

MANAGEMENT OF EARLY STAGE CERVICAL CANCER

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LEARNING OBJECTIVES

- Definition of Early Stage Cervical Cancer
- Management of Pre-invasive lesions
- Management of Early stage invasive lesions
- Comparisons- advantages/disadvantages of treatment modalities
- Summary and recommendations





DISCLAIMER

- CONFLICT OF INTEREST : NONE



DISCLAIMER

- DISCLOSURES : NONE

International Federation of Gynecology and Obstetrics (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 [≡]
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 [¶]
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 nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes ^Δ
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 nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes (including micrometastases), irrespective of tumor size and extent (with r and p notations) ^Δ
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 edema, as such, does not permit a case to be allotted to Stage IV.)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

When in doubt, the lower staging should be assigned.

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

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

^Δ 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.

From: Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. *Int J Gynaecol Obstet* 2018; 143 S2:22. Available at: <https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/ijgo.12611>. Reproduced under the terms of the [Creative Commons License 4.0](#).

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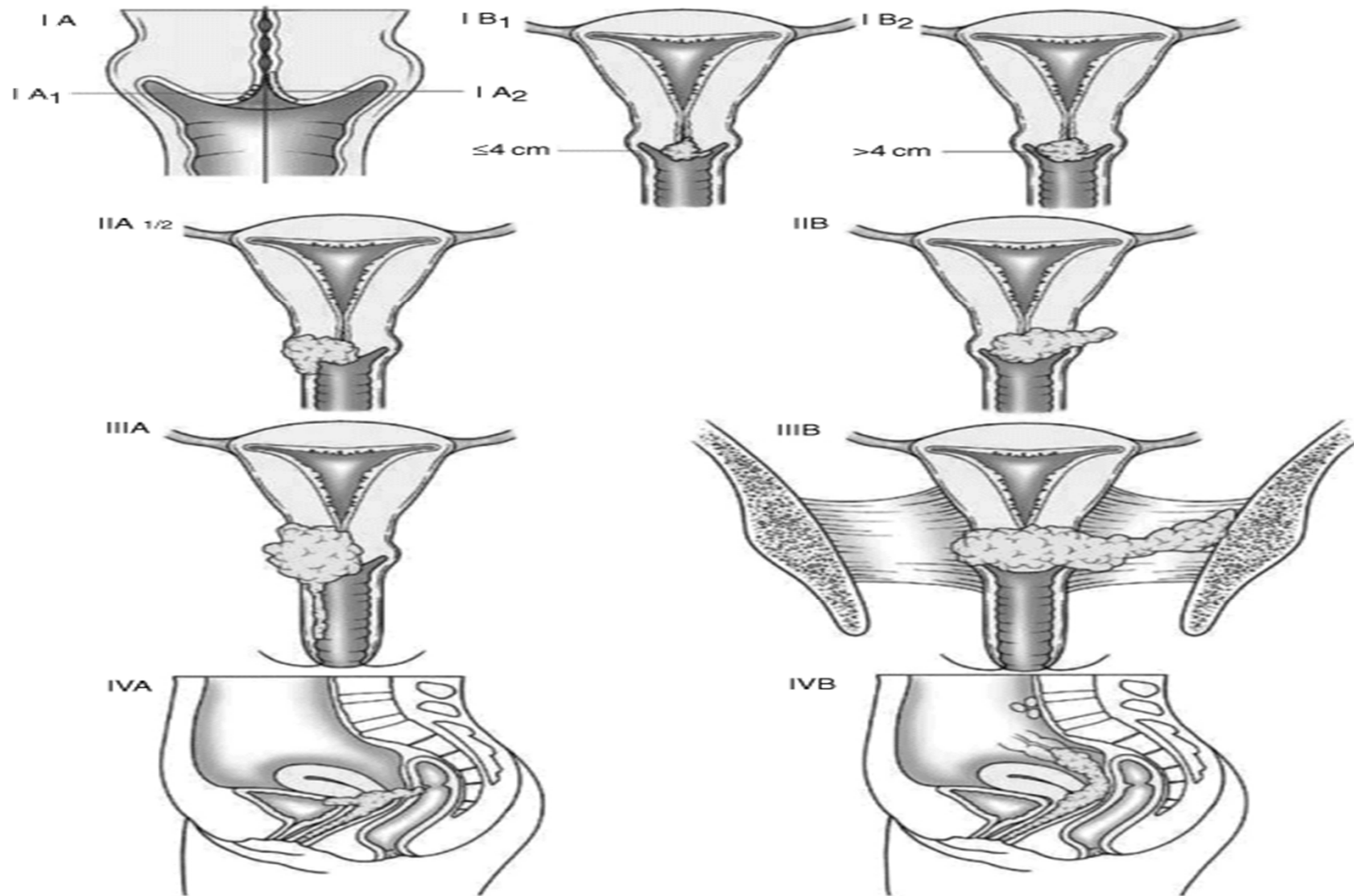
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STAGING OF CERVICAL CANCER

- Stage-1- The carcinoma strictly confined to uterus (extension to uterine corpus should be disregarded)
- Stage-2- The carcinoma invades beyond the uterus but has not extended into lower third of vagina or to the pelvic wall
- Stage-3- The carcinoma involves the lower third of vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves the pelvic and/or para-aortic lymphnodes
- Stage-4- The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) mucosa of bladder or rectum

Early-stage cervical cancer

Refers to FIGO stage IA, IB1, and IB2 disease

- Stage IA – Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm.
 - IA1 – Measured stromal invasion ≤ 3 mm in depth.
 - IA2 – Measured stromal invasion >3 mm and ≤ 5 mm in depth.
- Stage IB1 – Invasive carcinoma with >5 mm depth of stromal invasion, and ≤ 2 cm in greatest dimension.
- Stage IB2 – Invasive carcinoma >2 cm and ≤ 4 cm in greatest dimension.

Treatment Options

- Stage IA1 – Cone biopsy or extra-fascial hysterectomy without lymphadenectomy. If intermediate- or high-risk factors are present, a modified radical hysterectomy should be performed.
- Stage IA2 and IB1 - Modified radical hysterectomy with pelvic lymphadenectomy
- Stage IB2 - Radical hysterectomy with pelvic lymphadenectomy

Types of hysterectomy

Subtotal/supracervical
Subtotal/supracervical hysterectomy. The uterus is removed. The superior portion of the cervix is amputated; the remainder of the cervix is conserved. Intrafascial hysterectomy is a subtype of subtotal hysterectomy in which the uterosacral ligaments are conserved. ^[1]
Piver-Rutledge-Smith Classification [2]
Class I
Extrafascial hysterectomy. The fascia of the cervix and lower uterine segment, which is rich in lymphatics, is removed with the uterus.
Class II
Modified radical hysterectomy. The uterine artery is ligated where it crosses over the ureter, and the uterosacral and cardinal ligaments are divided midway towards their attachment to the sacrum and pelvic sidewall, respectively. The upper one-third of the vagina is resected.
Class III
Radical hysterectomy. The uterine artery is ligated at its origin from the superior vesical or internal iliac artery. Uterosacral and cardinal ligaments are resected at their attachments to the sacrum and pelvic sidewall. The upper one-half of the vagina is resected.
Class IV
Radical hysterectomy. The ureter is completely dissected from the vesicouterine ligament, the superior vesical artery is sacrificed, and three-fourths of the vagina is resected.
Class V
Radical hysterectomy. There is additional resection of a portion of the bladder or distal ureter with ureteral reimplantation into the bladder.

References:

1. Semm K. Hysterectomy via laparotomy or pelviscopy. A new CASH method without colpotomy (German). *Geburtshilfe Frauenheilkd* 1991; 51:996.
2. Piver MS. Five classes of extended hysterectomy for women with cervical cancer. *Obstet Gynecol* 1974; 44:265.

Treatment Options cont...

- **Women who wish to preserve fertility** – Appropriately selected women of reproductive age with early-stage disease who wish to preserve fertility may be candidates for fertility-sparing surgery.
- **Women who are not surgical candidates due to poor functional status** – Primary radiation therapy (RT) with or without chemotherapy.

Adjuvant chemo-radiation

- **Intermediate-risk factors** (ie. tumor size >4 cm, the presence of lympho-vascular space invasion [LVSI] and/or deep cervical stromal invasion)
- **High-risk factors** (ie, pathologically involved lymph nodes, parametrial invasion, or positive surgical margins)
- In these patients, chemoradiation, rather than observation or RT alone, results in an improvement in progression-free survival (PFS) and may improve overall survival (OS)

Surgery versus primary RT

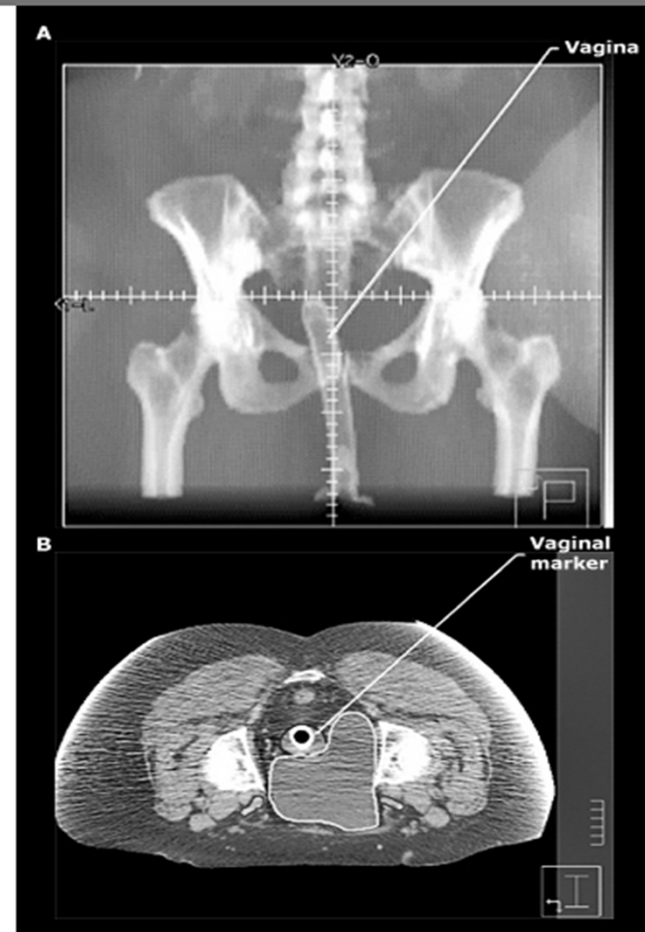
- An important factor in the decision between surgery and RT is that premature ovarian insufficiency and long-term sexual dysfunction- Both are more with RT
- Reserve primary RT with or without chemotherapy for women who are not candidates for primary surgery due to medical comorbidities or poor functional status
- A RCT (n = 343) in women with stage IB and IIA cervical cancer found that **radical surgery** compared with RT had **equivalent rates of five-years survival** (83 percent for both) and **disease-free survival** (DFS; 74 percent for both), and comparable **recurrence rates** (surgery: 25 percent; RT: 26 percent) . Severe **morbidity was higher with surgery**.
- Retrospective study of 4885 women with stage IB1 to IIA cervical cancer showed **surgery** to be associated with a **survival benefit** compared with RT alone (hazard ratio [HR] 0.41, 95% CI 0.35-0.50) .

- Landoni F, Maneo A, Colombo A, et al . Randomized study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet. 1997;350(9077):535.
- Bansal N, Herzog TJ, Shaw RE, et al. Primary therapy for early-stage cervical cancer: radical hysterectomy vs radiation. Am J Obstet Gynecol. 2009;201(5):485.e1.

PRIMARY RT

- Can be aided by the placement of a marker at the time of simulation

Pelvic radiation therapy field with vaginal marker



Radiograph (A) and computed tomography (CT) scan (B) demonstrating a radiopaque vaginal marker, placed to aid in localization of the vagina for treatment planning.

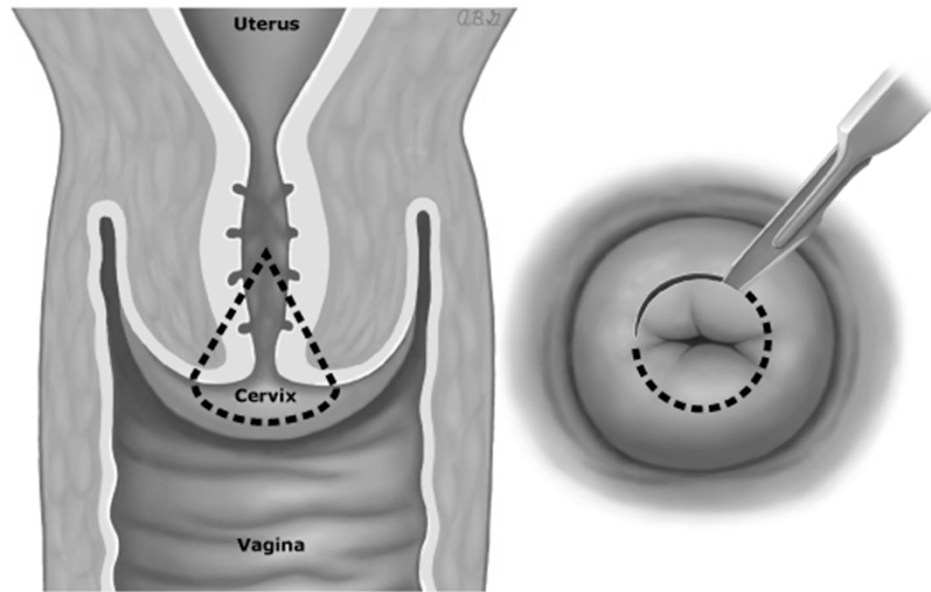
Courtesy of Kristin Bradley, MD and Derek McHaffie, MD.

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TREATMENT OF STAGE IA1

- **Extra-fascial hysterectomy or conization** — Treatment is limited to women with micro-invasive disease with stromal invasion ≤ 3 mm in depth (stage IA1) who have no evidence of intermediate- or high-risk features
- Conization- is often performed as part of the diagnostic evaluation and staging procedure for cervical cancer. Repeat conization is required if there is a positive margin. As there is low risk for lymph node involvement, pelvic lymphadenectomy is not indicated.
- Conization alone for women who wish to preserve their fertility, and extrafascial hysterectomy for women who desire definitive treatment.
- The surgical approach for extra-fascial hysterectomy may be vaginal (preferred), laparoscopic, robotic-assisted laparoscopic, or abdominal.

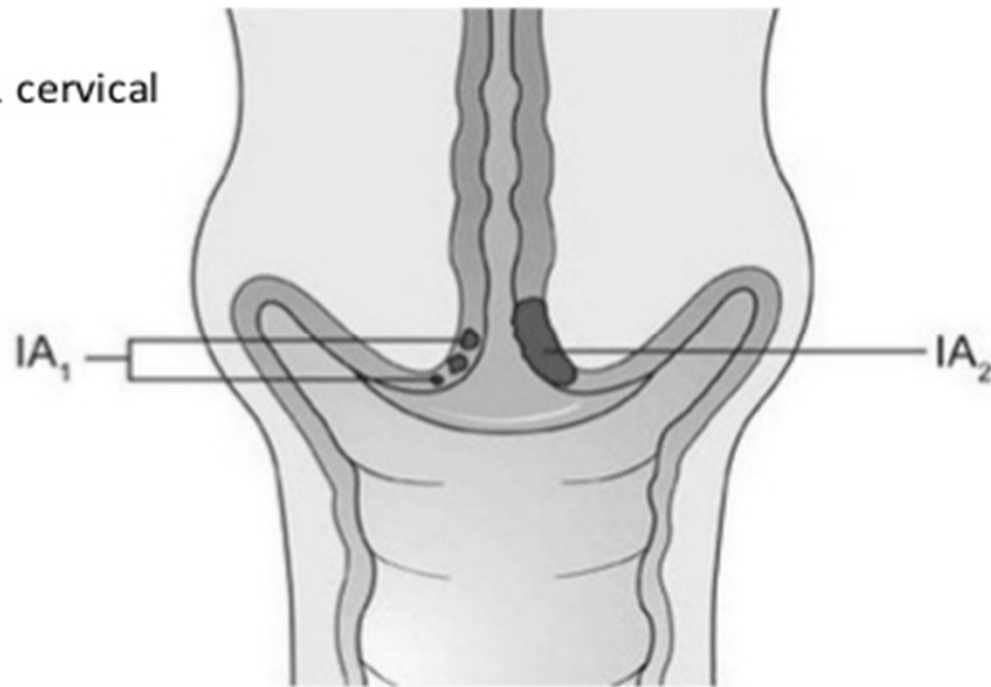
CERVICAL CONIZATION



- It is the surgical removal of a cone-shaped portion of cervix.
- This can be done in order to diagnose cervical cancer (called a "cone biopsy") or, to treat very early-stage cervical cancer by removing the cancerous area.
- It is performed through the vagina, under anesthesia.

Simple Hysterectomy (Type I)

- Also known as an *extrafascial hysterectomy*, removes the uterus and cervix, but does require excision of the parametrium.
- It is appropriately selected for stage IA1 cervical cancer.



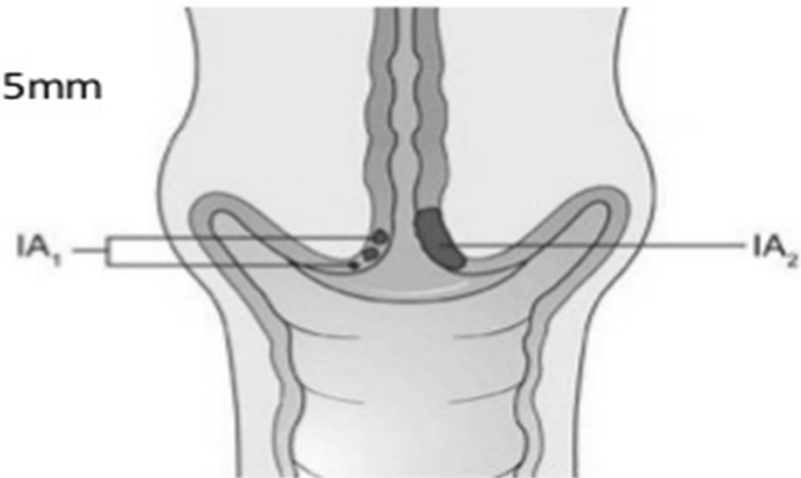
TREATMENT OF STAGE IA2 AND IB1

- The standard treatment for stage **IA2** and stage **IB1** cervical cancers is a modified radical hysterectomy (class II hysterectomy)
- in a retrospective series of 1253 women treated, the rate of recurrence at 12-year follow-up was: stage IA (1 of 104; 0.1 percent) and IB1 (40 of 762; 5 percent) [11].
- Pelvic lymphadenectomy is performed at the time of radical hysterectomy; para-aortic lymphadenectomy is performed if the pelvic nodes are suspicious for metastatic disease. Sentinel lymph node evaluation can be done. Ovaries are typically preserved in women with squamous histology as ovarian metastases are less common with squamous cell histology

- Suprasert P, Srisomboon J, Charoenkwan K, et al. Twelve years experience with radical hysterectomy and pelvic lymphadenectomy in early stage cervical cancer. *J Obstet Gynaecol.* 2010 Apr;30(3):294-8.
- Shimada M, Kigawa J, Nishimura R, Yamaguchi S, et al. Ovarian metastasis in carcinoma of the uterine cervix. *Gynecol Oncol.* 2006;101(2):234.

Modified Radical Hysterectomy (Type II)

- Modified radical hysterectomy removes the cervix, proximal vagina(1-2cm), and parametrial and paracervical tissue.
- This hysterectomy is well suited for tumors with 3- 5mm depths of invasion and smaller stage IB tumors.

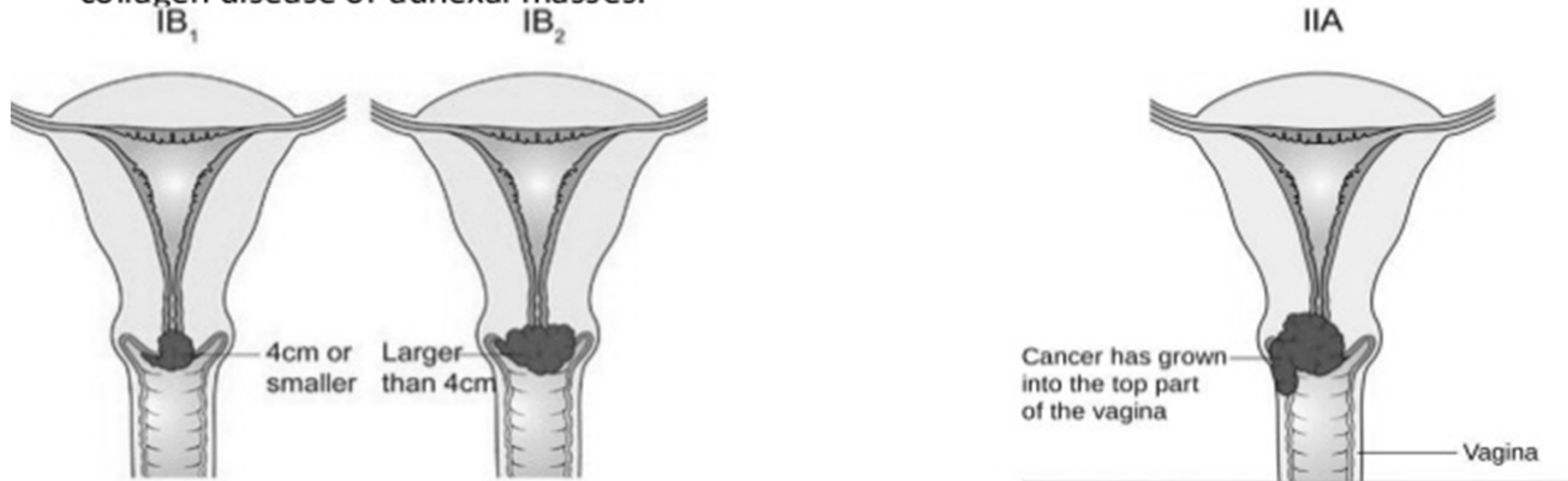


TREATMENT OF STAGE IB2

- Radical hysterectomy (class III hysterectomy) that includes removal of more vaginal tissue
- Stage IB2 was an independent risk factor for poor prognosis (relative risk [RR] 2.4, 95% CI 1.4-4.1) and increased the rate of disease recurrence (11 of 78 patients; 14 percent)

Radical Hysterectomy (Type III)

- Requires greater resection of the parametria, and excision extends to the pelvic sidewall .
- In addition, at least 2 to 3 cm of proximal vagina is resected.
- This procedure is performed for larger IB lesions/IIA lesions, and for patients with relative contraindications to radiation such as diabetes, pelvic inflammatory disease, hypertension, collagen disease or adnexal masses.



Mode of surgery

- Radical hysterectomy for cervical cancer with tumors ≥ 2 cm in diameter-laparotomy approach is preferred
- Radical hysterectomy for patients with smaller tumors (< 2 cm) -minimally invasive surgery(MIS) or robotic-assisted surgery is preferred
- A meta-analysis of 15 observational studies including almost 9500 patients undergoing radical hysterectomy for stage IA1 to IIA cervical cancer, MIS compared with open surgery was associated with a higher risk of recurrence or death (pooled HR 1.71, 95%CI 1.36-2.15)
- Robotic radical hysterectomy is associated with significantly less operative time and blood loss than laparotomy. The two procedures have similar complication rates, OS, and progression-free survival time.

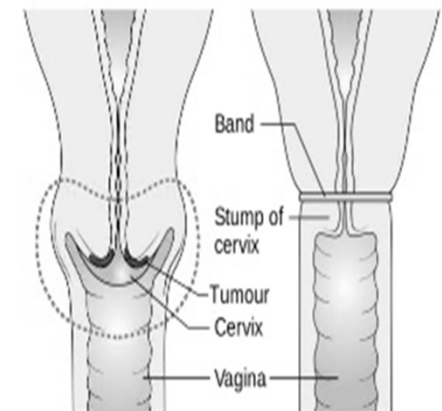
- Nitecki R, Ramirez PT, Frumovitz M, et al. Survival After Minimally Invasive vs Open Radical Hysterectomy for Early-Stage Cervical Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol.* 2020;6(7):1019.
- Chen L, Liu LP, Wen N, et al. Comparative analysis of robotic vs laparoscopic radical hysterectomy for cervical cancer. *World J Clin Cases.* 2019;7(20):3185-3193. doi:10.12998/wjcc.v7.i20.3185

Fertility-sparing surgery

- Considered for women with early-stage disease (stage IA1 with LVSI or stage IA2 to IB1) at low risk of cancer recurrence (ie, lesion size ≤ 2 cm; no lymph node metastases) .
- The surgical options include conization and trachelectomy

Radical Trachelectomy

- Also known as cervicectomy, is a surgical removal of the uterine cervix.
- As the uterine body is preserved, this type of surgery is a fertility preserving surgical alternative to a radical hysterectomy and applicable in selected younger women with early cervical cancer
- It is appropriately selected for stage IA1/IA2/IIA cervical cancer.



- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Cervical cancer. http://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf
- <https://image.slidesharecdn.com/surgicalmanagementofcarcinomacervix-160709112013/95/surgical-management-of-carcinoma-cervix-7-638.jpg?cb=1468063301>

SPECIAL CIRCUMSTANCES

- **Pregnancy-** Decisions regarding timing of treatment and delivery require careful consideration of the stage of disease, the trimester in which the diagnosis is made, and the patient preferences regarding the pregnancy.
- **Incidentally diagnosed cancer** — If early-stage disease detected after a simple hysterectomy- no additional therapy. However, if more advanced disease are identified ,further surgical or medical treatment may be required.
- **Considerations during the COVID-19 pandemic** — The COVID-19 pandemic has increased the complexity of cancer care. Important issues include balancing the risk from treatment delay versus harm from COVID-19, ways to minimize negative impacts of social distancing during care delivery, and appropriately and fairly allocating limited health care resources.

REFERENCES

- Revised FIGO Staging for Carcinoma of the Cervix Uteri." *Int J Gynaecol Obstet* 2019; 147:279.
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- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Cervical cancer. http://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf
- <https://image.slidesharecdn.com/surgicalmanagementofcarcinomacervix-160709112013/95/surgical-management-of-carcinoma-cervix-7-638.jpg?cb=1468063301>
- Nitecki R, Ramirez PT, Frumovitz M, et al. Survival After Minimally Invasive vs Open Radical Hysterectomy for Early-Stage Cervical Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol.* 2020;6(7):1019.
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- Shimada M, Kigawa J, Nishimura R, Yamaguchi S, et al. Ovarian metastasis in carcinoma of the uterine cervix. *Gynecol Oncol.* 2006;101(2):234.
- Mota F. Microinvasive squamous carcinoma of the cervix: treatment modalities. *Acta Obstet Gynecol Scand.* 2003;82(6):505.
- Ahmed, A., Tan, L., & Shafi, M. (2009). Cervical and vaginal cancer. In M. Shafi, H. Earl, & L. Tan (Eds.), *Gynaecological Oncology* (pp. 147-162). Cambridge: Cambridge University Press. doi:10.1017/CBO9780511691799.012