enlarged nodes must be removed regardless of findings at SLN mapping.
- Long-term safety of SLNB alone has yet to be established in prospective studies comparing SLNB with SLNB and full lymphadenectomy and women considering SLNB should be informed of this. (Grade B)

6. Pathology of cervix cancer

Detailed guidelines are available on Royal College of Pathologists (RCPath) website (https://www.rcpath.org/profession/publications/cancer-datasets.html). This section addresses some areas of clinical importance in the pathology of cervical cancer.

6.1 Clinical information required on the specimen request form

Given the increasing centralization of laboratories this may result in pathology departments being sited away from the clinical areas and not always sharing the same information systems. The request form has become an important medium of communication. In addition to demographic details, the request form should contain cervical screening history (at least the latest cytology result), results of previous biopsies including the dimensions of the cancer, radiology results and the details of all specimens sent.

6.2 Reporting of small biopsy specimens

Recording of dimensions of a large loop excision of the transformation zone (LLETZ) or loop biopsy of the cervix should be in three dimensions. The diameter of the ectocervix (two dimensions) and the depth (thickness) should be recorded. This should be as accurate and reproducible as possible, as it is relevant for staging, assessing adequacy of colposcopy (66) and therapeutic decision-making. A cervical LLETZ specimen is usually trimmed by serial slicing at 2-3 mm in a sagittal/parasagittal plane. The slices are submitted in sequential, individually labelled cassettes such that the sequence of slices is unambiguous. This enables assessment of a carcinoma whose third dimension may exceed 7 mm. Core histological data items that should be present in all histological reports of cervical carcinoma include tumour type, tumour grade, tumour dimensions, lymphovascular invasion, resection margins and FIGO stage.

All cervical carcinomas should be typed according to the 2014 WHO classification (67). Although a detailed description of different tumour types is beyond the scope of these guidelines, a few points should be noted. Nearly all-squamous carcinomas of the cervix are aetiologically related to HPV infections; although rare HPV-negative cancers have been described [68]. HPV-negative cervical adenocarcinomas are increasingly recognized, and it is now well established that gastric type adenocarcinomas of the cervix are unrelated to HPV. A new classification, based on HPV association, has been proposed (69). A system of assessing cervical adenocarcinomas based on the pattern of invasion has been developed and has been shown to be reproducible amongst pathologists and to correlate with the risk of lymph node involvement and outcomes (70).

Measurement of tumour dimensions in cervical carcinomas is important for accurate FIGO staging of early cervical cancers. Carcinomas must be measured in millimetres in three dimensions. Accurate measurements are paramount in distinguishing between the different early FIGO stages (71). Tumour measurements are one of the parameters, which affect decisions regarding type of surgery and need for adjuvant therapy.

The measurements must be provided in three dimensions, depth of invasion can be replaced by thickness of tumour in some cases especially in ulcerated cancers and adenocarcinomas. The term ‘microinvasive carcinoma’ does not feature in the FIGO staging systems and should not be used. Detailed descriptions of preferred methods of measurement are beyond the scope of these guidelines.

6.3 Reporting lymphovascular space invasion

Lymphovascular space invasion (LVSI) does not affect staging of cervical carcinoma. Correlation of LVSI with outcome has been difficult to assess due to variability in recognition (72). Variability in fixation leading to retraction around tumour groups is a well-recognized mimic. Assessment is difficult in fragmented and diathermized specimens. Features that may help in recognition of LVSI are presence of endothelial lining, adherence of the tumour cells to the side of the space, presence of adherent fibrin and matching of tumour contours to the outline of the space. LVSI has been shown as an independent predictive factor of adverse outcome although there is not yet enough evidence to support quantification of LVSI, distinguishing between blood and lymphatic channels or description of site of LVSI (73-75).

6.4 Reporting of frozen sections

In most institutions in the United Kingdom, frozen sections for cervical tumours are not routinely used for the assessment of resection margins. However, in some specialist centres, frozen sections are used for the intraoperative evaluation of the upper limit of trachelectomy specimens. The resected cervix is sent for frozen section evaluation of the proximal margin with a recommended tumour (invasive and in-

situ) clearance of 5-10 mm [76]. If this clearance is not achieved, additional cervical tissue is excised to obtain that clearance, or a completion hysterectomy is performed if intraoperative assessment indicates that an adequate margin clearance is not possible (77).

There are limitations of frozen section on trachelectomy specimens and the discrepancies are mainly due to inherent difficulties in discrimination of subtle invasion from benign mimics. Tubo-endometrioid metaplasia, which commonly occurs- particularly after loop excisions, may simulate cervical glandular intraepithelial neoplasia on frozen section [77] giving rise to a false positive report on frozen section. Assessment of margins in trachelectomy specimens is possible in some macroscopically visible tumours (78). In cervical cancers, lymph node involvement is a strong predictor of survival [79]. The 5-year survival rate decreases from 92% to 64% in cases of positive pelvic lymph nodes (80-81). In the context of fertility-preserving procedures, the intra-operative assessment of clinically suspicious lymph nodes may be of value. Frozen section is also highly crucial within the context of Sentinel LN technique (83). (Grade B)

6.5 Testing for HPV/p 16

6.5.1 HPV testing

The causative role of distinct types of human papilloma viruses (HPVs), referred to as high risk (HR) HPV types, in most types of cervical cancer has been unequivocally established [84]. The oncogenic potential of these viruses is quite divergent: HPV16, 18 and 45 are clearly very potent oncogenic agents, whereas oncogenicity of most of the other viruses of this group is less potent [85]. Molecular testing for HPV may occasionally be useful in a diagnostic scenario when, for example, in the context of a metastatic neoplasm the differential includes an HPV-related versus a non-HPV-related primary carcinoma. PCR based assays are usually sufficiently sensitive, but when the viral load is low, in-situ hybridization (ISH) techniques may be needed. HPV typing may be of value when considering patient selection for immunotherapy trials (86).

6.5.2 P16 staining

In cervical pre-neoplastic and neoplastic lesions associated with high-risk human papillomavirus (HPV) infection, there is functional inactivation of Rb by HPV E7 protein. This results in an accumulation of p16 protein, because normally Rb inhibits transcription of p16 (88). As a consequence, in the cervix diffuse p16 positivity can be regarded as a surrogate marker of the presence of high-risk HPV (84). This is of value in that most histopathology laboratories do not have the facilities to undertake molecular techniques to identify HPV, whereas p16 immunohistochemistry is easy to perform. It is also clear that focal, or even diffuse, p16 expression may occur as a result of non-HPV- related mechanisms (89). Diffuse (as opposed to focal) positivity with p16 in the cervix can be regarded as surrogate marker of the presence of high-risk HPV. Most cervical carcinomas (squamous, glandular and high grade neuroendocrine) are p16 positive, as a result of their association with high risk HPV (89). Some types of endocervical adenocarcinoma have been reported to be p16-negative (90). P16 is a useful marker to help in grading intraepithelial neoplasia. (90). It can be used to ascertain the tumour origin as endocervical adenocarcinoma, as discussed, is usually associated with high-risk HPV, whereas this is rarely the case with an endometrial adenocarcinoma (91). As a consequence, most cervical adenocarcinomas exhibit diffuse positivity with p16 whereas endometrial adenocarcinoma of endometrioid type is usually negative or there is focal positivity.

Recommendations:

- These would adhere to the RCPath guidance. (Grade B)

7 Surgical management of cervical cancer per stage (the new FIGO classification version 2018 applies)

7.1. Stage IA1

Conisation for stage IA1 cervical cancer

Conisation for stage IA1 cervical cancer has been recommended by numerous authors and is included in other established guidelines. The aim of conisation is to achieve negative margins to both cancer and dysplasia. Cold knife conisation used to be seen as having the advantage over loop conisation (LLETZ) with the margins being easier to assess. However, LLETZ is now the acceptable and preferred option in the UK, as long as adequate margins are achieved along with a non-fragmented specimen, correct histological orientation, and no electrosurgical artefact interfering with marginal assessment.

Conisation (LLETZ, knife, & LASER) has been systematically reviewed extensively in patients with cervical intra-epithelial neoplasia (CIN). Complications include cervical incompetence and stenosis, risks of premature delivery, leading to neonatal death and complications of extreme prematurity. A detailed assessment of these risks is outside the scope of this guideline, but it should be noted that when treating stage IA1 disease, patients often receive more than one conisation or large cones greater than 15mm deep, which are associated with a greater risk of these complications. This must be explained to patients undergoing conisation for cervical cancer (92-96). Especially in view of the fact that the lateral extent of the lesion is no longer taken into consideration for the early stages IA1 and 2, lesions with wider lateral extent will need larger cones. individual discussions and decision-making processes will need to happen whether a cone excision alone would be sufficient for the larger tumours, although they will probably represent a rarity.

When the patient has completed her family or does not require fertility sparing approach, a simple hysterectomy may be advised.

Recommendations:

- Conisation (cold knife or LLETZ) is an acceptable treatment for stage IA1 squamous cell and adenocarcinoma of the cervix (Grade B)
- Re-conisation is recommended if there are positive margins to intra-epithelial neoplasia (Grade A)
- Re-conisation is recommended if the specimen cannot be orientated, is fragmented, or has diathermy artefact that makes margin assessment impossible
- Conisation (LLETZ, knife, & LASER) for cervical cancer is often large or multiple and carries a higher risk of obstetric complications in the future. This must be explained to women who have this treatment and alternative options discussed
- Recent evidence has indicated that SLND approach may be extended to use in Stage IA1 (Grade C)
- In patients with LVSI a pelvic LND and/or SLNB should be performed (Grade A)
- https://bgcs.org.uk/news/sentinel-consensus-document-for-endometrial-and-cervical-cancer-bgcs.html

7.2 Stage IA2 – IB2 cervical cancer (FIGO 2018)

The standard management for patients with FIGO stages IA2, IB1 and Ib2 (FIGO 2018) cervical cancer is radical hysterectomy and bilateral salpingectomy +/- bilateral oophorectomy with bilateral pelvic lymphadenectomy. For younger patients who wish to preserve their ovarian function, opportunistic bilateral salpingectomy should be discussed and offered. The extent of radicality of the local resection has been an issue of debate for decades, however two randomised controlled trials found that following a less radical approach in terms of a Piver-Rutledge type I instead of III (Piver 1 or 2 – Class A/B) has equal oncologic safety, but a lower surgical morbidity profile (97,98). Wright et al found that patients with stage IB1 cervical cancer (FIGO 2018) with no LVSI and negative pelvic nodes had only 0.4% risk for

parametrial invasion and, therefore, could have received simple hysterectomy (95-96). Based on this and similar retrospective studies (101-103), three prospective randomised clinical trials have been designed to study the role of less radical surgery in this patient group. Patients eligible for these trials should be offered trial participation. The largest ongoing trial is the SHAPE Trial (ClinicalTrials.gov Identifier: NCT01658930), a randomized phase III trial comparing radical hysterectomy and pelvic node dissection vs simple hysterectomy and pelvic node dissection in patients with low risk early stage cervical cancer less than 2cm, including those with IA1 disease. The study has completed recruitment with seven hundred patients in 2019 and survival results are awaited.

Traditionally, the removal of lymph nodes is recommended from the following anatomical regions: external iliac lymph nodes from the bifurcation of common iliac artery to the deep circumflex iliac vein; the nodes around the internal iliac vessels; the nodes from the obturator fossa down to the level of the obturator nerve. (For SLN protocols and value please see section five.)

For women with stage IA2 disease who wish to preserve their fertility, individualised management should be discussed ranging from simple cone excision , simple or radical hysterectomy depending on the patient's previous cervical surgeries, lateral extension of the tumour, and presence of LVSI.

Recommendations:

- Women with stage IA2 cervical carcinoma who wish to preserve their fertility are eligible for conization/ simple or radical trachelectomy irrespective of grade and lymph-vascular space invasion, as long as clear margins can be achieved, and no pathological LN are identified in staging. (Grade B)
- The standard management for stage IB1 and IB2 cervical cancer (FIGO 2018), outside of clinical trials, is radical hysterectomy and bilateral salpingectomy with bilateral pelvic lymphadenectomy +/- bilateral oophorectomy. (Grade A)
- Patients eligible for clinical trials evaluating extent of surgery should be offered trial participation
- SLNB is a promising way of diagnosing lymph node metastases and reducing the morbidity of systematic pelvic LND (Grade C)
- Young patients with adenocarcinoma should be counselled carefully regarding bilateral salpingoophorectomy, due to the higher risk of metastases and/or relapse in the adnexa compared to squamous cell histology (Grade A)
- Chemoradiotherapy is a valid alternative to radical surgery but usually offered for those unfit for surgery or where a double treatment modality (i.e., surgery and radiotherapy) is to be avoided (Grade A)
- Radical trachelectomy with cerclage and bilateral pelvic lymphadenectomy and/or SLN is an option for patients with cervical cancer up to stage Ib1 (FIGO 2018) who wish to preserve their fertility. Trachelectomy may be an option also for Ib2 (FIGO 2018) tumours if patients are properly counselled by an experienced team about the higher oncologic risks. The estimated figures of global outcomes following trachelectomy can be seen in Table two below. There are protocols that apply neoadjuvant chemotherapy followed by trachelectomy, however these are not standard practice. Adjuvant chemoradiotherapy is recommended for patients with high-risk pathological prognostic factors (positive nodes, positive/close surgical margin, positive parametrium) (Grade C)

Table Two, Recommended Estimated Figures of Global Outcomes Following Different Types of Trachelectomy for Stage IB1 Cervical Cancer to be used During Patient Counselling.

	RVT	ART (open)	Minimally invasive ART
Does not receive fertility sparing surgery	Circa 11%	Circa 17%	Circa 8%
Recurrence rate	Circa 5%	Circa 5%	Circa 6%**
Cervical erosion rate	Circa 3%	Circa 3%	Circa 5%
Cervical stenosis rate	Circa 8%	Circa 11%	Circa 5%
Achieves at least one pregnancy	Circa 50%	Circa 50%	Circa 66%
Proportion of pregnancies secondary to fertility treatment	About a ¼	About a ½	About a 1/3
Women who achieve a live birth	Circa 50%	Circa 25%	Circa 57%
Premature delivery rate *	Circa 40%	Circa 50%	Circa 49%
Extreme premature delivery rate	Circa 17%	Circa 20%	Circa 22%

*This figure is affected by the proportion of elective Caesarean Sections before 37 weeks' gestation.

7.3. Ovarian conservation

The incidence of ovarian metastasis is not significant in patients with stage IB squamous cell carcinoma (0.2%) and therefore, ovarian preservation in young patients is safe (104). Published data on rates of ovarian metastasis in cervical adenocarcinomas are conflicting. Shimada et al found that 3.72% of patients with stage IB adenocarcinoma had ovarian metastases, which suggests that clinicians should be cautious offering ovarian preservation (104). Others, however found no difference in outcomes in patients with adenocarcinoma (105-108). One recent study of 312 patients found ovarian metastases in 14 women (4.5%) (109). Nine of these had stage IIA (FIGO 2009) disease or above and would not have qualified for fertility sparing surgery. Of the five patients with stage IB (FIGO 2009) disease, all had uterine corpus involvement at final histology and would also have been unsuitable for fertility-sparing surgery. The fact that most series include patients with disease greater than 4cm makes the estimation of risk of ovarian metastasis in smaller cases, so patients should be counselled carefully. Ovarian preservation is acceptable in adenocarcinoma patients who wish to preserve their fertility as on the balance of probability, women at risk of ovarian metastases will have completion treatment including the ovaries.

7.4. Laparoscopy versus laparotomy

Recent evidence from a prospective randomized trial (311) and a large SEER meta-analysis (312) showed a significant compromise of overall oncologic outcome in terms of both progression-free and overall survival of the minimal invasive compared to the open approach for patients with early stage cervical cancer up to 4cm. The surgical morbidity and mortality, as well as quality of life scores were all similar between the two modalities. These data are in contradiction with previous retrospective studies which showed equivalent oncologic outcome and even lower morbidity in the minimal invasive arm.

The UK National Cancer Registration and Analysis Service in their analysis of 929 patients who underwent either open or minimally invasive radical hysterectomy replicated the impaired overall survival outcome of the minimally invasive surgery group. (https://bgcs.org.uk/news/ncras-cervical-cancer-radical-hysterectomy-analysis.html). In their May 2019 statement, ESGO advised that in radical hysterectomy, open approach is the gold standard. (https://www.esgo.org/explore/council/esgo-statement-laparoscopic-radical-hysterectomy/).

Following the recently published evidence, patients should be carefully counselled about existing evidence to enable them to make an informed decision about their treatment. In light of this analysis from English data, the BGCS recommends that clinicians and patients exercise caution, taking into

account factors such as tumour size, when considering laparoscopic surgery for cervical cancer. We recommend that gynaecological cancer surgeons and nurse specialists discuss in detail the risks and benefits of the different surgical options with patients to enable women to make an informed choice. NCRAS analysis of the size of cervical tumour as a variable in predicting survival is ongoing and will provide very useful data in guiding future BGCS recommendations in this area.

Furthermore, In an effort to further elucidate variations in practice in Europe and the impact of minimally invasive surgery (MIS) in cervical cancer in European Centres; the European Society of Gynecological Oncology (ESGO), has launched the SUCCOR Study NCT03958305 (313): "An international european cohort observational study comparing MIS versus open abdominal radical hysterectomy in patients with stage IB1 cervical cancer operated in 2013-2014". The FIGO staging that applied was still the one from FIGO 2009. Even though this retrospective study also confirmed, that patients with IB1 (FIGO 2009) cervical cancer that underwent radical hysterectomy by MIS showed a significantly higher risk of relapse and death, patients with tumours smaller than 2 cm and those with previous cone biopsy did not show differences in disease free survival (DFS) by the surgical approach. Furthermore, the investigators showed that the use of a uterine manipulator in MIS impacted the DFS negatively in this population. Patients that underwent radical hysterectomy by MIS without the use of a manipulator showed the same outcome as those operated by open surgery and even more, protective manoeuvres to avoid tumour spillage at the time of the colpotomy in MIS improved the DFS in these patients.

The currently ongoing phase III prospective randomised controlled international trial has been established (Robot-assisted Approach to Cervical Cancer "RACC" NCT03719547) to further assess the risks and compare oncologic and surgical outcomes of open radical hysterectomy versus robotic hysterectomy in centres with strictly established quality assurance criteria of surgical training and appropriate infrastructure.

7.5 Adjuvant treatment after surgery

There will be some patients post operatively who, despite adequate preoperative staging, at final pathology have adverse prognostic factors that will require discussion about adjuvant treatment, such as microscopically involved margins, positive LN or larger tumour size. The following histopathological risk factors should be considered when considering postoperative adjuvant chemoradiotherapy.

High-risk factors:

- Positive pelvic/para-aortic lymph nodes
- Parametrial spread
- Positive surgical margins (microscopic)
- Patients with high-risk factors present in the radical hysterectomy specimen should be offered adjuvant concurrent chemoradiotherapy. Concurrent chemoradiation therapy is superior to radiation alone (118)

Intermediate-risk factors:

- Presence of LVSI
- Tumour maximum diameter >4cm at final pathology
- Deep cervical stromal invasion (>1/3)

The GOG 92 prospective trial recruited patients with two or more intermediate-risk factors (according to Sedlis-criteria, which can be seen below in Table Three) after radical hysterectomy and pelvic lymphadenectomy and compared outcomes of patient groups with or without adjuvant pelvic radiotherapy (but no chemotherapy) (118-124). Patients who received adjuvant radiotherapy had a significantly improved recurrence-free survival, but no statistically significant overall survival benefit. It is unknown if the addition of chemotherapy would increase the overall survival.

Table Three. Sedlis Criteria (117)

LVSI	Depth of invasion in thirds	Tumour size in cm
+	Deep	Any
+	Middle	≥2
+	Superficial	≥5
-	Middle or deep	≥4

Patients with intermediate-risk factors, therefore, should be considered for adjuvant chemoradiotherapy or observation and the GOG 92 results should be discussed. Patients were eligible for the trial according to the Sedlis-criteria (121). This study was carried out some time ago and more recent studies show better surgical outcome without the need for adjuvant treatment (122).

8 Management of locally advanced cervix cancer stage IB3-IVA (FIGO 2018)

The standard treatment for locally advanced cervical cancer is currently chemo-radiotherapy consisting of external beam radiotherapy (EBRT), intracavitary brachytherapy (BT) and concomitant chemotherapy with Cisplatin (125-128). A randomised controlled trial by Landoni et al (126) compared radical surgery with radical radiotherapy in patients with stage IB-IIA and found no survival difference in patients with squamous cell carcinoma but higher morbidity in patients with a combined treatment modality. For that reason, combined treatment should be avoided, and surgery should not be pursued in patients who are expected to need postoperative chemoradiotherapy. There is controversy about how to manage patients with positive nodes and whether the proposed surgery should be abandoned, or completion carried out. No trial has ever been completed to address this and individual MDTs/tumour boards should determine a local policy.

8.1 Stage IB3/IIA2 cervical cancer (FIGO 2018)

1) Treatment strategy should aim to avoid the combination of radical surgery and postoperative EBRT, due to significant increase of morbidity and no impact on survival. (Grade A)
2) Definitive platinum-based chemo-radiotherapy and brachytherapy is preferred (see Principles of radiotherapy). (Grade A)
3) Pelvic exenteration is an option in selected cases with stage IVA disease. This should be especially considered when need for symptom control applies, eg for fistulae. (Grade C)

8.2 Locally advanced disease and involved lymph nodes on radiological staging

1) Definitive chemoradiotherapy and brachytherapy with an additional radiation boost to the involved lymph nodes is recommended in patients with unequivocally involved pelvic lymph nodes on imaging (see principles of radiotherapy)
2) Para-aortic (at least up to the inferior mesenteric artery) lymph node dissection maybe considered before treatment for staging purposes if no evidence of disease on imaging (PET-CT recommended for imaging nodes).

8.3 Stage IIB, IIIA/IIIB, IVA cervical cancer (FIGO 2018)

1) Definitive chemoradiotherapy and brachytherapy with an additional radiation boost to the involved lymph nodes is recommended in patients with unequivocally involved pelvic lymph nodes on imaging (see principles of radiotherapy). The Uterus-11 trial, (NCT01049100) a

multicentre phase III Intergroup trial of the German Radiation Oncology Group (ARO) and the Gynaecologic Cancer Group (AGO) was designed to evaluate the role of surgical staging in patients with stage IIB-IV cervical cancer before primary chemoradiation therapy within a prospective randomised design. The study has finished recruiting, results are awaited.

2) Paraaortic (at least up to the inferior mesenteric artery) lymph node dissection maybe considered before treatment for staging purposes if no evidence of disease on imaging (PET-CT recommended for imaging nodes).
3) Pelvic exenteration is an option in selected cases with stage 4A (T4M0) disease.

8.4 Cervical stump cancer

Management of cervical stump cancer follows the recommendations for patients with subtotal hysterectomy. Adaptation of radiotherapy and brachytherapy may be necessary.

8.5 Principles of radiotherapy

8.5.1 Definitive chemoradiotherapy and brachytherapy: general aspects

Definitive management (without tumour related surgery) consists of concomitant pelvic radiotherapy (platinum-based) and brachytherapy or pelvic EBRT alone and brachytherapy.

1) Overall treatment time for the definitive treatment should not exceed 7-8 weeks. Overall treatment time for EBRT should not exceed 5-6 weeks (Grade A).
2) Delay of treatment and/or treatment interruptions must be avoided, i.e. patients should be treated as category 1 patients (Grade A).

There is evidence that overall treatment time (OTT), including brachytherapy, should be as short as possible and should not exceed 56 days for squamous carcinoma (124). Recent data from retro EMBRACE study indicates that the effect of OTT shortening by one week was equivalent to escalating CTVHR dose by 5 Gy (D90), resulting in increase of local control by 1.0% (small tumours) to 2.5% (large tumours). The EMBRACE data (125) is based on a treatment time of 7 weeks and ideally OTT should be less than 7 weeks.

It is recommended to use pelvic intensity modulated radiotherapy to deliver EBRT with an appropriate IGRT (image guided radiotherapy) programme (Grade B).

Pelvic EBRT is currently delivered with different techniques: 3D conformal EBRT, intensity modulated radiotherapy (IMRT), volumetric arc techniques (VMAT), and tomotherapy (131-135). Application of IMRT in cervix cancer significantly reduces the volume of tissue irradiated to intermediate doses such as 30-40 Gy for bladder, rectum, sigmoid and bowel (133). The progress from 3D conformal EBRT to IMRT has demonstrated a reduction of treatment related morbidity in mono-institutional and retrospective settings (135-137). Furthermore, EMBRACE quality of life data has shown a significantly lower incidence of bowel symptoms in patients treated with IMRT compared to 3D conformal EBRT with the four-field box technique (131). However studies of intra and inter-fraction motion show that there is significant internal motion of the cervix and uterus due to rectal and bladder filling and tumour regression as shown by Beadle (132), Van de Bunt (136), Taylor & Powell (137) and adequate margins must allow for this when using IMRT as well as a comprehensive online cone beam based imaging protocol ideally including daily imaging with a back-up plan.

1) A total dose of 45-50 Gy using 1.8-2 Gy per fraction should be used.

Randomised studies of radiotherapy have utilised fractionation regimens of 40-50.4 Gy in daily 1.8-2Gy fractions (Grade B) (RCR Guidelines). An RCR audit by Forrest & Clarke in 2012 (140) showed the most common UK regimens were 45 Gy in 25 fractions or 50.4 Gy in 28 fractions. Pelvic EBRT dose should be 45-50.4 Gy in 1.8 Gy per fraction to the central disease and the elective nodes. The central CTV volume

should include all known disease (GTV), entire cervix, parametrium, upper half of the vagina / at least 2 cm below GTV and entire uterus. The elective nodal volume should include all involved nodes, common iliac lymph nodes, internal and external iliac lymph nodes, obturator nodes and pre-sacral lymph nodes. These should be contoured as per a contouring atlas (Taylor and Powell 2008) (134-139,135).

2) Tumour and lymph node related target volume for IMRT includes the primary cervical tumour, the parametria, uterine corpus, upper half vagina (at least 2 cm below disease) and the pelvic lymph nodes (obturator, internal, external, common iliac and pre-sacral). In case of extensive pelvic node involvement / common iliac/ para aortic lymph node involvement the nodal target should include the para-aortic lymph node at least up to the level of the renal vessels.

3) Data from the EMBRACE studies (132) showed a significant incidence of para-aortic failure in patients with known pelvic nodes (11.5%) and the role of para-aortic nodal irradiation electively is being studied in EMBRACE II. Significant risk factors for para-aortic nodal recurrence is common iliac lymph node involvement and >/=3LN involved.
4) A reduced target volume for EBRT excluding the common iliac nodes may be considered in low and intermediate risk IB1 patients with negative nodes on imaging.

5) Boost treatment for involved lymph node(s) may be applied by simultaneous integrated boost within the IMRT or as a sequential boost. The total dose including the contribution from brachytherapy should be 55-60Gy (EQD2). An alternative treatment option is debulking of enlarged nodes.

The role of dose escalation to involved nodes is being explored in the DEPICT trial (137). Other studies indicate that pelvic nodes are a poor prognostic marker with increased likelihood of pelvic and para-aortic nodal recurrence. At this time nodal dose escalation can be considered but there is no good data to recommend this definitely. There is no definite survival advantage to treating the para-aortic area electively in patients at high risk of lymph node involvement.

Single agent radio-sensitising chemotherapy, preferably cisplatin (weekly 40 mg/m^2) should be used unless contraindicated. If cisplatin is not applicable alternative options are 5FU and carboplatin.

6) The benefit of concurrent chemo-radiotherapy is seen across all tumour stages. Standard treatments would be weekly cisplatin chemotherapy but where cisplatin is contra-indicated 5FU based chemotherapy is an alternative option (CCMAC 2008 & 2009) (141,142).

The currently recruiting INTERLACE study (NCT01566240) is a phase III multicentre trial comparing weekly induction chemotherapy followed by standard chemoradiation versus standard chemoradiation alone in patients with locally advanced cervical cancer (143) and the OUTBACK study (NCT01414608) which is a Phase III Trial of Adjuvant Chemotherapy Following Chemoradiation as Primary Treatment for Locally Advanced Cervical Cancer Compared to Chemoradiation Alone (144). Results are awaited.

8.6 Definitive brachytherapy

1) Image-guided adaptive brachytherapy (IGABT) is recommended, preferably using MRI at the time of brachytherapy (Grade A).
2) The tumour-related target for brachytherapy includes the residual gross tumour volume, the adaptive high-risk clinical target volume and the intermediate risk clinical target volume (Grade B).
3) Intracavity and combine intracavity / interstitial brachytherapy should be performed under anaesthesia.
4) The brachytherapy applicator should consist of a uterine tandem and vaginal applicator (ovoid's or ring). Combined intracavity / interstitial brachytherapy should be used where appropriate

(such as significant residual disease in parametria) in order to achieve a sufficiently high radiation dose to the target and / or reduce dose to organs at risk (Grade B).

5) In IGABT the aim should be to deliver a brachytherapy dose of 40-45 Gy (EQD2)(D90)to reach a total EBRT + brachytherapy dose of 85-90 Gy to the high-risk volume and 60 Gy (D98) to the intermediate risk volume. 3D dose volume constraints for rectum, vagina, sigmoid and bowel are recommended as published in the literature (Grade B).
6) Generally, point A dose normalisation should be used as the starting point for stepwise treatment plan optimisation.
7) Brachytherapy should be delivered in several fractions as high dose rate (usually 3-4) or in 1-2 fractions as pulsed dose rate (Grade A).

Evidence from cohort series supports the use of image guided brachytherapy to maximise survival and local control while minimising late toxicity. Results from EMBRACE and retro EMBRACE supports the recommended dose of > /= 85 Gy EQD2 to the high-risk CTV D90 which is predicted to lead to a 3-year actuarial local control of >96% in tumours ≦30 cm^3 and >91% in tumours >30 cm^3. Utilization of combined intracavitary / interstitial applicators is an essential tool for dose escalation in large tumours. The EMBRACE studies provide the best data on doses to organs at risk based on organ volume rather than point doses (D2cc Bladder 80 Gy, D2cc rectum 70-75 Gy, D2cc Bowel / sigmoid 70 Gy). These should be the treatment aim where possible but should not preclude adequate tumour doses. Of note there is not a good correlation between bowel / sigmoid dose and toxicity due to the mobility of this organ.

Recommendations:

- External beam radiation should be planned to use newer technologies
- Concurrent platinum-based chemotherapy should usually be administered
- Brachytherapy remains an integral part of the treatment
- Treatment times should not exceed 56 days (Grade A)

9 Adjuvant treatment post hysterectomy: Use of external beam radiotherapy, vagina vault brachytherapy, chemotherapy and combinations

This section provides evidence-based information on the adjuvant treatment options post hysterectomy for cervical cancer. In this setting, it describes the role of external beam radiotherapy, vaginal vault brachytherapy, chemotherapy and combinations after a hysterectomy for early stage cervical cancer. The purpose of adjuvant treatment is to reduce recurrence risk, increase chance of cure and prolong life if possible. It is therefore important to understand the risk factors that contribute to higher recurrence and lower survival rates.

9.1 External beam radiotherapy

Large tumour size, LVSI and deep stromal invasion have been shown to independently predict local recurrence after surgery in FIGO stage I cervical squamous cell cancer (123). The GOG 92 phase 3 trial therefore randomized patients with stage IB disease with at least two of these poor prognostic features to post-operative pelvic radiotherapy (46-50.4 Gy) or observation alone (121). The adjuvant radiotherapy arm showed a 46% reduction of recurrence (HR 0.54) and a reduction in risk of progression or death (HR 0.58). Both local recurrence (13.9% vs 20.7%) and distant recurrence (2.9% vs 8.6%) were reduced with the use of radiotherapy. This progression free survival benefit was balanced against a 6.6% grade 3 or 4 adverse event rate, (haematological RR 2.38; gastrointestinal RR 7.32) compared with 2.1% without radiotherapy. Post–operative radiotherapy was most beneficial in patients with adenocarcinoma or adenosquamous histology (120). A subsequent 2012 Cochrane Review which pooled this trial with a German randomized controlled trial (148) evaluated 397 patients and concluded that

although progression free survival was improved, overall survival was not affected by adjuvant radiotherapy in stage IB disease (149).

In this cohort of patients, it remains unclear whether concurrent chemotherapy with radiation is superior. Retrospective data suggests lower recurrence rate but no definite survival improvement with the addition of chemotherapy concurrently (150). The answer may hopefully be provided by the currently recruiting GOG 263 prospective randomised study of chemo-radiation versus radiation alone. Post-operative radiotherapy in patients with LVSI, deep cervical stromal invasion and large tumour size is associated with a progression free survival benefit. It can therefore be recommended to well-informed women with these risk factors providing they fully understand the risk of toxicity.

The addition of concurrent chemotherapy in this setting should be investigated within a clinical trial or on an individual patient basis.

9.2 Concurrent chemotherapy with external beam radiotherapy

High risk factors for recurrence after surgery for early stage cervical cancer include pathological confirmation of lymph node positivity, parametrial involvement and positive surgical margins. The recurrence risk in this setting is in the region of 40% if treated with surgery alone. The landmark randomized phase III intergroup trial {SWOG 8797, RTOG 91-12, GOG 109} (151) evaluated concurrent chemotherapy with radiation or radiation alone in patients with any of these risk factors. The chemotherapy was 4 cycles of 3 weekly cisplatin and fluorouracil started with radiotherapy. Progression free survival (HR 2.01 4yr PFS 80% vs 63%) and overall survival (HR 1.96, 4yr OS 81% vs 71%) were both significantly improved with the addition of chemotherapy (146). Interestingly, the 5-year survival benefit was significantly higher in tumours >2cm (19% vs 5%) and if more than 1 lymph node was involved compared to only one (20% vs 4%). Grade 3 and 4 haematological and gastrointestinal toxicity was increased with chemotherapy with 17% of chemo-radiation patients experiencing grade 4 toxicity, mainly hematologic compared to 4% with radiation alone. The use of single agent cisplatin is likely to reduce this toxicity risk and, as seen in locally advanced disease, may be equivalent in efficacy. A 2016 Cochrane analysis combined this phase III intergroup trial with three other randomised controlled studies to evaluate 401 patients in total. This concluded that use of concurrent platinum-based chemotherapy seems appropriate (153).

High risk patients, defined as lymph node positive, parametrial involvement and positive margins, gain a survival benefit from receiving post-operative cisplatin-based chemo-radiation. This should therefore be recommended to women with these pathological risk factors.

9.3 Radiotherapy technique

Guidance regarding the delivery of postoperative radiotherapy should be followed. Consensus guidelines have been published for delineation (153).

Newer radiotherapy techniques such as Intensity Modulated Radiotherapy (IMRT) can facilitate reduced toxicity with radiotherapy and achieve equivalent survival outcomes (155-157). The role of IMRT has been investigated in the phase III trial of IMRT versus standard therapy in postoperative treatment of endometrial and cervical cancer (TIME-C/RTOG 1203 CCOP), now closed to recruitment.

As for locally advanced cervical cancer patients, the radiotherapy field includes the para-aortic nodes if the common iliac nodes or the para-aortics themselves are proven positive.

Treatment time between surgery and start date is important. A recent National Cancer Database multivariate analysis of 3051 patients revealed a surgery to radiotherapy interval of more than 8 weeks is a poor prognostic factor (HR 1.20). Along with the overall radiotherapy treatment time of more than 7 weeks (HR 1.21). (157)

9.4 Vaginal vault brachytherapy

Within the GOG 92 and SWOG 8797/GOG 109/RTOG 91-12 protocols no brachytherapy was permitted (120-124). However, in cases of vaginal margin involvement or suboptimal surgery (less than radical hysterectomy) it is recommended to deliver a vaginal vault brachytherapy boost of an additional 10-15 Gy in view of the risk of residual tumour cells (158,159). There is no randomised evidence proving the additional role of brachytherapy in this situation. A retrospective analysis of 142 women who underwent post-operative radiotherapy for cervical cancer found the use of a brachytherapy boost in patients with close or involved vaginal resection margins did not have inferior local control, distant control or survival. This suggests a benefit, but patient numbers were small (160). In this cohort parametrial resection margin positivity was associated with a very poor prognosis (5 yr. OS 19%) and the majority of these patients did not receive brachytherapy. A further retrospective analysis of 292 patients demonstrated that systematic application of vaginal vault brachytherapy after EBRT (10-14 Gy) in patients with at least 2 of the following, (adenocarcinoma, nodal involvement and parametrial extension) significantly reduced the poor prognostic impact of histology on local and distant recurrence. This was not associated with any increase in complication risk (161). Without a significant increase in complication risk it is therefore reasonable to consider brachytherapy boost in all high-risk patients (158).

Vaginal vault brachytherapy boost (10-15 Gy) after adjuvant EBRT should be administered if less than radical hysterectomy has been performed or there are close or involved vaginal margins. It should also be considered in other high-risk patients with appropriate counselling of patients regarding the uncertain benefit and potential toxicity; adenocarcinoma, parametrial or vaginal involvement, extensive LVSI, larger tumours or deeply invasive tumours.

In the unlikely scenario of vaginal margin involvement following adequate surgery with no other high-risk factors then consideration of adjuvant vaginal vault brachytherapy boost alone could be discussed (162).

9.5 Adjuvant chemotherapy

The four randomised controlled trials analysed within the 2016 Cochrane review compared differing chemotherapy regimens in addition to radiotherapy post-operatively (152). Only one study compared chemoradiation with chemoradiation plus further adjuvant chemotherapy (163). Unfortunately, due to significant toxicity with the combination chemotherapy (topotecan and cisplatin) this study was terminated early with only 39 patients being recruited. The benefit of further chemotherapy after chemo-radiation in high risk patients is therefore still unknown. The currently recruiting joint GOG and RTOG 0724 trial is addressing that question by randomising patients to receive concurrent cisplatin with radiotherapy with or without 4 cycles of adjuvant carboplatin and paclitaxel. The NCT 00806117 is a similar randomised study recruiting in China.

Retrospective reviews have analysed the potential role of post-operative chemotherapy in certain high-risk patients (e.g. node positive, adenocarcinoma) as an alternative to chemo-radiation (164-166). They have demonstrated feasibility of platinum-based chemotherapy, but there is no randomised evidence to support its application. Adenocarcinomas have a worse prognosis than squamous cell cancers with a retrospective review suggesting adjuvant chemotherapy improves progression free survival compared to chemo-radiation in this cohort (167). A non-statistically significant improvement in survival of 9% was reported for node positive patients treated with chemotherapy after surgery compared to a historical cohort managed surgically only (164). As chemo-radiation has now been shown to provide a survival benefit in node positive patients the relevance of this result is unclear.

Adjuvant chemotherapy (not concurrent with radiation) in early stage cervical cancer should only be used in the context of a clinical trial. (Grade B)

10 Neoadjuvant chemotherapy in cervix cancer

Recommendations:

Neoadjuvant chemotherapy is not standard practise and was shown to have poorer oncologic outcome in earlier studies compared to cisplatin-based concomitant chemoradiation (Grade A). However more recent use of combinations which include a taxane has challenged this, hence current clinical studies such as INTERLACE comparing NACT followed by CCRT with CCRT alone (168-170).

Neoadjuvant chemotherapy (NACT) is usually defined as the use of chemotherapy prior to the definitive treatment. Thus, it may be used as an induction or neoadjuvant prior to planned surgery or prior to planned radiation therapy. The rationale for NACT is that it may:

- Reduce the size of the tumour and convert it from being surgically unresectable to resectable,
- Allow a lesser surgical procedure to be carried out such as fertility-preserving surgery or
- Shrink the tumour to allow definitive chemoradiation a more effective chance of achieving improved tumour control.

Furthermore, it may have a systemic effect and reduce risk of metastatic spread and/or eliminate micro-metastatic disease. NACT may also be considered in some low-income nations where there are scarce radiotherapy facilities and chemotherapy is given prior to surgery, but this is beyond the scope of this chapter.

As discussed below, NACT may also have a place in management of cervix cancer in pregnancy. (Grade D)

10.1 Neoadjuvant chemotherapy followed by surgery

Two large randomised clinical trials have been conducted, the first by the EORTC GCG study 55994 which although this began in 1999 and results were presented at ASCO 2019. This trial compared neoadjuvant chemotherapy with cisplatin or cisplatin-based chemotherapy (minimal cisplatin dose of 225 mg/m² over 9 weeks) followed by radical hysterectomy with pelvic node dissection (RHND) and compared it with concomitant cisplatin chemoradiation. The second trial was a large single-centre, phase III, randomized controlled trial by Gupta et.al (171) comparing the efficacy and toxicity of neoadjuvant chemotherapy followed by radical surgery versus standard cisplatin-based chemoradiation in patients with locally advanced squamous cervical cancer in stage IB2, IIA, or IIB squamous cervical cancer showing the 5-year disease free survival in the neoadjuvant chemotherapy plus surgery group was 69.3% compared with 76.7% in the concomitant chemoradiation group (HR, 1.38; 95% CI, 1.02 to 1.87; P = 0.038), whereas the corresponding 5-year OS rates were 75.4% and 74.7%, respectively (HR, 1.025; 95% CI, 0.752 to 1.398; P = 0.87). The delayed toxicities at 24 months or later after treatment completion in the neoadjuvant chemotherapy plus surgery group versus the concomitant chemoradiation group were rectal (2.2% v 3.5%, respectively), bladder (1.6% v 3.5%, respectively), and vaginal (12.0% v 25.6%, respectively). This study showed that cisplatin-based concomitant chemoradiation resulted in superior progression free survival (PFS) compared with neoadjuvant chemotherapy followed by radical surgery in locally advanced cervical cancer. (165). The EORTC 55994 study (172) was presented at ASCO 2019 and shows remarkably similar results and would suggest no advantage to NACT prior to surgery for larger tumours, whereas for stage IB2 tumours (FIGO 2009) there may be a small benefit to NACT. Thus, concomitant chemoradiation should be the current standard of care until INTERLACE is concluded and reported.

Recommendations:

- Concomitant chemoradiation should be the current standard of care for locally advanced cervical cancers. Results of further studies are awaited. (Grade A)

11 Management of cervical cancer in pregnancy

Cancer of the cervix is the most common gynaecological malignancy diagnosed in pregnancy with an incidence rate of 0.1 to 12 per 10,000 pregnancies. (173) At present, management is mostly based on small case series, expert opinion and anecdotal case reports. (174, 175)

11.1 Pre-invasive disease in pregnancy

11.1 a Cytology

An abnormal cytology in pregnancy should trigger a colposcopy and/or gynaecological oncology referral; investigation should not be deferred until after pregnancy (176-178). (Grade C)

11.1 b Colposcopy

The aim of colposcopy during pregnancy is to exclude invasion, and in appropriate patients, i.e. with pre-invasive disease, defer treatment until after delivery (176,177). If there is suspicion of invasion at colposcopy then a biopsy adequate for diagnosis should be performed (176). (Grade C)

The colposcopic features of invasive cancer do not differ between pregnant and non-pregnant women although colposcopy may be more challenging during pregnancy. These features may include abnormal vessels, irregular surface contour, mosaicism and punctation. The absence of histological invasion cannot be guaranteed by a punch biopsy only demonstrating CIN (176,177). If a loop biopsy is to be performed, it should be carried out where there are facilities to manage haemorrhage (177) and a vaginal pack can be inserted post procedure, which may reduce the risk of bleeding (179). Published case series have demonstrated the risk of significant bleeding to be as high as 25% (180), this is due to the increased vascularisation of the cervix (179).

11.2 Diagnosis of cervical cancer in pregnancy

Almost two-thirds of cervical cancer cases in pregnancy are diagnosed in the first two trimesters (181). The symptomatology of cervical cancer does not differ between the pregnant and the non-pregnant state (182). Cancer related symptoms, such as painless vaginal bleeding, pelvic and lower back pain and urinary frequency, may mimic pregnancy complications (183). Consequently, a delay may mean the cancer is at a higher stage when diagnosis occurs (184). Conversely, there is evidence to show that regular examinations during pregnancy can result in earlier diagnosis (185). Some studies have suggested the chances of cervical cancer being diagnosed in its early stages are three times more likely in pregnancy compared to controls; 76% of lesions diagnosed in pregnancy are a stage IB1(186).

All women presenting with a suspected cervical abnormality in pregnancy require an accurate pelvic examination (speculum and bimanual examination) including colposcopic assessment, regardless of gestational age (183,186). (Grade D). ESGO has a registry for cancers in pregnancy, refer to website, www.esgo.org.

11.2 a Signs and symptoms

The clinical stage and size of tumour will dictate the symptoms of cervical cancer. Early stages of disease may be an incidental finding on routine pelvic examination or cytological investigations. However, symptoms could also include painless vaginal bleeding, abnormal vaginal discharge, post-coital bleeding and dyspareunia. Patients with more advanced disease may complain of urinary dysfunction, pelvic pain, changes in bowel habit, back pain and swelling of legs (187,188).

11.2 b Examination

Examination should assess bleeding, discharge and the presence of lesions in the vagina/ on the cervix. Any lesions should be assessed in terms of size, shape and consistency (187). Cervical ectopy may make the assessment of a pregnant woman's cervix more challenging. Necrotic, friable and exophytic lesions

are suspicious and require further investigation. (187) A woman with suspicious invasive disease in pregnancy should undergo careful biopsy to establish diagnosis (187).

11.2 c Referral pathway

Women with any suspicious cervical pathology during pregnancy should be referred urgently to an experienced colposcopist or gynaecologist under the two-week rule (176,183). (Grade D)

11.3 Staging of cervical cancer in pregnancy

Magnetic resonance imaging (MRI)

MRI is the first line for staging of cervical cancer in pregnancy (190). (Grade D). In experienced centres, Ultrasound may be considered as an alternative which avoids ionizing radiation. MRI is safe in pregnancy (191) and currently the mainstay in staging of cervical cancer. It is essential to consider the challenges pregnancy poses when interpreting MRI. These difficulties can include dilated pelvic veins being misinterpreted as pelvic adenopathy (184), or a reduction in image quality due to fetal movements. (192)

Computed tomography (CT)

CT may be considered essential to gain diagnostic information about maternal wellbeing. Where there is a high suspicion of lung or pleural spread the benefits of undertaking the investigation can outweigh the risks to the fetus. In situations such as these, all efforts should be made to limit fetal exposure to radiation and not compromise the baby's health. Abdominal shielding and low dose radiation should be considered (193). MRI is preferred as there is no ionizing radiation.

Laparoscopic lymphadenectomy and sentinel lymph node biopsy

Lymph node status is an important prognostic factor. (188). (Grade D). The agents used for SLNB are blue dye and radio-colloid technetium. Certain blue dyes, such as lymphazurine, have not been tested in pregnancy and should be avoided. There is limited evidence on the use of radio-colloids in pregnancy, however, recent studies show fetal exposure to radiation is low and pregnancy should not be considered an absolute contraindication (190,191). The use of ICG has shown safety for retinal angiography and to measure hepatic blood flow in pregnant women. At present, the role of SLNB in these patients remains unclear; more trials are needed to clarify the issues of safety and for now the routine use of SLNB should not be performed, unless in the context of clinical trials (198).

11.4 Treatment options

Currently, gynaecological oncologists performing vaginal or laparoscopic radical trachelectomies routinely perform cervical cerclage as part of the procedure (199). However, radical trachelectomy undertaken via laparotomy is different, as cerclage was not included in the initial technique described. (200-205). Given the blood loss and poor fetal outcome, trachelectomy during pregnancy is not advised, in contrast, NACT maybe advocated.

There is limited level A evidence demonstrating prophylactic cerclage reduces the risk of fetal loss and prematurity (199). Despite this, one study demonstrated a reduced risk of fetal loss from 50% to 22% when used after vaginal radical trachelectomy (206). Patients who have undergone trachelectomy should be delivered by caesarean section. (207)

Delivery by caesarean section will aim to avoid damage to the reconstructive procedures performed, hence reducing prematurity in case of subsequent pregnancy. In addition, massive vaginal bleeding has been reported after vaginal delivery (208).

For patients with locally advanced cervical cancer neoadjuvant chemotherapy can help treat and control disease. This should be formally discussed within the local MDT. This will allow for fetal maturation and delivery at an appropriate gestation by caesarean section (209). (Grade D). Carboplatin is the first line chemotherapeutic agent (210). (Grade C)

Carboplatin has a similar efficacy but less nephrotoxicity and ototoxicity to cisplatin (66). There is evidence to show if paclitaxel is used in conjunction with a single platinum agent, the treatment has superior outcomes with a longer period of remission (211). Though studies are limited, those that do exist have demonstrated minimal trans-placental spread of paclitaxel (212).

Breastfeeding during chemotherapy treatment is contraindicated (213,214). (Grade C). Chemotherapy drugs cross into breast milk and may cause neonatal leucopenia. In turn increasing the risk of infection to the baby. An interval of 14 days from the last chemotherapy session is recommended before breastfeeding, allowing time for drug clearance from the breast milk (213). There is evidence to suggest that a short period of lactation after a stressful pregnancy can be of psychological benefit to the woman. (214)

Route of delivery is determined by the presence or absence of visible tumour. If tumour is still present, delivery by caesarean section is preferable to reduce risk of cancer cell implantation in episiotomy scar (212). (Grade D)

Delivery options must be discussed with the patient and obstetric contraindications to vaginal delivery also considered. Recurrence of tumour in episiotomy scars, haemorrhage and infection are well-documented complications of vaginal delivery in this cohort of women. Although less frequent, abdominal wall recurrences have also been described (215). If the tumour itself is very large, consideration to a wound protective system or corporeal uterine incision may be of benefit. In this circumstance, performing a classical caesarean section is likely to reduce blood loss.

Delivery should take place in a hospital with a level three neonatal unit, (173,175,185,188) and the placenta should be sent for histology to exclude metastases (216) (Grade D)

12 Surgical management of relapsed cervical cancer

The management of relapse will be influenced by the choice of initial therapy. Usually salvage surgery is considered after primary chemo-radiation, where the reverse is considered if primary management was surgical management. Surgical treatment of relapsed cervical cancer is challenging due to the commonly palliative situation of the disease, the complex disease-related clinical symptoms and the high surgical complexity associated with any surgical intervention. In the majority of cases, metastatic cervical cancer is not curable, but for some patients who present with locoregional recurrence or with limited distant metastatic disease, surgical treatment may be potentially curative.

12.1. Intra-pelvic relapse

Patients with intrapelvic relapse should be considered for exenterative surgery with curative intent, including laterally extended endopelvic resection (LEER), only if a complete tumour resection with microscopically clear tumour margins is anticipated (Grade B).

A PET/CT prior to exenterative surgery should exclude the presence of distant metastases. (Grade B). Patients with radiologically or clinically positive pelvic lymph nodes should not be excluded as surgical candidates, if disease appears resectable, since pelvic lymphadenopathy has been shown not to affect prognosis, as opposed to paraaortic lymphadenopathy which has been demonstrated to be a negative prognostic indicator of survival (Grade C).

For women who have undergone primary chemoradiotherapy, subsequent radical hysterectomy or pelvic exenteration, with the aim to achieve clear surgical margins, as management of local recurrence, is the preferred approach, as it has been shown to have five-year survival rates ranging between 30 and 40 percent (217,218). Careful patient selection is required given the perioperative and postoperative morbidity associated with this extensive surgical approach and should include psycho-sexual considerations. These should be part of the specialist team doing the procedures.

Intraoperative radiation therapy (IORT) is an additional potential option for women undergoing exenterative procedures for relapse, where available. However, the efficacy of IORT has not yet been shown in prospective trials and not routinely available in clinical practice (219,220).

Pelvic relapse can be divided into central versus pelvic side wall relapse. Central relapse can affect the anterior, posterior or both compartments. Pelvic side wall relapse also varies in terms of the affected structures and extent of clinical symptoms.

The probability of complete resection is higher in the case of a central relapse where exenterative surgery tailored to the affected compartment can achieve microscopically clear resection margins. The most common type of central relapse is a vaginal vault relapse and hence affecting both compartments and often necessitating total exenteration. Brunschwig was the first to publish in 1948 the first successful results of pelvic exenteration in patients with central cervical cancer relapse (221,222). The original procedure included the en bloc resection of the internal and external reproductive organs including the bladder, urethra, both ureters, rectosigmoid colon together with the anus and perineum. The ureters were then implanted into the colon upstream of the colostomy site in terms of a wet colostomy. (221)

There are three types of exenteration: total, anterior and posterior. Total exenteration refers to removal of the uterus and parametria, bladder, rectum, vagina, urethra, and a part of the levator muscles. In an anterior exenteration, the rectum is spared, while in a posterior exenteration, the bladder and urethra are preserved. A perineal phase, resecting the anus, urethra, and portions of the vulva, may also be required in cases where the distal part of the vagina and/ or vulva and perineum are affected. The type of procedure chosen for the patient depends on the site of relapse, previous treatment, anatomy, and the patient's wish and expectations.

There are no prospective randomized studies to assess the impact of exenterative surgery on patient's survival. In a systematic review of 21 studies of pelvic exenteration for gynaecological malignancy, one-third to one-half of women were found to have unresectable or extra pelvic disease found at exploration resulting in abortion of the procedure (223). Those who had negative resection margins and no metastatic disease had an approximately 50% cure rate; the remainder died of recurrent cancer.

One of the largest monocentric case series to date is by Egger et al, which evaluated the outcome of 282 patients with various types and extents of advanced or relapsed cervical cancer (222). The majority of patients (75%) had undergone exenteration for relapsed disease. Anterior or posterior exenteration alone cleared the disease in only 5% and 2% of the cases, respectively, and 93% of the patients required a total exenteration to achieve clear margins. The 5- and 10-year overall survival (OS) rates of all patients were 41% and 37%, respectively. The 5-year disease-free survival (DFS) for all patients was 61%. The 5- and 10-year OS rates of the 133 patients that were operated on with a curative intent, was 64% and 57% compared to those that were operated on with a palliative intent, who had a 5-year OS of 19% and a 10-year OS rate of 18%. No significant OS difference was found in the patients with positive pelvic lymph nodes compared to those with clinically and radiologically normal appearing pelvic lymph nodes. In contrast, para-aortic lymph node metastasis had a highly significant negative impact on the OS constituting a prognostically unfavourable group that should not therefore undergo major exenterative procedures.

A preoperative PET CT is an accurate imaging tool to demonstrate extra pelvic disease that should preclude patients from pelvic exenteration and is useful for preoperative assessment of disease extent (224,225). (Grade C)

12.2 Laterally extended endopelvic resection in pelvic side wall relapse

Laterally extended endopelvic resection (LEER) is a potential therapeutic option for patients with limited pelvic disease fixed to the pelvic side wall. Careful patient selection is crucial to keep surgical morbidity and mortality in limits. (Grade C)

In the presence of novel surgical advances, a new surgical approach has been developed in the last decade, based on developmentally derived surgical anatomy and aiming to increase the curative resection rates, even of tumours extending to and fixed to the pelvic side wall. The so called 'laterally extended endopelvic resection' or LEER has been developed with the potential to salvage selected patients, traditionally not considered for surgical resection (219,226). LEER as described by Höckel, is performed in combination with at least two of the following procedures: total mesorectal excision, total mesometrial resection, and total mesovesical resection. In cases of lateral tumour fixation, the inclusion of pelvic side wall and floor muscles, such as the obturator internus muscle and pubococcygeus, iliococcygeus and coccygeus muscles, and eventually of the internal iliac vessel system assures the completeness of the multi-compartmental resection (227). Resection of major vessels such as the common or external iliac arteries, requires surgical bypass grafts post-resection. Höckel described the outcome of 91 patients with locally advanced primary (n=30) and recurrent or persistent (n=61) carcinoma of the cervix and vagina who were treated with LEER. No LEER treatment was aborted and R0 resection was histopathologically confirmed in all cases, suggestive of careful patient selection. The authors concluded that LEER could definitively control the locoregional disease in 92% of the patients. Five-year OS was up to 61% despite 74% of the patients having tumours fixed to the pelvic side walls (226,227). LEER was developed on the concept of ontogenetic anatomy.

12.3. Surgical morbidity and mortality of pelvic exenteration

Due to the high surgical morbidity and mortality rates of exenterative procedures, especially following previous radiotherapy, careful patient selection and team specialization is key to optimal outcomes. (Grade C).

Post-operative leaks and haemorrhage should be preferably treated conservatively with endoscopic procedures and interventional radiology, rather than re-laparotomy wherever possible, to avoid additional morbidity from the re-operation (Grade C)

The significant surgical morbidity of exenterative procedures in relapsed cervical cancer is very common and can be as high as 50% (223,228,229). In retrospective reviews the most common complications are infections and wound healing problems ranging from 39% to 86%, gastrointestinal and/ or urinary fistula (10%-23%) and small bowel obstruction (11%-33%) (229,230). Perioperative mortality varies between series and patient cohorts, ranging from less than 5% to 10% (231). Sepsis, adult respiratory distress syndrome, heart failure, pulmonary embolus, and multi-organ system failure are typical terminal events. Intraoperative complications are predominantly related to haemorrhage and problems associated with pelvic reconstruction requiring high rates of blood transfusion. A significant issue can be delayed haemorrhage, even weeks following the operation, in association with pelvic abscesses leading to erosion and bleeding from major pelvic vessels, especially after previous pelvic radiotherapy. Delayed haemorrhage is best managed with percutaneous embolisation via interventional radiology, as re-laparotomy is associated with significant morbidity and mortality. (232)

Gastrointestinal or urinary tract fistulas should be treated conservatively, with endoscopic procedures such as stents, total parenteral nutrition and decompression with for example percutaneous catheters. Low output fistulas, in the absence of distal obstruction, may spontaneously heal (233).

Delayed complications include bowel obstruction (especially small bowel that is torted around the ileal conduit), gastrointestinal fistulas, ureteral obstruction with renal compromise, and stomal stenosis. Initial conservative management is recommended, where appropriate.

Multidisciplinary management and counselling with dedicated psychotherapists and clinical nurse specialists are strongly recommended prior to indication for exenteration in surgical candidates. (Grade D)

Body image and sexual function are significantly affected by exenterative procedures and should therefore be discussed with surgical candidates preoperatively, even though the degree of impairment varies strongly. A study of 16 women found sexual function and body image declined during the first three postoperative months before returning to baseline by 12 months in accordance with studies evaluating quality of life after ultra-radical surgery for ovarian cancer (234). Counselling of the patient regarding postoperative changes in anatomy, body function and involvement of the patient's sexual partner are important parts of exenterative surgery care.

In a recent retrospective, multicentric study investigating quality of life issues and emotional distress in 91 gynaecological cancer survivors submitted to pelvic exenteration, the following parameters have been identified as independent predictors of lower body image levels (235): Older age (HR, 11.235; P = 0.003), vaginal/vulvar cancer (HR, 7.369; P = 0.013), total/posterior pelvic exenteration (HR, 7.393; P = 0.013), higher number of ostomies (HR, 7.613; P = 0.012), the creation of a non-continent bladder (HR, 8.230; P = 0.009), and of definitive colostomy (HR, 8.516; P = 0.008).

12.4. Reconstructive procedures

Reconstructive procedures of the urinary, gastrointestinal tract and the vagina are as important as the procedure of exenteration itself. It should be carefully discussed preoperatively with those requiring consideration of exenteration to identify the adequate reconstructive techniques according to patient’s needs and wishes. (Grade C)

12.4.1 Urinary system

Urinary conduits and reservoirs are typically constructed from an isolated segment of bowel. Any segment of bowel can be theoretically used to form a urinary diversion, however, there are metabolic consequences to using each bowel segment, determined by its absorptive function, especially in patients with chronic renal failure (235). The most commonly used bowel segments in urinary diversions include the distal ileum and/or caecum and the ascending or sigmoid colon; these sites are associated with the fewest metabolic consequences.

There are two main types of urinary diversions: incontinent and continent (237).

Incontinent urine diversion is the most commonly used type of diversion and includes implanting the ureters into an isolated segmented loop of bowel, so the urine is drained via a cutaneous stoma. There, urine drains continuously and is collected by an external appliance adhered to the skin surface (stoma bag). The most common and widely used type of incontinent urinary diversion is the ileal conduit. Other types and the years where they were initially described are: Ureteroproctostomy (Simon, 1851), Ureterosigmoidostomy (Smith, 1878), Rectal bladder (Gersuny, 1898), Ileal loop (Bricker, 1950s), Ileal neobladder (Camay, 1959) Koch pouch (1970), Indiana pouch (early 1980s), Orthotopic diversion (late 1980s). Diversion into a non-continent conduit is considered less technically demanding and hence is associated with fewer postoperative complications and is the most widely used.

By contrast, continent reservoirs collect and store urine internally which is then actively emptied by the patient via catheterization of a cutaneous stoma. The patient is thereby freed from the need for an external appliance. The most commonly used bowel segments for continent urinary diversion are either ileum or a combination of terminal ileum and ascending colon with the appendix.

The process of selecting a particular urinary diversion option is multifactorial and addresses many levels: oncological surgical complexity and patient-related factors (co-morbidities, lifestyle, and quality of life expectations).

In an attempt to reduce morbidity from an additional anastomosis in the area of harvesting of the ileal conduit, an option is to implant the ureters into the distal part of the sigmoid and/ or descending colon after total exenteration. In patients where surgery is with palliative intent, or in those who do not want to have two stomatas, a safe and simple alternative is the double-barrelled wet colostomy. The technique is relatively easy to learn and reduces the time for urinary and faecal diversion, length of stay, and morbidity rate (238).

12.4.2 Gastrointestinal system

The indication to perform an end-sigmoid colostomy or a low rectal anastomosis depends on the level of the resection, length of the rectal stump, the extent of surgery and the radiotherapy induced bowel damage. Due to the radiotherapy-induced changes on the bowel wall and the deeper extent of dissection into the pelvis the leak and fistula rates are higher compared to those following debulking surgery for ovarian cancer. A protective temporary, double-barrelled ileostomy can be formed in an attempt to reduce postoperative morbidity from fistula formation, even though no randomised trials have proven that such an approach is protective. An omental flap can be used to cover the resulting empty pelvis and may help prevent adhesion and possibly subsequent fistulation or obstruction of the small bowel in the empty pelvis, and functions as a carpet for the raw surfaces of the exenterated pelvis.

12.4.3 Neovagina

Young and/ or sexually active women should have a discussion pre-operatively about neovaginal reconstruction. Several methods for vaginal and pelvic reconstruction have been described. Myocutaneous grafts, including rectus and gracilis muscle flaps, can be brought into the pelvis and perineum to create pelvic support and a neovagina. Split-thickness skin grafts have also been used to create neovaginas. A further technique is the sigmoid neovagina, even though radiotherapy induced changes need to be taken into consideration to avoid morbidity from anastomotic leaks. An advantage of bowel neovagina is that is does not need regular dilatation to avoid stenosis (239).

12.5. Fistulation / Cloaca (urinary or colonic)

Management of urinary or colonic fistulation depends on the oncological situation of the patient and her overall prognosis. In palliative settings where prognosis is likely to be shorter, the primary approach should be conservative with diverting nephrostomies or double-barrelled stomatas. (Grade C).

There are two main causes of fistula formation: cancer-induced or radiotherapy-induced. Depending on the extent of fistulation, the entire clinical picture, symptoms and the overall prognosis of the patient's treatment options range from minimally invasive nephrostomies and double-barrelled ileostomies or colostomies to total pelvic exenteration (240). Patients with limited prognosis should not undergo the high surgical risk of an extenterative procedure but are better managed with diverting nephrostomies in case of a urinary fistula and/ or a diverting bowel stoma in case of a gastrointestinal fistula, that can be also performed minimally invasive, where clinically appropriate. While quality of life comparative data is largely lacking, the patient's prognosis and overall clinical picture should dictate radicality of any therapeutic approach.

13. Re-Irradiation of cervix cancer

The need for pelvic re-irradiation is increasing, this is mainly due to improved cure rates with modern cancer treatments. In the context of recurrent gynaecological malignancies, we are likely to encounter two scenarios:

1. Patients cured of their cervix cancer developing a new vaginal cancer more than a decade later
2. Patients treated for cervical cancer develop a pelvic recurrence
   a) isolated recurrence, either side wall or central
   b) widespread recurrence within the pelvis.

The radiotherapy technique and dose/fractionation applied depends on the individual case. For example, for patients in scenario 2b, the recurrence is likely to be within a 5-year period and therefore further EBRT is unlikely to be either feasible, or indeed advisable, and such patients are better treated with systemic therapies either standard or within clinical trials. The following articles cover more recent events and developments including intra-operative and stereotactic ablative approaches as discussed below (241-245).

13.1 Vaginal cancer following radiotherapy for cervix cancer

Almost by definition, these patients will be 10-20 years post previous treatment. Disease is often localised to the vagina and, PET/CT, where available and used for staging, shows no pelvic nodal involvement. Such patients should be treated with a combination of small field radiotherapy, encompassing the whole of the vagina but not treating pelvic nodes. Brachytherapy boost is provided either with intracavity brachytherapy or interstitial implant. Selected cases may be treated with brachytherapy alone, often this would be interstitial brachytherapy. EBRT dose would be 40-45Gy in 20-25 fractions and brachytherapy dose 24Gy/4# for intracavitary and 15Gy/3# for Interstitial. Stereotactic Ablative (Body) Radiotherapy [SABR or SBRT] is not of much use in this setting.

13.2 Isolated recurrence following previous pelvic radiotherapy

This is more frequently seen less than 5 years from previous radiotherapy, either a side wall recurrence (often nodal) or a central recurrence (cervix or parametrium). A central recurrence would be amenable to re-treatment with brachytherapy which would, indeed, be the optimal choice in this setting. The most appropriate modality may either be intracavitary alone or a combination of intracavitary/interstitial. For side wall recurrences, brachytherapy is not an option. This is the group of patients who would benefit most from SABR/SBRT. The literature on this is limited although expanding (243-245). Doses used range from 21Gy/3# to 42Gy/6#, recent publications point to even higher doses.

There is no robust organ-at-risk (OAR) tolerance data although the COMET trial did provide some guidance and the author has utilized this in his own practice. The reported literature is very encouraging with little or no Grade 3 toxicity in any of the reports. This is therefore a very promising area of further enquiry and clinical trials are being planned, although not in the setting of re-irradiation.

Recommendations:

- Discussion of management should take place through the MDT/Tumour Board. In selected cases re-irradiation may be advised but with increased risk of later toxicity.
- Surgical excision of isolated nodal recurrence should be discussed where appropriate.
- FDG PET imaging is essential before the procedures are discussed. (Grade D)

14 Chemotherapy in metastatic or advanced cervical cancer

All patients with newly diagnosed stage 4 or relapsed cervical cancer should be treated as part of a multidisciplinary team, due to the complexity of disease relapse, especially when in the pelvis, where morbidity can be severely debilitating. Along with the obvious physical impact of disease, these patients

are often young with small children and emotional support for patients and families is of paramount importance.

Those patients with a WHO performance status (WHO PS) 0/1 should be considered for systemic treatment, whereas those with lower performance status should be carefully risk assessed as to their suitability and likely benefit from treatment, with the patient fully informed of expectations and limitations of chemotherapy. Best supportive care or palliative radiotherapy may be a more preferable option for these patients.

Platinum paclitaxel doublet has been the standard of care for some time for advanced and recurrent cervical carcinoma (246) however since 2014, Bevacizumab has been FDA approved and SMC and NICE approved from 2016 to be used with either platinum/paclitaxel or platinum/topotecan. Given alongside the chemotherapy, there was an overall survival (OS) advantage of 3 months and median progression free survival (PFS) of 2 months, with a higher response rate when compared to platinum/paclitaxel or platinum/topotecan alone (247-249), as shown in the GOG 240 trial. With extended follow up, the benefit of the addition of bevacizumab was sustained, as the overall survival curves remained separated. Furthermore, after stopping bevacizumab there does not seem to be a flare in disease burden.

Blood pressure and urinary monitoring is mandatory, but bevacizumab is contra-indicated in patients with fistulas or those within 4 weeks of surgery. However, the addition of bevacizumab does not appear to impact significantly of patient's quality of life and is well tolerated (250-252).

Those patients with recurrent/persistent inoperable disease have in the majority already been exposed to chemotherapy, either in the neoadjuvant setting prior to radiotherapy, or concurrent chemotherapy in the form of Cisplatin with radiotherapy. Interestingly, bevacizumab showed benefit in those with short platinum-free intervals, in contrast with the experience in earlier GOG studies where platinum free intervals less than 12-15 months were associated with poorer response possibly due to platinum resistance.

Cisplatin and carboplatin have been recognised as being equivalent in efficacy in a number of tumour sites and with their differing toxicity profile can lend themselves to help tailor treatment depending on patients' comorbidities (253). Locally recurrent/persistent disease can involve the bowel and would make bevacizumab relatively contraindicated, however in those able to receive chemotherapy/bevacizumab combination even those with prior cisplatin exposure saw a significant benefit.

In those that have pelvic reoccurrence or persistent disease who are initially not deemed salvageable with exenterative surgery, the option of upfront chemotherapy with a view to reconsideration for surgery depending on response should not be overlooked. Frumovitz, in 2017 also demonstrated improved progression free survival could be seen in those patients with recurrent small cell neuroendocrine carcinoma of the cervix (254) using topotecan and bevacizumab.

Second line treatment and beyond is dependent on the interval of progression since first line treatment in those patients with a good partial response with first line treatment and are more than 6 months out, rechallenging with platinum/paclitaxel could be considered. Mitomycin/5FU, vinorelbine, docetaxel, gemcitabine, weekly paclitaxel and topotecan have some activity but there is no standard of care. Response rates are universally poor and entry into clinical trials where possible to assess novel and immunotherapeutic agents should be strongly considered depending on patient's fitness and desires. McLachlan recently published retrospective results from the Royal Marsden 2004-2014 showing 70 % of their advanced cervical cancer patients received second line treatment. Median PFS was 3.2 months and median OS of 9.3 months. Thirty nine percent went on to receive 3rd line treatment (255).

Of these newer agents and combinations some have shown promising results. The CIRCCa trial used standard carboplatin/paclitaxel with or without cediranib - a vascular endothelial growth factor (VEGF) inhibitor, this showed only a PFS of 6 weeks with no OS) but subgroups showing expression of VEGF seemed to show greater benefit (256). This has led on to the COMICE trial which is combining cediranib and olaparib – a PARP inhibitor vs placebo in second line patients with stage 4 or recurrent cervical cancer.

Immunotherapy using PDL1 inhibitors pembrolizumab, nivolumab and ipilimumab, pathways targeted for example Trametinib and HPV related therapy using therapeutic vaccines are in early phase one and two stages of trial and development. Recent data from the Keynote studies with pembrolizumab has also shown benefit but at time of writing is not approved or licenced in Europe. Studies with Tumour infiltrating lymphocytes (TILs) are also under development and show great potential.

Recommendations:

- For those patients who are chemotherapy naive with stage 4 disease, first line treatment would be systemic chemotherapy with cisplatin/paclitaxel or carboplatin/paclitaxel doublets with or without bevacizumab depending on any patient risk factors. However, bevacizumab may lead to prolonged benefit and should be offered if not contra-indicated. (Grade B)

15 Follow-up of cervical cancer

Follow-up may be clinical, imaging or biochemical. It may be consultant-led by a gynaecological oncologist or clinical oncologist working in a specialist Cancer Centre or maybe by a general gynaecologist in a district general hospital or some form of shared care. The purposes of follow-up are to detect recurrence and offer appropriate salvage treatment, and to monitor for toxicities, particularly when new treatments or techniques are introduced. It is also an opportunity to seek support and care from CNS to provide psycho-sexual counselling and advice. Recent advances in surgery and changes in radiotherapeutic and chemotherapy practice require careful assessment to ensure that these changes are truly beneficial. 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 of this is very low certainty evidence (257-259).

Following surgery without any added radiation, follow up is usually in the gynaecological oncology clinic supervised by specialist teams. Clinical examination will be undertaken, and smears may be taken. 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. Routine use of cervical screening after radiation therapy is not recommended. Following fertility-sparing surgery, cervical screening is advised. (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/cervical-cancer#heading-Zero)

Traditionally, most recurrences were thought to occur within the first 2 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, thus recurrences are more frequently documented after the second year. This has significant implications as historically follow-up was more closely observed in the first 2 years, but now patients may need to be seen more frequently for longer. The BGCS has issued a comprehensive paper about the value of patient initiated follow up in gynaecological cancers, including cervical cancer, that supports this approach in patients with early disease who have not experienced any relapse (Newton et.al. Int J Gynae Cancer 2020 in press).

15.1 Identifying relapsed disease

However, contrary to this, there is published evidence to show that the numbers of patients picked up with relapse at the time of a clinic visit is actually relatively small and that most recurrences are interval relapses. In times of limited resources, it may be better to use these services more efficiently. However, there are other reasons for follow up such as emotional and psychosocial/psycho-sexual support and management of any menopausal symptoms and management of delayed surgical or radiation-induced sequelae. Furthermore, there are opportunities to reinforce the importance of smoking cessation. Not only is this beneficial to an individual's health but will also reduce the risk of subsequent gynaecological tract malignancies (mainly vaginal and vulval/perineal) but also other smoking related squamous cancers in lung and head and neck. This will be discussed in the following chapter.

Tumour markers such as the squamous cell carcinoma antigen (SCCA) are available, but there are very few centres in the United Kingdom who use it and it is not recommended for routine use. There are no other recommended tumour markers in clinical practice.

15.2 Imaging

Imaging is also controversial in the follow up of patients with cervix cancers. This would only be useful if there is a salvage treatment option. Some experts recommend re-imaging with MRI at 3 months post chemoradiation to show whether there is residual disease or not. The only randomised trials that have looked at chemoradiation followed by hysterectomy have failed to show any survival advantage and were terminated early. Therefore, the evidence base for recommending this is dubious at best and is a questionable use of this resource. Salvage hysterectomy should be considered on an individual basis at the MDT. If surgery is considered, an MRI is essential to delineate extent of disease for optimal surgical planning.

Potentially more valuable is the use of follow-up FDG PET/CT imaging. Data from Grigsby and his colleagues in Washington Missouri have shown that follow-up scans can be highly predictive of the risk of recurrence (260,261). Positive uptake on the FDG PET/CT at 3 months was usually associated with premature death whereas patients with complete metabolic response were generally in remission at five years and considered to be cured. The use of FDG PET/CT scanning at 3-6 months after treatment may help to identify those at low risk of recurrence who could then be put on minimal intervention follow-up or even nurse-led clinics whereas those with positive scans would need a higher intensity follow-up as they would be at considerable risk of developing a recurrence.

Recommendations:

- Follow up should be undertaken by gynaecological or oncological specialist teams arranged according to local arrangements. Access to a CNS can help to provide psycho-social and sexual support. Routine imaging has no place and should be used in symptomatic patients. (Grade C)

16 Supportive care – psychological care for patients and carers with cervix cancer

Over 49,000 women are living with or beyond cervical cancer in the UK today. Every day nine women are diagnosed, and it is currently the most common cancer in women under 35 years of age. Survival is high with over two thirds of women living 10 years or more however for those affected, diagnosis and treatment can have a significant impact on a quality of life starting for many when abnormal cells are detected for the first time.

In addition to pain and uncertainty, many treatment types bring multiple, long term physical and psychological consequences which can be extreme in their presentation. Impact on finances, relationships and ability to carry out day to day functions such as employment, education, shopping, housework and leisure activities cannot be underestimated. Being given the 'all clear' is far from the end as many women may have to live with numerous side effects and emotional and physical scars for the rest of their life.

In a report, http://www.jostrust.org.uk/longtermconsequences using the largest known dataset of cervical cancer patients, Jo's Cervical Cancer Trust found that far higher than anticipated numbers are affected by multiple, often complex long-term consequences of their diagnosis and treatment. High numbers of women reported unmet physical and psychological needs with many simply suffering in silence. (262)

Almost ninety percent (88%) of women reported experiencing at least one long term physical problem, two thirds (63%) at least three, and a quarter (24%) six or more potentially life-changing physical problems including with bowel and urinary function (both 54%), pain (52%) and negative impact on their sex life (67%). Many problems were reported as presenting for the first time long after treatment was complete with many presenting at least a year after treatment. The further women were from treatment, the greater the number of problems they reported, clearly highlighting the longevity of the impact of a diagnosis and the need for ongoing care and support. (262)

In addition to physical problems, the psychological impact of a cervical cancer diagnosis is significant. 37% of the women questioned reported depression and among young women it is far more pronounced with 79% of 25-34-year olds feeling blue, sad, down or depressed compared to 57% across all ages. The impact of cervical cancer does not stop after treatment is finished or when the five-year milestone has passed but can often be long term.

For many women anxiety, fear and uncertainty start well before diagnosis with referral to colposcopy or even invitation to screening being a stressful experience. Lack of information or signposting to sources of support can contribute to anxiety over waiting for results or uncertainty over potential outcomes or next steps. Ensuring women are made aware of reliable sources such as Jo's Cervical Cancer Trust can reduce isolation and alleviate pressure on those working within primary and secondary care to be the sole source of information and support. This also ensures women feel in control of their treatment options, decision making and fully understand the potential consequences they may face as a result of those decisions. Increased awareness of long-term consequences will enable women to identify symptoms, seek early intervention and better self-manage their care. Cervical cancer remains a less common cancer therefore many women will often never have met someone in the same situation as themselves. Signposting to relevant charities, support networks and services can enable women to make contact with others with similar experiences for mutual support. This includes through forums and support groups have been shown to reduce isolation and can significantly increase psychological and emotional wellbeing.

Following completion of treatment, patients will have significantly reduced contact with their care team. For some women this may be a relief, for others it is a difficult transition leaving them feeling vulnerable. Instead of speaking with their oncologist or a familiar member of their care team, patients may present to unfamiliar healthcare professionals such as A&E or their GP. Again, this is where a key worker or CNS become invaluable. Without encouragement to seek help many women simply accept their physical or emotional challenges which can lead to poor self- management of conditions, where expert intervention is required. Without appropriate information and signposting, women are more likely to feel unsure of where to seek help, feel embarrassed or lack the confidence to speak out. Fear of having further tests and treatment can also contribute to women remaining silent. A lack of awareness of the long-term consequences of cervical cancer and treatment is contributing to women experiencing typical symptoms not being diagnosed or referred and even being told nothing can be done.

Minimal research and understanding in this field have contributed to gaps in expertise, literature and information available to both professionals and patients. Just 21% of women who looked for information on long-term consequences of cervical cancer and treatment report fully finding what they need. Of 67% of women who reported having negative changes in their sex life as a direct result of treatment, a shocking 68% had not spoken to a doctor and of those affected by changes to their bowel

or bladder (both 54%) 39% and 42% respectively had not spoken to a doctor about these issues. Only half of women who experienced bowel and urinary problems had received treatment (41% and 54% respectively) and for those who experienced negative changes in their sex life, just 10% had received treatment. Worryingly high numbers say their emotional (75%) and physical (70%) needs have not been fully met. Long term chronic conditions bring added psychological strain therefore early referral and treatment is essential to alleviating this.

The emotional impact of diagnosis and treatment is also often neglected with 34% reporting their emotional needs not being addressed at all with only 25% could say they had been completely addressed. Unmet needs were reported among women of all ages, however, was greater among younger women and women further from diagnosis. Only 7% of 25-34-year olds said that the long-term emotional impacts of their treatment had been completely addressed and treated, rising to 46% for 65-84-year olds. While women were more positive about the physical impacts being addressed, only 30% said they had been completely addressed with 20% saying they had not been addressed at all. This demonstrates a clear need for support and referral for women affected by cervical cancer. The disparity in emotional and physical impacts may demonstrate a lack of awareness about the emotional consequences of cervical cancer and treatment which urgently needs to change.

Ongoing provision of and access to information and support is essential to ensuring they receive the information at a time that is appropriate to the individual patient, this can be as simple as posters on walls signposting to charities including Macmillan, Maggie's and Jo's Cervical Cancer Trust.

The role of a designated CNS or key worker cannot be understated. This vital role offers consistent support from point of diagnosis, providing a holistic approach to the care and support needs of the patient.

Each patient should have a Recovery Package. This valuable tool can support health professionals in delivery of patient-centred care, helping to identify and address changing needs from diagnosis onwards. When a patient is discharged from oncology, a detailed treatment summary helps facilitate a seamless transition from secondary to primary care and a multidisciplinary approach to long term care. If every patient and health professional is encouraged to use it to its full potential, it could significantly improve quality of life, enabling the patient to feel better informed and in control in addition to reducing delays in referrals, subsequent diagnosis and treatment or management.

For women who work, lack of assistance and support to return to work can have an extremely detrimental impact not only on their financial situation but also on mental health. For women who work, or worked pre diagnosis, returning to work may be an important part of rebuilding life post cancer. Impact on employment status is high with 60% of women who have had negative changes to employment status attributing it to their diagnosis and treatment. More research is needed to fully understand the issues faced by women regarding employment and returning to work to identify where interventions are needed to assist both employers and employees.

It is impossible to separate the physical and psychological impacts of a diagnosis of cervical cancer as physical difficulties caused by treatment can in themselves lead to emotional and psychological conditions and they in turn can have an impact on physical wellbeing. Physical consequences can be lifelong meaning that the psychological needs of women following diagnosis may change or increase over time. For young women, where greater numbers of diagnoses are seen, coping with loss of fertility or early menopause can be devastating and exacerbated when dealing with changes in appearance and watching friends go through pregnancy. Societal pressures and expectations around women's ability to conceive only serve to heighten the isolation and distress that women affected by cervical cancer may already be experiencing. Avoiding psychological impact is impossible, and therefore ensuring women have the best possible experience of diagnosis, treatment and care along with continued access to support long term can alleviate some of the feelings of anxiety, fear and uncertainty. Feeling informed

and in control through the provision of information can lead to women feeling engaged and active in their treatment decisions leading to better patient outcomes.

Psycho-oncological support and CNS support should be offered to all women with the diagnosis of cervical cancer (Grade C)

16.1 Management of complications and late effect/quality of life

This section provides information on prevention, identification and management of complications, late effects and quality of life issues following a cancer of the cervix diagnosis and treatment. It aims to guide/signpost the reader to agencies/services that provide appropriate intervention and support for the woman and her family if needed.

Women should have the opportunity to address symptoms attributed to their cancer and its management before, during and after treatment. Predictable side-effects are dependent on treatment modality and can include but are not limited to sexuality/sexual morbidity, menopause, lymphoedema, effects on gastrointestinal and urinary systems and psychosocial concerns. Both physiological and psychosocial factors can impact on quality of life, addressing possible and actual problems as they arise may help to reduce the negative impact experienced by women. It is good practice to talk about symptoms that could be attributed to cancer and the consequence of treatment and this should also be addressed at each follow-up appointment or through holistic needs assessment.

Women should receive appropriate information so they are informed of the relevant risks of short- and long-term side-effects during the consenting process, this should be recorded on the consent form. Good quality information is available from both Macmillan and Jo's Cervical Cancer Trust charities which the patient can source themselves or be given in clinic (this is provided free of charge).

- http://www.macmillan.org.uk/information-and-support/cervical-cancer/
- https://www.jostrust.org.uk/about-cervical-cancer/cervical-cancer
- https://be.macmillan.org.uk/be/s-605-radiotherapy.aspx

Areas of specific concerns are:

16.2 Sexuality/Sexual morbidity

Factual information on possible anatomical changes due to surgery or radiotherapy should be given to the women prior to treatment. This will acknowledge that the subject of sexuality is open should she need to seek further information if difficulties occur. The use of vaginal dilators following radiotherapy should be recommended to reduce the risk of stenosis. If women experience sexual difficulties these should be addressed and where possible specific suggestions given e.g. use of lubrication during intercourse. Where available, women with ongoing difficulties should be referred to psychosexual services. Fertility can play an important role in a women's sexuality. Where possible, fertility sparing treatment should be considered in women who wish to maintain their fertility. Referral to fertility services to discuss other options should also be available.

16.3 Menopause and hormone replacement therapy

Hormone replacement therapy (HRT) should be considered in women who develop treatment induced premature menopause to reduce risks associated with early menopause including cardiovascular and skeletal morbidity and menopause symptoms. There is no evidence recommending specific HRT preparations however those women with an intact uterus should receive combined HRT, this includes those women who have had radiotherapy. In women who do not want HRT, alternative health and lifestyle therapies may help – signpost appropriately. Local vaginal oestrogen application can also be used to improve side-effects of vaginal stenosis/dryness; alternatively, vaginal moisturisers may be helpful.

16.4 Lymphoedema

Risk of developing lymphoedema ranges from 21% following surgery alone to 77.8% in those who have undergone both surgery and radiotherapy. Prophylactic information on reducing the risk of lymphoedema should be available to women (http://www.macmillan.org.uk/information-and-support/coping/side-effects-and-symptoms/lymphoedema). And those women who develop lymphoedema should be referred to specialist lymphoedema services.

16.5 Bowel/bladder function

At follow up ask if any new problems relating to bowel/bladder function, if present initially manage with simple solutions such as loperamide for diarrhoea, dietary changes for constipation, anticholinergics for bladder urgency. Consider referral to other services for persistent problems e.g. gastroenterology, colorectal, urodynamic, continence or urology as appropriate.

16.6 Psychosocial

The impact of cancer and treatment can affect quality of life, the psychosocial needs of women should be addressed throughout; health needs assessment should be performed at pivotal points in the cancer pathway. Women should have the opportunity to explore ways of improving their quality of life through appropriate support and signposting to survivorship/living with and beyond cancer, and psychological services where available. The following references are recommended for further reading (263-271).

Recommendations:

- Prevention, identification and management of complications, late effects and quality of life issues following a cancer of the cervix diagnosis and treatment are essential part of package of care – (Grade C)
- Recording of late side effects should be documented (Grade C)
- Written information should be provided about treatment choices and side effects including late effects. (Grade C)
- Access to a CNS or equivalent and psycho-sexual counsellors should be available as part of the multi-disciplinary team. (Grade C)

17 Rare malignancies: small cell, mucinous and clear cell carcinomas, and sarcomas of the uterine cervix

17.1 High grade NEC of small cell type

These are all very rare and uncommon cancers and as such there is no evidence from randomised clinical trials data to support the optimal management. Most experience and evidence will come from case reports, small series or the reports of experience from the larger cancer centres. Crucial to the management of these tumours is the availability of a dedicated expert gynaecological oncology pathologist and commonly surgical tissues may need to be looked at for second specialist opinion. Many of these rare tumours can be difficult to interpret histologically and require a panel of immunocytochemistry, and even then, may be difficult to identify the histological subtype. Molecular pathology is evolving and in the course of the next few years will probably characterise these tumours with greater precision.

A recent report looked at the genomic landscape of small cell carcinomas of the cervix. Aneuploidy was common, occurring in nearly of the cases reported (265). A variety of mutations were reported including MSH2, pi3kinase and pTEN whereas TP53 and RB1 most commonly seen in small cell lung cancer were relatively uncommon. It is hoped that identification of these mutations may eventually lead to better selection of new drugs. Currently these rare tumours include neuroendocrine tumours (small cell carcinomas and carcinoids), clear cell carcinomas, mucinous carcinomas and rare sarcomas.

17.2 Neuroendocrine tumours (NETs)

These are rare (orphan status) especially in the gynaecological tract and are classified differently. This terminology was introduced in the 1970s but WHO 2014 classifies neuroendocrine tumours as low grade NET to include typical and atypical carcinoid tumours, and high-grade neuroendocrine carcinomas (NEC) which includes small cell and mixed large cell NECs. (273-276).

Primary cervical carcinoids tumours are better differentiated and exceedingly rare. Usually it is necessary to exclude a primary of the gastro-intestinal tract. For detailed advice on carcinoids, reference should be made to the standard guidelines from National and International Societies (277,278). This guideline will focus primarily on small cell carcinoma of cervix. Small cell neuroendocrine carcinomas probably account for less than 1% of all cervix cancers and are amongst the most lethal. It is important to differentiate between pure small cell cancers and poorly differentiated squamous carcinomas that have neuroendocrine elements as these are probably best managed as G3 epithelial carcinomas. Pure small cell carcinomas are generally composed of small round cells and have characteristic immunocytochemical staining. Mixed large cell and small cell tumours are also seen and are currently included within the NET family of tumours. (279-281)

Clinical presentation is usually very similar to that of any other carcinoma of the cervix, but they are slightly more common in the younger age group. They are associated with HPV exposure but more commonly HPV 16 and 34 are found. Some patients may present with hypercalcaemia, which may be due to secretion of parathyroid hormone related peptide (PTHRP), without evidence of bony metastasis, and this is usually a poor prognostic factor. Occasional patients may present with hyponatraemia and SIADH. Staging and clinical investigation are the same for all types of cervix cancer with a biopsy, MRI pelvis and ^{18}FDG PET CT scanning. Cases should be presented to the MDT for further discussion of management on an individual basis but would not be a standard of care (279-281).

Early stage disease

In early stage cases the standard approach is a radical hysterectomy and lymph node dissection following further MDT discussion, these patients should be offered adjuvant chemotherapy and radiotherapy in virtually all cases, given the high risk of relapse. The published data shows that virtually no patients with bulky stage II disease or higher stage will be cured and only around 1/3 of the early-stage cases will have 5-year survival. Since no clinical trials have been carried out, there is no firm evidence to support the adjuvant treatment post-operatively, but many would advocate either concomitant cisplatin-based chemoradiation or adjuvant platinum and etoposide followed by pelvic irradiation. There is no evidence to support the use of prophylactic cranial irradiation which had been advocated by some in the past.

The usual schedule of chemotherapy will be a platinum and etoposide combination, with 4-6 cycles given at 3-weekly intervals. Either carboplatin or cisplatin can be given as determined by clinician's choice. There is no evidence to support whether 4 or 6 cycles should be given. Lung oncologists who treat small cell cancers tend to use 4 cycles whereas those treating gynaecological cancers more frequently favour up to 6 cycles.

Advanced stage disease

For more advanced disease, bulky stage IIB (>5cm) or higher stage, chemotherapy is normally recommended initially. Many experts would recommend that the chemotherapy drugs and doses used for small cell lung cancer are prescribed but again there is no hard evidence to support this. Most centres will use either cisplatin or carboplatin combined with etoposide and administer between 4 and 6 cycles of chemotherapy at 3 weekly intervals. In patients who have had a very good response to this induction chemotherapy and where the tumour may have shrunk to less than 4 cm and furthermore where there is no evidence of distant metastatic disease, discussion should take place at the MDT to consider the potential place of radical hysterectomy and lymph node dissection. A follow up FDG PET

scan should be considered before embarking on a radical surgical approach. These patients will then require adjuvant radiation post-operatively.

For patients who receive neoadjuvant chemotherapy but do not achieve sufficient shrinkage to permit surgery or whether there are other contraindications, high-dose (chemo-)radiotherapy should be considered with external beam radiotherapy and intracavitary brachytherapy. Very few patients however will go on to long-term remission or cure. Concomitant weekly cisplatin may be offered but be wary of risk of neuropathy. Doses of radiation will be similar to those used in squamous cancers of cervix.

Studies which have deployed high dose chemotherapy with marrow transplant and maintenance chemotherapy are unproven. Equally whilst bevacizumab has been shown to be active in squamous cell carcinomas of the cervix, there is no proven data to support its use in small cell NEC of cervix. However, a recent report of topotecan, paclitaxel and bevacizumab has suggested possible benefit, but the series was small and non-randomised.

Metastatic or recurrent disease
In those patients where scanning shows residual, persistent or progressive extra pelvic disease, options are very limited. Second line chemotherapy may be offered but is rarely effective. Topoisomerase inhibitors potentially should be effective but the use of topotecan has been very disappointing. Others have used the CAVE regimen used in small cell lung cancer but again with limited effect. Several small series in small cell ovarian cancers have reported on dose dense and dose intense weekly carboplatin and paclitaxel but again no long-term responders were identified. To date no new targeted agents have been identified as being effective but it is hoped that with new developments in molecular pathology over the course of the next few years, new targets will be identified leading to new drugs. As mentioned above, one small series has suggested topotecan, paclitaxel and bevacizumab may show promise and needs further assessment.

Fertility preserving options
Again, there is no widescale experience and these patients should be managed within a multi-disciplinary team with careful counselling that the use of fertility preserving surgery is unproven in this situation. Neoadjuvant chemotherapy with carboplatin and paclitaxel may be considered and some form of conservative surgery. Given the uncertainty of risk of recurrence, early attempts to conceive and elective post-partum surgery can be discussed.

Progress in the management of these tumours is difficult but collaboration by international groups such as the Gynaecological Cancer InterGroup (GCIG) may help to take forward the management of these rare and difficult tumours. Only these organisations can manage to conduct the kinds of clinical trials needed to improve care in these rare tumours.

17.3 Mucinous tumours
These are very rare, and it is important to ensure it is not an endometrial tumour that has extended down to the cervix. The clinical management would normally be very similar to that for squamous or adenocarcinoma of the cervix with standard pre-treatment workup. Recent pathology review has suggested that there is an intestinal sub-type, which behaves differently and may explain the poor responsiveness to standard chemotherapy-based approaches.

More recently has been the identification of gastric type adenocarcinoma, which appears to carry a worse prognosis. It is therefore important to recognise the gastric-type adenocarcinoma. They are the largest group of non-HPV associated carcinomas. They are often larger in size, of higher stage and poorer outcome than HPV associated carcinomas. They have an increased risk of disease recurrence and a decreased 5-year disease specific survival rate. They are characterised by the pressure of

abundant clear, foamy or pale cytoplasm, distinct cytoplasmic borders, pleomorphic nuclei and foci of minimal deviation architecture with minimal stromal response (282,283).

If the tumour is confined to the cervix and less than 4 cm, radical hysterectomy and pelvic lymph node dissection would normally be the treatment of choice. There are questions about the radio sensitivity of mucinous tumours at other sites but if the tumour is not considered suitable for surgical resection then concomitant chemoradiation would be considered for localised disease.

If there is evidence of distant metastatic spread, systemic treatment would be considered. Consideration should be given to the use of combination regimens as used in colorectal cancer such as oxaliplatin or irinotecan and capecitabine/5-Fluoro-uracil and folinic acid. There is of course no randomised data to support the use of any particular combination but intuitively for a mucinous tumour, regimens used for colorectal cancer are more likely to have a better outcome.

17.4 Clear cell carcinomas (CCC)

These again are rare, and the same basic principles of management apply as for mucinous or other rare tumours. These should be discussed at the multidisciplinary team and subjected to the usual clinical workup and examination. Where the tumour is suitable for surgery, the patient should be offered radical hysterectomy and lymph node dissection. If adjuvant treatment is required there is limited evidence that paclitaxel added to cisplatin or carboplatin may improve the response rates but again this is based on very limited series. Some of this is also extrapolated from Japanese experience in CCC of ovary.

Again, there is some suggestion that clear cell carcinomas may have reduced radio sensitivity compared to squamous cell carcinomas, but there is no evidence to support the view that higher doses of radiation may be more effective, and the patient should be treated in the same manner. For patients with advanced disease, with extra pelvic spread, chemotherapy with carboplatin and paclitaxel is probably the preferred schedule with some limited evidence suggesting that regimens including paclitaxel may confer a slightly higher benefit.

17.5 Basaloid and adenoid cystic carcinomas

These are again exceedingly rare and may include pure basaloid carcinomas, adenoid-basal carcinomas and adenoid cystic carcinomas. These are usually managed surgically and are often polypoidal. There is very little published data regarding the management. The older literature suggested these were less radio responsive.

17.6 Sarcomatous tumours of the cervix

These are very rare but include adenosarcoma, leiomyosarcoma, and even endometrial stromal sarcoma as well as high-grade undifferentiated sarcoma. Even rarer are rhabdomyosarcomas which may present as a polypoid mass although not like the botryoides pattern seen in childhood. Many of these start as polypoidal tumours and can be managed surgically with very limited evidence to suggest whether they need any adjuvant treatment and they should be discussed on an individual basis at the MDT. Consideration should be given to discussing with colleagues from other centres particularly in the case of these ultra-rare tumours.

Carcinosarcomas are not true sarcomas and should be managed as poorly differentiated carcinomas. It is beyond the scope of this article to go into further detail about their management.

Recommendations:

- These are rare tumours and all cases must be discussed at MDTs. Consideration should be given to supra-regional teams providing the treatment with shared care for follow up. (Grade D)

18. Fertility sparing surgery in cervical cancer

18.1 Service delivery

When offering fertility sparing treatments for cervical cancer it is important to consider the efficacy in treating cancer, the effectiveness in preserving fertility, and the complications of surgery. Complications may be to the patient, such as those secondary to parametrial resection, but they may also involve infertility from cervical stenosis and adverse effects on subsequent pregnancies such as premature labour and consequential harm to a neonate. It is a difficult balance for a woman who has every right to compromise on her chances of cure in order to maximise a subsequent favourable obstetric outcome if she achieves a cure. If this right is to be respected, then it is intuitive that centres offering these treatments should be able to provide adequate counselling and support services. A woman's perception of the relative importance of different outcomes (oncological and obstetric) must be respected by professionals. Where the issues to consider are complex, such as the risk and consequences of premature labour following trachelectomy, it seems sensible to offer support from a CNS and for treatment to occur in a centre experienced in providing fertility sparing surgery. A recent survey from Public Health England estimated that only 80 cases of trachelectomy occur in England annually (284) and as case numbers for a particular centre are likely to be low, it is considered good practice for units to prospectively audit their outcomes.

Full clinical history, initial colposcopic examination and possibly hysteroscopy for measuring cervical lengths prior to trachelectomy, are important tools for the decision-making process of a fertility sparing surgery and may be used in conjunction with some form of conisation to determine those patients who can have the most conservative of fertility sparing approaches.

Recommendations:

- Counselling for procedures should include details of the oncological and fertility-sparing efficacy as well as potential complications to the patient, risks to subsequent pregnancies, and adverse outcomes to children who might be born prematurely
- A patient who prioritizes one set of outcomes above another (oncological versus obstetric) should have their views respected and the direction of treatment modified appropriately if necessary
- Centres performing fertility sparing surgery should be experienced in the techniques they use and audit their outcomes regularly. (Grade C)

18.2 Treatment options

Conisation for stage IA cervical cancer

Conisation for stage IA cervical cancer has been recommended by numerous authors (285,286) and is included in another established guideline (287,288). The aim of conisation is to achieve negative margins to both cancer and dysplasia. A 3mm margin to cancer has been recommended in previous guidelines (280). Cold knife conisation has the advantage over loop conisation (LLETZ) in that the margins are easier to assess. However, LLETZ is acceptable as long as adequate margins are achieved along with a non-fragmented specimen, correct histological orientation, and no electrosurgical artefact interfering with marginal assessment (289-291).

A detailed assessment of these risks is outside the scope of this guideline, but it should be noted that when treating stage Ia disease, patients often receive more than one conisation or large cones greater than 15mm deep which are associated with a greater risk of these complications. This must be explained to patients undergoing conisation for cervical cancer.

Recommendations:

- Conisation (cold knife or LLETZ) is an acceptable local treatment for stage IA1 (FIGO 2018) squamous cell and adenocarcinoma of the cervix. In stage IA2 with LVSI a pelvic LND should also be performed
- Re-conisation is recommended if margins to the cancer are within 3mm, if there are positive margins to intra-epithelial neoplasia, if the specimen cannot be orientated, is fragmented, or has diathermy artefact that makes margin assessment impossible
- Conisation (LLETZ, knife, & LASER) for cervical cancer is often large or multiple and carries a risk of cervical incompetence, premature labour, and neonatal death. This must be explained to women who have this treatment

18.3 Simple trachelectomy and cone biopsy for selected subsets of women with stage IB1 (FIGO 2018) cervical cancer

A number of authors have identified a group of patients with stage IB1 cervical cancer in whom the risk of parametrial spread is low leading to the hypothesis that a more conservative approach to selected cases may be appropriate. Kinney et al (293) found no parametrial involvement in a group of women with less than 3mm depth of tumour irrespective of the width. Covens et al (294) found the risk of parametrial involvement in 536 women to be only 0.6% when the lesion was <20mm in maximum diameter with <10mm of stromal invasion and negative lymph nodes. Wright et al (295) found the incidence of parametrial involvement to be 0.4% in a group of 270 patients with no lymph-vascular space invasion and tumours less than 20mm while Frumovitz et al (296) found the incidence to be 0% in a similar group of 125 women.

Centres offering fertility sparing surgery should have a protocol in place to offer a select group of women more conservative surgery and audit their outcomes.

Recommendations :

- Selected women with low volume disease are suitable for treatment by conisation alone.
- A centre offering fertility sparing surgery should have a protocol for selecting women with low volume disease for cone biopsy or simple trachelectomy rather than radical trachelectomy.
- Centres offering cone biopsy or simple trachelectomy for stage IB1 (FIGO 2018) disease should audit their outcomes prospectively.

18.4.1 Radical vaginal trachelectomy (RVT) for stage IB1 (FIGO 2018) disease

The efficacy of RVT for the treatment of cervical cancer has been systematically reviewed (297,298). Published data on RVT includes women with stage IA1, IA2, and IB1 disease (299-301). Those patients with IB1 disease have both low volume and high-volume tumours. Where it is possible to define, only 922/1277 (72%) of women reported in the literature had the procedure performed for stage IB1 disease (300-302) . When additional treatment is reported in papers, 150/1355 (11.1%) never completed or retained fertility sparing treatment either because of adverse factors subsequently diagnosed as part of work up or because of the need for adjuvant treatment (further surgery or radiotherapy).

Specific complications of RVT include cerclage erosion and cervical stenosis. Cerclage erosion is not routinely reported in the literature but seems to occur in between 0 and 30% of cases (303-305). Disadvantages of trachelectomy are lower fertility rates and risk of preterm delivery. Alternative options include discussions to include the use of neoadjuvant chemotherapy followed by conisation or simple trachelectomy.

The probability of a woman achieving at least one pregnancy following RVT is unclear in the literature. This is because data is often confounded by patients not attempting a pregnancy; occasions when one woman had more than one pregnancy and this not being reported clearly; and instances of short follow-up periods. One group used an actuarial analysis to calculate the percent probability of conception to be

53% (305). When the numbers of women trying for a pregnancy are reported in the literature, we found 299 (54.5%) women achieved a pregnancy out of 549 trying to conceive (294,302). Where it was possible to interpret data, we found 293/541 women (54.2%) achieved at least one live birth (294,302). Although these numbers are similar, many women had more than one pregnancy and there were many cases of first and second trimester miscarriages, and even cases of pregnancies being terminated. When reported, and data possible to interpret, a pregnancy following RVT was secondary to fertility treatment in 41/159 (25.8%) of cases (305,306). It should be noted that fertility in this group of women is not only compromised by the RVT and cervical stenosis, but also by the fact that on average, women are over the age of 30 years.

Of babies born to women who have had RVT, where it is possible to glean the data, 113/295 (38.3%) are born prematurely (36 weeks and less) (294,304,305). In addition, where it is possible to interpret the data 44/259 (17.0%) of babies born to women who had had RVT are born very prematurely (<32 weeks) (294,307). For this reason and because delivery is likely to be by caesarean section (possibly through a classical incision), it is advised that pregnancies are supervised by an obstetric team experienced in high risk obstetrics. Furthermore, women need to be advised of the above risks and counselled as to the risks of prematurity.

Recommendations:

- Radical vaginal trachelectomy is an acceptable fertility sparing treatment for women with stage IB1 (FIGO 2018) disease
- At histological review, those with low risk and low volume tumours should be considered for cone biopsy instead of radical trachelectomy
- When patients are considered for RVT, the risk of eventually receiving treatment that is fertility sacrificing (such as radiotherapy) is in the region of 11%. This figure should be presented to patients who should be counselled appropriately taking in to account other prognostic markers such as grade, LVSI, tumour size, and audit figures from the centre providing treatment
- The risk of recurrence following RVT is in the region of 5%. This figure should be presented to patients who should be counselled appropriately taking in to account other prognostic markers such as grade, LVSI, tumour size, and audit figures from the local centre providing treatment
- Prior to surgery, a woman scheduled for an RVT should be informed in detail about all surgical risks and the impact of the procedure on her fertility and future obstetric outcomes
- Prior to surgery, a woman scheduled for RVT should be warned that if they do conceive, and a cerclage is in situ, a caesarean section will be required
- Centres offering RVT should audit their outcomes regularly. This should include recurrence rates, complications, fertility rates, and obstetric outcomes
- Given the rarity of these cases most of the above is based on expert opinion

18.4.2. Abdominal radical trachelectomy (ART) for stage IB1 disease

The efficacy of ART for the treatment of cervical cancer has been systematically reviewed (297-298) for women with stage IA1 – IB1 disease for both low and high volume tumours. As with RVT, it is difficult to calculate the exact figure for recurrence following ART for stage IB1 lesions. This is as the figures reported in the literature are contaminated with patients with stage IA1, IA2 & IIA lesions and in many cases it is impossible to dissect these patients out of reported results (297,298). For those patients included in systematic reviews in which a recurrence rate can be calculated, the overall recurrence rate from all people who were selected for trachelectomy (whether or not they had completion treatment) was 31/866 (3.6%) (297). If an assumption is made that all recurrences existed in women with stage IB1 or greater, than the figure for recurrence would be 31/699 (4.4%) for this group (297). As with RVT, this figure is further distorted by series containing patients with short follow-up durations and influenced by tumour grade, presence of LVSI, tumour volume and other established prognostic factors. With the data

available, it seems sensible that the figure presented to patients as to the risk of recurrence should be in the region of 5% but also taking into account all the other prognostic markers available for an individual patient.

Cerclage erosion as a surgical complication is not routinely reported in the literature but when reported occurs in 13/433 (3.0%) of cases (303). There was a total of 50/433 (11.3%) cases of cervical stenosis in papers where it was possible to assess for this complication.

As with RVT the probability of a woman achieving at least one pregnancy following ART is not clear in the literature (303,309-312). This is for similar reasons to RVT that women not attempting a pregnancy often confound the results; there are occasions when one woman had more than one pregnancy and this is not clearly reported; and there are instances of short follow-up periods. When the numbers of women trying for a pregnancy are reported in the literature, we found 136 (41.6%) women achieved a pregnancy out of 327 trying to conceive (310-312). Of women who successfully conceived and where data could be interpreted, we found that 75/134 (56.0%) of pregnancies were secondary to fertility treatment. Where it was possible to interpret data, we found 35/142 women (24.6%) achieved at least one live birth (310-312). However, these numbers are small because much data was excluded as it was not clear in the literature how many of the live births were born to how many women. In total, 119/169 (72.6%) of pregnancies resulted in some form of live birth.

Of babies born to women who had an ART, where it is possible to glean the data, 59/118 (50.0%) are born prematurely (36 weeks and less) (310-312). However, as with RVT, the data is affected by women having elective caesarean sections at 36 weeks' gestation.

Recommendations:

- Abdominal radical trachelectomy (ART) is an acceptable fertility sparing treatment for women with stage IB1 disease. Especially those with larger tumours
- At histological review, those with low risk and low volume tumours should be considered for cone biopsy, simple trachelectomy, or radical vaginal trachelectomy
- When patients are considered for ART, the risk of receiving treatment that is fertility sacrificing (such as radiotherapy) is in the region of 17%. This figure should be presented to patients who should be counselled appropriately taking in to account other prognostic markers such as grade, LVSI, tumour size, and audit figures from the centre providing treatment
- The risk of recurrence following ART is in the region of 5%. This figure should be presented to patients who should be counselled appropriately taking into account other prognostic markers such as grade, LVSI, tumour size, and audit figures from the local centre providing treatment
- Prior to surgery, women should be warned of the risk of cerclage erosion in the region of 3% and the risk of cervical stenosis in the region of 11%
- Prior to surgery, women scheduled for an ART should be informed that the current data suggests the proportion of women who eventually achieve a pregnancy is over 42% but over 50% of these pregnancies are secondary to fertility treatment. The proportion of women trying for a baby who have a live birth is about 25%
- Prior to surgery, a woman scheduled for an ART should be informed that the premature delivery rate if a baby is achieved is just about 50% and the extreme premature labour rate about 20%. Women should also be informed that prematurity is associated with learning difficulties and slow development in children
- Prior to surgery, a woman scheduled for an ART should be warned if they do conceive, with a stitch is in situ they will need a caesarean section
- Centres offering ART should audit their outcomes regularly. This should include recurrence rates, complications, fertility rates, and obstetric outcomes

18.6 Ovarian transposition

Ovarian transposition has been considered to preserve ovarian function in women who require pelvic radiotherapy. The aim is not just to preserve hormonal production but also to preserve function so that egg collection can occur, and surrogacy be considered. Ovarian transposition has been systematically reviewed (313). Of the twenty-four papers included in the systematic review, much of the data is contaminated by patients who did not actually undergo subsequent radiotherapy (314-316). Of women who had external beam radiotherapy (EBRT) 65% preserved their ovarian function but 5% of women developed ovarian cysts. Ovarian cyst development is often associated with subsequent severe pain and difficult surgery to remove entrapped ovaries. The meta-analysis did not include case reports and did not report any recurrences in this specific group of patients.

There are a few unanswered questions regarding ovarian transposition. It seems sensible that not only the ovary but also the vascular pedicle needs to be moved away from the radiation field. Therefore, the ovarian ligament should be cut. Transposition of the Fallopian tube would preserve blood supply from the mesosalpinx but might carry cancer cells with it. High stage and poor histological type adenocarcinomas might have already metastasised to the ovary resulting in recurrence and perhaps this is the occasion when women with adenocarcinomas need to be treated differently. It seems intuitive that women with an adenocarcinoma and uterine spread should not have their ovaries transposed.

Ovarian transposition is particularly difficult after ovarian stimulation due to the size of the ovaries.

Opportunistic removal of tubes as risk reduction strategy should be discussed with the patient prior to the surgery.

Recommendations:

- Women due to receive external beam radiotherapy should be offered ovarian transposition if the radiation field will be away from the vascular pedicle
- Opportunistic removal of tubes should be discussed with the patient
- Prior to surgery a woman should be warned that the failure rate is in the region of 35%
- Prior to surgery a woman should be advised that the risk of ovarian cyst formation and entrapment is in the region of 5%
- Prior to surgery a woman should be warned of the potential risk of metastases to the transposed ovary
- A surgeon should note that transposition following ovarian stimulation is more difficult due to the size of the ovaries (Grade D)

18.7 Neo-adjuvant chemotherapy prior to fertility sparing surgery

Current literature

A number of studies has looked at neo-adjuvant chemotherapy (NAC) in an attempt to reduce tumour size and allow fertility sparing surgery when otherwise it might not be possible (311,317). Studies have included a variety of different histological types, and treatment modalities.

Recommendations:

- Women who would not normally qualify for fertility sparing surgery may be considered for NAC to reduce the size of the tumour
- Use of a NAC protocol in this setting should either be audited within a registered service evaluation project or in a clinical study

Bibliography

1) National Institute for Health and Clinical Excellence. NICE Guidelines (NG12) Suspected cancer: recognition and referral. June 2015. Available at: https://www.nice.org.uk/guidance/ng12
2) Scottish Intercollegiate Guidelines. Network Management of cervical cancer. A national clinical guideline. Jan 2008. http://www.sign.ac.uk/assets/sign99.pdf
3) NHSCP20 guidance
4) Pretorius R, Semrad N, Watring W, Fotheringham N. Presentation of cervical cancer. Gynecol Oncol 1991;42(1):48-53.
5) Scottish Intercollegiate Guidelines Network (SIGN). Management of genital Chlamydia trachomatis. Edinburgh: SIGN; 2000. (SIGN publication no. 42). (Nov 2007).
6) Shapley M, Jordan J, Croft PR. A systematic review of postcoital bleeding and risk of cervical cancer. Br J Gen Pract 2006;56(527):453-60.
7) Shalini R, Amita S, Neera MA. How alarming is post-coital bleeding—a cytologic, colposcopic and histopathologic evaluation. Gynecol Obstet Invest 1998;45(3):205-8.
8) Viikki M, Pukkala E, Hakama M. Bleeding symptoms and subsequent risk of gynecological and other cancers. Acta Obstet Gynecol Scand 1998;77(5):564-9.
9) Jha S, Sabharwal S. Outcome of colposcopy in women presenting with postcoital bleeding and negative or no cytology--results of a 1-year audit. J Obstet Gynaecol 2002;22(3):299-301.
10) Adjunctive colposcopy technologies for examination of the uterine cervix – DySIS and the Niris Imaging System (2012) NICE diagnostics guidance 4.
11) Adjunctive colposcopy technologies for assessing suspected cervical abnormalities- The NICE Diagnostics Assessment Programme will assess the clinical and cost-effectiveness of the adjunctive colposcopy technologies in order to make recommendations on their use in the NHS. Due for publication Dec 2017, as update to ref 10.
12) NCIN. Cancer Waiting times, http://www.ncin.org.uk/collecting_and_using_data/data_collection/gfocw. 2010
13) NCIN. Routes to diagnosis 2015 update: cervical cancer. www.ncin.org.uk/publications/routes_to_diagnosis. 2016
14) NHS England. Complex Gynaecology - Specialist Gynaecological Cancers, https://www.england.nhs.uk/wp-content/uploads/2014/04/e10-cancer-gynae-0414.pdf. 2013.
15) National Peer Review programme: Manual for Cancer Services Gynaecology Measures, www.cquins.nhs.uk/download.php?d=resources/measures/Gynaecology_January2014.pdf. 2014.
16) Sasieni P, Castanon A. NHSCSP Audit of Invasive Cervical Cancer: National Report 2009-2013. 2014.
17) Cancer Services Collaborative, British Gynaecological Cancer Society. Cancer reform strategy: Gynaecological Cancers Annexe D. 2007.
18) Public Health England. Trachelectomies for the treatment of cervical cancer, England: National Cancer Registration and Analysis Service Data Briefing. 2017.
19) Bipat S, Glas AS, van der Velden J, Zwinderman AH, Bossuyt PM, Stoker J. Computed tomography and magnetic resonance imaging in staging of uterine cervical carcinoma: a systematic review. Gynecol Oncol. 2003 Oct;91(1):59-66.
20) de Boer P, Adam JA, Buist MR, van de Vijver MJ, Rasch CR, Stoker J et al. Role of MRI in detecting involvement of the uterine internal os in uterine cervical cancer: systematic review of diagnostic test accuracy. Eur J Radiol. 2013 Sep;82(9):e422-8.

21) Sheu M, Chang C, Wang J, Yen M. MR staging of clinical stage I and IIa cervical carcinoma: a reappraisal of efficacy and pitfalls.Eur J Radiol. 2001 Jun;38(3):225-31.
22) Togashi K, Nishimura K, Sagoh T, Minami S, Noma S, Fujisawa I et al. Carcinoma of the cervix: staging with MR imaging. Radiology. 1989 Apr;171(1):245-51.
23) Boss EA, Barentsz JO, Massuger LF, Boonstra H. The role of MR imaging in invasive cervical carcinoma. Eur Radiol. 2000;10(2):256-70
24) Thomeer MG, Gerestein C, Spronk S, van Doorn HC, van der Ham E, Hunink MG. Clinical examination versus magnetic resonance imaging in the pretreatment staging of cervical carcinoma: systematic review and meta-analysis. Eur Radiol. 2013 Jul;23(7):2005-18.
25) Sahdev A, Sohaib SA, Wenaden AE, Shepherd JH, Reznek RH. The performance of magnetic resonance imaging in early cervical carcinoma: a long-term experience. Int J Gynecol Cancer. 2007 May-Jun;17(3):629-36. Epub 2007 Feb 9.
26) Kaji Y, Sugimura K, Kitao M, Ishida T. Histopathology of uterine cervical carcinoma: diagnostic comparison of endorectal surface coil and standard body coil MRI. J Comput Assist Tomogr. 1994 Sep-Oct;18(5):785-92.
27) Rockall AG, Ghosh S, Alexander-Sefre F, Babar S, Younis MT, Naz S, Jacobs IJ et al. Can MRI rule out bladder and rectal invasion in cervical cancer to help select patients for limited EUA? Gynecol Oncol. 2006 May;101(2):244-9. Epub 2005 Nov 28.
28) Mitchell DG, Snyder B, Coakley F, Reinhold C, Thomas G, Amendola MA et al. Early invasive cervical cancer: MRI and CT predictors of lymphatic metastases in the ACRIN 6651/GOG 183 intergroup study. Gynecol Oncol. 2009 Jan;112(1):95-103. doi: 10.1016/j.ygyno.2008.10.005. Epub 2008 Nov 20.
29) Shen G, Zhou H, Jia Z, Deng H. Diagnostic performance of diffusion-weighted MRI for detection of pelvic metastatic lymph nodes in patients with cervical cancer: a systematic review and meta-analysis. Br J Radiol. 2015 Aug;88(1052):20150063.
30) Choi HJ, Ju W, Myung SK, & Kim Y. Diagnostic performance of computer tomography, magnetic resonance imaging, and positron emission tomography or positron emission tomography/computer tomography for detection of metastatic lymph nodes in patients with cervical cancer: meta-analysis. Cancer Sci. 2010;101.(6.):1471.-9
31) Selman TJ, Mann C, Zamora J, Appleyard TL, Khan K. Diagnostic accuracy of tests for lymph node status in primary cervical cancer: a systematic review and meta-analysis. CMAJ. 2008;178.(7.):855.-62.
32) Kang S, Kim SK, Chung DC, Seo SS, Kim JY, Nam BH et al. Diagnostic value of (18)F-FDG PET for evaluation of paraaortic nodal metastasis in patients with cervical carcinoma: a metaanalysis. J.Nucl.Med. 2010.Mar.;51.(3):360.-7.
33) Addley H, Moyle P, Freeman S. Diffusion-weighted imaging in gynaecological malignancy. Clin Radiol. 2017 Aug 22. pii: S0009-9260(17)30389-6. doi: 10.1016/j.crad.2017.07.014. [Epub ahead of print]
34) Dappa E, Elger T, Hasenburg A, Düber C, Battista MJ, Hötker AM. The value of advanced MRI techniques in the assessment of cervical cancer: a review. Insights Imaging. 2017 Aug 21. doi: 10.1007/s13244-017-0567-0. [Epub ahead of print]
35) Hancke K, Heilmann V, Straka P, Kreienberg R, Kurzeder C. Pretreatment staging of cervical cancer: is imaging better than palpation?: Role of CT and MRI in preoperative staging of cervical cancer: single institution results for 255 patients. Ann Surg Oncol. 2008 Oct;15(10):2856-61.

36) Lakhman Y, Akin O, Park KJ, Sarasohn DM, Zheng J, Goldman DA et al. Stage IB1 cervical cancer: role of preoperative MR imaging in selection of patients for fertility-sparing radical trachelectomy. Radiology. 2013 Oct;269(1):149-58.
37) Mitchell DG, Snyder B, Coakley F, Reinhold C, Thomas G, Amendola M et al. Early invasive cervical cancer: tumor delineation by magnetic resonance imaging, computed tomography, and clinical examination, verified by pathologic results, in the ACRIN 6651/GOG 183 Intergroup Study. J Clin Oncol. 2006 Dec 20;24(36):5687-94.
38) Noël P, Dubé M, Plante M, St-Laurent G. Early cervical carcinoma and fertility-sparing treatment options: MR imaging as a tool in patient selection and a follow-up modality. Radiographics. 2014 Jul-Aug;34(4):1099-119
39) Prasad TV, Thulkar S, Hari S, Sharma DN, Kumar S. Role of computed tomography (CT) scan in staging of cervical carcinoma. Indian J Med Res. 2014 May;139(5):714-9.
40) Rockall A, Sohaib A, Sala E. Carcinoma of the cervix, vagina and vulva. In: Nicholson T (ed). Recommendations for cross-sectional imaging in cancer management, Second edition. London: The Royal College of Radiologists, 2014
41) Salani R, Backes FJ, Fung MF. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. Am J Obstet Gynecol. 2011 Jun;204(6):466-78. doi: 10.1016/j.ajog.2011.03.008. Review.
42) Atri M, Zhang Z, Dehdashti F. Utility of PET-CT to evaluate retroperitoneal lymph node metastasis in advanced cervical cancer: Results of ACRIN6671/GOG0233 trial. Gynecol Oncol. 2016 Sep;142(3):413-9.
43) Rajendran JG, Greer BE. Expanding role of positron emission tomography in cancer of the uterine cervix. J Natl Compr Canc Netw. 2006 May;4(5):463-9. Review.
44) Lakhman Y, Akin O, Park KJ. Stage IB1 cervical cancer: role of preoperative MR imaging in selection of patients for fertility-sparing radical trachelectomy. Radiology. 2013 Oct;269(1):149-58.
45) Elit L, Reade CJ. Recommendations for Follow-up Care for Gynecologic Cancer Survivors. Obstet Gynecol. 2015 Dec;126(6):1207-14.
46) Sala E, Rockall AG, Freeman SJ. The added role of MR imaging in treatment stratification of patients with gynecologic malignancies: what the radiologist needs to know. Radiology. 2013 Mar;266(3):717-40.
47) Balleyguier C, Sala E, Da Cunha T. Staging of uterine cervical cancer with MRI: guidelines of the European Society of Urogenital Radiology.Eur Radiol. 2011 May;21(5):1102-10.
48) Sala E, Micco M, Burger IA. Complementary Prognostic Value of Pelvic Magnetic Resonance Imaging and Whole-Body Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in the Pretreatment Assessment of Patients with Cervical Cancer. Int J Gynecol Cancer. 2015 Oct;25(8):1461-7.
49) Bats AS, Mathevet P, Buenerd A, Orliaguet I, Mery E, Zerdoud S et al. The Sentinel Node Technique Detects Unexpected Drainage Pathways and Allows Nodal Ultra staging in Early Cervical Cancer: Insights from the Multicenter Prospective SENTICOL Study. Ann Surg Oncol. 2013; 20: 413-422.

50) Van de Lande J, Torrenga B, Raijmakers PG, Hoekstra OS, van Baal MW, Brölmann HA et al. Sentinel lymph node detection in early stage uterine cervix carcinoma: a systematic review. Gynecol Oncol. 2007 Sep;106(3):604-613.
51) Wu Y, Li Z, Wu H, Yu J. Sentinel lymph node biopsy in cervical cancer: A meta-analysis. Mol Clin Oncol. 2013 Nov;1(6):1025-1030.
52) Wang XJ, Fang F, Li YF. Sentinel-lymph-node procedures in early stage cervical cancer: a systematic review and meta-analysis. Med Oncol. 2015 Jan;32(1):385.
53) Kadkhodayan S, Hasanzadeh M, Treglia G, Azad A, Yousefi Z, Zarifmahmoudi L et al. Sentinel node biopsy for lymph nodal staging of uterine cervix cancer: a systematic review and meta-analysis of the pertinent literature. Eur J Surg Oncol. 2015 Jan;41(1):1-20.
54) Furukawa N, Oi H, Yoshida S, Shigetomi H, Kanayama S, Kobayashi H. The usefulness of photodynamic eye for sentinel lymph node identification in patients with cervical cancer. Tumori. 2010 Nov-Dec;96(6):936-940.
55) Van der Vorst JR, Hutteman M, Gaarenstroom KN, Peters AA, Mieog JS, Schaafsma BE et al. Optimization of near-infrared fluorescent sentinel lymph node mapping in cervical cancer patients. Int J Gynecol Cancer. 2011 Nov;21(8):1472-1478.
56) Rossi EC, Ivanova A, Boggess JF. Robotically assisted fluorescence-guided lymph node mapping with ICG for gynecologic malignancies: a feasibility study. Gynecol Oncol. 2012 Jan;124(1):78-82.
57) Dargent D, Martin X, Mathevet P. Laparoscopic assessment of the sentinel lymph node in early stage cervical cancer. Gynecol Oncol. 2000 Dec;79(3):411-415.
58) Plante M, Renaud MC, Têtu B, Harel F, Roy M. Laparoscopic sentinel node mapping in early-stage cervical cancer. Gynecol Oncol. 2003 Dec;91(3):494-503.
59) Fader AN, Edwards RP, Cost M, Kanbour-Shakir A, Kelley JL, Schwartz B et al. Sentinel lymph node biopsy in early-stage cervical cancer: utility of intraoperative versus postoperative assessment. Gynecol Oncol. 2008 Oct;111(1):13-17.
60) Bats AS, Buénerd A, Querleu D, Leblanc E, Daraï E, Morice P et al. Diagnostic value of intraoperative examination of sentinel lymph node in early cervical cancer: a prospective, multicenter study. Gynecol Oncol. 2011 Nov;123(2):230-235
61) Slama J, Dundr P, Dusek L, Cibula D. High false negative rate of frozen section examination of sentinel lymph nodes in patients with cervical cancer. Gynecol Oncol. 2013 May;129(2):384-388.
62) Mathevet P, Lecuru F, Magaud L, Bouttie F. Sentinel lymph node biopsy for early cervical cancer: Results of a randomized prospective, multicenter study (Senticol 2) comparing adding pelvic lymph node dissection vs sentinel node biopsy only (Abstract). Gynecol Oncol. 2017, June; 145: S1 : 2-3.
63) SHAPE: A randomised phase III trial comparing radical hysterectomy and pelvic node dissection vs simple hysterectomy and pelvic node dissection in patients with low risk early stage cervical cancer. http://www.ctc.ucl.ac.uk/TrialDetails.aspx?Trial=106&
64) Dostálek L, Zikan M, Fischerova D, Kocian R, Germanova A, Frühauf F. SLN biopsy in cervical cancer patients with tumors larger than 2cm and 4cm. Gynecol Oncol. 2018 Mar;148(3):456-460.

65) Salvo G, Ramirez PT, Levenback CF, Munsell MF, Euscher ED, Soliman PT et al. Sensitivity and negative predictive value for sentinel lymph node biopsy in women with early-stage cervical cancer. Gynecol Oncol. 2017 Apr;145(1):96-101.
66) https://assets.publishing.service.gov.uk/.../NHSCSP_colposcopy_management. Accessed on 29 April 2018
67) Kurman RJ, Carcangiu ML, Herrington CS, Young RH (2014) WHO classification of tumours of the Female Reproductive Organs (4th edition) Lyon: IARC.
68) Rodríguez-Carunchio L, Soveral I, Steenbergen RD, Torné A, Martinez S, Fusté P et al. HPV-negative carcinoma of the uterine cervix: a distinct type of cervical cancer with poor prognosis. BJOG. 2015;122(1):119-27
69) Stolnicu S, Barsan I, Hoang L, Patel P, Terinte C, Pesci A et al. International Endocervical Adenocarcinoma Criteria and Classification (IECC): A New Pathogenetic Classification for Invasive Adenocarcinomas of the Endocervix. Am J Surg Pathol. 2018 Feb;42(2):214-226
70) Roma AA, Diaz De Vivar A, Park KJ, Alvarado-Cabrero I, Rasty G, Chanona-Vilchis JG et al. Invasive endocervical adenocarcinoma: a new pattern-based classification system with important clinical significance. Am J Surg Pathol.2015;39(5):667-72
71) McCluggage WG, Judge MJ, Alvarado-Cabrero I, Duggan MA, Horn LC, Hui P et al. Data Set for the Reporting of Carcinomas of the Cervix: Recommendations from the International Collaboration on Cancer Reporting (ICCR). Int J Gynecol Pathol.2018 May;37(3):205-228
72) Noviello MB, Silva-Filho AL, Traiman P, Triginelli SA, Noviello M, Pedrosa MS et al. Inter- and intraobserver variability in the assessment of tumour grade and lymphovascular space invasion in patients with squamous cell carcinoma of the cervix. Eur J Obstet Gynecol Reprod Biol. 2008;138(2):246-8
73) Wuntakal R, Papadopoulos AJ, Montalto SA, Perovic M, Coutts M, Devaja O. Location of Sentinel Lymph Node in Cervical Carcinoma and Factors Associated with Unilateral Detection. Int J Gynecol Cancer. 2015 Nov;25(9):1663-8]
74) Pol FJ, Zusterzeel PL, van Ham MA, Kuijpers DA, Bulten J, Massuger LF. Satellite lymphovascular space invasion: An independent risk factor in early stage cervical cancer. Gynecol Oncol. 2015 Sep;138(3):579-84
75) Winer I, Alvarado-Cabrero I, Hassan O, Ahmed QF, Alosh B, Bandyopadhyay S et al. The prognostic significance of histologic type in early stage cervical cancer - A multi-institutional study. Gynecol Oncol. 2015 Jun;137(3):474-8
76) Tanguay C, Plante M, Renaud MC, Roy M, Têtu B. Vaginal radical trachelectomy in the treatment of cervical cancer: the role of frozen section. Int J Gynecol Pathol. 2004 Apr;23(2):170-5
77) Park KJ, Soslow RA, Sonoda Y, Barakat RR, Abu-Rustum NR. Frozen-section evaluation of cervical adenocarcinoma at time of radical trachelectomy: pathologic pitfalls and the application of an objective scoring system. Gynecol Oncol. 2008 Sep;110(3):316-23.
78) Ganesan R, Brown LJ, Kehoe S, McCluggage WG, El-Bahrawy MA. The role of frozen sections in gynaecological oncology: survey of practice in the United Kingdom. Eur J Obstet Gynecol Reprod Biol. 2013 Feb;166(2):204-8
79) Lai CH, Hong JH, Hsueh S, Ng KK, Chang TC, Tseng CJ et al. Preoperative prognostic variables and the impact of postoperative adjuvant therapy on the outcomes of Stage IB

or II cervical carcinoma patients with or without pelvic lymph node metastases: an analysis of 891 cases. Cancer. 1999 Apr 1;85(7):1537-46
80) Quinn MA, Benedet JL, Odicino F, Maisonneuve P, Beller U, Creasman WT et al. Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet. 2006 Nov;95 Suppl 1:S43-103
81) Kim SM, Choi HS, Byun JS. Overall 5-year survival rate and prognostic factors in patients with stage IB and IIA cervical cancer treated by radical hysterectomy and pelvic lymph node dissection. Int J Gynecol Cancer. 2000 Jul;10(4):305-312
82) Lv X, Chen L, Yu H, Zhang X, Yan D. Intra-operative frozen section analysis of common iliac lymph nodes in patients with stage IB1 and IIA1 cervical cancer. Arch Gynecol Obstet. 2012 Mar;285(3):811-6
83) Fotopoulou C, Ind T, Baldwin P, Crawford R, Devaja O, Dobbs S et al. Sentinel lymph node consensus document of the British Gynaecological Cancer Society for endometrial, vulvar, and cervical cancers. Int J Gynecol Cancer. 2019 Nov;29(9):1348-1350. doi: 10.1136/ijgc-2019-000798.
84) Khan MJ, Castle PE, Lorincz AT, Wacholder S, Sherman M, Scott DR et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. J Natl Cancer Inst. 2005 Jul 20;97(14):1072-9
85) Mabuchi Y, Yahata T, Kobayashi A, Tanizaki Y, Shiro M, Ota N et al. Clinicopathologic Factors of Cervical Adenocarcinoma Stages IB to IIB. Int J Gynecol Cancer. 2015 Nov;25(9):1677-82
86) Klaes R, Friedrich T, Spitkovsky D, Ridder R, Rudy W, Petry U et al. Overexpression of p16INK4a as a specific marker for dysplastic and neoplastic epithelial cells of the cervix uteri. Int J Cancer. 2001;92:276–284
87) Keating JT, Cviko A, Reithdorf S, Reithdorf L, Quade BJ, Sun D et al. Ki-67, cyclin E and p16 are complimentary surrogate biomarkers for human papillomavirus-related cervical neoplasia. Am J Surg Pathol. 2001;25:894–991
88) Milde-Langosch K, Reithdorf S, Kraws-Poppinghaus A. Expression of cyclin-dependent kinase inhibitors p16, p21 and p27 in HPV-positive and HPV-negative cervical adenocarcinomas. Virchows Arch. 2001;439: 55–61
89) O'Neill CJ, McCluggage WG. p16 expression in the female genital tract and its value in diagnosis. Adv Anat Pathol. 2006 Jan;13(1):8-15
90) Clinton LK, Miyazaki K, Ayabe A, Davis J, Tauchi-Nishi P, Shimizu D. The LAST guidelines in clinical practice: implementing recommendations for p16 use. Am J Clin Pathol. 2015 Dec;144(6):844-9
91) Zaino RJ. The fruits of our labors: distinguishing endometrial from endocervical adenocarcinoma. Int J Gynecol Pathol. 2002; 21:1–3
92) Maneo A, Sideri M , Scambia G, Boveri S, dell'Anna T, Villa M et al. Simple conization and lymphadenectomy for the conservative treatment of stage IB1 cervical cancer. An Italian experience. Gynecologic Oncology 123 (2011) 557–560
93) Ramirez P, Pareja R, Rendón G, Millan C, Frumovitz M, Schmeler K. Management of low-risk early-stage cervical cancer: Should conization, simple trachelectomy, or simple

hysterectomy replace radical surgery as the new standard of care? Gynecol Oncol. 2014 Jan; 132(1): 254–259.
94) Xu L, Sun FQ, Wang ZH. Radical trachelectomy versus radical hysterectomy for the treatment of early cervical cancer: a systematic review. Acta Obstet Gynecol Scand. 2011 Nov;90(11):1200-9.
95) Girardi F, Burghardt E, Pickel H. Small FIGO stage IB cervical cancer. Gynecol Oncol. 1994 Dec;55(3 Pt 1):427-32.
96) Biliatis I, Kucukmetin A, Patel A, Ratnavelu N, Cross P, Chattopadhyay S et al. Small volume stage 1B1 cervical cancer: Is radical surgery still necessary? Gynecol Oncol. 2012 Jul;126(1):73-7.
97) Landoni F, Maneo A, Zapardiel I, Zanagnolo V, Mangioni C. Class I versus class III radical hysterectomy in stage IB1-IIA cervical cancer. A prospective randomized study. Eur J Surg Oncol. 2012 Mar;38(3):203-9.
98) Landoni F, Maneo A, Cormio G, Perego P, Milani R, Caruso O et al. Class II versus class III radical hysterectomy in stage IB-IIA cervical cancer: a prospective randomized study. Gynecol Oncol. 2001 Jan;80(1):3-12.
99) Wright JD, Grigsby PW, Brooks R, Powell MA, Gibb RK, Gao F et al. Utility of parametrectomy for early stage cervical cancer treated with radical hysterectomy. Cancer. 2007 Sep 15;110(6):1281-6.
100) Covens A, Rosen B, Murphy J, Laframboise S, DePetrillo AD, Lickrish G et al. How important is removal of the parametrium at surgery for carcinoma of the cervix? Gynecol Oncol. 2002 Jan;84(1):145-9.
101) Schmeler KM, Frumovitz M, Ramirez PT. Conservative management of early stage cervical cancer: is there a role for less radical surgery? Gynecol Oncol. 2011 Mar;120(3):321-5.
102) Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet. 1997 Aug 23;350(9077):535-40.
103) Baalbergen A, Veenstra Y, Stalpers L. Primary surgery versus primary radiotherapy with or without chemotherapy for early adenocarcinoma of the uterine cervix. Cochrane Database Syst Rev. 2013 Jan 31;(1):CD006248. doi: 10.1002/14651858.CD006248.pub3.
104) Shimada M, Kigawa J, Nishimura R, Yamaguchi S, Kuzuya K, Nakanishi T et al. Ovarian metastasis in carcinoma of the uterine cervix. Gynecol Oncol. 2006 May;101(2):234-7.
105) Chen J, Wang R, Zhang B, Lin X, Wei J, Jia Y et al. Safety of ovarian preservation in women with stage I and II cervical adenocarcinoma: a retrospective study and meta-analysis. Am J Obstet Gynecol. 2016 Oct;215(4):460.e1-460.e13.
106) Lyu J, Sun T, Tan X. Ovarian preservation in young patients with stage I cervical adenocarcinoma: a surveillance, epidemiology, and end results study. International Journal of Gynecological Cancer. 24(8):1513-20, 2014 Oct.
107) Geetha P, Nair MK. Laparoscopic, robotic and open method of radical hysterectomy for cervical cancer: A systematic review. J Minim Access Surg. 2012 Jul;8(3):67-73.

108) Sutton GP, Bundy BN, Delgado G, Sevin BU, Greasman WT, Major FJ et al. Ovarian metastases in stage IB carcinoma of the cervix: a gynecologic oncology group study. Am J Obstet Gynecol 1992;166:50–3.
109) Touhami O, Plante M. Should ovaries be removed or not in (early-stage) adenocarcinoma of the uterine cervix: A review. Gynecologic Oncology 136 (2015) 384–388.
110) Cibula D, Abu-Rustum NR. Pelvic lymphadenectomy in cervical cancer-surgical anatomy and proposal for a new classification system. Gynecol Oncol. 2010 Jan;116(1):33-7.
111) Höckel M, Horn LC, Tetsch E, Einenkel J. Pattern analysis of regional spread and therapeutic lymph node dissection in cervical cancer based on ontogenetic anatomy. Gynecol Oncol. 2012 Apr;125(1):168-74.
112) Frumovitz M, Plante M, Lee PS, Sandadi S, Lilja JF, Escobar PF et al. Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers (FILM): a randomised, phase 3, multicentre, non-inferiority trial. Lancet Oncol. 2018 Aug 21. pii: S1470-2045(18)30448-0.
113) Jewell EL, Huang JJ, Abu-Rustum NR, Gardner GJ, Brown CL, Sonoda Y et al. Detection of sentinel lymph nodes in minimally invasive surgery using indocyanine green and near-infrared fluorescence imaging for uterine and cervical malignancies. Gynecol Oncol. 2014 May;133(2):274-7.
114) Lécuru F, Mathevet P, Querleu D, Leblanc E, Morice P, Daraï E et al. Bilateral negative sentinel nodes accurately predict absence of lymph node metastasis in early cervical cancer: results of the SENTICOL study. J Clin Oncol. 2011 May 1;29(13):1686-91.
115) Mathevet P, Lecuru F, Magaud L, Bouttitie F. Sentinel lymph node biopsy for early cervical cancer: Results of a randomized prospective, multicenter study (Senticol 2) comparing adding pelvic lymph node dissection vs sentinel node biopsy only. Gynecologic Oncology June 2017 Vol145, Suppl 1, pages 2-3.
116) Cibula D, Abu-Rustum NR, Dusek L, Zikán M, Zaal A, Sevcik L et al. Prognostic significance of low volume sentinel lymph node disease in early-stage cervical cancer. Gynecol Oncol. 2012 Mar;124(3):496-501.
117) Cibula D, Pötter R, Planchamp F, Avall-Lundqvist E, Fischerova D, Haie Meder C et al. The European Society of Gynaecological Oncology/ European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the Management of Patients with Cervical Cancer. Int J Gynecol Cancer. 2018 May;28(4):641-655.
118) Sevin BU, Nadji M, Lampe B, Lu Y, Hilsenbeck S, Koechli OR et al. Prognostic factors of early stage cervical cancer treated by radical hysterectomy. Cancer. 1995 Nov 15;76(10 Suppl):1978-86.
119) Rogers L, Siu SSN, Luesley D, Bryant A, Dickinson HO. Radiotherapy and chemoradiation after surgery for early cervical cancer. Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD007583.
120) Rotman M, Sedlis A, Piedmonte MR, Bundy B, Lentz SS, Muderspach LI et al. A phase III randomized trial of postoperative pelvic irradiation in stage IB cervical carcinoma with poor prognostic features: follow-up of a gynaecologic oncology group study. International Journal of Radiation Oncology and Biological Physics 2006;65(1):169-76.

121) Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a gynecologic oncology group study. Gynecologic Oncology 1999; 73:177–83.
122) Cibula D, Abu-Rustum NR, Fischerova D, Pather S, Lavigne K, Slama J et al. Surgical treatment of "intermediate risk" lymph node negative cervical cancer patients without adjuvant radiotherapy-A retrospective cohort study and review of the literature. Gynecol Oncol. 2018 Dec;151(3):438-443.
123) Delgado G, Bundy B, Zaino R, Sevin BU, Creasman WT, Major F. Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol. 1990 Sep;38(3):352-7.
124) Peters WA, Liu PY, Barrett RJ, Stock RJ, Monk BJ, Berek JS et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol. 2000 Apr;18(8):1606-13.
125) Martin-Hirsch P, Wood N, Whitham NL, Macdonald R, Kirwan J, Anagnostopoulos A et al. Survival of women with early-stage cervical cancer in the UK treated with minimal access and open surgery. BJOG. 2019 Jul;126(8):956-959. doi: 10.1111/1471-0528.15617. Epub 2019 Mar 1.
126) Landoni F, Maneo A, Colombo A et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet 1997, 350:535-540
127) ESGO Cervical Cancer Guidelines 2017: guidelines.esgo.org
128) Monk BJ, Wang J, Im S, Stock RJ, Peters WA, Liu PY et al. Gynaecologic Oncology Group; Southwest Oncology Group; Radiation Therapy Oncology Group. Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical pathologic analysis of a gynaecologic Oncology Group/ Southwest Oncology group/ Radiation Therapy Oncology Group trial. Gynaecol Oncol 2005, 96:721-728.
129) Fyles A, Keane TJ Barton, Simm J. The Effect of treatment duration in the local control of cervix cancer. Gynaecologic Oncol 1996 60 42-48
130) EMBRACE study. www.embracestudy.dk. (retrieved 18.08.2017).
131) Forrest J, Presutti J, Davidson M, Hamilton P, Kiss A, Thomas G. A dosimetric planning study comparing intensity-modulated radiotherapy with four-field conformal pelvic radiotherapy for the definitive treatment of cervical carcinoma. Clin Oncol (R Coll Radiol).2012 May;24(4):e63-70.
132) Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity modulated whole pelvic radiation therapy. Int J Radiat Oncol Biol Phys. 2003 Aug 1;56(5):1354-60.
133) Pötter R, Haie-Meder C, Van Limbergen E, Barillot I, De Brabandere M, Dimopoulos J et al; GEC ESTRO Working Group. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol. 2006 Jan;78(1):67-77.

134) Pötter R, Dimopoulos J, Georg P, Lang S, Waldhäusl C, Wachter-Gerstner N et al. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. Radiother Oncol. 2007 May;83(2):148-55.
135) Pötter R, Haie-Meder C, Van Limbergen E, Barillot I, De Brabandere M, Dimopoulos J et al; GEC ESTRO Working Group. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol. 2006 Jan;78(1):67-77.
136) Van de Bunt L, Jurgenliemk-Schulz IM, de Kort GAP, Roesink JM, Tersteeg RJHA, van der Heide UA. Motion and deformation of the target volumes during IMRT for cervical cancer: what margins do we need? Radiother Oncol 2008;88(2):233e240
137) Taylor A, Powell MEB.(2008) An assessment of interfraction uterine and cervical motion: implications for radiotherapy target volume definition in gynaecological cancer. Radiother Oncol 2008;88; 250-257
138) https://www.rcr.ac.uk/clinical-oncology/audit-and-qi/audit-projects and https://www.rcr.ac.uk/system/files/audit_leads_report.pdf
139) Xu KM, Rajagopalan MS, Kim H, Beriwal S. Extended field intensity modulated radiation therapy for gynecologic cancers: Is the risk of duodenal toxicity high? Pract Radiat Oncol. 2015 Jul-Aug;5(4):e291-7.
140) Viswanathan AN, Kirisits C, Erickson BE, Pötter R. (Eds.). Gynecologic Radiation Therapy. Novel Approaches to Image-Guidance and Management. Springer-Verlag Berlin Heidelberg 2011.
141) Chemoradiotherapy for cervical cancer meta-analysis collaboration (CCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. Cochrane database of systemic reviews (online) (10 (ppCD008285), 2010
142) CCMAC 2008 Reducing uncertainties about the effect of chemoradiotherapy for cervix cancer: A systemic review and metanalysis of individual patient data from 18 randomized trials. Journal of Clinical Oncology vol 26 number 35 2008
143) The INTERLACE trial. http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-chemotherapy-before chemoradiation-for-cervical-cancer-interlace (retrieved 18.08.2017)
144) DEPICT: https://clinicaltrials.gov/ct2/show/NCT01793701 (retrieved 18.08.17)
145) The OUTBACK trial. https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1174 (retrieved 18.08.2017)
146) Taylor A, Rockall AG, Powell MEB. (2007) An atlas of the pelvic lymph node regions to aid radiotherapy target volume definition. Clin Oncol 2007;19:542e550.
147) Beadle BM, Jhingran A, Salehpour M, Sam M, Iyer R, Eifel PJ. Cervix regression and motion during the course of external beam chemoradiation for cervical cancer. Int J Radiat Oncol Biol Phys 009;73(1):235e241
148) Bilek K, Ebeling K, Leitsmann H, Seidel G. Radical pelvic surgery versus radical surgery plus radiotherapy for stage IB carcinoma of the cervix uteri: preliminary results of a

prospective randomised clinical study. Archiv fur Geschwulstforschung., 1982. 52(3): p. 223-29.
149) Rogers L, Siu SS, Luesley D, Bryant A, Dickinson HO. Radiotherapy and chemoradiation after surgery for early cervical cancer. The Cochrane database of systematic reviews. 2012. 5: p. CD007583.
150) Okazawa M, Mabuchi S, Isohashi F, Suzuki O, Yoshioka Y, Sasano T et al. Impact of the addition of concurrent chemotherapy to pelvic radiotherapy in surgically treated stage IB1-IIB cervical cancer patients with intermediate-risk or high-risk factors: a 13-year experience. Int J Gynecol Cancer, 2013. 23(3): p. 567-75.
151) Monk BJ, Wang J, Im S, Stock RJ, Peters WA, Liu PY et al. Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical-pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial. Gynecol Oncol, 2005. 96(3): p. 721-8.
152) Falcetta FS, Madeiros LR, Edelweiss MI, Pohlmann PR, Stein AT, Rossa DD. Adjuvant platinum-based chemotherapy for early stage cervical cancer. Cochrane Database Syst Rev, 2016. Nov 22(CD005342).
153) Small W Jr, Mell, LK, Anderson P, Creutzberg C, De Los Santos J, Gaffney D et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int J Radiat Oncol Biol Phys, 2008. 71(2): p. 428-34.
154) Klopp AH, Moughan J, Portelance L, Miller BE, Salehpour MR, Hildebrant E et al. Hematologic toxicity in RTOG 0418: a phase 2 study of postoperative IMRT for gynecologic cancer. Int J Radiat Oncol Biol Phys, 2013. 86(1): p. 83-90.
155) Lan ML, Yu, X, Xiao H, Zhou P, Hu N, Li J et al. Clinical outcomes and toxicity of postoperative intensity-modulated versus three-dimensional conformal radiation therapy in patients with cervical cancer. Asia Pac J Clin Oncol, 2016. 12(4): p. 430-436.
156) Folkert MR, Shih KK, Abu-Rustum NR, Jewell E, Kollmeier MA, Makker V et al. Postoperative pelvic intensity-modulated radiotherapy and concurrent chemotherapy in intermediate- and high-risk cervical cancer. Gynecol Oncol, 2013. 128(2): p. 288-93.
157) Jhawar S, Hathout L, Elshaikh MA, Beriwal S, Small W, Mahmoud O. Adjuvant Chemoradiation Therapy for Cervical Cancer and Effect of Timing and Duration on Treatment Outcome. Int J Radiat Oncol Biol Phys, 2017. 98(5): p. 1132-1141.
158) NCCN. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN.Guidelines®). Cervical cancer (version 1.2017). 2017 [cited 2017 September 3]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf.
159) Small W Jr, Beriwal S, Demanes DJ, Dusenbery KE, Eifel P, Erikson B et al. American Brachytherapy Society consensus guidelines for adjuvant vaginal cuff brachytherapy after hysterectomy. Brachytherapy, 2012. 11(1): p. 58-67.
160) Kim YJ, Lee KJ, Park KR, Kim J, Jung W, Lee R et al. Prognostic analysis of uterine cervical cancer treated with postoperative radiotherapy: importance of positive or close parametrial resection margin. Radiat Oncol J, 2015. 33(2): p. 109-16.

161) Davila Fajardo, R, van Os R, Buist MR, Uitterhoeve L, Westermann AM, Kenter GG et al. Post-operative radiotherapy in patients with early stage cervical cancer. Gynecologic oncology, 2014. 134(1): p. 52-9.
162) Huertas A, Oldrini S, Nesseler JP, Courrech F, Retif P, Charra-Brunaud C et al. FIGO stage IB1 cervical carcinoma: Place and principles of brachytherapy. Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique, 2017. 21(2): p. 155-163.
163) Sun W, Wang T, Shi F, Wang J, Hui B, Zhang Y et al. Randomized phase III trial of radiotherapy or chemoradiotherapy with topotecan and cisplatin in intermediate-risk cervical cancer patients after radical hysterectomy. BMC Cancer, 2015. 15: p. 353.
164) Mossa B, Framarino ML, Napolitano C, Marziani R, Imperato F, Marzetti L. Does adjuvant chemotherapy improve the prognosis of cervical carcinoma with lymph-node metastasis? A long-term follow-up. Eur J Gynaecol Oncol, 2003. 24(1): p. 33-40.
165) Takeshima N, Umayahara K, Fujiwara K, Hirai Y, Takizawa K Hasumi K. Treatment results of adjuvant chemotherapy after radical hysterectomy for intermediate- and high-risk stage IB-IIA cervical cancer. Gynecol Oncol, 2006. 103(2): p. 618-22.
166) Seki T, Tanabe H, Nagata C, Suzuki J, Suzuki K, Takano H et al. Adjuvant therapy after radical surgery for stage IB-IIB cervical adenocarcinoma with risk factors. Jpn J Clin Oncol, 2017. 47(1): p. 32-8.
167) Sato S, Shimada M, Ohta T, Kojimahara T, Tokunaga H, Takano T et al. Feasibility Study of Adjuvant Chemotherapy Using Taxane Plus Carboplatin for High-Risk Patients With Uterine Cervical Non-Squamous Cell Carcinoma After Radical Hysterectomy. Int J Gynecol Cancer, 2016. 26(3): p. 561-7.
168) Duenas-Gonzales A, Zarba JJ, Patel F, Alcedo JC, Beslija S, Casanova Lu, et al. Phase III, open-label, randomised study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIIB to IVA carcinoma of the cervix. J Clin Oncol 29: 1678-1685, 2011.
169) McCormack M, Ledermann, JA, Hall-Craggs MA, Symonds RP, Warwick V, Simmonds H et al. A phase II study of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer. Presented as an abstract at ASCO, Chicago, USA, May 2009. J Clin Oncol 27: 15s (no. 5586)
170) Scambia G, Benedetti Panici P, Foti E, Amoroso M, Salerno G et al. Squamous cell carcinoma antigen: prognostic significance and role in the monitoring of neoadjuvant chemotherapy response in cervical cancer. J Clin Oncol 12:2309-2316, 1994
171) Shrivastava S, Mahantshetty U, Engineer R, Chopra S, Hawaldar R, Hande V et al. Cisplatin Chemoradiotherapy vs Radiotherapy in FIGO Stage IIIB Squamous Cell Carcinoma of the Uterine Cervix: A Randomized Clinical Trial. Gynecologic Disease Management Group. JAMA Oncol. 2018 Apr 1;4(4):506-513. doi: 10.1001/jamaoncol.2017.5179
172) Kenter G. ASCO Results from neoadjuvant chemotherapy followed by surgery compared to chemoradiation for stage Ib2-IIb cervical cancer, EORTC 55994.Annual meeting 2019, J Clin Oncol 37, 2019, (abstr Suppl 5503)

173) Al-Halal H, Kezouh A, Abenhaim H. Incidence and obstetrical outcomes of cervical intraepithelial neoplasia and cervical cancer in pregnancy. Arch Gynecol Obstet 2013;287: 245-250.
174) Hunter MI, Tewari K, Mouk BJ. Cervical neoplasia in pregnancy. part 2: current treatment of invasive disease. Am J Obstet Gynecol 2008;2008199(1)10-18
175) Amant F, Brepoels L, Halaska M, Gziri M, Van Calsteren K. Gynaecological cancer complicating pregnancy: an overview. Best Pract Res Clin Obstet Gynaecol 2010;24(1):61-79.
176) British Society of Colposcopy and Cervical Pathology (2016) Document 20: 3rd edition
177) Dobbs SP, Asmussen T, Nunns D, Hollingsworth J, Brown LJ, Ireland D. Does histological incomplete excision of cervical intraepithelial neoplasia following large loop excision of transformation zone increase recurrence rates? A six-year cytological follow up. BJOG 2000;107(10)1298–1301.
178) Sood AK, Sorosky Jl. Invasive cervical cancer complicating pregnancy. How to manage the dilemma. Obstet Gynecol Clin North Am 1998;25(2):343-52.
179) Coleman CA. Evaluation and management of abnormal cervical cytology during pregnancy. Clint Obstet Gynecol 2013;56(1):51-4.
180) Robinson WR, Webb S, Tirpack J, Degefu S, O'Quinn AG. Management of cervical intraepithelial neoplasia during pregnancy with loop excision. Gynecol Oncol,1997;64(1):153– 155.
181) Kyrgiou M, Tsoumpou I, Vrekoussis T, Martin-Hirsch P, Arbyn M, Prendiville W et al. The up-to-date evidence on colposcopy practice and treatment of cervical intraepithelial neoplasia: the Cochrane colposcopy & cervical cytopathology collaborative group (C5 group) approach. Cancer Treat Rev. 2006;32(7):516-23.
182) Scottish Intercollegiate Guidelines Network (2008) Management of cervical cancer.
183) Nguyen C, Montz FJ, Bristow RE. Management of stage 1 cervical cancer in pregnancy. Obstet Gynecol Surv 2000;55(10):633-43.
184) Sadugor, M, Palmer J, Reinhard M. Carcinoma of the cervix concomitant with pregnancy. Am J Obstet Gynecol .1949;57:933-938.
185) Zemlickis D, Lishner M, Degendorfer P, Panzarella T, Sutcliffe S, Koren G. Maternal and foetal outcome after invasive cervical cancer in pregnancy. J Clin Oncol. 1991;43:1956-1961
186) Van Calsteren K, Vergote I, Amant F. Cervical neoplasia during pregnancy: diagnosis, management and prognosis. Best Pract Res Clin Obstet Gynaecol. 2005;19(4):611-30.
187) La Russa M, Jeyarajah AR. Invasive cervical cancer in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2016;33:44-57.
188) Han SN, Gziri M, Van Calsteren K, Amant F. Cervical cancer in pregnant women: treat, wait or interrupt? Assessment of current clinical guidelines, innovations and controversies. Ther Adv Med Oncol 2013; 5(4) 211-219.
189) Xia T, Gao Y, Wu B, Yang Y. Clinical analysis of twenty cases of cervical cancer associated with pregnancy. J Cancer Res Clin Oncol. 2015;141(9):1633-7.
190) Hricak H, Powell CB, Yu KK, Washington E, Subak LL, Stern JL et al. Invasive cervical carcinoma: role of MR imaging in pretreatment work-up-cost minimisation and diagnostic efficacy analysis. Radiology 1996; 198:403-409.

191) Nagayama M, Watanabe Y, Okumara A, Amoh Y, Nakashita S, Dodo Y. Fast MR imaging in obstetrics. Radiographics 2002;22:563-580.
192) Balleyguier, C, Fournet C, Ben Hassen W, Zareski E, Morice P, Haie-Meder C et al. Management of Cervical selected during pregnancy: role of magnetic resonance imaging. Clin Imaging 2013;37: 70-76.
193) Stabin M, Xu X, Emmons M, Segars W, Shi C, Fernald M. RADAR reference adult, paediatric, and pregnant female phantom series for internal and external dosimetry. J Nucl Med 2012;53:1807-1813.
194) Morice P, Uza, C, Gouy, S, Verschraegen C, Haie-Meder C. Gynaecological cancers in pregnancy. Obstet Gynecol Surv 2012;55:633-643.
195) Giammarile F, Fani Bozkurt M, Cibula D, Pahisa J, Oyen W, Paredes P et al. The EANM clinical and technical guidelines for lymphoscintigraphy and sentinel node localization in gynaecological caner. Eur J Nucl Med Mol Imaging 2014;41:1463-1477.
196) Lyman GH, Giuliano AE, Somerfield MR, Renson AB, Bodurka DC, Burstein HJ et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol 2005;23(20):7703-20.
197) Gentilini O, Cremonesi M, Trifiro G, Ferrari M, Baio SM, Caracciolo M et al. Safety of sentinel node biopsy in pregnant patients with breast cancer. Ann Oncol. 2004;15:1348–1351.
198) Filippakis G, Zografos G. Contraindications of sentinel lymph node biopsy: Are there any really? World J Surg Oncol. 2007 29;5:10.
199) Bentivegna E, Maulard A, Pautier P, Chargari C, Gouy S, Morice P. Fertility results and pregnancy outcomes after conservative treatment of cervical cancer: a systematic review of the literature. Fertil Steril 2016 ;106(5):1195-1211
200) Smith JR, Boyle DC, Corless DJ, Ungar L, Lawson AD, Del Priore G et al. Abdominal radical trachelectomy: a new surgical technique for the conservative management of cervical carcinoma. Br J Obstet Gynaecol 1997;104: 1196–200.
201) Palfalvi L, Ungar L, Boyle DC, Del Priore G, Smith JR. Announcement of healthy baby boy born following abdominal radical trachelectomy. Int J Gynecol Cancer 2003;13:250.
202) Ungar L, Palfalvi L, Hogg R, Siklos P, Boyle DC, Del Priore G et al. Abdominal radical trachelectomy: a fertility-preserving option for women with early cervical cancer. BJOG 2005;112:366–9.
203) Saso S, Ghaem-Maghami S, Chatterjee J, Naji O, Farthing A, Mason P et al. Abdominal radical trachelectomy in West London. BJOG 2012; 119:187–93.
204) Lintner B, Saso S, Tarnai L, Novak Z, Palfalvi L, Del Priore G et al. Use of abdominal radical trachelectomy to treat cervical cancer greater than 2 cm in diameter. Int J Gynecol Cancer 2013;23:1065–70.
205) Del Priore G, Ungar L, Boyle D, Smith R. Abdominal radical trachelectomy for fertility preservation in cervical cancer. Obstet Gynecol 2003;101(3 Suppl 2):S2–3.
206) Mathevet P, Laszlo de Kaszon E, Dargent D. Fertility preservation in early cervical cancer. Gynecol Obstet Fertil 2003; 31:706–12.
207) Speiser D, Mangler M, Kohler C, Hasenbein K, Hertel H, Chiantera V et al. Fertility outcome after radical vaginal trachelectomy: a prospective study of 212 patients. Int J Gynecol Cancer 2011;21:1635–9.

208) Kasuga Y, Nishio H, Miyakoshi K, Sato S, Sugiyama J, Matsumoto T et al. Pregnancy outcomes after abdominal radical trachelectomy for early-stage cervical cancer: a 13-year experience in a single tertiary-care center. Int J Gynecol Cancer 2016;26:163–8.
209) Karam A, Feldman N, Holschneider C. Neoadjuvant cisplatin and radical caesarean hysterectomy for cervical cancer in pregnancy. Nat Clin Pract Oncol 2007;4:375-380.
210) Moore KN, Herzog TJ, Lewin S, Guintoli, RL, Armstrong DK, Rocconi RP et al. A comparison of cisplatin/paclitaxel and carboplatin/paclitaxel in stage IVB, recurrent or persistent cervical cancer. Gynaecol Oncol 2007;105(2):299-303.
211) Fruscio, R, Villa A, Chiari S, Vergani P, Ceppi L, Dell/Orto F et al. Delivery delay with neoadjuvant chemotherapy for cervical cancer patients during pregnancy: a series of nine cases and literature review. Gynecol Oncol 2012;126:192-197.
212) Alouni S, Rida K, Mathevet P. Cervical cancer complicating pregnancy: implications of laparoscopic lymphadenectomy. Gynecol Oncol 2008;108:472-477.
213) Egan PC, Costanza ME, Dodion P, Egorin MJ, Bachur NR. Doxorubicin and cisplatin excretion into human milk. Cancer Treat Rep 1985;69:1387–9.
214) Leung AKC, Sauve RS. Breast is best for babies. J Natl Med Assoc 2005;97:1010–9.
215) Heron DE, Axtel A, Gerszten K, Amartegui A, Kelley J, Commerce J et al. Villoglandular adenocarcinoma of the cervix recurrent in an episiotomy scar: a case report in a 32-year-old female. Int J Gynecol Cancer 2005;15:366-371.
216) Alexander A, Harris RM, Grossman D, Bruggers CS, Leachman SA. Vulvar melanoma: diffuse malanosis and metastases to the placenta. J Am Acad Dermatol 2004;50(2):293-298.
217) Rutledge S, Carey MS, Prichard H, Allen HH, Kocha W, Kirk ME. Conservative surgery for recurrent or persistent carcinoma of the cervix following irradiation: is exenteration always necessary? Gynecol Oncol. 1994;52(3):353.
218) Maneo A, Landoni F, Cormio G, Colombo A, Mangioni C. Radical hysterectomy for recurrent or persistent cervical cancer following radiation therapy. Int J Gynecol Cancer. 1999;9(4):295.
219) Barney BM, Petersen IA, Dowdy SC, Bakkum-Gamez JN, Klein KA, Haddock MG. Intraoperative Electron Beam Radiotherapy (IOERT) in the management of locally advanced or recurrent cervical cancer. Radiat Oncol. 2013;8:80. Epub 2013 Apr 8.
220) Martínez-Monge R, Jurado M, Aristu JJ, Moreno M, Cambeiro M, Pérez-Ochoa A et al. Intraoperative electron beam radiotherapy during radical surgery for locally advanced and recurrent cervical cancer. Gynecol Oncol. 2001;82(3):538.
221) Brunschwig A. Complete excision of pelvic viscera for advanced carcinoma. Cancer 1948;1:177–83.
222) Schmidt AM, Imesch P, Fink D, Egger H. Indications and long-term clinical outcomes in 282 patients with pelvic exenteration for advanced or recurrent cervical cancer. Gynecologic Oncology 125 (2012) 604–609.
223) Höckel M, Dornhöfer N. Pelvic exenteration for gynaecological tumours: achievements and unanswered questions. Lancet Oncol. 2006;7(10):837.7.
224) Burger IA, Vargas HA, Donati OF, Andikyan V, Sala E, Gonen M et al. The value of 18F-FDG PET/CT in recurrent gynecologic malignancies prior to pelvic exenteration. Gynecol Oncol. 2013 Jun;129(3):586-592. doi: 10.1016/j.ygyno.2013.01.017. Epub 2013 Jan 29.

225) Meads C, Davenport C, Małysiak S, Kowalska M, Zapalska A, Guest P et al. Evaluating PET-CT in the detection and management of recurrent cervical cancer: systematic reviews of diagnostic accuracy and subjective elicitation. BJOG. 2014 Mar;121(4): 398-407. doi: 10.1111/1471-0528.12488. Epub 2013 Dec 3. Review.
226) Höckel M, Horn LC, Einenkel J. (Laterally) extended endopelvic resection: surgical treatment of locally advanced and recurrent cancer of the uterine cervix and vagina based on ontogenetic anatomy. Gynecol Oncol. 2012 Nov;127(2):297-302. doi: 10.1016/j.ygyno.2012.07.120. Epub 2012 Aug 1.
227) Höckel Michael. Laterally extended endopelvic resection (LEER)—Principles and practice Gynecologic Oncology 111 (2008) S13–S17
228) Berek JS, Howe C, Lagasse LD, Hacker NF. Pelvic exenteration for recurrent gynecologic malignancy: survival and morbidity analysis of the 45-year experience at UCLA. Gynecol Oncol. 2005;99(1):153.
229) Goldberg GL, Sukumvanich P, Einstein MH, Smith HO, Anderson PS, Fields AL. Total pelvic exenteration: the Albert Einstein College of Medicine/Montefiore Medical Center Experience (1987 to 2003). Gynecol Oncol. 2006;101(2):261.
230) Salom EM, Penalver MA. Pelvic exenteration and reconstruction. Cancer J. 2003;9(5):415
231) Fotopoulou C, Neumann U, Kraetschell R, Schefold JC, Weidemann H, Lichtenegger W et al. Long-term clinical outcome of pelvic exenteration in patients with advanced gynecological malignancies. J Surg Oncol. 2010 May 1;101(6):507-12. doi: 10.1002/jso.21518.
232) Naik R, Dostalek L, Bizzarri N, Kucukmetin A, Tinelli G, Scambia G et al. Laterally Extended Pelvic Resection for Gynaecological Malignancies: A Multicentric Experience with Out-of-the-Box Surgery. Ann Surg Oncol. 2019 Feb;26(2):523-530.
233) Bladou F, Houvenaeghel G, Delpéro JR, Guérinel G. Incidence and management of major urinary complications after pelvic exenteration for gynecological malignancies. J Surg Oncol 1995; 58:91.
234) Rezk YA, Hurley KE, Carter J. A prospective study of quality of life in patients undergoing pelvic exenteration: interim results. Gynecol Oncol 2013; 128:191.
235) Dessole M, Petrillo M, Lucidi A, Naldini A, Rossi M, De Iaco P et al. Quality of Life in Women After Pelvic Exenteration for Gynecological Malignancies: A Multicentric Study. Int J Gynecol Cancer. 2018 Feb;28(2):267-273. doi: 10.1097/IGC.0000000000000612.
236) Gosalbez R Jr, Woodard JR, Broecker BH, Warshaw B. Metabolic complications of the use of stomach for urinary reconstruction. J Urol. 1993;150(2 Pt 2):710.
237) Lee RK, Abol-Enein H, Artibani W, Bochner B, Dalbagni G, Daneshmand S et al. Urinary diversion after radical cystectomy for bladder cancer: options, patient selection, and outcomes. BJU Int. 2014 Jan. 113 (1):11-23.
238) Pavlov MJ, Ceranic MS, Nale DP, Latincic SM, Kecmanovic DM. Double-Barreled Wet Colostomy versus Ileal Conduit and Terminal Colostomy for Urinary and Fecal Diversion: A Single Institution Experience. Scand J Surg. 2014 Sep;103(3):189-194. Epub 2014 Feb 11.
239) Fotopoulou C, Neumann U, Klapp C, Lichtenegger W, Sehouli J. Long-term effects of neovaginal reconstruction with sigmoid loop technique on sexual function and self-image

in patients with gynecologic malignancies: results of a prospective study. Gynecol Oncol. 2008 Dec;111(3):400-6. doi: 10.1016/j.ygyno.2008.09.018. Epub 2008 Oct 22.

240) Lapitan MC, Buckley BS. Impact of palliative urinary diversion by percutaneous nephrostomy drainage and ureteral stenting among patients with advanced cervical cancer and obstructive uropathy: a prospective cohort. J Obstet Gynaecol Res. 2011 Aug;37(8):1061-70. doi: 10.1111/j.1447-0756.2010.01486.x. Epub 2011 Apr 12

241) Tran PT, Su Z, Hara W, Hussain A, Teng N, Kapp DS. Long-term survivors using intra-operative radiotherapy for recurrent gynaecological malignancies. Int J Radiat Oncol Biol Phys 2007;69:504-511

242) Mendez LC, Leung E, Cheung P, Barbera L. The role of stereotactic ablative radiotherapy in gynecological cancers: a systematic review. Clin Oncol 2017; 29:378-384

243) Krengli M, Pisani C, Deantonio L, Surico D, Volpe A, Surico N et al. Intraoperative radiotherapy in gynecological and genito-urinary malignancies. Radiation Oncology 2017;12-18

244) Seo Y, Kim MS, Yoo HJ, Jang WI, Rhu SY, Choi SC et al. Salvage stereotactic body radiotherapy for locally recurrent uterine cervix cancer at the pelvic sidewall: Feasibility and complication. Asia-Pacific J of Clin Oncol 2016;12:e280-288

245) Abusaris H, Hoogeman M, Nuttyens JJ. Re-irradiation: outcome, cumulative dose and toxicity in patients treated with stereotactic radiotherapy in the abdominal or pelvic region. Technol Cancer Res Treat 2012;11:591- 597.

246) Leath CA, Straughn JM Jr. Chemotherapy for advanced and recurrent cervical carcinoma: results from cooperative group trials. Gynecol Oncol. 2013 Apr;129(1):251-7. doi: 10.1016/j.ygyno.2012.12.035. Epub 2012 Dec 30. Review

247) Rosen VM, Guerra I, McCormack M, Nogueira-Rodrigues A, Sasse A, Munk VC et al. Systematic Review and Network Meta-Analysis of Bevacizumab Plus First-Line Topotecan-Paclitaxel or Cisplatin-Paclitaxel Versus Non-Bevacizumab-Containing Therapies in Persistent, Recurrent, or Metastatic Cervical Cancer. Int J Gynecol Cancer. 2017 Jul;27(6):1237-1246. doi: 10.1097/IGC.0000000000001000.

248) Tewari KS, Sill MW, Penson RT, Huang H, Ramondetta LM, Landrum LM et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). Lancet. 2017 Oct 7;390(10103):1654-1663. doi: 10.1016/S0140-6736(17)31607-0. Epub 2017 Jul 2

249) Penson RT, Huang HQ, Wenzel LB, Monk BJ, Stockman S, Long HJ et al. Bevacizumab for advanced cervical cancer: patient-reported outcomes of a randomised, phase 3 trial (NRG Oncology-Gynecologic Oncology Group protocol 240). Lancet Oncol. 2015 Mar;16(3):301-11. doi: 10.1016/S1470-2045(15)70004-5. Epub 2015 Jan 29. Erratum in: Lancet Oncol. 2016 Jan;17(1):e6.

250) Minion LE, Tewari KS. Cervical cancer - State of the science: From angiogenesis blockade to checkpoint inhibition. Gynecol Oncol. 2018 Mar;148(3):609-621. doi: 10.1016/j.ygyno.2018.01.009. Epub 2018 Feb 3. Review

251) Tewari KS, Monk BJ. New strategies in advanced cervical cancer: from angiogenesis blockade to immunotherapy. Clin Cancer Res. 2014 Nov 1;20(21):5349-58. doi: 10.1158/1078-0432.CCR-14-1099. Epub 2014 Aug 7. Review. PMID:

252) Monk BJ, Tewari KS. Evidence-based therapy for recurrent cervical cancer. J Clin Oncol. 2014 Sep 1;32(25):2687-90. doi: 10.1200/JCO.2014.56.8733. Epub 2014 Jul 28. No abstract available
253) Lorusso D, Petrelli F, Coinu A, Raspagliesi F, Barni S. A systematic review comparing cisplatin and carboplatin plus paclitaxel-based chemotherapy for recurrent or metastatic cervical cancer. Gynecol Oncol. 2014 Apr;133(1):117-23. doi: 10.1016/j.ygyno.2014.01.042. Epub 2014 Jan 31. Review.
254) Frumovitz M, Munsell MF, Burzawa JK, Byers LA, Ramalingam P, Brown J et al. Combination therapy with topotecan, paclitaxel, and bevacizumab improves progression-free survival in recurrent small cell neuroendocrine carcinoma of the cervix. Gynecol Oncol. 2017 Jan;144(1):46-50. doi: 10.1016/j.ygyno.2016.10.040. Epub 2016 Nov 4.
255) McLachlan J, Boussios S, Okines A, Glaessgen D, Bodlar S, Kalaitzaki R et al. The Impact of Systemic Therapy Beyond First-line Treatment for Advanced Cervical Cancer. Clin Oncol (R Coll Radiol). 2017 Mar;29(3):153-160. doi: 10.1016/j.clon.2016.10.002. Epub 2016 Nov 9.
256) Symonds RP, Gourley C, Davidson S, Carty K, McCartney E, Rai D et al. Cediranib combined with carboplatin and paclitaxel in patients with metastatic or recurrent cervical cancer (CIRCCa): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Oncol. 2015 Oct 13. pii: S1470-2045(15)00220-X. doi: 10.1016/S1470-2045(15)00220-X. [Epub ahead of print]
257) Lanceley A, Fiander A, McCormack M, Bryant A. Follow-up protocols for women with cervical cancer after primary treatment. Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD008767. DOI: 10.1002/14651858.CD008767.pub2.
258) Elit L, Fyles AW, Devries MC, Oliver TK, Fung-KeeFung M. Follow-up for women after treatment for cervical cancer: a systematic review. Gynecologic Oncology 2009;114: 528–35.
259) Zola P, Macchi C, Cibula D, Colombo N, Kimmig R, Maggino T et al. Follow-up in Gynecological Malignancies: A State of Art. Int J Gynecol Cancer. 2015 Sep;25(7):1151-64. doi: 10.1097/IGC.0000000000000498. Review
260) Rao YJ, Grigsby PW. The Role of PET Imaging in Gynecologic Radiation Oncology. PET Clin. 2018 Apr;13(2):225-237. doi: 10.1016/j.cpet.2017.11.007. Review
261) Schwarz JK, Siegel BA, Dehdashti F, Grigsby PW. Metabolic response on post-therapy FDG-PET predicts patterns of failure after radiotherapy for cervical cancer. Int J Radiat Oncol Biol Phys. 2012 May 1;83(1):185-90. doi: 10.1016/j.ijrobp.2011.05.053. Epub 2011 Oct 17
262) http://www.jostrust.org.uk/longtermconsequences
263) Hadwin R, Petts G, Olaitan A. 2010. Treatment-related morbidity in gynaecological cancers. The Obstetrician & Gynaecologist, 12(2), pp. 79-86.
264) Hareyama H, Hada K, Goto K, Watanabe S, Hakoyama M, Oku K et al. 2015. Prevalence, classification, and risk factors for postoperative lower extremity lymphedema in women with gynecologic malignancies: a retrospective study.. International journal of gynecological cancer, 25(4), pp. 751-757.

265) Hayes S, Janda M, Ward LC, Reul-Hirche H, Steele ML, Carter J et al. 2017. Lymphedema following gynecological cancer: Results from a prospective, longitudinal cohort study on prevalence, incidence and risk factors.. Gynecologic Oncology., 146(3), pp. 623-629.
266) Holmes L, Miles T, White I. 2015. Female sexual health after a cancer diagnosis.. Cancer Nursing Practice, 14(7), pp. 16-22.
267) Kim J, Choi JH, Ki EY, Lee SJ, Yoon JH, Lee KH et al. 2012. Incidence and risk factors of lower-extremity lymphedema after radical surgery with or without adjuvant radiotherapy in patients with FIGO stage I to stage IIA cervical cancer.. International Journal of Gynecological Cancer, 22(4), pp. 606-691.
268) MacmillanCancerSupport, 2014. Part 1: Guidelines on Late Effects of Gynaecological Cancer: Pelvic Radiotherapy, London: Macmillan Cancer Support.
269) Miles T. 2012. International guidelines on vaginal dilation after pelvic radiotherapy., Brook Hill, Woodstock, Oxon: Owen Mumford Ltd.
270) O'Donnell R, Clement K, Edmondson R. 2016. Hormone replacement treatment for a gynaecological malignancy. Current Opinion Obstetrics Gynaecology, 28(1), pp. 32-41.
271) Singh P, Oehler M. 2010. Hormone replacement after gynaecological cancer. Maturitas, Volume 65, pp. 190-197.
272) Patibandla JR, Fehniger JE, Levine DA, Jelinic P. Small cell cancers of the female genital tract: Molecular and clinical aspects. Gynecol Oncol. 2018
273). Kurman RJCM, Herrington CS, Young RH. WHO classification of tumours of female reproductive organs. Bosman FTJE, Lakhani SR,Ohgaki H,editors. Lyon:International Agency for Research on Cancer; 2014. 307 p. 103.
274) Howitt BE, Kelly P, McCluggage WG. Pathology of Neuroendocrine Tumours of the Female Genital Tract. Curr Oncol Rep. 2017;19:59.
275) Lloyd RV, Osamura RY, Klöppel G, Rosai J. WHO Classification of Tumours of Endocrine Organs. 4th ed. Lyon: International Agency for Research on Cancer; 2017. 355 p.
276) Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol. 2018 Aug 23. doi: 10.1038/s41379-018-0110-y. [Epub ahead of print]
277) Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME et al; UK and Ireland Neuroendocrine Tumour Society. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut. 2012 Jan;61(1):6-32.
278) Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R et al; all other Vienna Consensus Conference participants. Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology. 2016 Jan 5 Neuroendocrinology. 2016;103(2):172-85. doi: 10.1159/000443167. Epub 2016 Jan 5 [Epub ahead of print]
279) Reed NS, Gomez-Garcia E, Gallardo-Rincon D, Barrette B, Baumann K, Friedlander M et al. Gynecologic Cancer InterGroup (GCIG) consensus review for carcinoid tumours of the

ovary. Int J Gynecol Cancer. 2014 Nov;24(9 Suppl 3):S35-41. doi: 10.1097/IGC.0000000000000265

280) Satoh T, Takei Y, Treilleux I, Devouassoux-Shisheboran M, Ledermann J, Viswanathan AN et al. Gynecologic Cancer InterGroup (GCIG) consensus review for small cell carcinoma of the cervix. Int J Gynecol Cancer. 2014 Nov;24(9 Suppl 3):S102-8. doi: 10.1097/IGC.0000000000000262

281) Reed NS. Neuroendocrine tumours of the gynecological tract. Curr Opin Oncol. 2016 Sep;28(5):412-8. doi: 10.1097/CCO.0000000000000321 PMID: 27467970

282) Kojima A, Mikami Y, Sudo T, Yamaguchi S, Kusanagi Y, Ito M et al. Gastric morphology and immunophenotype predict poor outcome in mucinous adenocarcinoma of the uterine cervix. Am J Surg pathol 2007; 31 (5): 664-672

283) Milami Y, McCluggage WG. Endocervical glandular lesions exhibiting gastric differentiation: an emerging spectrum of benign, premalignant and malignant lesions. Adv Anat Pathol 2013 Jul;20 (4):227-237

284) England PH. Trachelectomies for treatment of cervical cancer, England - National Cancer Registration and Analysis Service Data Briefing. PHE publications gateway number: 2016384. 2017:1 - 2.

285) Diaz ES, Aoyama C, Baquing MA, Beavis A, Silva E, Holschneider C et al. Predictors of residual carcinoma or carcinoma-in-situ at hysterectomy following cervical conization with positive margins. Gynecologic oncology. 2014 Jan;132(1):76-80. PubMed PMID: 24262876.

286) Yoneda JY, Braganca JF, Sarian LO, Borba PP, Conceicao JC, Zeferino LC. Surgical treatment of microinvasive cervical cancer: analysis of pathologic features with implications on radicality. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2015 May;25(4):694-8. PubMed PMID: 25742569.

287) Oncology NCPGi. Cervical Cancer. NCCN. 2016;Version 1.2017.

288) ESGO. Algorithms for the management of Cervical Cancer. ESGO. 2010.

289) Sevin BU, Nadji M, Averette HE, Hilsenbeck S, Smith D, Lampe B. Microinvasive carcinoma of the cervix. Cancer. 1992 Oct 15;70(8):2121-8. PubMed PMID: 1394041.

290) Ueki M, Okamoto Y, Misaki O, Seiki Y, Kitsuki K, Ueda M, et al. Conservative therapy for microinvasive carcinoma of the uterine cervix. Gynecologic oncology. 1994 Apr;53(1):109-13. PubMed PMID: 8175008.

291) Webb JC, Key CR, Qualls CR, Smith HO. Population-based study of microinvasive adenocarcinoma of the uterine cervix. Obstetrics and gynecology. 2001 May;97(5 Pt 1):701-6. PubMed PMID: 11339919. Epub 2001/05/08. eng.

292) Zhou J, Chen Y, Zhang P, Lou H. Ovarian preservation in adenocarcinoma of the uterine cervix. Journal of ovarian research. 2017 Jul 24;10(1):48. PubMed PMID: 28738842. Pubmed Central PMCID: PMC5525268. Epub 2017/07/26. eng.

293) Kinney WK, Hodge DO, Egorshin EV, Ballard DJ, Podratz KC. Identification of a low-risk subset of patients with stage IB invasive squamous cancer of the cervix possibly suited to less radical surgical treatment. Gynecologic oncology. 1995 Apr;57(1):3-6. PubMed PMID: 7705699. Epub 1995/04/01. eng.

294) Covens A, Rosen B, Murphy J, Laframboise S, DePetrillo AD, Lickrish G, et al. How important is removal of the parametrium at surgery for carcinoma of the cervix? Gynecologic oncology. 2002 Jan;84(1):145-9. PubMed PMID: 11748991. Epub 2001/12/26. eng.
295) Wright JD, Grigsby PW, Brooks R, Powell MA, Gibb RK, Gao F et al. Utility of parametrectomy for early stage cervical cancer treated with radical hysterectomy. Cancer. 2007 Sep 15;110(6):1281-6. PubMed PMID: 17654664. Epub 2007/07/27. eng.
296) Frumovitz M, Sun CC, Schmeler KM, Deavers MT, Dos Reis R, Levenback CF et al. Parametrial involvement in radical hysterectomy specimens for women with early-stage cervical cancer. Obstetrics and gynecology. 2009 Jul;114(1):93-9. PubMed PMID: 19546764. Epub 2009/06/24. eng.
297) Bentivegna E, Gouy S, Maulard A, Chargari C, Leary A, Morice P. Oncological outcomes after fertility-sparing surgery for cervical cancer: a systematic review. The Lancet Oncology. 2016 Jun;17(6):e240-e53. PubMed PMID: 27299280. Epub 2016/06/15. eng.
298) Zhang Q, Li W, Kanis MJ, Qi G, Li M, Yang X et al. Oncologic and obstetrical outcomes with fertility-sparing treatment of cervical cancer: a systematic review and meta-analysis. Oncotarget. 2017 Jul 11;8(28):46580-92. PubMed PMID: 28418849. Pubmed Central PMCID:
299) Kim M, Ishioka S, Endo T, Baba T, Akashi Y, Morishita M et al. Importance of uterine cervical cerclage to maintain a successful pregnancy for patients who undergo vaginal radical trachelectomy. International journal of clinical oncology. 2014 Oct;19(5):906-11. PubMed PMID: 24170246.
300) Lanowska M, Mangler M, Spek A, Grittner U, Hasenbein K, Chiantera V et al. Radical vaginal trachelectomy (RVT) combined with laparoscopic lymphadenectomy: prospective study of 225 patients with early-stage cervical cancer. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2011 Nov;21(8):1458-64. PubMed PMID: 21701392.
301) Mangler M, Lanowska M, Kohler C, Vercellino F, Schneider A, Speiser D. Pattern of cancer recurrence in 320 patients after radical vaginal trachelectomy. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2014 Jan;24(1):130-4. PubMed PMID: 24362717.
302) Dargent D, Martin X, Sacchetoni A, Mathevet P. Laparoscopic vaginal radical trachelectomy: a treatment to preserve the fertility of cervical carcinoma patients. Cancer. 2000 Apr 15;88(8):1877-82. PubMed PMID: 10760765. Epub 2000/04/13. eng.
303) Persson J, Imboden S, Reynisson P, Andersson B, Borgfeldt C, Bossmar T. Reproducibility and accuracy of robot-assisted laparoscopic fertility sparing radical trachelectomy. Gynecologic oncology. 2012 Dec;127(3):484-8. PubMed PMID: 22935472. Epub 2012/09/01. eng.
304) Schlaerth JB, Spirtos NM, Schlaerth AC. Radical trachelectomy and pelvic lymphadenectomy with uterine preservation in the treatment of cervical cancer. American journal of obstetrics and gynecology. 2003 Jan;188(1):29-34. PubMed PMID: 12548192. Epub 2003/01/28. eng.
305) Shepherd JH, Spencer C, Herod J, Ind TE. Radical vaginal trachelectomy as a fertility-sparing procedure in women with early-stage cervical cancer-cumulative pregnancy rate

in a series of 123 women. BJOG : an international journal of obstetrics and gynaecology. 2006 Jun;113(6):719-24. PubMed PMID: 16709216. Epub 2006/05/20. eng.

306) Uzan C, Gouy S, Desroque D, Pomel C, Duvillard P, Balleyguier C et al. Analysis of a continuous series of 34 young patients with early-stage cervical cancer selected for a vaginal radical trachelectomy: should "staging" conization be systematically performed before this procedure? International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2013 Feb;23(2):331-6. PubMed PMID: 23358180. Epub 2013/01/30. eng.

307) Yoon A, Choi CH, Lee YY, Kim TJ, Lee JW, Kim BG et al. Perioperative Outcomes of Radical Trachelectomy in Early-Stage Cervical Cancer: Vaginal Versus Laparoscopic Approaches. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2015 Jul;25(6):1051-7. PubMed PMID: 25675039. Epub 2015/02/13. eng.

308) Abu-Rustum NR, Neubauer N, Sonoda Y, Park KJ, Gemignani M, Alektiar KM et al. Surgical and pathologic outcomes of fertility-sparing radical abdominal trachelectomy for FIGO stage IB1 cervical cancer. Gynecologic oncology. 2008 Nov;111(2):261-4. PubMed PMID: 18708244. Pubmed Central PMCID: PMC4994885. Epub 2008/08/19. eng.

309) Pareja FR, Ramirez PT, Borrero FM, Angel CG. Abdominal radical trachelectomy for invasive cervical cancer: a case series and literature review. Gynecologic oncology. 2008 Dec;111(3):555-60. PubMed PMID: 18829092. Epub 2008/10/03. eng.

310) Tokunaga H, Watanabe Y, Niikura H, Nagase S, Toyoshima M, Shiro R et al. Erratum to: Outcomes of abdominal radical trachelectomy: results of a multicenter prospective cohort study in a Tohoku Gynecologic Cancer Unit. International journal of clinical oncology. 2015 Aug;20(4):781. PubMed PMID: 25471660. Epub 2014/12/05. eng.

311) van Gent MD, van den Haak LW, Gaarenstroom KN, Peters AA, van Poelgeest MI, Trimbos JB et al. Nerve-sparing radical abdominal trachelectomy versus nerve-sparing radical hysterectomy in early-stage (FIGO IA2-IB) cervical cancer: a comparative study on feasibility and outcome. International journal of gynecological cancer . 2014 May;24(4):735-43. PubMed PMID: 24651626. Epub 2014/03/22. eng.

312) Vieira MA, Rendon GJ, Munsell M, Echeverri L, Frumovitz M, Schmeler KM et al. Radical trachelectomy in early-stage cervical cancer: A comparison of laparotomy and minimally invasive surgery. Gynecologic oncology. 2015 Sep;138(3):585-9. PubMed PMID: 26095894. Epub 2015/06/23. eng.

313) Gubbala K, Laios A, Gallos I, Pathiraja P, Haldar K, Ind T. Outcomes of ovarian transposition in gynaecological cancers; a systematic review and meta-analysis. Journal of ovarian research. 2014;7:69. PubMed PMID: 24995040. Pubmed Central PMCID:

314) Hwang JH, Yoo HJ, Park SH, Lim MC, Seo SS, Kang S et al. Association between the location of transposed ovary and ovarian function in patients with uterine cervical cancer treated with (postoperative or primary) pelvic radiotherapy. Fertility and sterility. 2012 Jun;97(6):1387-93 e1-2. PubMed PMID: 22464082. Epub 2012/04/03. eng.

315) Morice P, Juncker L, Rey A, El-Hassan J, Haie-Meder C, Castaigne D. Ovarian transposition for patients with cervical carcinoma treated by radiosurgical combination. Fertility and sterility. 2000 Oct;74(4):743-8. PubMed PMID: 11020517. Epub 2000/10/06. eng.

316) Pahisa J, Martinez-Roman S, Martinez-Zamora MA, Torne A, Caparros X, Sanjuan A et al. Laparoscopic ovarian transposition in patients with early cervical cancer. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2008 May-Jun;18(3):584-9. PubMed PMID: 18476952. Epub 2008/05/15. eng.
317) Lanowska M, Mangler M, Speiser D, Bockholdt C, Schneider A, Kohler C et al. Radical vaginal trachelectomy after laparoscopic staging and neoadjuvant chemotherapy in women with early-stage cervical cancer over 2 cm: oncologic, fertility, and neonatal outcome in a series of 20 patients. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2014 Mar;24(3):586-93. PubMed PMID: 24469326. Epub 2014/01/29.
318) Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R et al. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. N Engl J Med. 2018 Nov 15;379(20):1895-1904. doi: 10.1056/NEJMoa1806395. Epub 2018 Oct 31.
319) Melamed A, Margul DJ, Chen L, Keating NL, Del Carmen MG, Yang J et al. Survival after Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer. N Engl J Med. 2018 Nov 15;379(20):1905-1914. doi: 10.1056/NEJMoa1804923. Epub 2018 Oct 31.
320) Chiva L, Zanagnolo V, Kucukmetin A et al SUCCOR study. An international European cohort observational study comparing minimally invasive surgery versus open abdominal radical hysterectomy in patients with stage IB1 (FIGO 2009, <4 cm) cervical cancer operated in 2013–2014 International Journal of Gynecologic Cancer 2019;29:A1-A2.

Appendices

Box 1 FIGO staging of carcinoma of the cervix uteri (2018).

Stage I:

The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded)

- **IA** Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm[a]
  - **IA1** Measured stromal invasion <3 mm in depth
  - **IA2** Measured stromal invasion ≥3 mm and <5 mm in depth
- **IB** Invasive carcinoma with measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to the cervix uteri[b]
  - **IB1** Invasive carcinoma ≥5 mm depth of stromal invasion and <2 cm in greatest dimension
  - **IB2** Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
  - **IB3** Invasive carcinoma ≥4 cm in greatest dimension

Stage II:

The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall

- **IIA** Involvement limited to the upper two-thirds of the vagina without parametrial involvement
  - **IIA1** Invasive carcinoma <4 cm in greatest dimension
  - **IIA2** Invasive carcinoma ≥4 cm in greatest dimension
- **IIB** With parametrial involvement but not up to the pelvic wall

Stage III:

The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes[c]

- **IIIA** Carcinoma involves the 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 known to be due to another cause)
- **IIIC** Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[c]
  - **IIIC1** Pelvic lymph node metastasis only
  - **IIIC2** Paraaortic lymph 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 edema, 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

[a]Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumor size and extent, in all stages.

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

[c]Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be stage IIIC1r and, if confirmed by pathological findings, it would be Stage IIIc1p. The type of imaging modality or pathology technique used should always be documented. When in doubt, the lower staging should be assigned.

Revised FIGO staging for carcinoma of the cervix uteri. Neerja Bhatla, Jonathan S. Berek, Mauricio Cuello Fredes, Lynette A. Denny, Seija Grenman, Kanishka Karunaratne, Sean T. Kehoe , Ikuo Konishi, Alexander B. Olawaiye, Jaime Prat. **https://doi.org/10.1002/ijgo.12749**

Stage	Description
0	Tumor confined to the surface layer (the cell lining) of the cervix; also called carcinoma in situ
I	Extension deeper into the cervix with no spread beyond (extension to the corpus is disregarded)
IA	Invasive carcinoma; may only be diagnosed at microscopy
IA1	Stromal invasion 3.0 mm deep and extension 7.0 mm
IA2	Stromal invasion >3.0 mm and 5.0 mm with extension ≤7.0 mm
IB	Clinically visible lesions limited to the cervix uteri or preclinical cancers higher than stage IA
IB1	Clinically visible lesion 4.0 cm in greatest dimension
IB2	Clinically visible lesion >4.0 cm in greatest dimension
II	Cervical carcinoma extends beyond the uterus but not to the pelvic wall or the lower one-third of the vagina
IIA	No parametrial invasion
IIA1	Clinically visible lesion 4.0 cm in greatest dimension
IIA2	Clinically visible lesion >4.0 cm in greatest dimension
IIB	With obvious parametrial invasion
III	Extension to the pelvic wall, involvement of lower one-third of the vagina, or hydronephrosis or nonfunctioning kidney
IIIA	Involvement of lower one-third of the vagina with no extension to the pelvic wall
IIIB	Extension to the pelvic wall, hydronephrosis, or nonfunctioning kidney
IV	Extension beyond the true pelvis or involvement of the bladder or rectal mucosa (biopsy proved); bullous edema does not convey stage IV disease
IVA	Spread to adjacent organs
IVB	Spread to distant organs

FIGO COMMITTEE ON GYNECOLOGIC ONCOLOGY. Previous FIGO staging for carcinoma of the vulva, cervix, and endometrium. Pecorel li S. International Journal of Gynecology and Obstetrics 105 (2009) 103–104