Statement of Recommended Practice: Sentinel Lymph Node Mapping in Patients with Cervical Cancer

New Zealand Gynaecologic Cancer Group (NZGCG)

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On behalf of the SLN in cervical cancer working group - NZGCG

Contents

1. Abbreviation Table

AC	Adenocarcinoma
BAGP	British Association of Gynaecological Pathologists
BGCS	British Gynaecological Cancer Society
CAP	College of American Pathologists
CRT	Chemo-radiation treatment
CT	Computed tomography
DFS	Disease-free survival
DSS	Disease specific survival
ENP	Empty node packet
ESGO	European society of gynaecological cancer
ESTRO	European society for radiotherapy and Oncology
ESP	European society of Pathology
FIGO	International federation of gynecology and obstetrics
H&E	Haematoxylin and Eosin
HPV	Human Papilloma Virus
ICG	Indocyanine green
IHC	Immunohistochemistry
ITC	Isolated Tumour Cells
LVSI	Lympho-vascular space invasion
PLND	Pelvic lymphadenectomy
MAC	Macro-metastasis
MIC	Micro-metastasis
MIS	Minimally invasive surgery
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NPV	Negative predictive value
NZGCG	New Zealand Gynaecologic Cancer Group
OS	Overall survival
PET-CT	Positron emission tomography – Computed tomography
RFS	Recurrence free survival
RT	Radiation treatment
SCC	Squamous Cell Carcinoma
SLN	Sentinel lymph node
Tc99	Technetium-99

2. Background and Introduction

Cervical Cancer is a major public health problem with overrepresentation of Māori wāhine, Pacific people and people from lower socioeconomic backgrounds. Persistent HPV infection is the predominant cause for the development of cervical cancer. Squamous cell carcinoma (SCC) accounts for the majority of cervical cancer histology (+/- 80% of all cases) followed by Adenocarcinoma (AC) (+/- 20% of all cases).

Cervical cancer incidence and mortality has been reducing over time in Aotearoa New Zealand, due to the implementation of Human Papillomavirus (HPV) vaccination and cervical screening programmes. Despite this, 177 people are still diagnosed with cervical cancer, and 54 people demise due to the disease in Aotearoa New Zealand annually. (Ora, 2017-2021)

Early-stage cervical cancer is traditionally treated with uterine/cervical resection (radical hysterectomy or simple hysterectomy) and lymph node staging by performing a systematic pelvic lymphadenectomy (PLND).

Lymph node metastasis are identified in the minority of patients with presumed early-stage (Stage IA-IB) cervical cancer. Therefore, more than 80% of patients will undergo a systematic PLND, and exposed to the associated morbidity, for negative lymph nodes. (Lécuru F, 2011)

In recent years a growing understanding and body of evidence with regards to sentinel lymph node (SLN) mapping in early cervical cancer has developed, with multiple international guidelines stating the consideration and recommendation of its use in early cervical cancer patients. (Cibula D R. M., 2023) (Abu-Rustum N, 2024)

SLN mapping in cervical cancer is an alternative or addition to systematic PLND in the surgical staging of early-stage cancer. It relies on the concept of identification of the first lymphatic drainage of the cervix and removal of only the first lymph node drainage echelon. Its usage has been associated with reduce the extent of surgery and associated morbidity, increase in the ability to detect lymph node metastasis by more than 40% otherwise missed by standard systematic PLND and identifies possible lymph node metastasis outside of traditional lymph node boundaries. (Spinholtz S, 2022) (Kocian R, 2024) (Bats A, 2013)

This statement of recommended practice is largely based on the ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer - Update 2023, which unequivocally recommends SLN mapping in cervical cancer. (Cibula D R. M., 2023) The current recommendation statement is tailored to the clinical practice in Aotearoa New Zealand by the use of consensus, with the aim for a national implementation of SLN mapping in patients with early stage and surgically treated cervical cancer.

3. Equity considerations

3.1 Te Tiriti o Waitangi

The working group developing the ‘statement of recommendation practice: SLN mapping in cervical cancer’, is obligated to uphold Te Tiriti o Waitangi, and actively works towards honouring the principles. Te Tiriti o Waitangi is a founding document of Aotearoa New Zealand with it’s principles shaping this kaupapa.

- Researchers can use the principles of Te Tiriti o Waitangi, the theory of Āta- Creating respectful relationships and the Consider Statement, to help them work in a whānau centred way. (Pohatu, 2013) (Huria, 2019)
- Māori Data sovereignty is a taonga/treasure and refers to the rights and interests of Māori in the collection, ownership, and application of their own data.
- Researchers and Clinicians need to understand and be aware that the patient and their whānau are connected and therefore whānau will be part of the clinical trial and plan being offered.
- Consent is never implied or assumed; it is always sought. This includes consent for patient body tissue that maybe used at a later date.
- Clear, whānau friendly language is used to ensure the patient has been made fully aware of what being involved in research means.
- All researchers and members of the team will be fluent or on a journey cultural competency,
- Where possible clinical trials will be informed by whānau voice.

3.2 Commitment to equity in health outcomes

The Ministry of Health defines equity as “In Aotearoa New Zealand, people have differences in health that are not only avoidable but unfair and unjust. Equity recognises different people with different levels of advantage require different approaches and resources to get equitable health outcomes” (Health, 2019)

Ethnic disparities in cervical cancer incidence are notable in Aotearoa New Zealand, with Māori and Pacific people experiencing disproportionately high cancer rates. Reducing the morbidity associated with surgical staging through sentinel node support better outcomes for high-risk groups. The working group recommends implementing evidence-based, culturally responsive strategies to ensure equitable access and outcomes.

This statement of recommended practice is expected to enhance equity of health among cervical cancer patients and is aimed to ensure equitable clinical use of SLN mapping in cervical cancer nationally.

4. Responsibilities

The aim of this statement of recommended practice is to present a national consensus on the role of SLN mapping in early-stage cervical cancer and to help guide clinicians and patients on its use in clinical practice as an alternative or addition to PLND.

This statement of recommended practice is aimed to aid clinicians implementing SLN mapping as a treatment strategy in early-stage cervical cancer within their respective local setting. This statement of recommended practice solely comments on topics related to lymphatic staging in early cervical cancer and does not guide on the overall management of patients diagnosed with cervical cancer.

Although this statement of recommended practice is a representation of current evidence and consensus within the NZGCG, we acknowledge that there may be variations in resources, practices, infrastructure, access to surgical technology, training, and surgical experience between centres in Aotearoa New Zealand that may impact the implementation of the statement of recommended practice.

5. Methods

The statement of recommended practice has been developed using a 6-step process by the "SLN in cervical cancer working group" (Figure 1).

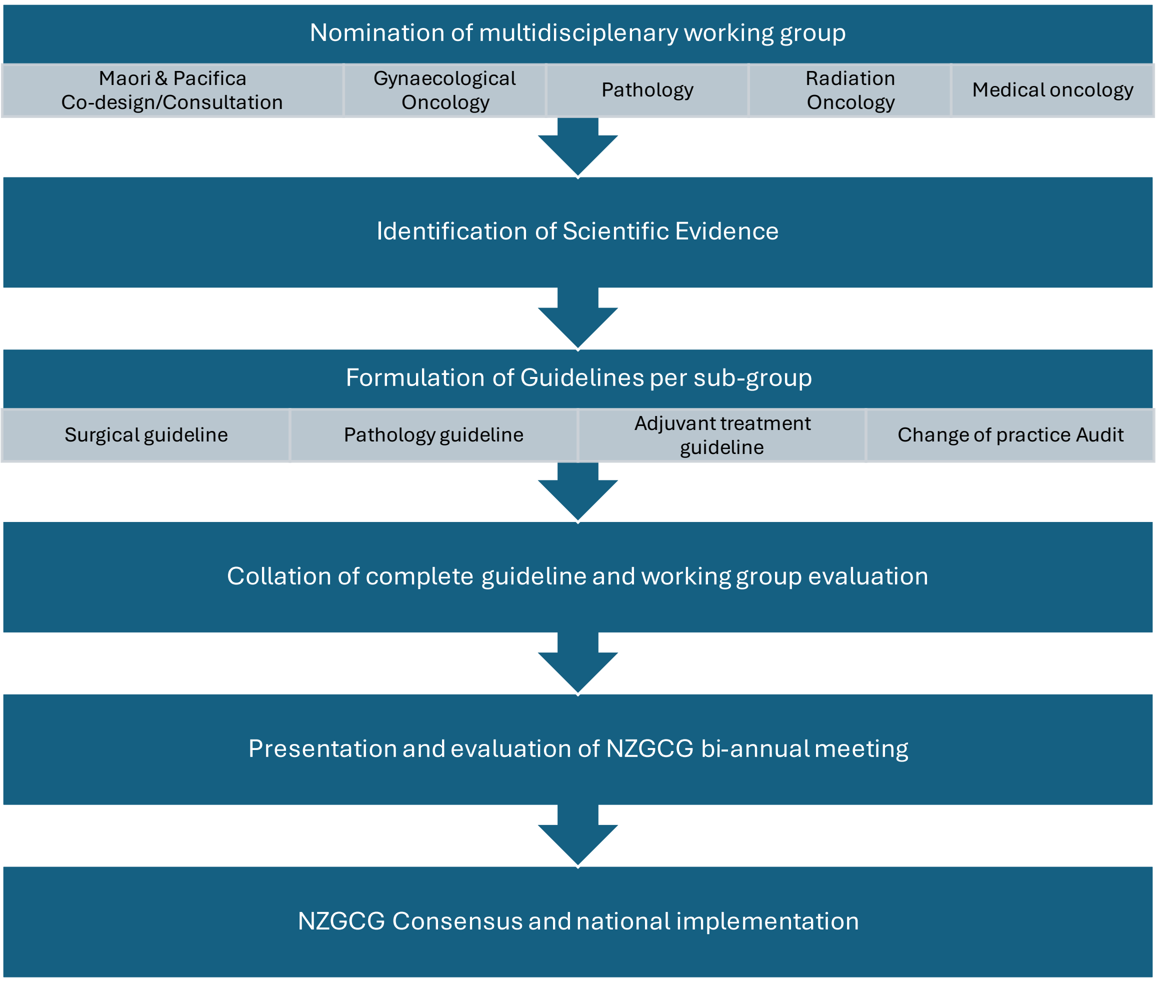

Figure 1: *Guideline development process.*

Nominations for this working group have been requested during and after the NZGCG meeting in June 2024. Māori and Pacific co-design/consultation is ensured by nominating individuals with cultural, clinical, and patient advocacy expertise. Nominating practising clinicians are required to manage patients with early cervical cancer and be member of the NZGCG. Nominations have ensured representation of all 3 major gynaecological oncology centres in Aotearoa New Zealand (Auckland, Christchurch, and Wellington) and include professionals from relevant disciplines (gynaecological oncology, pathology, radiation oncology and medical oncology). Nominated members of the working group are stated in table 1.

Name	Specialty/expertise	Work location	Function in working group
Tom De Greve	Gynaecological Oncology	Auckland	Chair, Surgical group lead
Tania Batley	Māori consultant and patient advocate	Christchurch	Māori Consultation, Patient advocacy consultation
Silipa Naiqiso	Gynaecological Oncology, Pacific consultant	Auckland	Pacific Consultation
Roberta Hager	Pathology	Christchurch	Pathology group lead
April Xu-Holland	Radiation Oncologist	Wellington	Adjuvant treatment group lead
Peter Sykes	Gynaecological Oncology	Christchurch	Audit group lead
Rachael van der Griend	Pathology	Christchurch	
Mayada Kellow	Pathology	Auckland	
Mollie Kain	Radiation Oncologist	Auckland	
Dorothy Lombe	Radiation Oncologist	Palmerston North	
Carol Johnson	Radiation Oncologist	Wellington	
Komeela Naidoo	Radiation Oncologist	Waikato	
Kathryn Chrystal	Medical Oncologist	Auckland	

***Table 1**: Nominated members of working group.*

6. Literature review

Lymph node staging is an integrate part of the primary management of patients with early stage and surgically treated surgically. In recent years SLN mapping in cervical cancer has become an alternative or addition to systematic PLND in the surgical staging of early-stage cancer. It relies on the concept of identification of the first lymphatic drainage of the cervix and removal of only the first lymph node drainage echelon. Its usage has been associated with reduce the extent of surgery and associated morbidity, increase in the ability to detect lymph node metastasis by more than 40% using ultra staging techniques otherwise missed by standard systematic PLND and identifies possible lymph node metastasis outside of traditional lymph node boundaries. (Spinholtz S, 2022) (Kocian R, 2024) (Bats A, 2013)

International guidelines advocate for the use of SLN mapping. The ESGO/ESTRO/ESP 2023 guidelines consider SLN mapping without additional PLND to be acceptable for patients with 2018 FIGO stage IA1 with LVSI and stage IA2 cervical cancer. (Cibula D R. M., 2023) However, due to the lack in long term survival data, SLN mapping alone in stage IB cervical cancer is not recommended. In contrast the 2024 National Comprehensive Cancer Network (NCCN) states to consider SLN mapping in patients with stage IA1 with LVSI to stage IB2 without the addition of PLND. (Abu-Rustum N, 2024) The 2019 Consensus document from the British Gynaecological Cancer Society (BGCS) has a similar statement to consider SLN mapping in patients with a tumour size less than 2 cm and to omit systematic PLND if successful SLN mapping if the resources are available. (Fotopoulou C, 2019)

6.1 Detection rates, sensitivity, and techniques

Multiple retrospective and prospective studies support the feasibility of SLN mapping in patients with early-stage cervical cancer.

Meta-analysis and pooled data have confirmed acceptable detection rates ranging between 89% and 92% and sensitivity of 89% - 90%. (Wu Y, 2013) (Kadkhodayan S, 2015)

The prospective SENTICOL-1 study in 2011 reported a unilateral and bilateral detection rate of 98% and 77%, respectively, by using blue dye and Technetium-99 (Tc99). (Lécuru F, 2011) The more recent SENTIX trial reported a bilateral detection rate of 91%. (Cibula D K. R., 2020) The prospective randomised FILM trial demonstrated an improved in overall and bilateral detection rates with the use of ICG compared to blue dye. (Frumovitz M, 2018) Unilateral and Bilateral detection rates are reported as 98% and 81% with ICG compared to 76% and 32% with blue dye, respectively. (Frumovitz M, 2018)

6.2 Reduced morbidity

Reduced morbidity of SLN mapping in patients with cervical cancer has been demonstrated in the prospective SENTICOL-2 study. (Mathevet P, 2021)

A significant reduction in lymphatic morbidity (31% vs. 51%) and post-operative neurological symptoms (7.8% vs. 20.6%) was observed in favour of the SLN mapping only arm. (Mathevet P, 2021) These findings have been further confirmed by the Prospective SENTIREC study, which demonstrated a reduction in 3-month lymphatic complications from 32.3% to 5.6% in the patients undergoing SLN and PLND compared to SLN mapping only. (Spinholtz S, 2022)

6.3 Improved detection of lymph node metastasis in SLN mapping

6.3.1 Detection of lymph node metastasis outside of traditional surgical boundaries

Systematic PLND in cervical cancer is defined as the removal of all fatty lymphatic tissue from the predicted areas of high incidence of lymph nodes with metastatic involvement. In cervical cancer the area is proposed as the common iliac, external iliac, internal iliac, obturator, and sacral (or presacral) areas. (Cibula D A.-R. N., 2010) Due to the low incidence of lymph node metastasis in lymph nodes cranially to the iliac bifurcation (common iliac and presacral) and the high morbidity associated with extensive lymphadenectomy, the ESGO guideline recommends to limit the boundaries of the systematic PLND to a level I (external iliac, internal iliac, obturator). (Cibula D R. M., 2023) (Cibula D K. R., 2020)

SLN mapping can detect “unexpected” or “unusual” lymph node drainage pathways in areas outside of the usual surgical boundaries. The SENTICOL data has shown that up to 38% of patients had at least one SLN in an unexpected area and 5% had a SLN only in an unexpected area. (Bats A, 2013) These lymph nodes would have been missed by the conventional systematic PLND, thus SLN mapping has the ability to improve nodal staging.

6.3.2 Detection of low volume metastasis

In comparison with systematic PLND, SLN mapping has been reported to have an increased detection of low-volume metastasis compared to systematic PLND due to the practical application of pathological ultra-staging. Pathological ultra-staging is a labour and resource intensive process; thus, it can only be performed in a limited number of nodes making this technique unpractical and non-sustainable in the setting of systematic PLND.

Pathological ultra-staging compared to routine pathological lymph node examination has, in addition to macro-metastasis (MAC) (>2mm), the ability to detect low volume metastasis defined as micro-metastasis (MIC) (>0.2mm - ≤2mm) and isolated tumour cells (ITC) (≤0.2mm). Between 39% and 60% of lymph node metastasis are identified by pathological ultra-staging alone, thus SLN mapping has the ability to improve nodal staging. (Bats A, 2013) (Cibula D K. R., 2020)

6.4 Frozen section of sentinel lymph node

Frozen section of lymph nodes in cervical cancer is a common practice in the setting of intra-operative unexpected suspicious appearing lymph nodes. In the setting of SLN mapping/staging this is controversial.

A possible advantage of SLN mapping is the opportunity to identify a small number of lymph nodes, allowing a frozen section to be performed as intra-operative pathological assessment. This would allow clinicians to avoid unnecessary radical surgery in the case of a positive frozen section of the SLN, and triage towards primary concurrent chemo-radiation treatment (CRT) rather than surgery.

Literature, however, shows poor accuracy in detecting metastasis in SLN. Data from the SENTICOL and SENTIX trials reported only 56% of MAC and MIC being detected on frozen section. In addition, frozen section increases the surgical time and has a risk of tissue loss during the frozen section process. (Balaya V G. B., 2020) (Cibula D K. R., 2020)

Therefore, frozen section of macroscopically normal lymph nodes in the setting of SLN mapping remains controversial and not widely utilised.

6.5 Completion systematic pelvic lymphadenectomy

Extrapolating data from advanced stage disease with MAC, adjuvant CRT should be at least equivalent to PLND in terms of pelvic nodal control. Omitting PLND in the case of MAC may lose information in terms of highest involved node but again this is similar to the treatment of advanced disease with definitive CRT so long as PET scan performed.

The ongoing PHENIX II trial, looking into the role of PLND in the setting of positive SLN may provide prospective evidence that CRT is non-inferior to PLND with CRT when a SLN is positive. (Tu H & group., 2020)

6.6 Prognostic effect of low volume metastasis

MAC is a well-known prognostic factor in patients with a presumed early-stage cervical cancer, with most guidelines recommending adjuvant CRT. (Cibula D R. M., 2023)

A large retrospective study has demonstrated that the presence of MIC is significantly associated with a reduction in OS similar to patient with MAC, no effect of ITCs on survival was reported in this series. (Cibula D A.-R. N., 2012) This multicentre international retrospective series highlights the importance of SLN mapping and ultra-staging. In contrast the combined data from the prospective SENTICOL I and II trials suggest that MIC and ITC do not decrease disease-free survival (DFS) in early-stage cervical cancer patients, however only 24 patients with low-volume metastasis were included in the analysis. (Guani B B. V., 2020)

Adjuvant treatment in the setting of low-volume metastasis (MIC and ITC) is a subject of debate, with a lack of prospective randomised data. The ongoing prospective SENTIX and SENTICOL III trials have therefore different indications for adjuvant treatment, with MIC being an indication for CRT in the SENTIX and not in the SENTICOL III trial. (Cibula D D. J., 2019) (Lécuru FR, 2020)

Despite the insufficient data that exist with regards to adjuvant treatment in low-volume metastasis in early-stage cervical cancer, the ESGO guidelines recommends adjuvant CRT in the case of MIC due to the majority of retrospective data indicating a reduced survival in the setting of MIC in SLN, and adjuvant treatment may be considered in ITC, however with an uncertain prognostic impact. (Cibula D R. M., 2023) The NCCN guideline does not specify any recommendation with regards to low-volume metastasis. (Abu-Rustum N, 2024)

6.7 Survival data

Although a large number of retrospective and several prospective studies have demonstrated the high sensitivity of SLN ultra-staging for pelvic LN status, there is currently only one prospective study in which SLN biopsy was not followed by a systematic pelvic lymphadenectomy. (Balaya V & Group, 2022) This post-hoc analysis of the prospective SENTICOL I and II has reported no difference between lymph node negative patient undergoing SLN mapping alone compared to SLN mapping and systematic PLND, with a 7-year DFS and disease-specific survival (DSS) of 85% vs. 80% and 91% vs. 97% respectively. (Balaya V & Group, 2022)

A recent systematic review and meta-analysis has shown no difference in 5-years DFS and overall survival (OS) between SLN mapping alone compared to SLN mapping and systematic PLND. (Parpinel G, 2023)

Currently there is a lack of randomised controlled data looking into the long-term outcomes of patients undergoing SLN mapping only compared to systematic PLND. We are awaiting the results from 3 ongoing prospective studies looking into the survival of patients undergoing SLN mapping compared to systematic PLND – SENTICOL III, SENTIX and PHENIX trials. (Lécuru FR, 2020) (Cibula D D. J., 2019) (Tu H & group., 2020) The first result from these trials is expected to be published in 2025/2026.

7. Indications

7.1 General indications

- SLN mapping should be performed in gynaecological oncology centres with experience and expertise in SLN mapping. In centres not familiar with using this technique, it is recommended to perform SLN in combination with systematic PLND until appropriate experience is gained.
- This statement of recommended practice is only applicable to the common histological types of cervical cancer, including SCC, AC (HPV associated) and Adeno-squamous cell carcinoma. There is limited data to support the use of SLN mapping in rare cervical cancer histological types and can therefore not be supported in this statement of recommended practice.

7.2 Contra-indications for SLN mapping

- Provisional FIGO (2018) stage >IB2
- Indocyanine green (ICG) allergy
- History of pelvic radiation
- History of pelvic lymph node dissection
- Status post hysterectomy
- Pregnancy

7.3 FIGO 2018 cervical cancer - Stage related indications

Considerations and recommendations are visualised in figure 2.

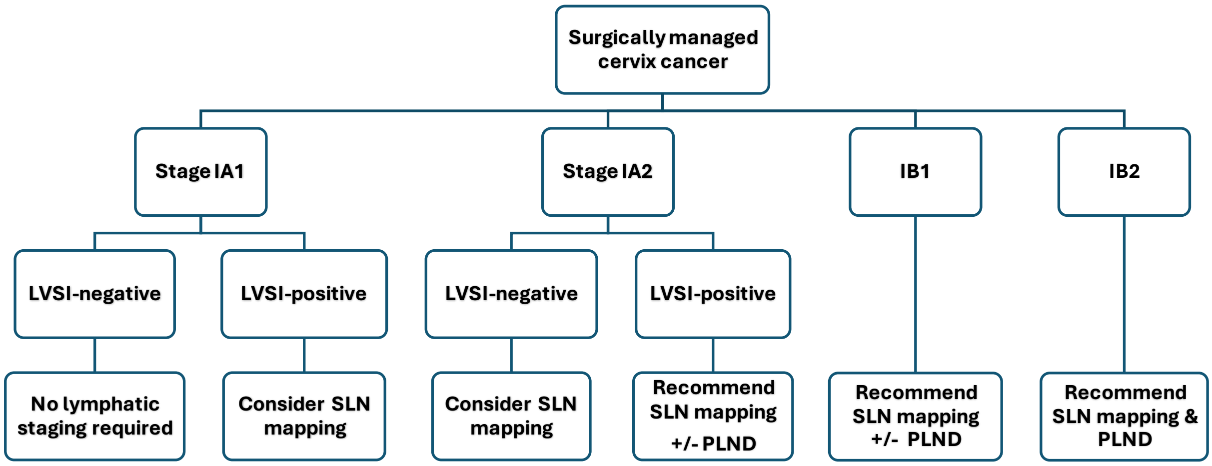

***Figure 2**: SLN mapping in cervical cancer indication algorithm.*

7.3.1 Stage IA1, LVSI-negative

Lymph node staging is not recommended in patients with stage IA1, LVSI-negative and negative margins on conisation. The frequency of pelvic lymph node metastasis in this stage without LVSI is reported to be <1%. (Benedet JL, 1996) (Margolis B, 2020)

7.3.2 Stage IA1, LVSI-positive

Pelvic lymph node metastasis in patients with stage IA1, LVSI-positive is reported to be 7.8% - 8.2%. (Margolis B, 2020) (Benedet JL, 1996) Therefore, lymph node staging can be considered in these patients. We recommend to perform SLN mapping if lymph node staging is performed in this situation. (Cibula D R. M., 2023)

7.3.3 Stage IA2, LVSI-negative

Pelvic lymph node metastasis in patients with stage IA2, LVSI-negative is reported to be between 1.3 – 8.3%. (van Meurs H, 2009) (Benedet JL, 1996) (Margolis B, 2020)Therefore, lymph node staging can be considered in these patients. We recommend to perform SLN mapping if lymph node staging is performed in this situation. (Cibula D R. M., 2023)

7.3.4 Stage IA2, LVSI-positive

Lymph node staging is recommended in patients with stage IA2, LVSI-positive, cervical cancer. Pelvic lymph node metastasis in patients with stage IA2, LVSI-positive is reported to be between 7.5 – 14.6%. (Benedet JL, 1996) (van Meurs H, 2009) (Margolis B, 2020) We recommend to perform SLN mapping (with consideration of additional PLND) in this situation as an alternative to PLND. (Cibula D R. M., 2023)

The addition of PLND to SLN mapping can be considered as prospective randomised long-term data on the safety of SLN mapping in early-stage cervical cancer is being awaited and the lymph node metastatic risk exceeds 10%. (Lécuru FR, 2020) (Cibula D D. J., 2019) (Tu H & group., 2020)

7.3.5 Stage IB

Pelvic lymph node assessment is a critical component of patients undergoing surgical management for a stage IB1 – IB2 cervical cancer. Lymph node metastasis is reported in 12-22% of patients with stage IB cervical cancer. (Sakuragi, 2007)

SLN mapping has shown to have high sensitivity ranging between 89-96% and negative predictive value (NPV) of 98%. (Lécuru F, 2011) (Sponholtz SE, 2021) (Wu Y, 2013) (Kadkhodayan S, 2015) Combined data and post-hoc analysis from two prospective studies has shown no difference in 7-year DFS or DSS between patients undergoing SLN mapping alone compared to SLN and PLND. (Balaya V & Group, 2022) In addition, a systematic review and meta-analysis in 2023 has confirmed no difference in 5-year DFS and OS between patients undergoing SLN mapping alone compared to SLN and PLND. (Parpinel G, 2023)

Currently we are awaiting prospective randomised long-term data on the safety of SLN mapping in early-stage cervical cancer, with the expected publication of the SENTICOL III, SENTIX and PHENIX trials in 2025/2026. (Lécuru FR, 2020) (Cibula D D. J., 2019) (Tu H & group., 2020)

7.3.5.1 Stage IB1

Lymph node staging is recommended in patients with stage IB1 cervical cancer. We recommend to perform SLN mapping (with consideration of additional PLND) in this situation as an alternative to PLND.

The addition of PLND to SLN mapping can be considered as we are awaiting completion of three prospective long term randomised trials on the safety of SLN mapping in early-stage cervical cancer. (Lécuru FR, 2020) (Cibula D D. J., 2019) (Tu H & group., 2020)

7.3.5.2 Stage IB2

The benefits of detection of unexpected drainage pathways / metastasis and increase in detection of low-volume metastasis with SLN mapping is counterbalanced with the lack of long-term safety data of SLN mapping in cervical cancer. Thus, we recommend to perform SLN mapping in combination with systematic PLND in patients with stage IB2 cervical cancer undergoing surgical management.

8. SLN mapping technique

8.1 Pre-operative workup

- Standard pre-operative work-up is recommended prior to provisional staging of any cervical cancer (including examination, biopsy +/- Colposcopy)
- Pelvic imaging (Computed tomography (CT) or Pelvic magnetic resonance imaging (MRI)) is <u>recommended</u> to assess for possible lymph node metastasis. (Imaging can be omitted in patients with stage IA cervical tumour, LVSI-negative and with negative margins after conisation).
- Positron emission tomography – Computed tomography (PET-CT) is recommended if suspicious pelvic lymph nodes are identified on pelvic imaging.
- Equivocal extra-uterine disease on imaging should be considered for biopsy to avoid inappropriate treatment.

8.2 Surgical technique

Surgical technique recommended is based on NZGCG consensus and a consensus statement of international experts published in 2024. (Bizzarri N, 2024)

8.2.1 Tracer injection technique

- Tracer injection is <u>recommended</u> to be performed after abdominal entry is obtained.
  - Injection before abdominal entry is acceptable but can be associated with a delay between injection and surgical SLN mapping. Causing ICG migration to non-SLNs, making identification of the "true" SLN more difficult.
- ICG is the <u>recommended</u> tracer for SLN mapping in cervical cancer patients.
- Dilution of ICG is <u>recommended</u> as 1.25mg/ml
  - Dilute 25mg of ICG with 20ml sterile water
- Total volume of ICG dilution is advised to be 4ml.
- ICG injection of the cervix is <u>recommended</u> to be performed at 3 and 9 o'clock, using a superficial 1mm submucosal injection and a deep 5-10mm injection.
- Injection should be performed at the margins of involved stroma avoiding vaginal fornices.
  - It is not advisable to inject through the cervical tumour.
- Grasping of the cervix is <u>recommended</u> to assist the injection only if part of the cervix is tumour free.

8.2.2 Intra-abdominal surgical technique

- Minimally invasive surgical (MIS) approach for SLN mapping is acceptable in cases with no vaginal-peritoneal cavity opening. (Vaginal simple trachelectomy, conisation, two-stage procedure)
- A two-stage procedure, with MIS SLN mapping and awaiting final histopathology, followed by the surgical management of cervical cancer in the case of negative SLNs can be considered but is limited due to:
    - Time sensitive surgical planning of second stage
        - It is <u>recommended</u> to perform second surgery within 10 days or after 6 weeks of SLN mapping after completion of SLN ultra-staging histopathology.
    - Risk of increased surgical complexity due to retroperitoneal fibrosis
    - Low rate of lymphatic metastasis in selected patients
- 360^0 evaluation of the abdomen is <u>recommended</u> to be performed prior to SLN mapping, with specific focus on the pelvic, pre-sacral, aortic/caval lymphatic areas and posterior lymphatic channels along the ureter (with and without the use of the fluoroscopy).
- Identification of following structures are <u>recommended</u> prior to identification and removal of SLN:
    - Ureter
    - Obliterated umbilical artery
    - Internal iliac artery
    - External iliac artery and vein
    - Advisable to open the para-rectal, para-vesicle and obturator space prior to SLN identification and removal
- Dissection and identification of SLN is <u>recommended</u> to start at uterine artery and continue laterally following the traced lymphatic channels (care not to disrupt lymphatic channels)
    - The first lymph node(s) mapped after following lymphatic tracer after crossing the obliterated umbilical artery is defined as the SLN and should be excised. (There can be more than one SLN per hemipelvis)
        - Note must be made of possible unexpected/unusual lymphatic pathways (posterior pathway) along the ureter to a SLN at common iliac, presacral or para-aortic/para-caval areas.
    - A parametrial SLN is defined as a SLN medial to the obliterated umbilical artery and should be excised and separately labelled in addition to "true" pelvic SLN mapping.
- Manipulation of the SLN should be performed by grasping the afferent/efferent channels. It is <u>recommended</u> to avoid grasping the body of the lymph node to reduce the risk of lymph node rupture.

- In the case of MIS approach, removal of lymph nodes is recommended to be performed using a protective manoeuvre (Endocath bag, finger of sterile glove, 'cup forceps')
- SLN should be labelled as per location and side: (figure 3.) (Bats A, 2013)
    - Expected/usual SLN location:
        - Obturator / interiliac SLN
        - External iliac SLN
    - Unexpected/Unusual SLN location
        - Parametrial SLN
        - Internal iliac SLN
        - Common iliac / Presacral SLN
        - Para-aortic/Para-caval SLN
- Any suspicious lymph nodes for metastasis encountered during SLN mapping, regardless of mapping, is recommended to be removed.
    - It is recommended to perform a frozen section to identify macroscopic metastatic disease with the aim to abandon the surgical management of cervical cancer and limit the need for dual modality treatment and its associated increase in toxicity. (Cibula D D. L., 2021)
- SLN mapping and excision is recommended to be completed in one hemi-pelvis before proceeding to the contralateral side.

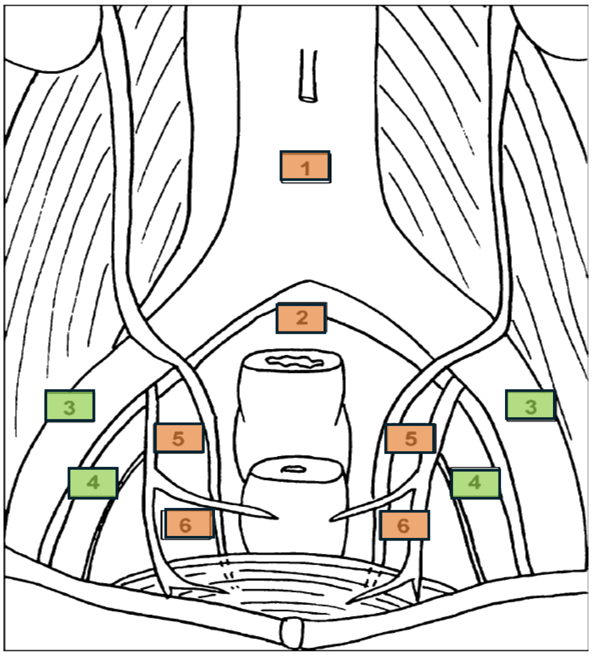

Figure 3*: SLN in cervical cancer location. 1: Para-aortic/Para-caval, 2: Common iliac/Presacral, 3: External iliac, 4: Obturator/Interiliac, 5: Internal iliac, 6: Parametrial. Green: expected / usual SLN location, Orange: Unexpected / unusual SLN location. (Bats A, 2013)*

8.2.3 Steps in case of failed SLN mapping

- Perform a contra-lateral SLN mapping and return to side of failed mapping to identify delayed SLN mapping
- Explore atypical location for SLN mapping (common iliac, pre-sacral and para-aortic/para-caval retroperitoneal spaces)
- Second injection of ICG dilution in the cervix.
- A side-specific systematic PLND is <u>recommended</u> in case of a failed SLN mapping.

8.2.4 Empty node packet

- Empty node packet (ENP) is defined as the absence of lymph node tissue at final histopathology examination. This has been described in between 2.6% and 5% of SLN mapping cases. (Vila A, 2024) (Frumovitz M, 2018)
- Ex-vivo inspection and palpation of the SLN specimen for the presence of lymphatic tissue is recommended to reduce the risk ENP.
    - Consideration can be made for pathological examination of the fresh specimen if uncertainty of ex-vivo examination of SLN presence occurs.
- In the setting of an ENP, it is recommended that a re-operation with systematic LND is performed in cases where the cervical factors, other ipsilateral SLN and contra-lateral SLN information is not sufficient to define adjuvant treatment.

8.2.5 Role of frozen section

- Frozen section is <u>recommended</u> in the case of unexpected intra-operative clinically suspicious lymph nodes. (as stated in <u>Intra-abdominal surgical technique</u>) Pre-operative imaging as stated in <u>Pre-operative workup</u> should be performed to categorise lymphatic status prior to surgery.
- Intra-operative frozen section of clinically non-suspicious SLN is <u>not recommended</u> in this statement due to controversial usage and limitations (as stated in <u>Frozen section of sentinel lymph node</u>).
    - Low sensitivity (56%) for the identification of macro- (MAC) and Micro-metastasis (MIC) (Balaya V G. B., 2020) (Cibula D D. J., 2019)
    - Loss of tissue during frozen section process.
    - Significant increase in pathology service workload
    - Increase in surgical time
- For all these reasons consideration can be made for a two-stage procedure as stated in <u>Intra-abdominal surgical technique</u>.

9. Pathology protocol

9.1 Rationale

Pathological ultra-staging is a crucial component of the sentinel lymph node biopsy.
Tumour metastases are classified by size into MAC (>2 mm), MIC (>0.2 - ≤ 2.0 mm) and ITCs (single cells or clusters ≤0.2 mm).
This definition of lymph node metastasis is based on breast cancer data, which has been extrapolated to many other tumour types, although has not been specifically validated for cervical cancer. (L.H. Sobin, 2009)

Lymph nodes should be sliced at 2mm intervals, and completely processed, to maximise detection of MAC. Based on a mathematical model to maximise detection of all MIC, each 2 mm block of lymph node tissue should be further sectioned at 0.2 mm (200 micron) intervals, at least. The addition of immunohistochemistry at each level, usually a broad-spectrum cytokeratin AE1/3, increases detection of low volume disease.
How many levels and how far apart to cut them remains an area of debate internationally. The more intensive the protocol, the more disease will be detected, but this must be balanced against workload, cost, and clinical benefit.
The detection rate of a positive sentinel lymph nodes directly correlates with the intensity of ultra-staging (Kocian R, 2024), however, no sentinel node protocol can detect 100% of disease or examine all the nodal tissue. Examining every section of tissue (cut at the standard 4 microns) would generate 500 slides per 2mm block.

9.2 International guidelines

A variety of international guidelines exist, with a wide spectrum of protocols.

The College of American Pathologists (CAP) recognise that currently there is no universal ultra-staging protocol but state that all institutions undertaking sentinel lymph node examination should have a standard procedure in place for sentinel lymph nodes and suggest the following: for any section that is negative on initial Haematoxylin and Eosin (H&E) section, 2 sections are taken from each of two levels that are 50 µm apart, with one for H&E and the second for pankeratin immunohistochemistry (IHC). (Krishnamurti UG, 2023) This potentially leaves up to 1.9 mm of lymph node in each block unexamined. At the other end of the spectrum are the guidelines from the British Association of Gynaecological Pathologists (BAGP), in conjunction with the BGCS, which recommend levelling through the entire node at 200-micron (0.2 mm) intervals with H&E and AE13 Cytokeratin at each level and two unstained spares. (Ganesan R, 2019)

As an example, a single sentinel lymph node, 8 mm in maximum dimension. The node is sliced at 2 mm intervals and all 4 pieces processed in one cassette. Applying the CAP protocol in this situation would generate 5 slides (3 H&E, 2 IHC) while applying the BAGP protocol would generate 44 slides (11 H&E, 11 IHC, 22 unstained spares). Considering that is it not uncommon to receive multiple sentinel nodes, exhaustive protocols quickly become untenable for laboratories.

The SENTIX protocol appears to offer a safe and reasonable compromise. This was a prospective multicentre study on 647 patients undergoing sentinel lymph node biopsy for cervical cancer. (Kocian R, 2024) All SLNs were fixed in 10% buffered formalin, cut at 2-mm intervals, embedded in paraffin, and fully examined. The protocol involved preparing pairs of consecutive sections (each 4-μm-thick), at 150-μm intervals between the pairs of sections, from each paraffin block until no lymph node tissue remained. The first section was stained with H&E and the second section was examined immunohistochemically using anti-cytokeratin antibodies (AE1/AE3). The levels at which metastases were found were documented and, analysing the results, 92.6% of all MAC and MIC were detected within the first 4 levels. Consequently, they recommend examining a minimum of four levels as this should detect >90% of N1 disease. Using the same example above, this would generate 16 slides (8 H&E, 8 IHC, 16 unstained spares).

9.3 NZGCG Consensus protocol

Standardisation of pathological process is desirable for the following reasons:

- Maximise patient safety by reducing variability
- Enable easier comparison between centres
- Aim for equity and efficient use of resources

9.3.1 Gross/macroscopic handling

- For frozen section protocol see Role of frozen section.
- Examine the lymph node and any adherent fat. It is preferable to avoid trimming fat, however, if there is excessive fat this can be carefully trimmed and placed in a separate cassette (single H&E only, not for ultra-staging)
- Record the presence and colour of any visible dye.
- Nodes 4 mm or more in greatest dimension should be sliced at 2mm intervals; perpendicular to the long axis. Nodes 2 – 4 mm should be bisected, and small lymph nodes < 2 mm can be submitted whole.
- All slices should be submitted for processing, do not overcrowd the block.

- When a node is trisected, the two end pieces should be placed cut surface down; the middle piece is placed randomly unless gross examination identifies a suspicious lesion.
- When more than three slices are submitted the non-apposing faces should form the cutting surface ensuring the microscopic sections are no more than 2 mm apart and to maximise detection of MAC.
- Each sentinel lymph nodes must be in a separate cassette.
- A block index must be maintained.

9.3.2 Protocol/Levels

A single H&E section of each block of lymph node, with minimal trimming, should be examined initially.

If no metastasis is identified, complete the remainder of the protocol as follows:

- *without trimming* take 1 x AE13 and 1 x unstained spares
- trim 150 microns and take 1 x H&E, 1 x AE13 and 1 x unstained spares
- repeat x 3, until 5 levels in total are completed

In a bilateral procedure, if one SLN is positive on initial H&E, but the nodes(s) on the contralateral side are negative, ultra-staging should be carried out only on the contralateral node(s).

9.3.3 Synoptic reporting

For each side it is recommended to report as synoptic report (Figure 4).

Macroscopic
- Number of nodes:
- Measurements (3 dimensions): …x…x… mm
- Sectioned, *at right angles to long axis*, into ……….. slices
- Morphological features (colour, nodularity, haemorrhage, necrosis etc):
- All slices embedded: Yes
- Each node in a separate block: Yes

Microscopic
- Anatomical Site:
- Sentinel Node: YES/NO
- Protocol: 4 pairs of sections cut 150 microns apart for 1xH&E, 1xAE1/3 at each level
- Number of nodes:
- Number containing metastatic deposits:
- Site of deposit: Subcapsular, Intraparenchymal, Sinusoidal
- Size of deposit: …mm (or single cells)
- Nature of deposit: Isolated Tumour Cells/ITCs (Single cells, or clusters less than or equal to 0.2 mm), Micrometastasis (> 0.2 mm but less than or equal to 2 mm), Metastasis (> 2 mm)
- Detection by: H&E/IHC/Both H&E and IHC
- Extracapsular spread: YES/NO
- Greatest dimension from capsule: …mm

Figure 4*: Synoptic SLN in cervical cancer pathology report.*

10. Adjuvant treatment guidelines

10.1 General statement on adjuvant treatment

Indications for adjuvant therapy based on primary tumour features is not part of this statement of recommended practice and remain unchanged and independent of lymph node status, local guidelines and consensus should be used in these indications.

Indications for adjuvant treatment based on lymph node status is shown in figure 5.

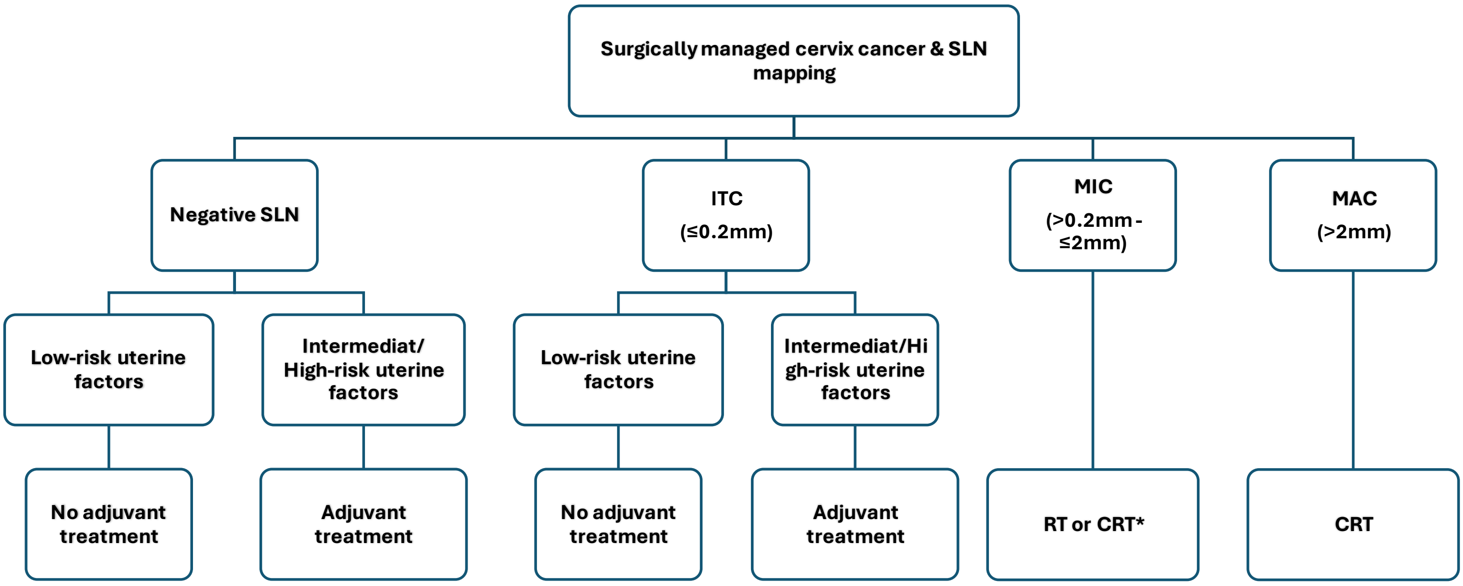

***Figure 5**: Adjuvant treatment recommendation based on SLN status. *Adjuvant chemotherapy in the setting of MIC should be discussed with the patient as this is based on observational data showing a decreased OS in patients with MIC (comparable to MAC) in the SLN.*

10.2 Negative sentinel lymph nodes

Where the SLN is negative on ultra-staging, adjuvant treatment is <u>not indicated</u> so long as there are no indications for adjuvant treatment based on primary tumour features and SLN+/-PLND is performed as per agreed selection criteria and protocol (SLN mapping technique).

10.3 Positive sentinel lymph nodes – Macrometastasis (MAC)

Where MAC is detected on SLN, adjuvant CRT is recommended.

- Extrapolating from advanced stage disease with MAC, adjuvant CRT should be at least equivalent to PLND in terms of pelvic nodal control.
- Omitting PLND may lose information in terms of highest involved node but again this is similar to the treatment of advanced disease with definitive CRT so long as PET scan performed.
- The ongoing PHENIX II trial, looking into the role of PLND in the setting of positive SLN may provide prospective evidence that CRT is non-inferior to PLND+CRT when SLN is positive. (Tu H & group., 2020)

10.4 Positive sentinel lymph nodes – Micrometastasis (MIC)

Where MIC is detected on SLN, adjuvant radiotherapy is recommended, and adjuvant chemotherapy should be considered. However, this recommendation is based on observational data showing a decreased OS in patients with MIC (comparable with MAC) in the SLN and should be discussed with the patient. Currently there is a lack of high-quality evidence on this topic.

- A large retrospective study has demonstrated the presence of MAC and MIC is significantly associated with decreased OS. (Cibula D A.-R. N., 2012)
- In contrast the combined data from the prospective SENTICOL I and II trials suggest that MIC and ITC do not decrease DFS in early-stage cervical cancer patients, however only 24 patients with low-volume metastasis were included in the analysis. (Guani B B. V., 2020)
- Despite the insufficient data that exist with regards to adjuvant treatment in low-volume metastasis in early-stage cervical cancer, the ESGO guidelines recommends adjuvant CRT in the case of MIC due to the majority of retrospective data indicating a reduced survival in the setting of MIC in SLN. (Cibula D R. M., 2023)
- No strong evidence for or against adjuvant chemotherapy and the use of chemotherapy for MIC nodal disease is extrapolated from the evidence for MAC nodal disease. High level evidence is not likely to become available.

10.5 Positive sentinel lymph nodes – Isolated tumour cells (ITC)

Where ITC is detected on SLN, adjuvant treatment is not recommended (unless there are other risk factors based on the primary tumour).

- Retrospective and prospective studies have not demonstrated worse outcomes for patient with ITCs. (Cibula D A.-R. N., 2012) (Guani B B. V., 2020)
- In patients with low volume metastasis in the SLN, only 3.6% were identified to have subsequent MAC after a systematic PLND was performed (n=23, ITC=4 MIC= 19) (Cibula D A.-R. N., 2012), and some of those cases may have qualified for adjuvant treatment base on primary features, so the likelihood of undertreating nodal disease by omitting adjuvant treatment for ITCs is expected to be very low.
- In the original SENTICOL trial, 7 patients had ITCs only, two had adjuvant treatment based on primary features and none had recurrence. (Guani B D. M., 2019)
- The ESGO guideline states that adjuvant treatment may be considered in the setting of ITC, however, also states that the prognostic impact remains uncertain. (Cibula D R. M., 2023)

11. Update, Evaluation & Audit

11.1 Update

Current evidence is evolving in the field of SLN mapping in early-stage cervical cancer. A mandatory review, update, and evaluation of this statement of recommended practice is planned once new evidence in published. This is expected to occur in January 2026/2027.

There will be a specific focus on:

- Randomised controlled data looking into the of long-term outcomes of patients undergoing SLN mapping only compared to systematic PLND. The first result from these trials is expected to be published in 2026.
  - SENTICOL III trial (Lécuru FR, 2020)
  - SENTIX trial (Cibula D D. J., 2019)
  - PHENIX trial (Tu H & group., 2020)
- Evolving data on Silva Pattern-based classification for HPV-associated adenocarcinoma of the cervix and effect on lymph node metastasis/SLN mapping.

- Feedback received from patients, clinicians, and stakeholders.

11.2 Audit

As a result of the success of cervical cancer prevention strategies including screening and vaccination, cervical cancer is a relatively uncommon disease in Aotearoa New Zealand and Australia. Consequently, caseloads for individual centres and individual surgeons are low. While audit has an important role in ensuring safe surgical care it has a particularly important role in the establishment of new surgical procedures. While the use of SLN mapping is familiar to most gynaecological oncologists in Endometrial and Vulvar cancer its use in cervical cancer is being established. As individual surgeons only have small caseloads institutional audit is of limited value combining data from multiple similar institutions has the potential to determine real world, utility, outcomes, and safety of uncommonly performed procedures.

Our group is familiar with the concept of prospective multi centre audit of sentinel node procedures having successfully conducted an audit of sentinel node biopsy in vulvar cancer.

We therefore propose a similar multicentre audit for sentinel node biopsy in cervical cancer in Aotearoa New Zealand and Australia. This Audit will be developed as a separate document and project to this statement of recommended practice.

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