Final PMB definition guideline for cervical cancer

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DISCLAIMER

The cervical cancer benefit definition has been developed for the majority of standard patients. The benefit definition is subject to the provisions of Regulations 15H and 15I. The benefit definition does not describe specific in-hospital management such as theatre, anaesthetists, anaesthetist drugs and nursing care. However, these interventions form part of care and are prescribed minimum benefits.

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ABBREVIATIONS

AC	Adenocarcinoma
BSO	Bilateral salpingo-opherectomy
CIN	Cervical intraepithelial neoplasia
CMS	Council for Medical Schemes
CT	Computed tomographic
DTPs	Diagnosis Treatment Pairs
EBRT	External beam radiation therapy
ECC	Endocervical curettage
FBC	Full blood count
FIGO	Federation of Gynecology and Obstetrics
HSIL	High squamous intraepithelial lesions
ICD	International Classification of Diseases
IMRT	Intensity-modulated radiation therapy
IV	Intravenous therapy
LLETZ	Large loop excision of the transformation zone
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PMB	Prescribed minimum benefit
RT	Radiation therapy
SCC	Squamous cell carcinoma
SDI	Socio-demographic index

DEFINITION OF TERMS

Terminology	Description
Conisation	Conisation of the cervix or cone biopsy may be done for various reasons - excisional procedures are warranted for diagnostic purposes and treatment. A diagnostic excisional procedure is warranted if there is a lesion that is suspicious for invasive cancer or an adenocarcinoma in situ of the cervix.
Simple hysterectomy	Simple (total) hysterectomy is the removal of the uterus (both the body of the uterus and the cervix) but not the structures next to the uterus (parametria and uterosacral ligaments) (American Cancer Society, 2016).
Radical hysterectomy	Radical hysterectomy with pelvic lymphadenectomy has evolved into the standard therapy for non-bulky disease. Radical hysterectomy refers to removal of the uterus along with the tissues next to the uterus (the parametria and the uterosacral ligaments) and the upper part (about 1 inch) of the vagina next to the cervix. The ovaries and fallopian tubes are not removed unless there is some other medical reason to do so (Roque, Wysham & Soper, 2014).
Trachelectomy	Trachelectomy is one of the options for small stage 1 cancers. The operation involves the removal of most of the cervix and the upper part of the vagina. The uterus is left in place (UK Cancer Research, 2017).
Pelvic exenteration	Pelvic exenteration involves en bloc resection of all pelvic structures, including the uterus, cervix, vagina, bladder, and rectum. It is usually performed for centrally recurrent gynaecologic cancers, but mostly for recurrent cervical cancers that have previously been treated with surgery and radiation or radiation alone (Ferenschild, Vermaas, Verhoef, Ansink, Kirkels, Eggermont & de Wilt, 2009).
Bilateral salpingo-oopherectomy (BSO)	Bilateral salpingo-oopherectomy (BSO) may be an option to reduce the risk of ovarian and breast cancer particularly in women with BRCA gene mutations, but side effects should be clearly explained to patients because it may trigger surgical menopause and therefore long-term side effects (Kovacs, 2014).
FIGO Staging	FIGO staging is used to assign the stage of the cervical cancer by evaluating the tumour and whether the cancer has spread to lymph nodes and other

	parts of the body. FIGO staging generally runs from Stage I to IV. In FIGO Stage I the cervical cancer has spread from the cervix lining into the deeper tissue but is still just found in the uterus. In Stage IV, the cancer has spread to other parts of the body.
External Beam Radiation Therapy (EBRT)	External beam radiation therapy (EBRT) is a non-invasive method of delivering radiation to a tumour and is the most common type of radiation therapy used for cancer treatment. It refers to the delivery of tightly targeted radiation beams from outside the body.
Brachytherapy	Brachytherapy, also known as internal radiation therapy, involves placement of a radioactive material directly inside or next to the tumour. Brachytherapy involves use of a higher total dose of radiation to treat a smaller area and in a shorter time than is possible with external beam radiation treatment.
Large loop excision of the transformation zone (LLETZ)	The LEETZ procedure (Loop) uses a small wire with an electrical current running through it to remove the affected layer of cancerous tissue and seal the wound at the same time. It is one of the most commonly utilised procedures to treat high grade cervical dysplasia on colposcopic examination.

1. INTRODUCTION

1.1. The legislation governing the provision of the Prescribed Minimum Benefits (PMBs) is contained in the regulations enacted under the Medical Schemes Act, No. 31 of 1998 (the Act). With regard to some of the Diagnosis Treatment Pairs (DTPs), medical scheme beneficiaries find it difficult to be fully aware of their entitlements in advance. In addition, medical schemes interpret these benefits differently, resulting in a lack of uniformity of benefit entitlements.

1.2. The benefit definition project is undertaken by the CMS with the aim of defining the PMB package, as well as to guide the interpretation of the PMB provisions by relevant stakeholders.

2. SCOPE AND PURPOSE

2.1. This is a recommendation for the diagnosis, treatment and care of individuals with cervical cancer in any clinically appropriate setting as outlined in the Act.

2.2. The purpose is to provide detailed clarification in respect of benefit and entitlements to members and beneficiaries of medical schemes.

2.3. A separate guideline will be published with detailed member entitlements for cervical cancer screening and non-invasive cervical cancer.

Table 1: Possible ICD10 codes for identifying cervical cancer

ICD 10 code	WHO description
C53.0	Malignant neoplasm, endocervix
C53.1	Malignant neoplasm, exocervix
C53.8	Malignant neoplasm, overlapping lesion of cervix uteri
C53.9	Malignant neoplasm, cervix uteri, unspecified

2.4. The CMS acknowledges that some patients will not qualify for PMB entitlements under the definition of treatable cancers as outlined in explanatory note 3, annexure A of the Act. In these instances, when the treatment intent is no longer curative, DTP 260S, may be applied depending on the clinical case.

Table 2: Applicable PMB code for a non-curative setting in cervical cancer

PMB Code	PMB Description		ICD10 Code	ICD10 Description
260S	# Imminent death regardless of diagnosis	# Comfort care; pain relief; hydration	Z51.5	Palliative care

3. EPIDEMIOLOGY AND BURDEN OF DISEASE

3.1. Cervical cancer is one of the leading causes of morbidity and mortality worldwide, and the incidence of cervical cancer is expected to increase by approximately 70% over the next two decades (Reynoso-Noverón et al, 2017; WHO 2017).

3.2. With an estimated 570,000 cases and 311,365 deaths in 2018 globally, cervical cancer ranks as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women. (GLOBOCAN).

3.3. Marked inequalities exist in cervical cancer incidence and mortality and are associated with disparities in socio-economic status. This is evidenced by 86% of all deaths (Aswathy, Reshma and Avani, 2015; Arbyn et al, 2011) due to cervical cancer being in developing, low- and middle-income countries (Yeole, Sunny, Swaminathan, Sankaranarayanan & Parkin 2001). Most women in developing countries present with advanced disease, often untreatable or suitable only for palliation (Denny and Anorlu, 2012).

3.4. In South Africa, it is estimated that 5 735 new cases of cervical cancer were diagnosed in 2014 (Nicd.ac.za, 2019) placing cervical cancer as the 2nd leading cause of female cancer in South Africa and the most common female cancer in women aged 15 to 44 years (Bruni et al, 2018).

4. PATHOLOGY

4.1. The World Health Organization (WHO) recognises three types of cervical cancer, namely, squamous cell carcinoma (SCC), adenocarcinoma (AC) and other epithelial tumours which includes adenosquamous carcinoma, neuroendocrine tumours and undifferentiated carcinoma (Marth et al, 2017).

4.2. Squamous cell carcinomas constitute 80% to 85% of all cases of cervical cancer with adenocarcinoma (AC), accounting for approximately 15 – 20 % of the cases (Wang, 2004). Most cervical cancers are recognised to arise in the squamocolumnar junction. Cervical carcinoma is, however, preceded by a spectrum of microscopic events ranging from acellular atypia to various grades of cervical intraepithelial neoplasia (CIN), denoting cellular atypia confined to the epithelium. The Bethesda System has replaced the 3 levels of CIN with the two-tiered system recognising low squamous intraepithelial lesions (LSIL) representing dysplastic lesions confined to the lower one third of the squamous epithelium and high squamous intraepithelial lesions (HSIL) with dysplastic changes beyond. The category of LSIL includes flat condyloma and CIN I, while HSIL includes CIN II and CIN III and carcinoma in *situ* of the older system.

4.3. The role of human papillomaviruses (HPVs) in the aetiology of invasive cervical carcinoma has been well established. Persistent HPV infection is the most important factor in the development of cervical cancer (Kjaer, Frederiksen, Munk & Iftner 2010; Rodriguez, 2010). Countries with a high incidence of cervical cancer, have a chronic HPV prevalence of approximately 10% to 20% (Parkin, Bray, Ferlay & Pisani, 2005).

4.4. HPV16 is reported to be the most prevalent genotype in both squamous cell carcinoma (59.3%) and adenocarcinoma (36.3%) across the world and HPV18, the second most common genotype, has been found in a higher proportion of adenocarcinoma (Li, Franceschi, Howell-Jones, Snijders & Clifford, 2010; Guan, Clifford & Franceschi, 2012). A history of smoking, parity, oral contraceptive use, early age of onset of coitus, larger number of sexual partners, history of sexually transmitted disease and chronic immunosuppression are all other epidemiological risk factors associated with cervical cancer (Dugue, 2013). HPV high risk type-16/18 are responsible for 64.2% of invasive cervical cancer and about 3.2% of women in South Africa are estimated to harbour HPV type-16/18 at any given time. (Bruni et al, 2018).

4.5. Although the role of HIV infection in the pathogenesis of cervical cancer is not fully understood, it is acknowledged that cervical cancer is more common in HIV-infected women, and this increased prevalence has remained essentially unchanged with the use of highly active antiretroviral therapy (National Cancer Institute, 2017).

5. SCREENING

Screening for cervical cancer is PMB level of care under DTP Code 960M. However, detailed member entitlements relating to screening intervals, screening tools, HPV screening vs cervical screening etc. are not within the scope of this document and will be addressed in a separate guideline for the afore-mentioned code.

6. DIAGNOSIS

6.1. Consultations

Table 3: Recommended consultations for the diagnosis, staging and risk assessment of cervical cancer

Treating provider	Number of consultations
GP or physician	1
Specialist (Gynaecologist / Gynaecology oncologist / Oncologist/ Surgeon)	4

6.2. Histopathology

6.2.1. To improve sensitivity of colposcopy, multiple cervical biopsies may be performed (Zuchna, Hager, Tringler, Georgoulopoulos, Ciresa-Koenig, Volgger, Widschwendter & Staudach, 2010).

6.2.2. It is important to acknowledge that immunohistochemistry is used as an adjunct to routine morphological examination and no marker is totally specific or sensitive for a given lesion (McCluggage, 2007).

6.2.3. p16 immunostain is used as an adjunct test in the diagnosis of lower genital tract squamous intraepithelial lesions and should always be interpreted in conjunction with the morphologic features of the H&E-stained lesions cervical intraepithelial neoplasia 3 (CIN3) cases have been reported at 8 – 28% (Agoff, Lin, Morihara, Mao, Kiviat, Koutsky, 2003).

6.2.4. p16 immunostaining is a good surrogate marker for high risk HPV infections (Kalof, 2005 & Kalof & Cooper, 2006) as well as for assessment of cervical biopsies that are histologically indeterminate for dysplasia (Kong, Balzer, Troxell, Patterson, Longacre, 2007) and therefore it should be considered that negative p16 staining does not rule out HSIL. Ki-67 immunostain has a role in separating benign findings from HPV-associated lesions (McCluggage, 2007).

6.2.5. Occasionally collagen IV (basement membrane) stain may be done to confirm invasion (breach of basement membrane) and p63 may be done to confirm squamous differentiation in a non-keratinising squamous cell carcinoma or an adenosquamous cell carcinoma (McCluggage, 2007).

Table 4: Recommended PMB level of care histopathology for cervical cancer

Procedure	Comment (where necessary)
Histology	
Staining	Nonsquamous cell malignancies (adenocarcinoma, small cell carcinoma, sarcoma, lymphoma) normally require additional stains for correct subtyping at diagnosis. Stains are not routine for squamous cell carcinoma
Immunohistochemistry	Not routine for the diagnosis of squamous cell carcinoma of the cervix. For endocervical adenocarcinoma, immunohistochemistry is routinely performed to confirm endocervical origin and exclude endometrial origin.

6.3. Diagnostic procedures

6.3.1. Diagnostic procedures described below are for obtaining a tissue confirmation. Radiological investigations can only be done after tissue confirmation.

Table 5: Recommended diagnostic PMB level of care procedures

Diagnostic procedures	Comment (where necessary)
Colposcopy with biopsy	
Cone biopsy	
Large loop excision of the transformation zone (LLETZ)	
Endocervical curettage (endocervical scraping)	Not recommended as routine for cervical cancer. Motivation may be considered in case of adenocarcinoma on pap smear with no mass clinically detected, a curettage may be performed to exclude endometrial cancer.
Cystoscopy, proctoscopy	Not routine. Only if bladder or rectal extension is suspected.

6.3.2. The earliest stages of cervical carcinoma may be asymptomatic or associated with a watery vaginal discharge and postcoital bleeding or intermittent spotting. Cervical small-cell neuroendocrine carcinoma has a particular propensity to spread distantly, as a result, patients can present with systemic symptoms such as weight loss, paraneoplastic syndrome such as the syndrome of inappropriate antidiuretic hormone secretion (SIADH), Cushing syndrome, hypercalcaemia or a neurological disorder (Marth et al, 2017, McCusker, 2003).

6.3.3. Workup for patients with suspicious symptoms includes history and physical examination with pelvic examination and a cervical cytology. Abnormal cervical cytology should lead to colposcopy and biopsy or excisional procedures such as loop electrosurgical excision and conisation.

6.3.4. A biopsy should be performed on any grossly visible or suspicious lesion on the cervix, because cervical cytology can be reported as negative when invasive cancer is grossly present.

6.3.5. Colposcopy is a diagnostic procedure used to identify precancerous and cancerous lesions so that treatment can be initiated early. Cytologically reported high-grade abnormalities such as HSIL and persistent LSIL which may be associated with an underlying invasive squamous cell cervical cancer or adenocarcinoma, all warrant colposcopic evaluation. If examination of the entire squamocolumnar

junction is visualised, endocervical curettage (ECC) is not necessary (Wright, Massad, Dunton, Spitzer, Wilkinson & Solomon, 2007).

6.3.6. Cone biopsy is a recommendation for those patients where the cervical biopsy is either inadequate to define invasiveness or accurate assessment of microinvasive disease is required.

6.3.7. Histological diagnosis of HSIL after biopsy may be followed by large loop excision of the transformation zone (LLETZ) which has the advantage of provision of a specimen for histological diagnosis thereby allowing for assessment of excision margins.

6.4. Laboratory investigations

The following laboratory investigations are recommended as PMB level of care for diagnostic work-up of cervical cancer:

- Full blood count
- Liver and renal function tests
- Urea, electrolytes and creatinine
- HIV diagnostic test. A CD4 T-cell count and an HIV viral load will be required if not already done within the previous 6 months

7. STAGING AND RISK ASSESSMENT

All women with histologically diagnosed cervical cancer must undergo staging before any treatment is initiated. The International Federation of Gynecology and Obstetrics (FIGO) staging system is widely used. The FIGO stages 2018 are as follows:

Table 6: FIGO staging of cancer of the cervix uteri (2018)

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine 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
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
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 para-aortic lymph nodes[c]
IIIA	The 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 para-aortic lymph nodes, irrespective of tumour size and extent (with r and p notations) [c]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous oedema, as such, does not permit a case to be allotted to Stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

[a] Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumour 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. Example: If imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r, and if confirmed by pathologic findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented.

7.1. Histopathology for the staging and risk assessment

Table 7: Recommended histopathology for the staging and risk assessment of cervical cancer

Description	Comment
Immunohistochemistry	Not recommended as routine for staging Already done during the diagnosis stage Motivation to be submitted if the diagnosis on the resection is suspected to differ from the biopsy diagnosis or to confirm micrometastasis
Histology	Recommended for both diagnosis and staging. Histology of the resection specimen is required for staging (e.g. extent of lymph node involvement, vaginal cuff involvement) and to assess margins.

7.2. Imaging radiology

7.2.1. Various procedures are used for staging the cancer and guiding treatment. Staging of cervical cancer is important in distinguishing patients with operable vs those with inoperable disease.

7.2.2. Early disease (stages IA and IB) can be treated with surgical resection whilst more advanced disease requires radiation and possibly chemotherapy (Pecorelli, Zigliani, & Odicino, 2009).

7.2.3. Cervical cancer is staged by clinical examination according to FIGO, however, this staging does not give information about the lymph node metastases. Lymph node metastasis is a major factor that correlates with a poor prognosis of cervical cancer. There is controversy over whether cervical cancer should be clinically, radiologically or surgically staged. Although surgical provides for precise lymph node status of the patients and as such is regarded regarded more accurate than clinical staging, use of surgical staging is limited in low-resource countries (Gold, Tian, Whitney, Rose & Lanciano, 2008; Pecorelli et al, 2009 & Moore, 2008).

7.2.4. Radiologic staging (magnetic resonance imaging (MRI), computed tomography scan (CT scan), PET scan) also does not allow with certainty for detection of lymph node involvement (Sakuragi, 2007).

7.2.5. Whilst MRI, CT or combined PET/CT have a role in treatment planning, these imaging modalities are not accepted for formal staging purposes, MRI, has however shown better accuracy as a staging method as it can evaluate the actual extent of the disease because of its high spatial and contrast

resolution for pelvic tissues and organs (Siegel, Andreotti, Cardenes, Brown, Gaffney, Horowitz, Javitt, Lee, Mitchell, Moore, Rao, Royal, Small, Varia, & Yashar, 2012; Moore ,2008; Hricak, Gatsonis, Coakley, Snyder, Reinhold, Schwartz, Woodward, Pannu, Amendola & Mitchell, 2007).

7.2.6. With its high contrast resolution, enabling differentiation between cancerous and normal tissue, the MRI has gained increasing use for pretreatment staging of uterine cervical cancer (Sala, Rockall, Freeman, Mitchell & Reinhold, 2013; Freeman, 2012 & Patel 2010).

7.2.7. MRI is not currently accepted as the gold standard and not recommended as routine PMB level of care (Testa, Ludovisi, Manfredi, Zannoni, Gui, Basso, Di Legge, Licameli, Di Bidino, Scambia & Ferrandina, 2009). However, a motivation can be submitted on a case by case basis as there is a role of MRI in identifying operable cases in early stages of cervical cancer and also identifying those with pelvic para aortic disease in the advanced stages.

7.2.8. CT imaging of the abdomen and pelvis also has use in defining lymph nodes status and to assess the extent of local disease and is recommended as PMB level of care for disease staging and treatment planning (Hricak, et al, 2007).

7.2.9. Findings from a CT of the abdomen and pelvis in HIV positive patients may avoid potential curative intent treatment if the cancer is metastatic, where the treatment intent becomes palliative.

7.2.10. CT chest is not recommended as PMB level of care. A motivation can be submitted for reimbursement only if the CT of the abdomen and pelvis shows para aortic nodes.

7.2.11. Compared to conventional imaging methods, positron emission tomography (PET) has some value in the detection of nodal metastatic disease and recurrent cervical cancer possibly being predictive of survival outcome. It is increasingly regarded as having a potential to accurately delineate the extent of disease, particularly in lymph nodes that are not macroscopically enlarged and in distant sites, with high sensitivity and specificity (Lin, 2015; Zhao, Feng, Mao & Qie, 2013). A sensitivity of 91% and specificity of 100% for FDG-PET scanning in nodal staging compared with a 73% sensitivity and 83% specificity for MRI was reported (Reinhardt, 2001). Patel et al reported that PET/CT has a sensitivity of 53%–73% and specificity of 90%–97% for the detection of lymph node involvement in early stage disease, while in more advanced stages the sensitivity for detecting the involvement of para-aortic nodes increases to 75% with 95% specificity (Patel, 2011).

7.2.12. PET scan is recommended as PMB level of care in select cases with squamous carcinoma for initial staging, restaging and suspected recurrence in locally advanced cervical cancer being considered for radical chemoradiotherapy (Vorster, Doruyter, Brink, Mkhize, Holness, Malan, Nyakale, Warwick & Sathekge, 2016).

Table 8: Recommended imaging radiology for the staging and risk assessment of cervical cancer

Description	Comment (when necessary)
Ultrasound abdomen and pelvis	

Transvaginal ultrasound	
Chest x-ray	
CT chest	Not recommended as routine Motivation on a case by case basis
CT abdomen and pelvis	Recommended for staging (routine)
Bone scan	Not recommended
MRI abdomen and pelvis	Not recommended as routine Motivation on a case by case basis
PET scan	On motivation on a case by case basis. Only for squamous carcinoma not adenocarcinomas

8. TREATMENT OPTIONS

8.1. Treatment of Early Stage Disease (FIGO IA1, IA2, IB1, IB2 and IIA1

The stage of a cervical cancer and various prognostic factors are the most important factors in choosing treatment. Both surgery and radiotherapy remain viable options for early stage disease. Some of the surgical interventions may also be used to assist in the diagnosis to determine how far the cancer has spread. Definitive radiotherapy or concurrent chemoradiation (CCRT) is preferred in patients likely to require postoperative radiotherapy to prevent compounding treatment-related morbidity. (Bhatla, Aoki, Sharma and Sankaranarayanan, 2018).

8.1.1. Treatment of Stage 1A1

8.1.1.1. For Stage IA1, if preservation of fertility is desired, then a fertility sparing cone biopsy with or without pelvic lymph node involvement dissection may be performed (Andikyan 2014, Koliopoulos 2004 & Wright 2010). For patients with negative margins after cone biopsy, observation would be appropriate if fertility is desired (NCCN 2016). For patients with positive margins after cone biopsy, options include a repeat cone biopsy to better evaluate the depth of invasion. The treatment is completed with cervical conisation unless there is lymphovascular space invasion (LVSI) or tumour cells are present at the surgical margin. Total extrafacial hysterectomy may be recommended (Bhatla, Aoki,

Sharma and Sankaranarayanan, 2018). When LVSI is evident, pelvic lymphadenectomy should be considered.

8.1.1.2. In the absence of lymphovascular where invasion and preservation of fertility is not relevant, a total hysterectomy may be an option with or without bilateral salpingo-oopherectomy (BSO). BSO may reduce the risk of ovarian and breast cancer particularly in women with BRCA gene mutations, but side effects should be clearly explained to patients because it may trigger surgical menopause and therefore long-term side effects (Kovacs, 2014).

8.1.2. Treatment of Stage IA2

8.1.2.1. When preservation of fertility is desired, Stage IA2 lesions can be treated with either a simple or radical trachelectomy with pelvic lymph node dissection. A prospective multicentre study of radical trachelectomy combined with laparoscopic pelvic lymphadenectomy with a median follow up of 29 months, reported three recurrences in 300 FIGO 1A1, IA2 and IB1 patients (Hertel, 2006). When there are no concerns over maintaining fertility, treatment can be with a modified radical hysterectomy (class II) and a pelvic lymphadenectomy with or without para-aortic lymph node dissection (NCCN, 2016).

8.1.3. Treatment of Stage IB1

8.1.3.1. For Stage IB1 lesions, a radical hysterectomy (class II) and pelvic lymphadenectomy with tailored post-operative adjuvant radiotherapy is recommended.

8.1.3.2. If preservation of fertility is desired, a radical trachelectomy may be performed (Bhatla, Aoki, Sharma and Sankaranarayanan, 2018).

8.1.4. Treatment of stages IB2 and IIA1

8.1.4.1. Surgery or radiotherapy is the primary treatment for stages IB2 and IIA1. A radical hysterectomy (class II) and pelvic lymphadenectomy with tailored post-operative adjuvant radiotherapy are recommended.

8.1.4.2. Definitive pelvic radiotherapy is also acceptable for these patients (Colombo et al, 2012).

8.1.4.3. PMB level of care for definitive radiotherapy includes external beam radiation therapy (EBRT), conformal radiation and brachytherapy. (Bagshaw, Tward & Gaffney 2013).

8.2. Treatment of locally advanced stage cervical cancer

The category of advanced stage cervical cancer traditionally includes patients with Stage IIB to IVB. However, IB2 and IIA2 have been included by some oncologists in the advanced disease category.

8.2.1. Treatment of stages IB3 and IIA2

8.2.1.1. Concurrent platinum-based chemo-radiotherapy is standard treatment for locally advanced cervical cancer. Radiotherapy includes external beam radiation therapy (EBRT) of primary tumour and pelvic and paraaortic lymph nodes (if involved) and may include intracavitatory brachytherapy for more

localised control. The treating provider may determine whether EBRT alone or in combination with intracavitatory brachytherapy is needed. (Eisenhauer et al, 2009; Gaffney, 2011; Monk, 2007).

8.2.1.2. Significant overall survival benefit of treatment with chemoradiation compared to radiation alone has been reported, with an absolute survival benefit for chemoradiotherapy compared with radiotherapy alone of 10% for FIGO stages I/II compared with 3% for those with stages III/IV. (Green et al, 2005).

8.2.1.3. There is no unanimity of view as to whether neoadjuvant chemotherapy improves prognosis compared with the standard treatment (Bhatla, Aoki, Sharma and Sankaranarayanan, 2018). Neoadjuvant chemotherapy is not recommended as PMB level of care.

8.2.2. Treatment of stages IIB - IVA

8.2.2.1. Concurrent chemoradiation is considered the standard treatment for patients with locally advanced cervical cancer (LACC) (Bhatla, Aoki, Sharma and Sankaranarayanan, 2018).

8.2.2.2. Simple hysterectomy after chemoradiation for locally advanced cervical cancer in patients with residual disease limited to the uterus (after chemoradiation) will result in a 50% cure rate and under these circumstances should be a PMB.

8.2.2.3. For patients without nodal disease or disease limited to the pelvis, treatment consists of pelvic EBRT and brachytherapy with or without concurrent cisplatin-based chemotherapy. (Gaffney 2011, Monk 2007).

8.2.2.4. The combination of EBRT and brachytherapy maximises the likelihood of locoregional control while minimising the risk of treatment complications. The primary goal of EBRT is to sterilise local disease and to shrink the tumour to facilitate subsequent brachytherapy (Bhatla, Aoki, Sharma and Sankaranarayanan, 2018).

8.2.3. Treatment of metastatic disease (Stage IVB)

8.2.3.1. For patients with positive paraaortic lymph nodes and pelvic lymph node involvement, imaging workup for metastatic disease would be warranted as it influences the choice of treatment.

8.2.3.2. Definitive radiotherapy with or without chemotherapy is recommended as PMB level of care.

8.2.4. Treatment of recurrent disease

8.2.4.1. Recurrence should be proven by biopsy before treatment planning for recurrent disease can be undertaken.

8.2.4.2. If there is extensive local disease or distant metastatic disease, the patient is assigned to palliative therapy, with best supportive care and symptom control the recommended management (Bhatla, Aoki, Sharma and Sankaranarayanan, 2018).

8.2.4.3. However, based on the evidence from the Moore study, Cisplatin in combination with Paclitaxel was shown to be superior to Cisplatin alone with respect to response rate and

progression free survival (Moore et al, 2004). Cisplatin in combination with Paclitaxel is also recommended on PMB level of care.

8.2.4.4. Patients with central pelvic recurrent disease after radiotherapy should be evaluated for pelvic exenteration with or without intraoperative radiotherapy. Surgical mortality is generally 5% or less with survival rates approaching 50% in carefully selected patients (Mamitz 2009, Berek 2005, Goldberg 2006, Tran 2007, Fleisch 2007).

9. FOLLOW-UP

In a review of 17 retrospective studies that followed up women treated for cervical cancer, the median time to recurrence ranged from 7 to 36 months after primary treatment. (Bhatla, Aoki, Sharma and Sankaranarayanan, 2018). The following follow up schedule is generally acceptable: 3 monthly for a year, every 4 months for 2 years, 6 monthly for the next 5 years and thereafter annually for 10 years.

Post treatment surveillance by a multidisciplinary team is important for all patients. Post surveillance should be based on patient's risk for recurrence (Salani 2011). Cytology (vaginal vault smears) often used in follow up is not recommended as PMBs level of care as it does not significantly improve the detection of early disease recurrence (Bhatla, Aoki, Sharma and Sankaranarayanan, 2018). Lymph node FNA may be performed if enlarged lymph nodes are found. Biopsy for histology is usually required if suspicious lesions are found on clinical examination.

10. BEST SUPPORTIVE CARE

CMS developed a PMB definition document on best supportive care for gastrointestinal oncology conditions (available at https://www.medicalschemes.com/files/PMB%20Definition%20Project/BestSupportivCare%20GIT3103docx.pdf). The document contains some guidance for the management of side effects of chemotherapy, which can be applied across all oncology conditions, i.e. management of nausea and vomiting, management of diarrhea and pain management. Other rehabilitation interventions specific to cervical cancers should be considered for funding when referred by the primary treating provider.

Table 9: Summary of PMB level of care for surgical management of cervical cancer

Procedure	Comment (where applicable)
Conisation	Early stage cervical cancer when preservation of fertility is desired.
Simple total hysterectomy (vaginal or abdominal)	Performed when fertility preservation is not desired and there is no lymphovascular node involvement.
Radical hysterectomy	Where fertility preservation is not desired. This is undertaken in conjunction with bilateral pelvic lymph node dissection.
Pelvic lymph node dissection	Closely related to the presence of lymph node metastasis.
Trachelectomy	May be used for carefully selected patients with lesions of 2 cm diameter or less.
Pelvic exenteration	In recurrent disease in the central pelvis following radiation therapy.
Bilateral salpingo-oopherectomy (BSO)	May be considered as an option to reduce risks of ovarian and breast cancer. Not routine in young patients.
Laparoscopic hysterectomy	Recommended based on basket of care given below
Diversion colostomy or urinary	For palliative and treatment procedures.
Exclusions	
Robotic assisted hysterectomy	Not PMB level of care.
Omentectomy	Not PMB level of care.

Table 10: Recommended basket for laparoscopic hysterectomy

Disposable
1xoptic standard port 10/11/12
3x5mm ports (preferably reusable port, but not necessarily)
Sutures: PDS/Vicryl/V-lock/J-needle
Ligasure/harmonic scalpel/Thunderbeat
Reusable
Suction and irrigation
Graspers
Bipolar forceps and cable
Monopolar cable
Uterine manipulator with colpotomy cuff

Table 11: Summary of PMB level of care for radiation therapy of cervical cancer

Indication	Recommendation
Definitive	EBRT Conformal + brachytherapy
Adjuvant	EBRT +/- Brachytherapy
Palliative radiation	Single fractions 10Gy – 40Gy
Exclusions	
Intensity-modulated Radiation Therapy (IMRT)	Limited evidence on use of IMRT in cervical cancer. Not recommended as PMB level of care.

Table 12: Summary of PMB level of care for chemotherapy of cervical cancer

Indication	Medicine names	Comment
Adjuvant / definitive	Cisplatin + Radiation	Addition of platinum-based chemotherapy (Cisplatin or Carboplatin) to adjuvant radiotherapy (chemoradiation) may improve survival in women with early stage cervical cancer (IA2-IIA) and risk factors for recurrence (Falcetta, Medeiros, Edelweiss, Pohlmann, Stein & Rosa, 2016).
Metastatic	Carboplatin	Carboplatin remains a reasonable option particularly in patients with compromised renal function (Green & Lainakis, 2006). The Japan Clinical Oncology Group conducted a randomised Phase III study to evaluate the clinical benefit of Carboplatin plus Paclitaxel compared with cisplatin plus Paclitaxel for patients with advanced or recurrent disease. The Carboplatin combination proved comparable with the Cisplatin combination in terms of its antitumour activity, however, the

		Carboplatin combination was more tolerable (Kamura & Ushijima, 2013; Saito, Kitagawa, Fukuda, Shibata, Katsumata, Konishi & Yoshikawa, 2012).
	Paclitaxel	A randomised Phase III study of with and without Paclitaxel, Cisplatin with Paclitaxel showed significantly better response rate and progression free survival (Kamura & Ushijima, 2013, Moore et al, 2004).
	Cisplatin	Recommended
	Gemcitabine	Inferior to Paclitaxel. Not recommended
Exclusions		
Biologicals Topotecan Vinorelbine		

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