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| [Brain Mets/Palliative/Oligo/Immuno](https://bit.ly/PalliativeRoR)| [Breast](https://bit.ly/BreastRoR) | [CNS/Peds](http://bit.ly/CNSandPeds) | [Constraints](https://bit.ly/RoRConstraints) | [GI](https://bit.ly/RoRGI) | [GU](https://bit.ly/GURoR) | [**Gyn**](https://bit.ly/RoRGyn)| [H&N/Skin](https://bit.ly/HNRoR) | [Heme](https://bit.ly/RoRHeme) | [Sarcoma](https://bit.ly/RoRSarcoma) | [Thorax](https://bit.ly/RoRThorax) | [Rad Phys/Bio](https://bit.ly/RORPhysBio)  [**www.RadOncReview.org**](http://www.radoncreview.org)  For best navigation, click on the Table of Contents (ToC) to navigate and click on a subheader or header to return to the ToC. Otherwise, use the Document Outline feature or control-F to search for a clinical trial or type ASCO '20 to see what's new. Best held horizontally on mobile.  **This document is a collaborative resource. All comments, corrections, and additions are welcome! Editing tips [**[**here**](https://docs.google.com/document/d/163jAwVLz8Wnno7jttJnDIM-4kTxkSSmj9XLP1W5pPJs/edit)**].**  Patterns of recurrence data found in the Follow Up section for most disease sites. Ongoing Trials are found in Future Directions.  2020 Gold Star Summary Box: [[General Overview](#_t4kv4aacj9qi)] of Gynecologic malignancies. |

See NCTN Trial Portfolios by Disease Site: [[Gyn](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_GYNE_Trials.pdf)]

# Gynecologic

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| [**General**](#_t4kv4aacj9qi)  [Uterine Cancer](#_83m96wfmlocl)  [Cervical Cancer](#_rtjdwwmi0dfj)  [Vulvar Cancer](#_k19a41x9sid8)  [Brachytherapy](#_qxjzzedoyoxn)  [Cervical cancer](#_bqy7544hnf4w)  [Endometrial cancer](#_uea73z4c4po1)  [Relapsed Gynecologic malignancies](#_hhogskebb6ms)  [Treatment Planning](#_cyceuqnig849)  [Post-Operative Consensus Guidelines](#_eb93f2h9mmw)  [Lymph node Boosts](#_y9l1m6e7xjg3)  [WPRT Fields](#_rdqhiroqx6vu)  [IMRT Trials](#_voic7ljxmng9)  [Toxicity](#_kwb29p841dr6)  [Radiation Proctitis](#_qre45bwvt8hy)  [**Cervical Cancer**](#_npqfvkgpavlm)  [Types of Hysterectomy](#_yrcjyvw6jf2d)  [Early Stage Cervical Cancer](#_5lk9il1h0h7r)  [Locally Advanced / Bulky (>4 cm) Cervical Cancer](#_yz77wn3eqois)  [Historical Studies](#_hn3lnpbyk3qu)  [Modern Studies](#_hu9bxcxl49uf)  [Recurrent disease](#_2bwhgio65uf3)  [Metastatic disease](#_ktoj0p128ndq)  [Toxicity](#_ud351cf7in4a)  [Brachytherapy](#_1nf811u0hkfi)  [Point based planning](#_452nd8rbg7bt)  [Volume based (3D) planning](#_ja7eh4sj5kkt)  [RetroEMBRACE](#_oz5ykvjkls6u)  [EMBRACE I](#_efhwb1dgreff)  [EMBRACE II](#_pik419qibug)  [Dosing regimens](#_tfoawe58l2ux)  [Volume-based Treatment Planning](#_6xguu6v0w1a2)  [Treatment Planning](#_a6plw395yelu)  [SBRT boost?](#_g1nbtfay0vog)  [Follow up](#_otbu8tgwul23)  [Future Directions](#_xgw4qyr3grr8)  [Organ Confined, High risk](#_ih3q475b5xt0)  [Newly diagnosed, Locally advanced](#_62ygxj6thrlj) | [**Endometrial Cancer**](#_3llouklhg1v3)  [Surgery](#_tswqoux8snp9)  [Lymph Nodes](#_l4vsoe7fdwuc)  [SLNB](#_8luavf34me13)  [Chemotherapy](#_i15tke1c82bc)  [Nomograms](#_m811c6vihx23)  [Early Stage Endometrial Cancer](#_x5yfx9juqx)  [Low risk Endometrial cancer](#_d5kt0vbcjfi)  [IBG3 disease](#_duv4qqb1j2a8)  [PORTEC vs. GOG in a nutshell](#_pqcmr8kiuidd)  [Advanced Stage Endometrial Cancer](#_70muvcsfz1v8)  [Recurrent Endometrial Cancer](#_z3gqjm7iu1m0)  [Toxicity](#_rcbajempumfm)  [Brachytherapy](#_oc4dol5dwo1z)  [Intact uterus](#_hfs8g2syw14i)  [Treatment planning](#_ce97gipx12r6)  [Follow up](#_1vm4pc34eiot)  [Future Directions](#_e9e7oz6ftgla)  [**Uterine Sarcoma**](#_aoxg7c5f2mcc)  [**Vulvar Cancer**](#_jvy8eyvc333a)  [Surgical margins](#_dx362qpsjtbt)  [Lymph Node Management](#_p6thujzfu6i0)  [Role of SLNB](#_9fm3d2nhu2al)  [Toxicity](#_oyrd18xw0vzg)  [Treatment Planning](#_dv2j8zcaqa9a)  [Follow up](#_n403ifh5ce3i)  [**Vaginal Cancer**](#_ngxza69hnb07)  [Toxicity](#_tluevzph8s0l)  [Treatment Planning](#_wwy9huh4bf08)  [Follow up](#_jxvffzvi81gh)  [Future Directions](#_ppa831wuylrl)  [**Ovarian Cancer & Fallopian tube Cancer**](#_2y4nw0w64v2o)  [Future Directions](#_b0dcq0tt2tp3) |

[**StatPearls: Cervical**](https://www.ncbi.nlm.nih.gov/books/NBK431093/) *Last update: 9/9/2019.*

[**StatPearls: Cervical Intraepithelial Neoplasm (CIN)**](https://www.ncbi.nlm.nih.gov/books/NBK544371/)*Last update: 6/16/2019.*

[**StatPearls: Cervical Screening**](https://www.ncbi.nlm.nih.gov/books/NBK537348/)*Last update: 1/4/2019.*

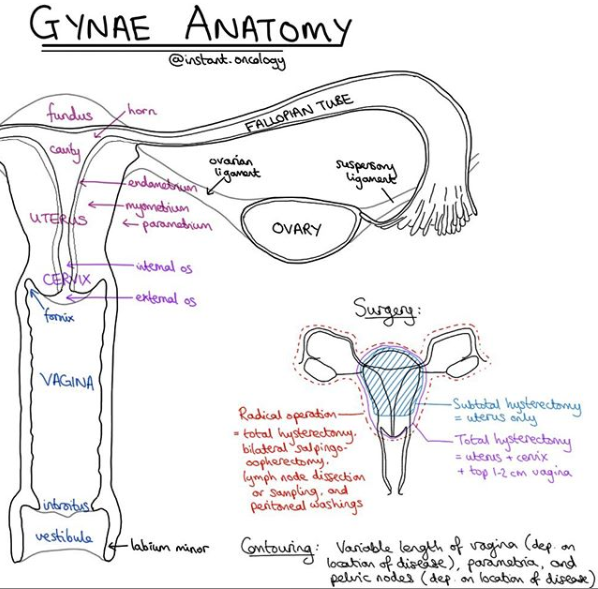
[**StatPearls: Endometrial**](https://www.ncbi.nlm.nih.gov/books/NBK525981/)*Last update: 7/22/2019.*

## 

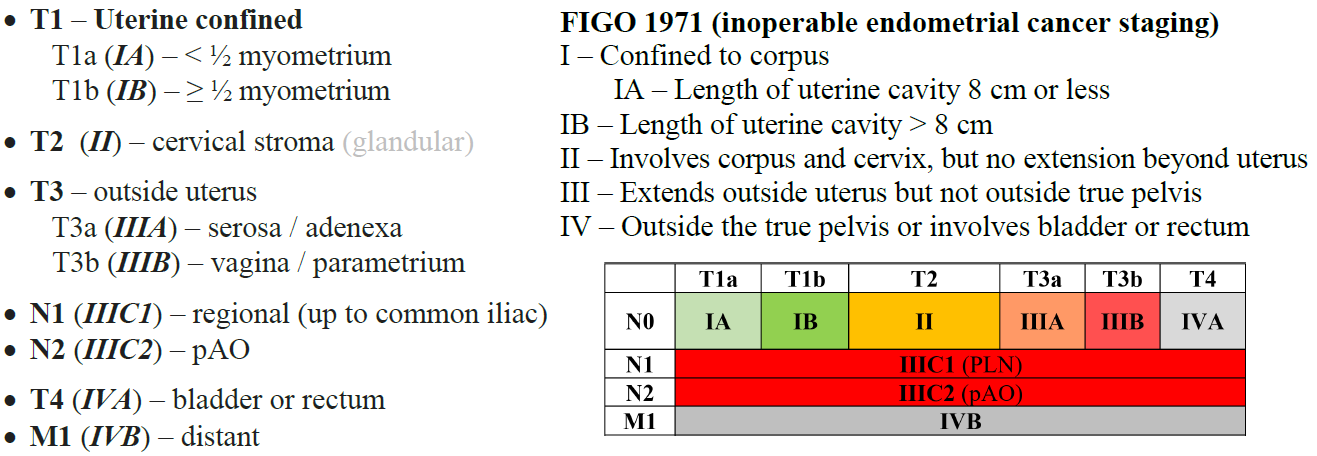
# General

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| **Gynecologic Malignancies** [[Suneja and Viswanathan Heme/Onc Clin N. Amer '20](https://www.sciencedirect.com/science/article/pii/S088985881930111X?via%3Dihub)]: **Excellent Summary Article**.  *See General Principles of Staging on the next page.*  Gyn staging [[Zaorsky](https://twitter.com/NicholasZaorsky/status/1219773291528884229?s=20)], comparison of hysterectomy subtypes and trachelectomy [[Zaorsky](https://twitter.com/NicholasZaorsky/status/1221824856834158592?s=20)], Gyn nodes [[Zaorsky AP](https://twitter.com/NicholasZaorsky/status/1221823861978693632?s=20), [Lat](https://twitter.com/NicholasZaorsky/status/1221824276740956162?s=20)]   * Gyn malignancies are among the most prevalent cancers worldwide.  [Uterine Cancer](#_t4kv4aacj9qi) *See General Principles of Staging on the next page.*  Endometrial staging [[Zaorsky](https://twitter.com/NicholasZaorsky/status/1221829707450195975?s=20)]  FIGO Summary Article: Cancer of the corpus uteri [[Amant IJGO '18](https://www.ncbi.nlm.nih.gov/pubmed/30306580)] *Note: Pre-PORTEC-3 final results.*  See [[High intermediate risk](#_gpdbaw92x9m0)] for an understanding of risk groups.  See [[PORTEC vs. GOG in a nutshell](#_pqcmr8kiuidd)] to understand the difference between GOG 249, PORTEC-3 and GOG 258 (Figure 2).   * 60k cases in the USA per year with a relatively stable rate of death (Figure 1). * Endogenous or exogenous estrogen exposure are risk factors, along with HNPCC (Lynch Syndrome). * Most are diagnosed at an early stage due to post-menopausal bleeding. * TVUS to evaluate endometrial thickness followed by endometrial biopsy is the main modality for evaluation. * Extrafascial hysterectomy (TAH) is standard unless there is cervical stromal involvement. * Grade and stage drive risk of recurrence. Depth, Grade, LVSI ("DGL") are risk factors, as is [[Older Age](#vo57kghm48ad)]. * Stage IA G1-2 disease endometrioid histology without LVSI may be cured by surgery alone. * Stage IB and stage II are candidates for ART with EBRT or VBT, particularly if DGL and older age.   + See the new (2020) [[Bayta.us](https://www.bayta.us/nomos/endometrial)] nomogram to guide recommendations for intermediate risk endometrial cancer. * Presence of LVSI typically favors EBRT, although [[focal LVSI](#iuwnoiy6bk4n)] may be treated with VBT alone if no other risk factors.   + One foci involving up to two vessels is focal, while multiple foci is substantial LVSI. * IBG3 disease: EBRT is standard, especially with [[substantial LVSI](#iuwnoiy6bk4n)]. Consider addition of VBT to EBRT (controversial), or potentially even adjuvant chemotherapy (controversial). * If risk factors guide you to lean towards delivery of EBRT, consider the addition of VBT to EBRT for lower uterine segment involvement (LUSI), although the addition of VBT to EBRT is "strongly recommended" for cervical stromal involvement in many trials. * [[PORTEC-4](#1ysyu0brf2hr)] is investigating observation vs. two HDR regimens (21/3 vs. 15/3 to 5 mm) for HIR up to IBG3. * [[PORTEC-4a](#3niegyeqx8u5)] is investigating VBT vs. [[molecular profile](#g2adkm90u58t)]-based treatments for up to microscopic stage II. * Figure 2: See [[PORTEC vs. GOG in a nutshell](#_pqcmr8kiuidd)]. See [[High intermediate risk](#_gpdbaw92x9m0)] for an understanding of risk groups.   + **•** [[**GOG 249**](#6rmy0whpf4lt)]: **WPRT vs. VBT→ CarboP x3c**. No difference in arms, more acute toxicity (heme) in VBT arm. More than 3c is preferred in order to affect development of DM.   + **•** [[**PORTEC-3**](#crqxu2jebdsq)]: **WPRT(B) ± CDDP→ CarboP x4c**. Overall survival advantage for CCRT and Stage III tumors and serous carcinoma. As of 2019, CCRT→ CarboP is standard of care! [QS](http://www.quadshotnews.com/2019/07/time-will-tell.html)   + **•** [[**GOG 258**](#kix.2wgy28yhajjf)]: **WPRT(B)/CDDP→ CarboP x4c vs. CarboP x6c**. Higher risk than PORTEC-3 (more nodal disease). Less pelvic/pAO relapses in CCRT arm. [QS](http://www.quadshotnews.com/2019/06/vintage-asco.html#more) * Optimal sequencing of chemotherapy and radiotherapy remains unknown, although upfront CCRT is common. * Survival varies from 80-90% for stage I disease to 20-40% for stage IV disease.  [Cervical Cancer](#_t4kv4aacj9qi) *See General Principles of Staging on the next page.*  Cervical cancer staging [[Zaorsky](https://twitter.com/NicholasZaorsky/status/1221828307068604417?s=20)], EBRT [[Zaorsky](https://twitter.com/NicholasZaorsky/status/1222649051235127296?s=20)] and brachytherapy [[Zaorsky](https://twitter.com/NicholasZaorsky/status/1222648780903849986?s=20)].   * Third most common gyn malignancy in the USA, although the second leading cause of death worldwide. * Most are squamous cell carcinoma, although adenocarcinoma is not all that uncommon (10-20%). * FIGO 2018 allowed PET/CT and MRI to be a component of staging, therefore LN mets are stage IIIC1/2. * Early stage cervical cancer is traditionally thought of as ≤ 4 cm (new IB2) without parametrial involvement (up to IIA1). * Surgery of choice is typically the modified radical hysterectomy (compare to extrafascial hysterectomy for endometrial).   + Deliver PORT alone for any two: Size ≥ 4 cm, Depth middle/outer third, or LVSI ("SDL" - [[SeDLis](#p8xcqpfzudaz)])   + Deliver POCCRT if 1+: positive nodes (III), positive margins, or parametrial involvement (IIB) ("3 P's" - [[Peters](#lfcem3d38zac)])   + [[GOG 0263](#jq4ldzxzuxcj)] is investigating the role of adjuvant RT vs CCRT in intermediate risk disease. * CCRT/B is recommended for tumors > 4 cm (IIA2, new IB3) and extension beyond upper vagina or nodal involvement.   + Adjuvant hysterectomy is typically not recommended [[GOG 71](#dxwom566rr6)].   + The utility of adjuvant CarboP x4c is being investigated for patients meeting Peters criteria after POCCRT(B) on [[RTOG 07-24](#vyhja2y0cn37)] and after definitive CCRT/B on the [[OUTBACK](#tgrkocfn51fu)] trial. * Cemiplimab (PD-1) is being evaluated in the metastatic setting for platinum-resistant disease [[EMPOWER-Cervical 1](#_xgw4qyr3grr8)]. * Survival varies from 80-95% for stage I disease to 16% for stage IVA disease.  [Vulvar Cancer](#_t4kv4aacj9qi) *See General Principles of Staging on the next page.*  Vulvar cancer staging [[Zaorsky](https://twitter.com/NicholasZaorsky/status/1222649476386578438?s=20)].   * Fourth most common gyn malignancy in the USA with 6k new cases per year. * Staging depends on size and DOI (if > 1 mm, or IB+, do nodal sampling). * Radical local excision is favored for smaller lesions. MRV may be required for large or multifocal lesions. * SLNB may be performed in stage IB-II disease if < 4 cm [[GROINSS-V](#gapq6vf7kmp7)]. All others get IFLND. * Adjuvant RT to vulva recommended for tumors > 4 cm or SM+ / ≤ 5- **8** mm [[Viswanathan '13](#ycth0x2iruaj), [Heaps '90](#owjsvsmvfryg)].   + Newer data says margin distance does impact local recurrence [[Raimond '19](#vz1hugs0vy1n)]. Instead, SM+ for dVIN and LS and stage II+ disease appears to have the greatest association with local recurrence [[GROINSS-V '19 analysis](#lnsp2bntimc4)].   + Surgical excision for close or positive SM appears to be a reasonable alternative to RT for stage I [[Bedell '19](#2ksf2g9o6m4k)] * Adjuvant RT to lymph nodes include: 2+ LN or ECE [[GOG 37](#8jvpsgbv0nv6)]. However, many experts will treat with adjuvant RT even with single lymph nodes due to low salvage rates for pelvic recurrences. * [[GROINSS-V II / GOG 270](#fb8a7u304m1p)] is evaluating the utility of completion IFLND versus adjuvant RT for women with early-stage vulvar cancer with a single positive lymph node after SLNB. * Some physicians perform a biopsy two mo after completion of CCRT and consider surgery if complete response is lacking, while others use CCRT as definitive treatment and reserve surgery for clearly progressing disease.   + [[GOG 279](#obi3l3lyiz4c)] is evaluating the feasibility of this approach.   [**Modern Radiotherapy Planning**](#_t4kv4aacj9qi)   * Simulate the patient with a full and empty bladder if IMRT is to be used. * Consider placing a marker at the vaginal apex if cuff. * Endometrial cancer: Common iliacs, EI, II, Obturators. * Cervical cancer: Common iliacs, EI, II, Obturators, Presacrals. * Include pAOs if common iliacs are involved. Isolated pAO involvement is rare at [[1-3%](#_l4vsoe7fdwuc)], even with fundal involvement. * Include inguinals if the lower vagina or vulva is involved. * Traditional vulvar fields include wide AP and narrow PA fields with supplemental electron dose to the inguinal nodes to achieve target dose while protecting the femoral heads. There is only retrospective vulvar data/interpolation from anal data for the use of IMRT in vulvar cancer. * Typical dose if 45 - 50.4 Gy. Gross nodal disease requires boost, either sequential or SIB. Integrated boosts have not been evaluated in the prospective setting. Parametrial boosts may be delivered as SIB, but are usually not required if interstitial needles are used with brachytherapy. * See Table 3 for excellent dose constraints. * IMRT decreases heme toxicity in the postoperative setting per [[RTOG 04-18](#kix.n1e5fah4ao76)] . * IMRT appears to demonstrate less frequent/almost constant diarrhea and antidiarrheal use in the acute setting [[TIME C](#kix.nqh4mp4cd7f2)].[QS](http://www.quadshotnews.com/2020/02/time-is-on-our-side.html) * There appears to be less bowel obstruction at 5 years with IMRT [[MSKCC](#kix.gn0w00l4s3l9)]. * See [[Verma IJROBP '14](#kix.osgibl16milg)] and [[George Clin Onc '20](#kix.bqagbt7h013l)] for retroperitoneal duodenal constraints for 50 Gy, 55 Gy and 60 Gy. * Frequently tested: Bone Marrow - V40 < 37% , V10 < 90% [[RTOG 04-18](#kix.n1e5fah4ao76)]. Bowel - V40 < 30% [[TIME C](#kix.nqh4mp4cd7f2)].   [**Brachytherapy**](#_t4kv4aacj9qi)  See the [[General Brachytherapy](#_qxjzzedoyoxn)] section, [[Cervical Brachytherapy](#_1nf811u0hkfi)] section, or the [[Uterine Brachytherapy](#_oc4dol5dwo1z)] section for more.   * ABS TG Report: Compendium of fractionation schedules for Gynecologic HDR BT [[Albuquerque BT '19](https://www.sciencedirect.com/science/article/pii/S1538472118306305?via%3Dihub)] * Cervical cancer: See Table 4 or [[EMBRACE II](#_pik419qibug)] [[Target definitions](#kix.8yrje68n0x79)] and [[Coverage recommendations and Constraints](#_6xguu6v0w1a2)]. * [[RetroEMBRACE](#_oz5ykvjkls6u)] demonstrated improved LC and reduced late toxicity for patients with large tumors treated by IGABT. * [[EMBRACE I](#_efhwb1dgreff)] identified improved DVH thresholds for urinary and rectovaginal toxicity. |

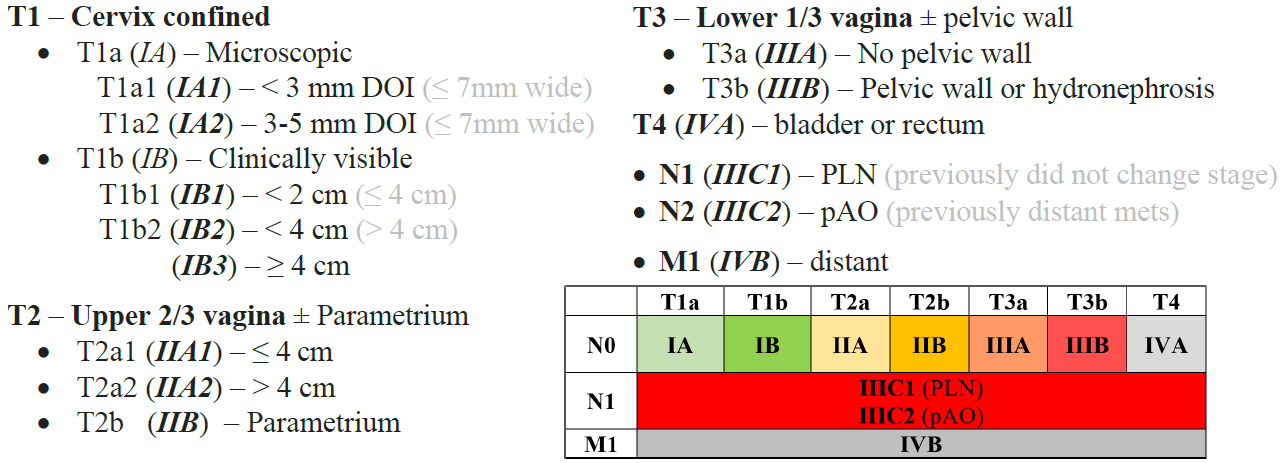
Gyn staging, although note lymph nodes on imaging now effect staging for cervical cancer [[Zaorsky](https://twitter.com/NicholasZaorsky/status/1219773291528884229?s=20)]

[](https://www.instagram.com/p/B8n4ET9geRC/?utm_source=ig_web_copy_link)

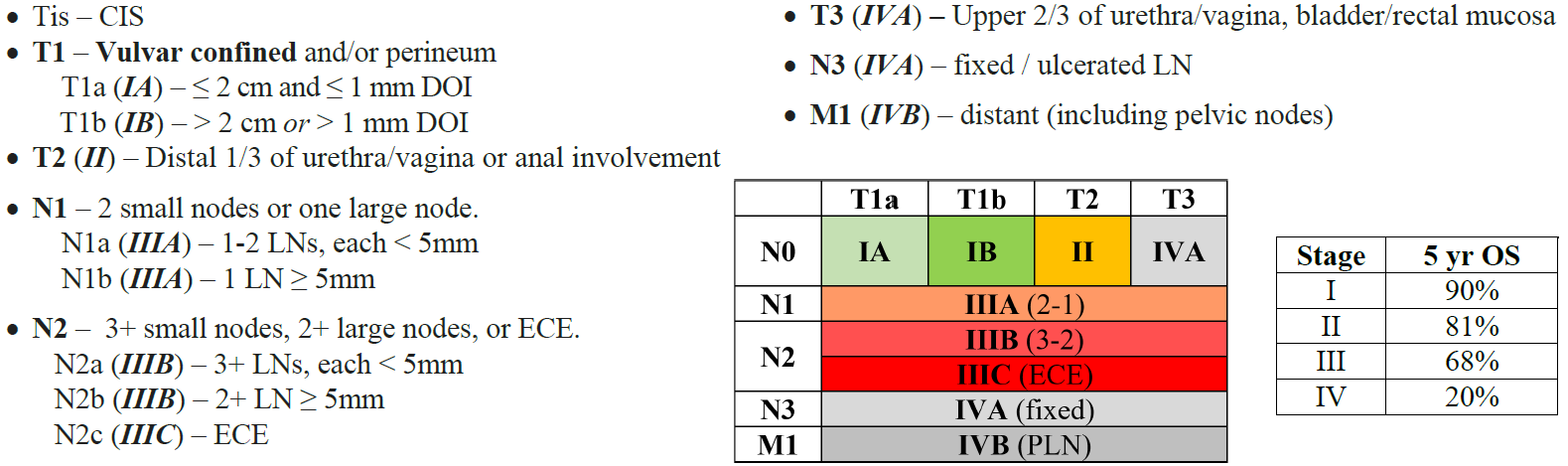
**Endometrial Staging**



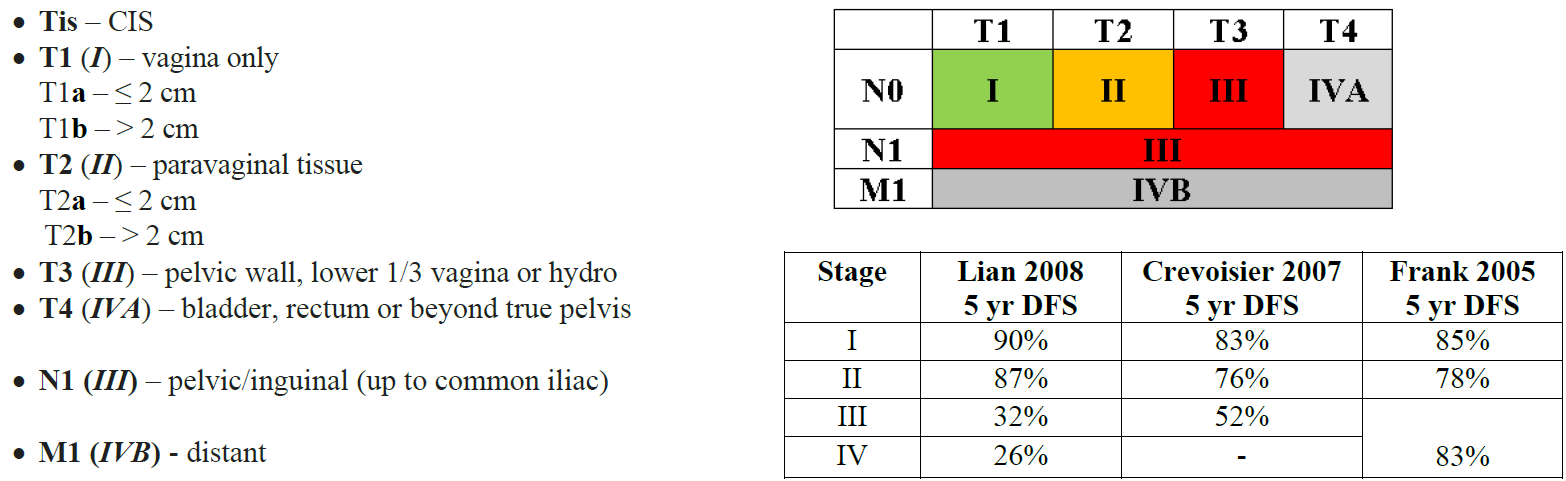
**Cervical Staging**



**Vulvar Staging**



**Vaginal Staging**



## 

## 

## [Brachytherapy](#_nz4p8uik7qem)

**ABS Task Group Report** [[Albuquerque BT '19](https://www.sciencedirect.com/science/article/pii/S1538472118306305?via%3Dihub)] **Compendium of fractionation schedules for Gynecologic HDR BT**.

### 

### [Cervical cancer](#_nz4p8uik7qem)

See the [[Cervical Brachytherapy](#_1nf811u0hkfi)] section for more.

For boards, it is reasonable to give 45 Gy followed by 30/5 (6 Gy - EQD210 84.3) in almost all\* cases.

\*Cases which might require > 87 Gy include large tumors > 30cc or tx delays one week beyond 50 days. Cases which might only require an EQD210 of 80 Gy (e.g., 27.5/5 after 45 Gy EBRT) are those with [[complete response](#1vb7u8jdcrdy)] to EBRT.

Also acceptable to Rx to Point A ( > 65 Gy) with DVH analysis (i.e. account for OAR D2cc).

[[RetroEMBRACE](#_oz5ykvjkls6u)] demonstrated improved LC and reduced late toxicity for patients with large tumors treated by IGABT.

[[EMBRACE I](#_efhwb1dgreff)] identified improved DVH thresholds for urinary and rectovaginal toxicity.

See [[EMBRACE II](#_pik419qibug)], [[Dosing regimens](#_tfoawe58l2ux)], [[Target definitions](#kix.8yrje68n0x79)] and [[Coverage recommendations and Constraints](#_6xguu6v0w1a2)].

**Adjuvant HDR-BT after 45 Gy EBRT**:

* **Point A based**: Use as a starting point to achieve D90 ≥ 100% to the HR-CTV for volume-based planning.
  + 24/3 (8 Gy - EQD2 80.3 Gy)
  + 28/4 (7 Gy - EQD2 83.9 Gy): Over 2 implants - used in Europe for template-based HDR as well.
  + **30/5** (6 Gy **-** EQD2 84.3 Gy).
  + 27.5/5 (5.5 Gy - EQD2 79.8 Gy): Used to be more common, but D90 HR-CTV goal now > 87 Gy EQD2\*.
  + 25/5 (5 Gy - CTV EQD2 75.5 Gy). *27.5-30/5 for cases recommended D90 between 85-95 Gy, but respect OARs.*
  + 30/6 (5 Gy - EQD2 81.8 Gy).
* Templated-based HDR after 45 Gy, treatment with a single application BID.
  + 31.5/9 (3.5 Gy - CTV EQD2 80 Gy).
  + 29.75/7 (4.25 Gy - CTV EQD2 80 Gy).
  + 25/5 (5 Gy - CTV EQD2 75.5 Gy). *27.5-30/5 for cases recommended D90 between 85-95 Gy, but respect OARs.*
* Templated-based HDR after 50.4 Gy, treatment with a single application BID.
  + 27/3 (9 Gy - CTV EQD2 78.8 Gy).
  + 22.5/5 (4.5 Gy - CTV EQD2 77 Gy).

### [Endometrial cancer](#_nz4p8uik7qem)

See the [[Uterine Brachytherapy](#_oc4dol5dwo1z)] section for more.

[[PORTEC-4](#1ysyu0brf2hr)] is investigating observation vs. two HDR regimens (21/3 vs. 15/3 to 5 mm) for HIR up to IBG3.

Nearly half of respondents to the [[2019 ABS survey](#vvscrycdosny)] utilized 21/3 prescribed to 0.5 cm depth for cuff alone, although some practitioners worry about the possibility of late toxicity especially with small cylinders.

ABS recommends to treat the proximal 3-5 cm of the vagina, consider length of vagina for IIIB.

* **VBT monotherapy**: See the [[Treatment of Early Stage endometrial cancer](#f362ka102v2f)] summary box.

See the new (2020) [[Bayta.us](https://www.bayta.us/nomos/endometrial)] nomogram to guide recommendations for intermediate risk endometrial cancer.

* + LDR if monotherapy: 60-65 Gy to vaginal surface.
    - PORTEC-2: HDR 21/3 or LDR 30 to 5mm (dose equivalent of 45-50 Gy).
  + HDR alone:
    - **21/3 to 5mm** (7 Gy - PORTEC 2): Most common scheme based on [[most recent survey](#vvscrycdosny)].

*Around 60 Gy to the vaginal surface and 30 Gy EQD210 to 5 mm with 3 cm cylinder.*

* + - * May be associated with late morbidity.
      * May adjust based on size. For a 2.5 cm cylinder, consider **18/3** **to 5mm** to reduce surface dose.
    - **22/4 to 5mm** (5.5 Gy - ABS survey).Equivalent to 38/4 to surface.

*Around 55 Gy to the vaginal surface and 28 Gy EQD210 to 5 mm with 3 cm cylinder.*

* + - 25/5 to 5mm (5 Gy - Michigan).
    - 15/6 to 5mm (2.5 Gy - Sorbe).
    - 31.5/3 to surface (10.5 Gy - UCSF).
    - 38/4 to surface (8.5 Gy - Australian series). Equivalent to 22/4 to 5 mm.
    - 30/5 to surface (6 Gy - MDACC): Second most common scheme based on [[most recent survey](#vvscrycdosny)].

*Around 40 Gy to the vaginal surface and 15 Gy EQD210 to 5 mm with 3 cm cylinder.*

* + - 24/6 to surface (4 Gy - DFCI/Harvard).
* **Adjuvant VBT after EBRT**:Consider for IBG3 (controversial), cervical (II), vaginal (IIIB) or in the recurrent setting.

See the new (2020) [[Bayta.us](https://www.bayta.us/nomos/endometrial)] nomogram to guide recommendations for intermediate risk endometrial cancer.

* + LDR 20 Gy at vaginal surface.
  + HDR, after 45 Gy EBRT: EQD210 65-70 Gy. If superficial SM+, 70-75 Gy.
    - 15-18/3 to surface after 45 Gy, 12/2 after 50.4/28 WPRT. *One less 6 Gy fraction after 50.4/28 WPRT.*
    - 15/3 to 5 mm after 45 Gy, 10/2 after 50.4/28 WPRT. *One less 5 Gy fraction after 50.4/28 WPRT.*
  + HDR for recurrence after 45 Gy EBRT: EQD210 ≥ 75 Gy .
    - 21/3 to 5 mm (7 Gy - 74 Gy).
    - 24/4 to 5 mm (6 Gy - 76 Gy).
    - 30/5 to surface (5 Gy - 84 Gy).
    - 28/4 to surface (4 Gy - 84 Gy).
* See [[Inoperable Endometrial cancer](#h7y4krhnstic)] for more on treatment of the intact uterus (rare).
  + **Intact IA**: VBT alone for stage IA G1-2. Rx to D90 CTV, goal 48-62.5 Gy EQD210. GTV to 80-90 Gy EQD210.

*Take home: 36/6 VBT (EQD210 only 48 Gy) is adequate for intact IA.*

* + **Intact > IA**: Rx to D90 CTV. Goal 65-70 Gy (stage IA) or 70-75 Gy (stage II+). GTV to 80-90 Gy EQD210.

*Take home: After 45 Gy, 25/5 VBT (EQD210 75 Gy) is adequate for intact > 1A.*

## 

## [Relapsed Gynecologic malignancies](#_nz4p8uik7qem)

Old dogma: nearly all pelvic recurrences are associated with widespread DM, and are invariably incurable [e.g. [PORTEC 2](#swo73a3wobd5)].

New dogma: Around HALF of patients will still be alive at 3 years for isolated pelvic/pAO recurrences!

* **Salvage curative intent reirradiation SBRT for isolated pelvic and/or paraaortic recurrences** [[Ling PRO '19](https://www.sciencedirect.com/science/article/abs/pii/S1879850019301584)]: **40-45/5**.  
  For isolated pelvic and/or pAO recurrences, there is suggestion that around half may be cured with reirradiation SBRT!
  + 20 patients who underwent 21 curative-intent reirradiation SBRT treatments. MFU 2.5y.
  + Median prior dose 45 Gy. Around 2/3 IFF, while 1/3 marginal failures.
  + 3y LC / DMPFS / OS of 61→ 44→ 52%.
  + At last follow up, nearly half of patients remained alive and NED.
  + 3y G2+ / G3+ toxicities of 38→ 14%.
* **ABS working group report on patterns of care for reirradiation** [[Sturdza BT '20](https://www.ncbi.nlm.nih.gov/pubmed/31917178)]:
  + Overall, local control ranged from 44-88% over 1-5 years with OS in the range of 40-82% at 2-5 years.

## Oligometastatic Disease

* **SBRT for oligometastatic or oligoprogressive Gyn malignancies** [[Onal IJCG '20](https://www.ncbi.nlm.nih.gov/pubmed/32273293)]: Retro.

MVA demonstrated patients with early progression ( ≤ 12 mo) and CR after SBRT were most significant for OS.

* + 29 patients with 35 lesions. 21 cervical, 8 ovarian. All 1-4 metastases, no brain mets. MFU 15 mo.
  + De novo in 25%, oligoprogression in 75%.
  + OS at 1 / 2y of 85→ 62%.
  + PFS at 1 / 2y of 27→ 18%.
  + LC at 1 / 2y of 84%.
  + Patients with a CR after SBRT had a significantly higher 2y OS and PFS.

## Treatment Planning

eContour: [[post op endo (pelvis)](http://econtour.org/cases/53), [VBT](http://econtour.org/cases/57)], [[post op cervix](http://econtour.org/cases/55)], [[EMBRACE 2 cervix](http://econtour.org/cases/111)], [[NRG cervix](http://econtour.org/cases/38)], [[Vaginal](http://econtour.org/cases/51)], [[Quad shot](http://econtour.org/cases/58)].

[[AVARO cervix](http://econtour.org/cases/84)], [[AVARO endometrium](http://econtour.org/cases/85)]

* Intrafraction motion (ASTRO refresher 2018): Cervical and uterine motion can exceed 2 cm in many situations.

Perform Daily soft tissue IGRT. May require replanning at short notice.

* + Pooled review of cervical motion: 18-63mm A/P, 18-36mm S/I. *Therefore, 1.5-2 cm PTV recommended.*
  + Pooled review of uterine motion: 20-48mm A/P, 32-45mm S/I.
  + Ask for daily IGRT for day 1-3, then weekly. Ensure cervix and uterus are within PTV.

### [Post-Operative IMRT Consensus Guidelines](#_nz4p8uik7qem)

See the [[Cervical](#_a6plw395yelu)] and [[Endometrial](#_ce97gipx12r6)] Treatment Planning sections for more.

* **IMRT Consensus guidelines for delineation of CTV in Endo/Cervical PORT** [[Small IJROBP '09](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2752724/), [RTOG Gyn Atlas](http://www.rtog.org/corelab/contouringatlases/gyn.aspx)].

TIME-C/RTOG 1203 [[Protocol (Supplement) Klopp JCO '18](http://ascopubs.org/doi/full/10.1200/JCO.2017.77.4273)]: Cervix/Endo (M)RH→ WPRT vs. IMRT. [RoR](#kix.nqh4mp4cd7f2)

RTOG 0418 [[Protocol](https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0418)] for post-operative cervical and endometrial. [RoR](#kix.n1e5fah4ao76)

See eContour cases on [[post op endo (pelvis)](http://econtour.org/cases/53)], [[post op cervix](http://econtour.org/cases/55)]

* + Supine, vaginal marker at apex. Simulate full and empty bladder.
  + **CTVn**: **7 mm** margin around common, EI, II, and obturators. Exclude bowel, bone, iliopsoas.
    - Superior extent 7 mm below L4/L5.
    - For Endometrial, only include presacrals (S2-3 interspace) only if cervical stromal invasion.
    - Obturator nodes are missing from the original atlas, but will be included in the newer atlas. Include until appearance of the obturator canal.
  + **CTV vagina/parametria**:
    - ≥ 1.5 cm at midline. May include anterior rectum if there is significant distention and posterior bladder.
    - Inferior border ≥ 3 cm from apex or 1 cm above bottom of obturator foramen.
  + **ITV vagina/parametria**:
    - Volume of vagina and paravaginal soft tissues in both full and empty bladder scans.
    - Empty rectum: Vaginal ITV extends anteriorly into bladder by at least 2 cm.
    - Distended rectum: Vaginal ITV extends posteriorly to within 1.5 cm of posterior rectal wall.
  + PTV\_45-50.4: CTVn + ITVv/p + **7 mm** margin.
    - Utilize IMRT w daily cone beam/5 mm PTV expansion (old PTV 8-10 mm) [[EMBRACE II](#_pik419qibug)].

### [Lymph Node Boosts](#_nz4p8uik7qem)

* Lymph nodes "USA ME LIES"
  + Upper uterine: Superficial inguinal and Aortic. *Also include inguinals if the lower vagina or vulva is involved.*
  + Middle portion (uterine body): External iliac nodes.
  + Lower portion (cervix): Internal iliac nodes, External iliac, Sacral nodes
* Isolated pAO involvement without pelvic lymph node involvement in endometrial cancer is only 1-3%. Recall: Fundus may drain straight to pAO, bypassing pelvic lymph nodes.
* Less than 5% of pAO lymph nodes are to the right of the IVC in cervical cancer (Figure 2) [[Takiar IJROBP '13](https://www.ncbi.nlm.nih.gov/pubmed/23332221)]
  + New Atlas coming soon (2020). May split IVC above renal hilum to spare bowel as nodal mets are rarely seen here.
* How high to take the pAO chimney?

Take pAO chimney higher if concerned, as nearly half of failures are marginal (read: cranial) to pelvic fields.

*Simple answer: cover one echelon of lymph nodes above gross nodal disease.*

* + Consider a higher chimney for ≥ 1 pathologic node at common iliac OR ≥ 3 pathologic nodes [[EMBRACE II](#_pik419qibug)].
  + Upper border to renal veins (e.g. L2) OR if pAO+, cover ≥ 3 cm above the highest node [[EMBRACE II](#_pik419qibug)].

Nodal boost with conventional fractionation:

* + We want at least 60 Gy (preferably 64 Gy). Nodal control is quite good above 60 Gy EQD2.
  + SIB is favored: 45/25 WPRT with 55/25 (2.2 Gy) or 57.5/25 (2.3 Gy) for EQD2 of 55.9 Gy and 58.9 Gy, respectively. Then, sequential 3-5 fx boost at 1.8-2 Gy.
  + Consider SIB in pts with LN involvement to avoid OTT > 50 days. Give an additional 5 Gy to compensate for every week OTT is extended to avoid OTT > 50 days [[EMBRACE II](#_pik419qibug)].
  + Issue: Bowel toxicity. Must keep point dose < 55-60 Gy, and that's pushing it. See [[Verma](#kix.osgibl16milg)] or [[George](#kix.bqagbt7h013l)] for retroperitoneal duodenal constraints. For non-retroperitoneal bowel, limit the bowel *bag* V55 to 5 cc (relative) or 10 cc (absolute) per word of mouth [[EMBRACE II](#n9hc7b9umqu)]. PRV on small bowel can be 3 cm, as it can be very mobile. Therefore, tread carefully when pushing constraints on non-retroperitoneal bowel.
  + Add 5 mm for CTV per [[EMBRACE II](#n9hc7b9umqu)].

### [WPRT Fields](#_nz4p8uik7qem)

See WPRT in the [[Cervical](#_ez35t5pn6x9y)] and [[Endometrial](#_p7g7lxw5oimq)] sections for more.

* Sup: L4-L5 (cervix) or L5-S1 (endometrium or non-bulky cervix). EFRT can extend to T12-L1.
  + Consider L3/L4 (bifurcation of the aorta) for cervical if common iliac involvement or take pAO chimney even higher if concerned, as nearly half of failures are marginal (read: cranial) to pelvic fields.
  + See Lymph Nodes section below for more discussion on the pAO chimney.
* Inf: Bottom of obturator foramen to cover proximal 2/3 of vagina or lowest extent of disease with 3 cm margin.
* Lateral: 2 cm beyond lateral margins of true bony pelvis.
  + If distal 1/3, widen to include inguinofemoral nodes
    - Lat: Greater trochanter.
    - Inf: Lesser trochanter (easiest) or inguinal crease or 2.5 cm below ischium.
    - Superolateral: ASIS.
* Ant: 1 cm anterior to pubic symphysis.
* Post: Include entire sacrum if cervical involvement (to cover presacrals), may split sacrum to 0.5 cm posterior to anterior border of S2/S3 junction for endometrium or non-bulky cervix.
* Weigh AP/PA beams 2:1 over laterals (converge closer together = better dose distribution).
* EFRT: Include 2 cm margin around uninvolved nodes. *IMRT is now used for SIB.* 
  + High common iliacs stop at L1. Usually EFRT stops at T10.
  + pAO: up to T12/L1. Lateral encompass tips of transverse processes.
    - If matching a PA field to pelvic fields, HBB each, or use IMRT.
* 4-field box technique. 23 MV for nearly everyone (deep).
* Weigh AP/PA beams 2:1 over laterals (converge closer together = better dose distribution).

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| **IMRT use in Gynecologic Cancers**  See the IMRT Trials section above.  Advantages: May spare bowel/duodenum/kidneys with EFRT (pAO coverage). For inguinal coverage, may spare femur and perform SIB. Potential for reduced bone marrow toxicity and potential to reduce pelvic fractures.   * The addition of concurrent chemo appears to increase G2+ heme toxicity in the setting of BM V40 > 37% [[RTOG 04-18](#kix.n1e5fah4ao76)]. * IMRT appears to demonstrate less frequent/almost constant diarrhea and antidiarrheal use in the acute setting [[TIME C](#kix.nqh4mp4cd7f2)].   + Patient reported diarrhea at 1 year and late GU effects at 3 years were improved with IMRT. * There appears to be less bowel obstruction at 5 years with IMRT [[MSKCC](#kix.gn0w00l4s3l9)]. * Limit retroperitoneal duodenum V60 < 2 cc and V55 < 15 cc for G2+ < 10% [[Verma IJROBP '14](#kix.osgibl16milg)]. * Limit retroperitoneal duodenum V55 < 1 cc or V50 < 4 cc for G2+ of 10% [[George Clin Onc '20](#kix.bqagbt7h013l)]. |

### [IMRT](#_nz4p8uik7qem) Trials

See the Summary Box above for information on IMRT toxicities..

See IMRT in the [[Cervical](#_c77gtbmlb1bd)] and [[Endometrial](#_1644wcbo0nsj)] sections for more.

* **RTOG 0418 hematologic toxicity** [[Protocol](https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0418), [Klopp IJROBP '16](https://pubmed.ncbi.nlm.nih.gov/23582248/)]: Phase II. (**M**)**RH**→ **IMRT ± weekly CDDP**.  
  Limit volume of marrow treated with IMRT, especially when using concurrent chemo.
  + 43 patients with AC of endometrium (no chemo cohort), 40 cervical ca treated with weekly cisplatin x4c (90%).
    - 50.4 Gy to vaginal and nodal PTV.
    - **Bowel**: **V40 ≤ 30%**. Same as [[RTOG 07-24](#vyhja2y0cn37)] and [[TIME-C](#kix.nqh4mp4cd7f2)].
    - **Bladder**: **V45 ≤ 35%**. V50 < 35%. Same as [[RTOG 07-24](#vyhja2y0cn37)] and [[TIME-C](#kix.nqh4mp4cd7f2)].
    - **Rectum**: V30 ≤ 60%. V50 < 35%. Compare to V45 ≤ 60% in [[RTOG 07-24](#vyhja2y0cn37)], or V40 ≤ 80% in [[TIME-C](#kix.nqh4mp4cd7f2)].
    - Femoral head: V30 < 15%. V30 < 20%.
  + G2 heme for ± weekly CDDP of 7→ 33%. G3 heme 16→ 25%.
  + Endometrial (WPRT alone, no chemo): G2 heme 7%, G3 heme 16%.
  + Cervical: G2+ heme for **bone marrow V40 ± 37%** of 40→ 75%. Same for median BM dose of 34.2 Gy.
    - Bone marrow: V20 ≤ 75%, V10 ≤ 90% [[Mell IJROBP '06](https://pubmed.ncbi.nlm.nih.gov/16757127/)].

* **TIME-C**/RTOG 1203 [[Protocol (Supplement) Klopp JCO '18](http://ascopubs.org/doi/full/10.1200/JCO.2017.77.4273), [Yeung JCO '20](https://www.ncbi.nlm.nih.gov/pubmed/32073955)]: (**M**)**RH**→ **WPRT vs. IMRT**.

PROs showed a reduction in symptoms, while clinician reported AEs reported no difference.

Less frequent/almost constant diarrhea and antidiarrheal use with IMRT at 1y, these differences disappeared by 3y.

Patient reported diarrhea at 1 year and late GU effects at 3 years were improved with IMRT.

TBL [QS](http://www.quadshotnews.com/2020/02/time-is-on-our-side.html): The reported frequency and perceived severity of acute pelvic radiation toxicity is much greater for patients than their clinicians, highlighting a more distinct (but still short-term) advantage with IMRT.

* + 280 pts. 2012-2015. Endometrial + CDDP for IA G3 or IBG1-2, Endometrial ± CDDP for IBG3, USC, CCC, any stage II or IIIC1. Cervix ± CDDP for [[SeDLis](#p8xcqpfzudaz)] criteria. Cervix + CDDP for PLN+ or parametrial disease.
  + Endpoint: Acute GI toxicity from baseline to 5 weeks. MFU 3y.
    - **Bowel: V40 < 30%**. Same as [[RTOG 04-18](#kix.n1e5fah4ao76)] and [[RTOG 07-24](#vyhja2y0cn37)].
    - **Bladder: V45 < 35%**. Same as [[RTOG 04-18](#kix.n1e5fah4ao76)] and [[RTOG 07-24](#vyhja2y0cn37)].
    - **Bone Marrow**: **V40 < 37%**, **V10 < 90%**. Same as [[RTOG 04-18](#kix.n1e5fah4ao76)], though 95%.
    - Rectum: V40 < 80%. Compare to V30 ≤ 60% in [[RTOG 04-18](#kix.n1e5fah4ao76)], or V45 ≤ 60% in [[RTOG 07-24](#vyhja2y0cn37)].
  + IMRT decreased acute pt reported GI/GU. Bowel summary mean score improved, but bowel bother NS.
    - At week 5 of RT, Mean EPIC bowel score declined 24→ 19 points.
    - At week 5 of RT, Mean EPIC urinary score declined 11→ 5 points. At 3y, 6→ 0 points.
    - At week 5 of RT, frequency of fecal incontinence of 9→ 1% (8% difference).
    - At week 5 of RT, interference of fecal incontinence of 13→ 4% (9% difference).
    - At week 5 of RT, frequent/almost constant diarrhea of 52→ 34% (18% difference).
      * At 1y, frequent/almost constant diarrhea of 15→ 6%.
      * This difference disappeared by 3y.
    - 1y after RT, taking antidiarrheal ≥ 2x per day of 13→ 5%.
  + QoL by FACT-Cx with less detriment on physical well being and less treatment related concerns.

* **Dosimetric predictors of duo toxicity after IMRT to pAO nodes** [[Verma IJROBP '14](https://www.sciencedirect.com/science/article/pii/S0360301613032793?via%3Dihub)].   
  Goal: D2cc 60 Gy and V55 < 15cc. A larger volume to a lower dose appears to have a greater impact.
  + 105 gyn pts. Nodal CTV 45-50 Gy with integrated IMRT boost to 60-66 Gy.
  + Duodenal toxicity 9%. 3y G2+ 11.7%
    - 3y G2+ for D2cc ± 60 Gy of 4→ 19%
    - 3y G2+ for V55 ± 15 cc of 7→ 49%

* **Dosimetric predictors of duo toxicity after IMRT** [[George Clin Oncol '20](https://www.ncbi.nlm.nih.gov/pubmed/31495648)]: Retro.
  + 258 pts. 2010-2015. Upper GI and gyn cancers with pAO involvement.
    - RT: 45 Gy to elective CTV and 52.5-60 Gy to gross nodal volume.
  + Overall, 12% of pts were detected to have G2-4 toxicity related to the duodenum on endoscopy.
  + G3 toxicity 7%, mostly duodenal ulceration.
  + G2+ for V55 ± 1 cc or V50 ± 4 cc of 4→ 8%.
  + G2+ for 1 / 10cc V55 of 10→ 20%.
  + G2+ for 4 / 10cc V50 of 10→ 14%.
  + Median time to toxicity 6 mo.

## [Toxicity](#_nz4p8uik7qem)

The addition of concurrent chemo appears to increase G2+ heme toxicity in the setting of BM V40 > 37% [[RTOG 04-18](#kix.n1e5fah4ao76)].

Limit retroperitoneal duodenum V60 < 2 cc and V55 < 15 cc for G2+ < 10% [[Verma IJROBP '14](#kix.osgibl16milg)].

Limit retroperitoneal duodenum V55 < 1 cc or V50 < 4 cc for G2+ of 10% [[George Clin Onc '20](#kix.bqagbt7h013l)].

* IMRT appears to demonstrate less frequent/almost constant diarrhea and antidiarrheal use in the acute setting [[TIME C](#kix.nqh4mp4cd7f2)].
  + Patient reported diarrhea at 1 year and late GU effects at 3 years were improved with IMRT.
* There appears to be less bowel obstruction at 5 years with IMRT [[MSKCC](#kix.gn0w00l4s3l9)].

* Wiltink [[JCO '15]](http://ascopubs.org/doi/abs/10.1200/JCO.2014.58.6693?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): **Secondary malignancies**. Pooled analysis of PORTEC 1/2 and Dutch TME study.

No increased risk of new cancer, within or outside RT field, in those who received RT versus no RT.

* + 2,554 endometrial and rectal cancer patients. MFU 13y.
  + 10y second malignancy ~15%, 15y second malignancy ~26%.
  + Age-matched new cancer rate was higher for all cancer patients with incidence ratio of 2.98.

* MSKCC **Bowel obstruction** in Endo/Cervical Cancer [[Shih Gyn Onc '16](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5031532/)]: Retro. **3D vs. IMRT.**
  + 224 pts. Endo or cervical.
  + G1/G2/G3 Bowel obstruction (BO) rates of 1→ 2→ 2%.
  + 5y actuarial rate of BO 5%.
  + 5y BO 9→ 1%.

* **PORTEC-2 QoL** (Figure 3) [[Nout JCO '08](http://ascopubs.org/doi/abs/10.1200/JCO.2008.20.2424?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed)]: **TAH/BSO/LND for *suspicious* LNs→ WPRT vs VBT**.  
  See [[PORTEC 2](#y035jmu41jo8)] in the Endometrial cancer section.

There is around a 1 in 8 chance of "bowel bother" after WPRT.   
Limitation of activities due to bowel symptoms in one of eight patients who received WPRT.

This 1 in 8 risk of "bowel bother" after WPRT holds true for [[prostate studies](https://docs.google.com/document/d/1j15zXLBPWwqty60Slm2jnHEiqaoT2iw5Gapp4iMWJsw/edit#bookmark=id.mgs2fxdka4pi)] as well.

Therefore, quote a 1 in 8 risk of long term "bowel bother" to your patients for WPRT, in general.

* + QoL at 2y demonstrated worse social fxn, more diarrhea and fecal leakage w EBRT.

*Note: Difference of 5-10% is considered clinically relevant.*

* + After RT need to remain close to the toilet 21→ 9%. 2y 13→ 8%. *Difference 5%.*
  + After RT limitation of ADLs due to bowel sx 22→ 6%, 2y 14→ 3%. *Difference >10%.*
  + After RT diarrhea 31→ 9%; 2y diarrhea 13→ 6%. *Difference >5%.*
  + After RT fecal leakage 9→ 4%, 2y 9→ 2%. *Difference >5%.*
  + After RT rectal blood loss 2→ 1%, 2y 2→ 1%.
* **Pelvic insufficiency fractures after EBRT for Gynecologic cancers** [[Sapienza IJROBP '19](https://www.ncbi.nlm.nih.gov/pubmed/31580930)]: Meta.   
  There is a 1 in 7 chance of pelvic insufficiency fracture after RT, with the majority affecting the sacral bone/joint. Post-treatment surveillance is indicated as close to 40% of patients are asymptomatic at the time of PIF diagnosis.
  + 3,929 pts from 21 studies.
  + Overall rate of pelvic insufficiency fractures (PIF) of 14%.
  + Symptomatic PIF rate of 61%.
  + Use of IMRT is associated with lower fracture rates.
  + Most common sites: SI joint (40%), pubis (13%), lumbar VB (7%), iliac bone (3%), acetabulum (2%), femoral head/neck (2%).
  + Median time to fracture 7.1 - 19 mo after RT.
* **RT-induced insufficiency fractures after pelvic RT for Gyn malignancies** [Razavian IJROBP '20]:

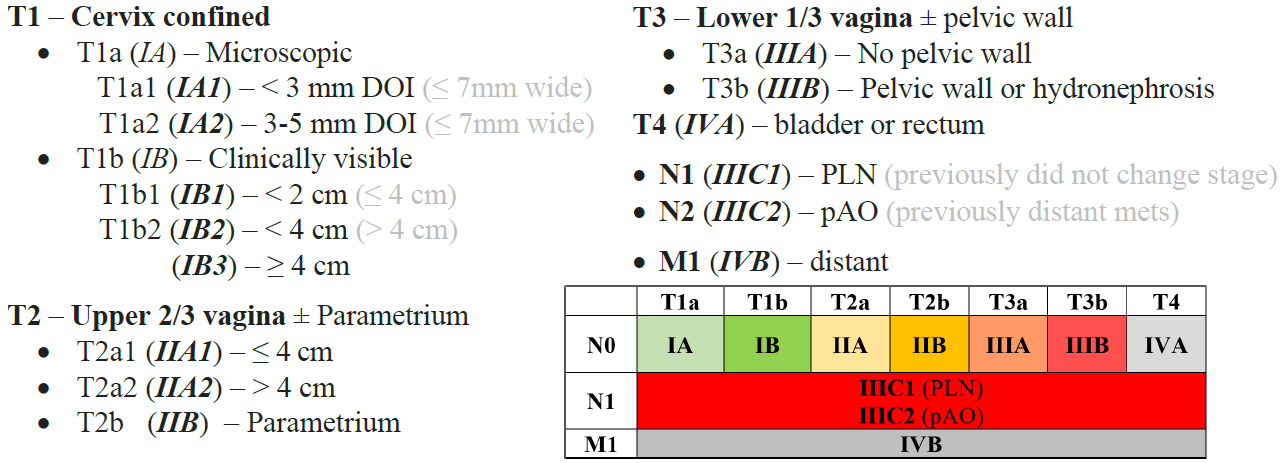
There is a 1 in 7 chance of pelvic insufficiency fracture after RT, with the majority affecting the sacral bone/joint. Post-treatment surveillance is indicated as close to 40% of patients are asymptomatic at the time of PIF diagnosis.

* + Crude incidence for pelvic insufficiency fractures (PIF) ranges from 9% (6,588 patients from 37 studies) to 15% (2,131 patients from 9 studies).
  + Risk factors include osteoporosis, postmenopausal state, and history of DM.
  + MTT PIF after RT of 8-39 mo, with sacrum being the most frequent location for fracture development (60%).
  + From 18 studies, 59% were symptomatic, with pain being the most common presenting symptom. 85% were treated conservatively, while 6% were treated with bone-directed therapy.

### [Radiation Proctitis](#_kwb29p841dr6)

* Chronic radiation proctitis: tricks to prevent and treat [[Vanneste Int J Colorectal Dis '15]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4575375/)
  + Three types: Inflammation predominant, Bleeding predominant, mixed.
    - Bleeding predominant most common form.
    - Likely to resolve with time.
  + Bleeding predominant
    - First, optimize bowel fxn and stool consistency.
    - Start **Vit A/E/C** or **Metronidazole**.
      * Vit A 10,000 IU,Vit E 400 IU TID,Vit C 500mg TID.
        + May have cytoprotective effects by reducing oxidative stress.
        + 90 day course! (E and C used for a year)
      * Metronidazole 400 mg TID.
        + Effective due to immune modulator effects and selective toxicity to microorganisms that contribute to pathogenesis of CRP.
        + 30 day course!
    - If bleeding effects QoL, **Sucralfate enema**: 2g BID and consider holding OAC.
      * Aluminum salt that adheres to mucosal cells and stimulates PG production, producing cytoprotective effects.
      * 30 day course! 77% improvement of bleeding by two grades.
    - Discuss **APC**, **formalin**, **HBO** (if accessible) if persistence of symptoms, but discuss iatrogenic problems.
      * APC considered tx of choice. Rectal ulcers after APC in 26%,with one series up to 52%
  + Inflammation predominant
    - Loperamide, fibers, stool bulking agents, corticosteroids.
      * Rectal betamethasone 5 mg BID vs. rectal hydrocortisone 90 mg BID with potential symptomatic improvement with the latter.

# [Cervical Cancer](#_nz4p8uik7qem)



Old FIGO:

IA2: 3-5 mm DOI, ≤ 7mm wide.

IIA1: Upper ⅔ vagina, < 4 cm (small size therefore group with IB1 for treatment).

New FIGO [[2018](https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/ijgo.12608)]: Any imaging counts!

IA: Horizontal spread no longer dictates staging. If SM+ after LEEP or cone, then IB1.

IB1 / IB2 / IB3 < 2 → < 4 → ≥ 4 cm.

IIIC1: PLN only. IIIC2: pAO.

See [[Cervical Cancer](#_rtjdwwmi0dfj)] in the Introduction to Gynecologic Malignancies section.

**Zaorsky**: [[Gyn staging](https://twitter.com/NicholasZaorsky/status/1219773291528884229?s=20)], [[Comparison of hysterectomy subtypes and trachelectomy](https://twitter.com/NicholasZaorsky/status/1221824856834158592?s=20)], [[Gyn nodes AP](https://twitter.com/NicholasZaorsky/status/1221823861978693632?s=20), [Gyn nodes Lat](https://twitter.com/NicholasZaorsky/status/1221824276740956162?s=20)], [[Cervical cancer staging](https://twitter.com/NicholasZaorsky/status/1221828307068604417?s=20)], [[Cervical cancer EBRT](https://twitter.com/NicholasZaorsky/status/1222649051235127296?s=20)], [[Cervical cancer brachytherapy](https://twitter.com/NicholasZaorsky/status/1222648780903849986?s=20)].

**ARRO**: [[Cervical cancer](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/CervicalCancer.pdf)].

**eContour**: [[AVARO cervix](http://econtour.org/cases/84)], [[post op cervix](http://econtour.org/cases/55)], [[EMBRACE 2 cervix](http://econtour.org/cases/111)] and [[NRG cervix](http://econtour.org/cases/38)].

FIGO Summary Article: Cancer of the cervix uteri [[Bhatla IJGO '18](https://www.ncbi.nlm.nih.gov/pubmed/30306584)]

[**StatPearls: Cervical**](https://www.ncbi.nlm.nih.gov/books/NBK431093/) *Last update: 9/9/2019.*

[**StatPearls: High Grade Squamous Intraepithelial Lesion (HGSIL)**](https://www.ncbi.nlm.nih.gov/books/NBK430728/)*Last update: 4/2/2019.*

[**StatPearls: Cervical Intraepithelial Neoplasm (CIN)**](https://www.ncbi.nlm.nih.gov/books/NBK544371/)*Last update: 6/16/2019.*

[**StatPearls: Cervical Screening**](https://www.ncbi.nlm.nih.gov/books/NBK537348/)*Last update: 1/4/2019.*

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| ASCO Guideline: Mgmt [and Care of Women with Invasive Cervical Ca Resource-Stratified Guideline](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/gynecologic-cancer#/11801) *May 25, 2016*  **ASCO Guideline:** [**Secondary Prevention of Cervical Ca Resource-Stratified Guideline**](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/gynecologic-cancer#/14021)*October 12, 2016*   * HPV DNA testing recommended in all settings. * Visual inspection with acetic acid may be used in basic settings.   **ASCO Guideline:** [**Primary Prevention of Cervical Ca Resource-Stratified Guideline**](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/gynecologic-cancer#/24681) *March 17, 2017*   * Two doses of HPV vaccines recommended if aged 9-14, with an interval of at least 6 mos and up to 12-15 mo. * HIV positive pts should receive 3 doses. * If no doses before age 15, three doses should be administered.   **ASTRO Guideline: Radiation Therapy for Cervical Cancer** [[Chino PRO '20](https://www.practicalradonc.org/article/S1879-8500(20)30094-1/fulltext)]  TBL [QS](http://www.quadshotnews.com/2020/06/gyn-guide.html): Here’s a nice updated guideline on cervical cancer radiation.   * PORT for intermediate risk factors and POCCRT for high-risk factors. * Definitive CCRT is recommended for IB3-IVA (≥ 4 cm), while RT or CCRT is conditionally recommended for IA1-IB2 (< 4 cm) if medically inoperable. * IMRT is recommended for PORT and conditionally recommended for definitive RT. * CT or MRI-based BT is strongly recommended for all women receiving definitive RT, with a conditional recommended to bump the cumulative EQD2 up from ≥ 80 Gy to ≥ 85 Gy when using volume based planning for poorly-responding or large-volume (> 4 cm) disease. * See Table 7 for cumulative dose constraints. |

* ~13,000 new cases and 4,100 deaths in the USA, the third most common cancer.
  + Worldwide, there were 527,000 new cases and 265,700 deaths in 2012. Second most common cancer, 3rd in deaths.
  + 85% of new cases and 90% of deaths occur in low-resource regions.
* **Anatomy**:
  + Ectocervix projects into vagina and is lined with squamous epithelium.
  + Endocervical canal extends from external os to internal os at junction of uterus and is lined with columnar epithelium.
  + Transformation zone is the site of almost all cases of cervical cancer.
* Retro and early patterns of care studies demonstrate LC with BT >> EBRT alone - there are no RCTs for why we use brachy.
* **HPV**: Causes >95% of cervical cancer [[Walboomers JPath '99](https://onlinelibrary.wiley.com/doi/abs/10.1002/%28SICI%291096-9896%28199909%29189%3A1%3C12%3A%3AAID-PATH431%3E3.0.CO%3B2-F)]. Considered ubiquitous. *99% of sexually active adults have it.*
  + Clearance occurs in more than 90% of healthy individuals. Transformation to cervical cancer takes ~10y to occur. Risk factors for persistence: Smoking, older age, HPV type, mutagens, immunosuppression, inflammation, hormones, genetic factors [[Kahn NEJM '09](https://www.nejm.org/doi/pdf/10.1056/NEJMct0806938)].
  + **Gardasil 9** for **ages 9-45 (male and female)**, covers against 6, 11, 16, 18, 31, 33, 45, 52, and 58.
    - >70% caused by 16/18, while 19% are attributable to 31 and 45. Less so 33, 45, 52, 58.
      * 16 is associated with SqCC (more common). 18 is associated with AC (more aggressive).
    - Low risk types: 6/11 MCC of warts.
    - 3 injections over 6 mo, or 2 injections over 12 mo if < 15y.
    - Reduces lesions by 30%.
* E6→ p53, E7→ Rb.
  + P53 around 23% of all cervical cancer.
* Racial disparity is now a washout for women < 40y.
* **Histology**: Incidence of SqCC / AC / Clear cell of 80-90→ 10-20→ 1-2%.
  + Obesity for AC; think endometrial for AC.
  + With spread to the cervix, it's automatically called cervical cancer.
  + **Rare**: Serous, Adenosquamous, Glassy cell, Adenoid cystic, Adenoid basal, Small cell, Undifferentiated.
  + Do adenocarcinoma patients do worse? Pooled study of GOG.
    - 1671 pts from 5 GOG studies. 11% had adeno or adenosquamous.
    - Adenocarcinoma is more likely to be stage IB2, fewer stage IIIB.
    - Squamous were larger, more poorly differentiated.
    - CCRT makes up for RT alone for adenocarcinoma.

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| **Cervical Cancer Screening**   * Regular pap screening decreases incidence and mortality by at least 80%. * **Several methods**: **Conventional cytology** (pap smear) **or liquid based cytology and HPV testing**. **Low-middle income countries favor visual inspection with acetic acid** (VIA) due to lack of resource intensive technology.   + VIA: Usee of 3-5% acetic acid to visualize acetowhite lesions on cervix one minute after application. * **General screening**:   + Screen ages 21-65y, earlier if sexually active.   + **In 20s, q3y Pap and no HPV if wnl**. If 3 consecutive negative tests:   + **In 30s**, **q5y Pap/HPV** [[USPTF '18]](https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/cervical-cancer-screening2), q3y Pap, or q5y HPV only. * **If pap reveals ASCUS**: **Colposcopy if HPV+**, otherwise repeat Pap **6-12** **mo**.   + ASCUS resolves ~70% of the time, < 1% progress to invasive. * **If pap reveals LGSIL** (CIN 1): **Colposcopy if age 25-29 or HPV+**, otherwise repeat Pap **6 mo**.   + LGSIL resolves ~50% of the time, 5% progress to invasive. * **If pap reveals HGSIL** (CIN 2/3, CIS, ASCUS-H): **Do colposcopy and LEEP/conization**.   + HGSIL: > 20% progress to invasive, so go straight to colpo. * **Risk of progression to cancer** for ASCUS / LGSIL / AGC-NOS / HGSIL of < 1→ 5→ 17→ 22%. |

* **Workup**
  + H&P with attention to onset and duration, post-coital bleeding.
  + Gyn hx: LMP, previous abnormal pap, HPV risk factors, number of partners, genital warts.
  + PE: Abd/Pelvis, speculum, bimanual, recto-vaginal, pap if not bleeding. Consider EUA with Gyn Onc.
    - EUA Cysto and sigmoid for suspicion of bladder/bowel involvement.
  + Labs: CBC, LFT, RFT, Pregnancy testing. HIV testing category 3.
    - Transfuse if Hgb < 7, goal > 10 (not 12).
  + FIGO: Previously only CXR, barium enema, IVP allowed. Now U/S, CT, PET/CT, MRI allowed! [[FIGO 2018](https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/ijgo.12608)]
    - Consider CXR and assessment of hydronephrosis for frank invasive disease.
  + The pelvic exam is accurate ~ 50% of the time .
  + MRI staging accuracy ~86% of the time.
  + **MRI**: **Best method to assess primary tumors > 1 cm**.
    - Add vaginal contrast to tell about vaginal involvement.
    - Get MRI for all pts >IB1 to r/o disease high in the endocervix/urinary tract.
    - Obtain MRI around 1 week pre-HDR. If disease is > 0.5 cm above mucosal surface, use interstitials
    - **Cervix tumors usually low T1, high T2 (dark)** [[Dimopoulos RTO '12](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3336085/)].
      * Cervix low T1, low (bright) T2. Parametrium high T1, high (dark) T2.
      * Uterine junctional zone: low (bright) T2 inner myometrium, if high (dark), think uterine invlmt.
      * Take home: Tumor low/high, cervix low/low, parametrium high/high.
  + **PET/CT**: **Best for nodes.** #1 and now medicaid approved: 85-90% Sn and 95-100% Sp for pAO. **FN rate 5-15%**.
    - In areas endemic for TB and HIV, large nodes may not necessarily be cancerous.
    - WashU [[Grisby JCO '01](http://ascopubs.org/doi/full/10.1200/JCO.2001.19.17.3745)]: Staging w **CT vs. PET/CT**.PET+ pAO is an independent prognostic factor!
      * 101 pts. Retro. Treated with CCRT. Observed at 3 mo intervals for median 15 mo.
      * PLN 20→ 67%, pAO 7→ 21%.
      * 2y PFS CT(+)PET(+) / CT(-)PET(+) /CT(-)PET(-) based on pAO status of 14→ 18→ 64%.
      * MVA demonstrated the most significant factor was the presence of pAO+ on PET/CT.
    - Ramirez [[Cancer '10](https://onlinelibrary.wiley.com/doi/full/10.1002/cncr.25739)]: No evidence of pAO on preop CT or MRI underwent **PET/CT w pAO dissection**.  
      Laparoscopic extraperitoneal pAO LND is safe and feasible. Should we be doing it?
      * 60 pts. IB2-IVA. 14 pts (23%) had pathologically involved pAO.
      * PET/CT w PLN-pAO-/PLN+pAO- had 12→ 22% pathologically involved pAO nodes.
        + These numbers correspond to 3 of 26 and 6 of 27 pts, respectively.
      * For those negative of preop CT or MRI, PET/CT Sn and Sp for pAO+ 36% and 96%, respectively.
    - **FN rate of 12%** [[Gouy JCO '12]](http://ascopubs.org/doi/full/10.1200/JCO.2012.47.3520) for pathologic pAO when PET/CT negative in IB2-IVA dz.
    - Wash U [[Kidd JCO '10](https://www.ncbi.nlm.nih.gov/pubmed/20308664)]: Retro. **Pre-operative PET-CT**.   
      PET detected nodes help predict DSS. Long term DSS is possible in advanced stages, even with supraclavicular metastasis. Even SCN and pAO nodes can have long term DSS.
      * 560 pts.
      * 5y DSS for +pAO of ~20-40%.
      * 5y DSS for +SCN of ~10-35%.
      * Frequency of lymph nodes metastases was similar to historic surgical series.
  + For stage IIIB, place **renal stent** prior to starting chemo (Creatinine > 3, no cisplatin!)
* **NRG/GOG Nomograms for cervical cancer** [[Rose JCO '15]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4477785/): **2y PFS, 5y OS and pelvic recurrence rate**.
  + 2042 pts with locally advanced cervical cancer treated with CDDP-based CCRT. Stage IIA/IIB ~PFS, IB/IIA ~OS.
  + 5y OS rates [[Quinn IJGO '06](https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1016/S0020-7292%2806%2960030-1)]

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| **Stage** | **LC** | **OS** | **PLN+** | **pAO+** |
| **IA1**  **IB1**  **IB2** | 95-100%  90-95%  60-80% | 95-100% 85-90%  60-75% | < 1% (IA2 5%)  **15%** | 0% (IA2 < 3%)  **7.5%** |
| **IIA**  **IIB** | 80-85%  60-80% | 75%  60-65% | **30%** | **15%** |
| **IIIA**  **IIIB** | 60%  50-60% | 25-50%  25-50% | **45%** | **30%** |
| **IVA**  **IVB** | 30% | 15-30%  <10% | 60% | 40% |
|  |  | **5y OS =** (**100 - PLN**) | **Risk of PLN =**  (**Stage x 15**) | **Risk of pAO =** (**Stage x 15**)**/2** |

* **Risk of PLN+ by DOI**
  + < 3 mm (IA1): < 1% if NO LVSI.Recall: LVSI doubles rate of PLN+.
  + 3-5 mm (1A2): 6-7%
  + 6-10 mm: 15%
  + 10-20 mm: 25%.
* **Lymph Nodes**: Gyn nodes [[Zaorsky AP](https://twitter.com/NicholasZaorsky/status/1221823861978693632?s=20), [Lat](https://twitter.com/NicholasZaorsky/status/1221824276740956162?s=20)]
  + Routes of drainage:
    - Lymph nodes "USA ME LIES"
      * Upper uterine: Superficial inguinal and Aortic.
      * Middle portion (uterine body): External iliac nodes.
      * Lower portion (cervix): Internal iliac nodes, External iliac, Sacral nodes
    - Lateral along uterine artery→ EI nodes→ pAO.
    - Posterior→ Cmn iliac and lateral sacral nodes (why our field extends behind sacrum).
    - Post-lat behind ureters→ II nodes→ pAO.
    - Fundus→ straight to pAO.
    - Distal vagina and round ligament→ superficial inguinal nodes.
  + LN drainage:
    - Pelvic LN+ risk for Stage I / II / III of 15→30→ 45%. *pAO risk ~½ that of PLNs. LVI doubles rate.*
    - Parametrial (paracervical) LNs important b/c if +, 75-80% have pelvic LN+ (if -, 25%)
    - Uterus (esp fundus) involvement increases pAO risk.
  + SLN mapping:
    - ~90% detection rate/sensitivity; appears to be better in tumors **≤ 2 cm**. SLN is still experimental, but may have some role in early stage cervical cancer, such as FIGO IA, IB1, and IB2 (≤ 4 cm).
    - **SENTICOL I and II** [[Balaya ASCO '20](https://meetinglibrary.asco.org/record/190091/abstract)]: **Bilateral SLN biopsy vs. bilateral PLND**.

Attempt to uncover unusual lymph drainage patterns. Do bilateral SLN biopsies. Generally, if both negative, ipsilateral lymphadenectomy was preferred.

SLNB alone is oncologically safe in early stage cervical cancer. Worse prognosis is associated with higher FIGO stage disease.

* + - * 259 pts. FIGO IA-IIB. 2005-2012. MFU 4y.
      * Tumor size > 2 cm in 11→ 23%. POCCRT in 2→ 11%.
      * 4y recurrence 8%, including 2% nodal recurrence. 4% (n=9) died of cervical cancer.
      * 5y DFS ~94→ 98% (p=0.14). 5y DSS ~88→ 94% (p=0.14).
      * After controlling for final FIGO stage and margin status, SLNB was not associated with DFS and DSS. Only the final FIGO stage was an independent predictor of DSS.
  + Para-aortic lymph nodes:
    - Related to PLN mets, tumors >2 cm, and mets to common iliac nodes.
    - GOG trials (85, 120, 165) - better prognosis if surgically excised vs. radiographic determination.
  + Pelvic failure rate IB = 5-8%, IIA 15-20% (which is why you start RT at these stages mostly).
    - When < 7 mm beyond basement membrane, PLN mets <1%.

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| **Caution with minimally invasive surgery**: Retrospective and RCT with decreased DFS and OS.   * Not for lack of trying, 21st century technology still hasn’t proven its worth against the tried (for 100 years) and true treatments of gyn cancers [QS](http://www.quadshotnews.com/2018/08/robot-takeover.html). |

* **Surgery**
  + **Advantages of surgery**: Shorter tx time, preserves ovarian fxn, possibly better sexual functioning after treatment, no secondary malignancy risk, possible superior tx of radioresistant tumors (may help to decide between surgery and RT for IB2 and IIA1), psychologically easier to understand, complete staging.
    - There is an 18-44% modification of fields after surgical staging. 20% IIB, 30% IIIB had positive nodes at time of surgical staging. There is a survival benefit of surgical staging.
  + **Caution with minimally invasive surgery**: Retrospective and RCT with decreased DFS and OS.
    - Melamed [QS](http://www.quadshotnews.com/2018/08/robot-takeover.html) [[NEJM '18](https://www.nejm.org/doi/full/10.1056/NEJMoa1804923)]: SEER. 2461 IA2-IB1 pts, 50% minimally invasive. 2000-2010.
      * Minimally invasive diagnosed later in era, smaller, lower grade tumors.
      * 4y mortality 5.3→ 9.1%.
      * Adoption of minimally invasive coincided w decline in 4y relative survival of 0.8%/y after 2006.
    - **LACC** [QS](http://www.quadshotnews.com/2018/08/robot-takeover.html) [[Ramirez NEJM '18](https://www.nejm.org/doi/10.1056/NEJMoa1806395)]: Phase III noninferiority. **Open vs. minimally invasive surgery**.
      * 740 pts with IA1 + LVSI or IB1 (92%). 84% laparoscopic, 16% robotic assisted.
      * 5y DFS 96→ 86%, 3y DFS 97→ 91%.
        + Almost 4x recurrences or deaths 7→ 27 pts, 6x deaths 3→ 19 pts.
      * 3y OS 99→ 94%.
  + **Risk of lymphedema after LND ~25%** regardless of if robotic.

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| [Types of Hysterectomy](#_npqfvkgpavlm) See the Surgery section above.  Comparison of hysterectomy subtypes and trachelectomy [[Zaorsky](https://twitter.com/NicholasZaorsky/status/1221824856834158592?s=20)].  All remove uterus/cervix: Simple/extrafascial hysterectomy *does not* remove vagina.   * **Type I**: **TAH** (extrafascial/simple). Uterus, cervix, small rim of vag cuff (outside pubocervical fascia). No parametrium.   This is the preferred surgery for [[endometrial cancer](#_tswqoux8snp9)], unless there is concern for cervical stromal involvement.   * + Consider for stage IA1 without LVSI, inner third stromal invasion (< 1% with lymph nodes). * **Type II**: **MRH**. Half parametrium (uterosacral/cardinal ligs **medial to ureter** border) + **1-2 cm** of vagina.   This and RH are the preferred surgeries for cervical cancer.   * + Consider for stage IA1 with LVSI, IA2 (< 8% with lymph nodes, double if LVSI), and IB1. * **Type III**: **RH**. Takes parametrium/cardinal ligament to **pelvic sidewall** w uterine artery ligated at internal iliac artery, uterosacral ligaments resected at attachment to sacrum, PLND. **Upper 1/4 to 1/3** of vagina.   This is the most common type of surgery for cervical cancer.   * + Perform for 2-4 cm or non-bulky parametrial involvement. * **Type IV**: ERH more paracervical/paravaginal tissue, remove superior vesicular artery, part of ureter/bladder. * **Type V**: Nearby organs removed e.g. bladder/rectum.   **2017 Update on the Querleu–Morrow Classification of Radical Hysterectomy** [[Querleu ASO '17]](https://link.springer.com/article/10.1245%2Fs10434-017-6031-z)  Great table on Q-M classification located in Table 4 [[Cibula Virchows '18](https://link.springer.com/article/10.1007%2Fs00428-018-2362-9)], risk groups guide degree of surgery:   * **Type A**: parametrium halfway to cervix and ureter. Minimal ventral/dorsal parametrium. * **Type B1**:Parametrium **to ureters**. Partial excision of vesicouterine and rectouterine/uterosacral ligaments.   + Consider for LR: < 2 cm, no LVSI, inner third stromal invasion. * **Type B2**: B1 + paracervical LNs.   + Consider for IR: ≥ 2 cm, no LVSI or < 2 cm with LVSI. * **Type C1**: Parametrium **to iliac vessels**, caudal preserved. Total vesicouterine and rectouterine. Most common Hys for cervical cancer.   + Consider for HR: ≥ 2 cm with LVSI. * **Type C2**: C1+ caudal parametrium at iliac vessels. Bladder and hypogastric nerves sacrificed. * **Type D**: Parametrium **to the sidewall**. |

* **Surgical resection based on ontogenetic cancer field theory** [[Höckel Lancet Onc '19](https://www.sciencedirect.com/science/article/pii/S1470204519303894?via%3Dihub)]: **Total mesometrial resection**.  
  Field theory is based on the idea that cancer is a form of reverse morphogenesis whereby devolved cancer cells migrate primarily along embryologically defined tissue layers. It would be natural, then, to direct surgical excision along these embryological planes. The Leipzig School of Radical Pelvic Surgery has pioneered the technique of radical, ontogenetic resections for gynecologic malignancies. Their rationale is that the reason conventional surgery fails and the reason radiation is needed is that the mullerian compartment is incompletely resected in your typical hysterectomy. Therefore, a radical ontogenetic approach obviates the need for adjuvant radiation therapy. The procedure is essentially a MRH with freakish attention to anatomic detail.

TBL [QS](http://www.quadshotnews.com/2019/08/craft-work.html): Radical surgery without radiation for up to FIGO stage IIB cervical cancer results in excellent clinical outcomes... at the Leipzig School of Radical Pelvic Surgery.

* + 500 patients with IB1 (51%) to IIB (31%) cervical cancer treated with TMMR and lymph node dissection.
  + 5y DSS nearly 90%, 5y RFS 83%. No adjuvant RT utilized.
  + G3+ toxicity 3%, just over 20% G2 toxicity.
* **Fertility preservation**: Conization/**Radical trachelectomy** (remove cancer, spare internal os)→ C/S.
  + **IA2/IB1** **< 2 cm**, may do radical trachelectomy (removal of cervix and parametrium) and nodes if LVSI.
    - < 2 cm for vaginal trachelectomy, < 4cm for abd trachelectomy (experimentalif > 2 cm).
    - Removes cervix, upper vagina, supporting ligaments and preserves uterine corpus.
    - Cone/Trachelectomy hard to tell if LVSI⇒ if positive, go back for PLND.
    - Except small cell neuroendocrine and adenoma malignum (minimal deviation adenocarcinoma).

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| **General treatment recommendations**   * Surgery for IA, IB1 and selected IIA1.   + Less commonly, HDR alone (5.5 Gy x 4 fx). * **IA1**: Without LVSI, IA1 has extremely low LN mets.  *Less than 3 mm invasion has < 1% chance of nodal mets.*   + **Conization is curative** unless LVSI or SM+. Prefer **3 mm** margins without LVSI or SM+.   + **If LVSI, TAH vs. radical trachelectomy** (if ≤ 2 cm) **+ PLND vs. RT alone ± pAO**. * **IA2**: Higher chance of LN metastasis.  *Less than 5 mm invasion has ≤ 8% of LN metastasis. Double that if LVSI.*   + **For fertility preservation, add LND to conization or trachelectomy**.   + **At least Type B/MRH** (to ureters) **+ PLND ± pAO sampling**→ risk stratified RT ± CT.   + Follow up after fertility preservation: Pap q3 mo pap x2y, then q6m x3y, then routine screening. * **IB1-IIA1** (non-bulky): RH preferred due to wider margin of resection: paracorpos, upper vagina, nodes ± pAO.   + **At least Type C/RH** (to side wall) **+ PLND ± pAO sampling**→ risk stratified RT ± CT.     - **Post-op WPRT** [[**Sedlis**](#p8xcqpfzudaz)]: For IB1-IIA1 (non-bulky). SeDLis criteria: Size ≥ 4 cm (bulky), Depth middle/outer third, LVI.       * If two of three SeDLis criteria met→ postop WPRT alone (no chemo).       * EBRT 45/25 (boost R2 nodes 10-20 Gy) ± CDDP.     - **Post-op CCRT** [[**Peters**](#lfcem3d38zac)]: If positive margins, >4cm (IIA2), positive LNs, or parametrium (IIB).       * EBRT 45 Gy + CDDP ± BT 6 Gy x 3 to vaginal surface (Peters paper didn't do brachy).         + Would add brachy for positive/close vaginal mucosal margins, can consider for surprise IIB or high risk histology.   + **Definitive RT** (**80-85** Gy to point A) ± concurrent chemo.     - Generally speaking, favor RH + PLND for non-bulky, CCRT for bulky, as they'll get RT.     - RT alone: Surgery preferred in younger pts to preserve ovarian fxn and prevent vaginal stenosis.   + Very small IB1 (< 1 cm) may rec ICBT alone in non-operable, bringing Point A to 65-75 Gy. * **IB2 or IIA1**: Either surgery or RT can be considered as equivalent outcomes.  This is new IB2 (i.e., 2-4 cm).   + Get a PET scan to r/o extrapelvic disease.   + Bulky disease: Definitive CCRT (**≥ 85** Gy to point A). * **IB3+: CCRT**, though select/limited IIB may be candidates for RH/Type C.  Around 80% of IB3/IA2 need PORT.   + GOG 71 with no benefit of adjuvant hysterectomy after RT alone except in case of residual disease. |

## [Early Stage Cervical Cancer](#_npqfvkgpavlm)

* **Italian** [[**Landoni** Lancet '97,](https://www.sciencedirect.com/science/article/pii/S0140673697022502?via%3Dihub) [JGO '17](https://www.ncbi.nlm.nih.gov/pubmed/28382797)]: **RT vs. RH ± RT**. Surgery and RT have similar efficacy for IB-IIA. Basis for doing WPRT + brachy OR surgery in IB1/IIA1. There appears to be a trend to OS benefit with RT over surgery for tumors > 4 cm at long term follow up. Morbidity worse with surgery likely due to CMT. This trial is prior to the era of concurrent chemotherapy.
  + 343 pts. IB-IIA. Adjuvant RT if parametrial, ≤ 3 mm of uninvolved cervical stroma, SM+, LN+.
    - Definitive RT: 47 Gy (40-53 Gy)→ LDR to 76 Gy (70-90 Gy) to Point A.
    - Adjuvant RT (64%): 50.4 Gy. pAO to 45 Gy.
  + 5y OS ~83%, 5y DFS ~77%, 5y LR ~25%.
  + 20y OS ~75%.
  + OS trend with RT for size ≥ 4 cm, with significant benefit at size ≥ 5 cm.
  + G2/3 higher in surgery arm 12→ 28% although likely due to side effects from CMT. Caveat: No chemo!
    - PORT delivered in 64% of the surgery arm, including 83% tumors > 4 cm.
* **Induction chemo→ surgery vs. surgery alone**
  + Three RCTs of induction chemo + surgery vs. definitive RT alone.
    - **GOG 141**: IB2 RH + LND ± NAC Vincristine/Cis x3. Closed early but ~LC and OS, PORT needed in ½ of patients.
    - Phase III Italian NAC+ surgery vs. RT alone for IB2-III w superior OS and PFS, but benefit only for stages IB2 to IIB.
  + Mixed results. Two suggest advantage for induction chemo→ surgery, one with equivalency.
  + Interestingly, meta failed to show clear benefit for induction chemo vs. surgery alone.
  + Two phase III trials for CCRT vs. induction→ surgery:
    - EORTC 55994
    - NCT 0019373

* **GOG 92** [[**Sedlis** Gyn Onc '99](https://www.sciencedirect.com/science/article/pii/S0090825899953878?via%3Dihub), [IJROBP '06](https://www.sciencedirect.com/science/article/pii/S0360301605028725?via%3Dihub)]: **RH/PLND ± 46-50.4 Gy WPRT** (fields slightly smaller, no pAO or BT).  
  Adjuvant RT improved PFS and LR in intermediate risk stage IB cervical cancer.

Give RT to 2+ SeDLis criteria (Size ≥ 4 cm (bulky), Depth middle/outer third, LVI) for LRC/PFS benefit.

* + 277 stage IB pts. +LVI, middle ⅓ and 2 cm or greater. MFU 10y.
  + **5y RFS 79→ 88%**, 5y LR 28→ 15%.
    - 78% of recurrences were local only (vagina and pelvis).
  + 10y LR 21→ 14%, 10y DR 9→ 3%, 10y PFS HR 0.58, 10y LR for ± AC or adenosquamous histo of 44→ 9%.
    - Results show RT may be even more valuable for AC (no LR w AC in RT arm).
  + 10y OS ~71→ 80% (p=0.07).
  + G3+ toxicity 6.6→ 2.1%.
* **STARS** [[Huang ASCO '20](https://meetinglibrary.asco.org/record/185461/abstract)]: **RH/PLND and 1 HR factor→ RT alone vs. CCRT vs. SCRT**.

Sequential SCRT may be preferred for early stage cervical cancer patients with 1 HR factor after radical surgery.

* + 1,048 pts. 2009 FIGO Stage IB1-IIA2 (75% IB1 or IIA1). MFU 4.5y.
    - CCRT with CDDP 30-40 q1w. SCRT CDDP 60-75 + paclitaxel 135-175 q3w x2c before/after RT.
    - Groups w similar LVSI, grade, rate of minimally invasive surgery. LN involvement lowest in RT alone.
  + 3y DFS 82→ 85→ 90%. Differences remained after adjustment for lymph-node involvement.
  + 5y OS for RT alone / SCRT of ~88→ 92%.

* **GOG 109** / SWOG 8797 / INT107 [[**Peters** JCO '00]](http://ascopubs.org/doi/abs/10.1200/JCO.2000.18.8.1606?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): **Surgery→ ± CCRT**.   
  Adjuvant CCRT with CDDP improves OS and PFS. There is a 10% OS advantage for the "3 P's".  
  Deliver post-operative CCRT for IB with PLN+ (85%), Parametria (33%), or Positive margins (5%).

It was not possible to determine the impact of the outback chemo component in this study.

* + 243 pts. IB (only 5% IA2, IIA). WPRT (45-50 Gy, no VBT, pAO if common iliacs +).
    - WPRT 49.3/29 (1.7 Gy) with 45 Gy to pAO if common iliacs are positive.
    - CDDP 70 and 5-FU 1g/m2 q3w x4c (2 concurrent, 2 adjuvant). *The first time outback chemo was used.*
  + 4y PFS 63→ 80%, 4y OS 71→ 81% esp with bad histology (adeno).
    - [Subset](https://www.sciencedirect.com/science/article/pii/S0090825804009011?via%3Dihub): 20% 5y OS benefit with CCRT for pts > 2 cm or 2+ nodes, no benefit for < 2 cm or 1 node.
* **Tata Memorial** [[Gupta JCO '18](https://www.ncbi.nlm.nih.gov/pubmed/29432076)]: **CarboP x3c→ RH vs. CCRT**.
  + 633 pts. IB2, IIA, or IIB SqCC. 2003-2015. MFU nearly 5y.
    - Neoadjuvant group received PORT or POCCRT if indicated.
    - CCRT: 40/20 with midline shield at 20 Gy, CDDP 40 Gy x5c→ ICBT LDR 30 Gy x2 or 35/5 HDR.
  + 5y DFS 69→ 77%.
  + 5y OS 75%.

* **GOG 263** [[NCT01101451](https://clinicaltrials.gov/ct2/show/NCT01101451)]: Phase III. **RH/PLND→ WPRT ± CDDP qwk**.

See NCTN Trial Portfolios by Disease Site: [[Gyn](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_GYNE_Trials.pdf)] and [[Future Directions](#_xgw4qyr3grr8)] section for more.

* + Stage I-IIA. Role of CCRT in intermediate risk disease (2+ Sedlis criteria).

**Adjuvant hysterectomy**

* **GOG 71** [[Keys Gyn Onc '03](http://www.gynecologiconcology-online.net/article/S0090-8258(03)00173-2/fulltext)]: **RT alone to 80 Gy vs. 75 Gy→ TAH**.  
  Don't routinely perform adjuvant hysterectomy after RT alone unless residual dz or tumor 4-6 cm in size.

Cons: Used relatively low dose of RT, protracted RT and no CCRT.

We now know there is an OS benefit with the addition of weekly CDDP to preoperative RT for tumors > 4 cm [[GOG 123](#c3zpxkfl8hoo)].

* + 256 pts. New IB3, old **IB2** (Bulky IB: Tumor or cervix ≥ 4 cm)
    - RT alone: 40 Gy WPRT alone→ LDR to 40 Gy to total 80 Gy at Point A.
    - HYS arm: 45 Gy WPRT alone→ LDR to 30 Gy to total 75 Gy at Point A→ MRH at 2-6 weeks.
  + 10y LR trend 26→ 14% (p=0.08) but OS ~62%. Equivalent G3/4.
    - On subset analysis, pts with tumor 4-6 cm appeared to have OS benefit with TAH, RR death 0.56-0.61.
    - pCR 48%, 40% microscopic, 12% grossly positive. The latter pts w 7x progression and death.

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## [Locally Advanced / Bulky (>4 cm) Cervical Cancer](#_npqfvkgpavlm)

* **CCRT Overview**
  + CCRT for IB2 to IVA based on the results of 6 trials: Keys, Rose, Bundy, Watkins, Morris, Whitney, Peters.
    - CCRT reduces risk of death 30-50% vs. RT alone.
    - Early stage disease: Several RCTs evaluated the utility of CMT, some included IB2-IIA. Most w OS advantage, except NCIC. There is no RCT for CCRT in IB1 or below.
    - Advanced disease = IIB-IVA; many oncs now include IB3 (old IB2) and IIA2 disease in the advanced disease category.
    - EBRT 45/20: 3D CRT, AP/PA, 4 fields with boost to parametrial or sidewall disease.
    - Brachytherapy 80-90 Gy to Point A.
* **Chemo regimen**
  + CDDP ± 5-FU q3-4w during RT, or weekly CDDP **40**.
  + Adjuvant, if given, is usually carboplatin/paclitaxel. *NOT doxorubicin/cisplatin as used in some endometrial trials.*
  + Theory that CDDP is radiosensitizer by preventing sublethal damage repair.

* **Tata Memorial** [[Shrivastava JAMA Onc '18](https://jamanetwork.com/journals/jamaoncology/article-abstract/2671607)]: **Stage IIIB WPRT/B ± concurrent CDDP 40 q1w**.  
  TBL [QS](http://www.quadshotnews.com/2018/02/cementing-cisplatin.html): Yes, we really need cisplatin concurrent to definitive radiation for FIGO IIIB cervical cancer--a regimen now cemented as standard of care.  
  The first time we have level I evidence for CCRT over RT alone in IIIB! (Diminished benefit w CCRT for IIIB as per below)
  + 850 pts. Stage IIIB cervical cancer suitable for CDDP. MFU 7y.
    - RT: AP/PA or box to 50/25 ± midline shield for final 10 Gy.
    - BT: 30 Gy LDR or 21/3 to point A HDR if primary to 40 Gy, otherwise 25 Gy LDR or 14/2 HDR.
      * Goal: Deliver 75-80 Gy to Point A.
  + 5y DFS 44→ 52%. 5y OS 46→ 54%. HR for relapse and/or death 0.81.

* **Meta** [[Chemo for Cervical Cancer Collaboration JCO '08](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2645100/)]: **RT alone vs. CCRT**.  
  **CCRT = 6% improvement in 5y OS** with HR 0.81. CCRT→ Consolidative chemo appears to have the [[greatest benefit](#rtabydz6rzkq)].  
  OS benefit diminishes with advancing stage, but benefit for CCRT for IIIB was finally prospectively validated in 2018 [[Tata](#hvllctskd97d)].

The benefit of consolidative chemo is being tested in [[RTOG 07-24](#vyhja2y0cn37)] after POCCRT and the [[OUTBACK](#tgrkocfn51fu)] trial after CCRT/B.

* + 3452 pts. 15 RCTs of CT+RT vs. RT. 11 platinum based, 3 non platinum.
  + Unlike previous metas, excluded trials that used non-chemo treatments in RT arm.
  + CCRT vs. RT: 8% absolute improvement in DFS (50→ 58%), 5y OS benefit of 6% (60→ 66%).
    - There was a trend towards larger benefits for addition of chemo in IB-IIA as compared to advanced stages.
      * Benefit decreases as the stage increases. I-IIA 10%. IIB 7%. IIIB 3%.
  + CCRT→ consolidative chemo vs. RT alone: 19% absolute improvement in OS (60-79%).
    - Results based on two smaller trials without mature data, but indicates some benefit for outback chemo.

### [Historical Studies](#_yz77wn3eqois)

|  |  |  |  |
| --- | --- | --- | --- |
| **Concurrent weekly CDDP/RT: Three studies - GOG 120, NCIC, GOG 123** | | | |
|  | **GOG 120**  **Rose, 1999** | **NCIC**  **Pearcey, 2002** | **GOG 123**  **Keys, 1999** |
| **Stage** | IIB-IVA | IA-IIA, >5 cm IIB | New IB3, old IB2 (> 4 cm) |
| **Arms** | WPRT/B + HU vs.  WPRT/B + CDDP/HU/5FU vs.  WPRT/B + CDDP q1w | WPRT/B vs.  WPRT/B + CDDPq1w | WPRT/B→ Hys vs. WPRT/B + CDDPq1w→ Hys |
| **OS** | 3y OS 47→ 65→ 65% | 5y OS ~60% (only 250 pts) | 3y OS 74→ 83% |
| **LR** |  |  | 3y LR 37→ 21% |
| **Notes** | Decreased toxicity arms 1 and 3 | Non-surgical staging of nodes | pCR 41→ 52% |

* **GOG 120** [[Rose NEJM '99](https://www.nejm.org/doi/full/10.1056/NEJM199904153401502), [JCO '07]](http://ascopubs.org/doi/abs/10.1200/JCO.2006.09.4532?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): 3 arm CCRT: **WPRT/B + (HU vs. CDDP/5FU/HU vs. CDDP)**.  
  This trial established CDDP-alone as the preferred concurrent chemotherapy.

Cisplatin-based chemo with OS advantage, particularly for Stage IIB and III.  
Cisplatin thought to be radiosensitizer by preventing sublethal damage repair

* + 526 pts. IIB-IVA with no pAO LNs.
    - LDR to 81 Gy Point A dose.
  + 2y PFS 47→ 64→ 67%. 3y OS 47→ 65→ 65%.
    - Stage IIB and III: 10y LR 34→ 21%, 10y PFS 26→ 43→ 46%, 10y OS 34→ 53→ 53%.
  + Equivalent G3/4 toxicity, although CDDP alone demonstrated less toxicity.
* [**NCIC** [Pearcey JCO '02]](http://ascopubs.org/doi/abs/10.1200/JCO.2002.20.4.966?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed):**WPRT/B ± CDDP q1w**.

**The only trial without an OS benefit for CCRT over RT. Power may have been too low to detect an OS benefit.**Results may be explained by statistical variation, presence of anemia in CCRT arm or absence of pAO LN surgical staging. Also, the NCIC trial achieved a shorter average tx duration which might have rendered RT more effective.  
This was also the only definitive trial with IB patients.

* + 250 pts. IA, IIA > 5 cm or IIB-IVA. Non-surgical staging of nodes.
    - WPRT 45 Gy + LDR 35 x1 or HDR 8 Gy x 3 ± CDDP q1w 40 x6c.
  + Equivalent 5y PFS and 5y OS ~60%.

* **GOG 123** [[Keys NEJM '99](http://www.nejm.org/doi/full/10.1056/NEJM199904153401503), ['07](https://www.sciencedirect.com/science/article/pii/S0002937807009696?via%3Dihub)]: **RT alone vs. CCRT/CDDP→ Surgery** in 3-6w.   
  The addition of weekly cisplatin to preoperative radiation therapy for > 4 cm cervical cancer provides a LC and OS benefit.

See [[GOG 71](#dxwom566rr6)] which suggested an OS benefit with preoperative RT alone for tumors > 4 cm prior to hysterectomy.

* + 370 pts. New IB3, old **IB2** (> 4 cm, new IB3).
    - 45 Gy EBRT→ 75 Gy Point A.
    - CDDP 40 q1w x6c→ Surgery at 3-6 weeks.
  + 3y OS 74→ 83%, 3y LR 37→ 21%.
  + 5y PFS 60→ 71%, 5y OS 64→ 78%.
  + pCR 41→ 52%.

|  |  |  |  |
| --- | --- | --- | --- |
| **Concurrent weekly CDDP/5FU and RT: Three studies - RTOG 9001, SWOG 8797, GOG 85** | | | |
|  | **RTOG 90-01**  **Morris, 1999** | **SWOG 8797**  **Peters, 2000** | **GOG 85**  **Whitney, 1999** |
| **Stage** | IIB-IVA, IB2-IIA2, PLN+ | IB (only 5% were IA2, IIA) | IIB-IVA |
| **Arms** | EFRT/B vs.  WPRT/B + Cis/5-FU q3w x3c | WPRT vs.  WPRT + Cis/5-FU q3w x4c (2/2) | RT + HU vs.  RT + Cis/5FU |
| **OS** | 8y OS 41→ 67% | 4y OS 71→ 81% | Latter with 3y OS 55%. |
| **LR** | 35→ 18% |  |  |
| **Notes** | NS increased failures in pAOs when withholding EFRT. | Postop CCRT for IB with PLN+ (85%), Parametria (33%), or Positive margins (5%). | Late complications 16% (equivalent). |

CDDP + 5-FU toxicity includes N/V/D, mouth sores, and myelosuppression.

* **RTOG 9001** (1990-1997) [[Morris NEJM '99](https://www.ncbi.nlm.nih.gov/pubmed/10202164), [Eifel JCO '04](http://ascopubs.org/doi/abs/10.1200/JCO.2004.07.197?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed)]: **EFRT/B vs. CCWPRT/B**.   
  The addition of concurrent chemo decreased LRF by 50%.

The addition of concurrent chemo improved OS, LR, and DM, especially for stage I-II disease.

OS benefit diminishes with advancing stage, but benefit for CCRT for IIIB was finally prospectively validated in 2018 [[Tata](#hvllctskd97d)]

* + 389 pts. IIB-IVA, IB3-IIA2 ≥ 5 cm, or PLN+ (no pAO, 10% common iliac).
    - EFRT/B to 85 Gy vs. CCWPRT/B with Cis q3wk + 5-FU.  
      EFRT pAO to **L1/L2** while WPRT to L4/5 w inf to mid-pubis or 4 cm below lowest extent of disease.   
      *Superior pAO field now set higher at T12/L1 (level of renal hilum)*
    - Brachy in both arms. Point A→ 85 Gy over 58 days, 16% major deviations.
    - Only 45 Gy delivered to nodal fields. Compared to [[RTOG 0116](#2s9lxocmlkr1)] which boosted nodes to 54 - 59.4 Gy.
  + Equivalent pAO failure (4 vs 7%), Equivalent long term toxicity but acute toxicity 1→ 11%.
    - Role of ppx EFRT is unclear due to **significant acute/late toxicity** with CCRT.
  + 8y OS 41→ 67%, 8y DFS 46→ 61%, 8y LRF 36→ 18%, 8y DM 35→ 20%. 5y OS 52→ 72%, 5y DFS 43→ 67%.
  + 5y LRR for stage IB or II of 31→ 13%. 5y LRR for stage III or IVA of ~44→ 29% (p=0.07)
  + Best OS advantage for stage I and II disease with CCRT… NS for III and IV!
* **RTOG 90-01 performed due to OS benefit with EFRT in RTOG 79-20**:

* + **RTOG 7920** [Rotman JAMA '95]: **WPRT vs. EFRT**.   
    There appears to be an OS benefit with EFRT. Impetus for RTOG 90-01. Prior to the IMRT era.
    - 337 pts. IB-IIA ≥ 4 cm or IIB without cNpAO+.
      * WPRT to 40-50 Gy, EFRT to 44-45 Gy→ 30-40 Gy IC-BT to Point A.
    - 10y OS 44→ 55%, LRC ~65%, DM ~25-30%.
    - G4-5 toxicity ~4→ 8% (p=0.06).
  + Vargo [IJROBP '14]: EFRT 45 Gy w 55 Gy to PET-avid LN + CDDP and HDR-BT.
    - 61 pts, retrospective. IB1-IVA with PET-avid LN, f/u PET/CT 12-16 weeks. MFU 2.5y.
    - Sites of persistent disease: Cervix 16.3%, regional nodes 5%, DM 23%.
    - pAO nodal failure in pts with PLN+ of 2.5%
    - Late G3 AE 4%.

* + **RTOG 0116** [[Protocol](https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileID=7534), [Small IJROBP '07](https://www.ncbi.nlm.nih.gov/pubmed/17398031), [IJCG '11](https://www.ncbi.nlm.nih.gov/pubmed/21892091)]: Phase I/II. **EFRT/B/CDDP ± amifostine**.

EFRT/B with CDDP for para-aortic or high common iliac metastasis from cervical cancer is associated with significant acute and late toxicity. Amifostine did not reduce acute toxicity.

* + - 26 patients in phase I. pAO+ in 21 pts, high common iliac in 5 pts. MFU 1.5y.
      * RT: EFRT 45/25. LDR point A to 85 Gy, HDR allowed. Positive nodes boosted to 54 - 59.4 Gy.
      * CDDP 40 mg q1w.
    - 8 patients underwent surgery for complications.
    - 16 patients (62%) had complete responses for both local and nodal disease.
    - The complete local response was 92%. The complete overall nodal response was 62%.
    - Regional / pAO nodal response rates of 60→ 71%.
    - 1.5y DFS / OS of 46→ 60%.
    - Acute G3/4 excluding G3 leukopenia of 81% and a late G3/4 toxicity of 40%.
* [**GOG 109** / SWOG 8797 [**Peters** JCO '00]](http://ascopubs.org/doi/abs/10.1200/JCO.2000.18.8.1606?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): **Surgery→ ± CCRT**.   
  Adjuvant CCRT with CDDP improves OS and PFS. There is a 10% OS advantage for the "3 P's".  
  Deliver post-operative CCRT for IB with PLN+ (85%), Parametria (33%), or Positive margins (5%).
  + 243 pts. IB (only 5% IA2, IIA). WPRT (45-50 Gy, no VBT, pAO if common iliacs +).
    - WPRT 49.3/29 (1.7 Gy) with 45 Gy to pAO if common iliacs positive.
    - CDDP 70 and 5-FU 1g/m2 q3w x4c (2 concurrent, 2 adjuvant).
  + 4y PFS 63→ 80%, 4y OS 71→ 81% esp w/ bad histology (adeno).
    - [Subset](https://www.sciencedirect.com/science/article/pii/S0090825804009011?via%3Dihub): 20% 5y OS benefit with CCRT for tumors > 2 cm or 2+ nodes, no benefit for < 2 cm or 1 node.
* **GOG 85** [[Whitney](http://ascopubs.org/doi/abs/10.1200/JCO.1999.17.5.1339?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed) JCO '99]:  **RT+HU vs. RT+CDDP/5FU**.   
  OS and PFS improved with CDDP/5FU over HU. There is also less acute toxicity with CDDP/5FU.
  + 368 pts. IIB-IVA with negative cytologic washings and PLN.
    - IIB 40.8/24 WPRT→ 40 Gy Point A, and if necessary, 55 Gy Point B.
    - III-IVA 51/30 WPRT→ 30 Gy Point A, 60 Gy Point B. No implant received 61.2 Gy.
  + 3y OS 43→ 55%. 3y PFS 47→ 57%.
  + G3+ 24→ 4%, Late complications ~16%.
* **GOG 165** [[Lanciano JCO '05](https://www.ncbi.nlm.nih.gov/pubmed/16230678?dopt=Abstract)]: **CCRT/B w CDDP vs. 5-FU**.   
  Concurrent 5-FU with 35% higher distant failure than CDDP.
  + 316 pts. IIB, IIIB and IVA.
    - WPRT 45 Gy + PMB + ICBT with CDDP 40 q1w vs. protracted venous infusion 5-FU x6c.
  + Study closed prematurely when planned interim analysis demonstrated 35% higher DM with 5-FU.
* **Korea Cancer Hospital** [[Kim Gyn Onc '08](https://www.sciencedirect.com/science/article/pii/S0090825807007792)]: **Monthly CDDP/5-FU vs. Weekly CDDP**.
  + 158 pts. IIB-IVA. No pAO nodes.
    - Monthly: 5-FU 1g and CDDP 20 mg d1-5 x3c.
    - Weekly: CDDP 30 x6c.
    - RT: 41.4-50.4 Gy with 30-35 Gy HDR in 6-7 fractions to point A w PMB.
  + G3/4 hematologic 43→ 26%. CR in 91%.
* **Korea Cancer Hospital** [[Ryu IJROBP '11](https://www.sciencedirect.com/science/article/pii/S0360301611006626)]: CCRT w **weekly vs. triweekly CDDP**.   
  Triweekly CDDP wins.
  + 104 pts. IIB-IVA.
    - Weekly CDDP 40 x6, Triweekly CDDP 75 x3.
  + G3-4 neutropenia 39→ 23%, 5y OS 66→ 89%.

### [Modern Studies](#_yz77wn3eqois)

**CCRT→ Adjuvant chemotherapy**

Suggestion from [[Meta](#3uyvy8g2t59o)] of 19% absolute OS improvement with CCRT and adjuvant chemo over RT alone, though small patient numbers. The Mexico City trial utilized non-standard, highly toxic chemotherapy (Gem/Cis).

Awaiting results of RTOG 07-24 (post-op CCRT) and OUTBACK (intact/definitive CCRT) which use adjuvant CarboP.

Conflicting evidence points towards a possibly higher likelihood of DM for non-squamous (adenocarcinoma and adenosquamous) histologies, suggesting a role for chemotherapy.

* **Mexico City / B9E-MC-JHQS** [[Duenas-Gonzales JCO '11]](https://www.ncbi.nlm.nih.gov/pubmed/21444871): **WPRT/B/Cis vs. Concurrent and adjuvant Gem/Cis**.  
  Concurrent and adjuvant Cis/gem improved PFS and OS compared to standard definitive CCRT. Was it the addition of gem to CCRT, adjuvant chemotherapy, or both that led to decreased DM?

Gem/Cis has not been widely adopted due to *doubling* of G3-4 toxicity (90%!) compared to conventional CCRT.

* + 515 pts. IIB-IVA. KPS ≥ 70. \*Adjuvant Gem/Cis arm also got Gem concurrently with CCRT.   
    CDDP 40mg/m2 q1w vs. CDDP 40/gem 125 q1w→ Cis 50 d1/gem 1g d1,8 q3w x2c.
    - CCRT and BT to total point a dose of 85 Gy.
    - CDDP 40 and gem 125 q1w while on RT, CDDP 50 and gem 1k adjuvantly.
    - EBRT 50.4→ VBT 30-35 Gy in 96h.
  + 3y PFS 65→ 74%, 3y OS 69→ 80%.
  + G3-4 toxicity 43→ 87% with two deaths related to treatment in gem/cis arm.
  + Hospitalizations 11→ 30%.

* **RTOG 0724** [[NCT00980954](https://clinicaltrials.gov/ct2/show/NCT00980954)]: Phase III. **RH→ CCRT**(**B**) **± CarboP x4c**.

See NCTN Trial Portfolios by Disease Site: [[Gyn](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_GYNE_Trials.pdf)] and [[Future Directions](#_xgw4qyr3grr8)] section for more.  
This trial investigates the use of adjuvant chemo in high risk, early stage cervical cancer. Primary endpoint DFS.

* + IA2, IB, IIA→ RH with Peters Postop criteria. Strat by VBT, 3D/IMRT, and WPRT dose (45 vs. 50.4 Gy).
    - WPRT/B/CDDP ± Carbo AUC5 with paclitaxel 155mg/m2 x4c
    - Superior: L4/5 Sup unless PLN+ (L1/L2) or pAO+ (T11/12).
    - Lateral: Ant 2 cm to VB and/or 1 cm ant to pAO. Post 1-1.5 cm into VB and/or 1 cm post to pAO.
    - **Bowel: V40 < 30%**. Same as [[TIME-C](#kix.nqh4mp4cd7f2)] and [[RTOG 04-18](#kix.n1e5fah4ao76)].
    - **Bladder: V45 < 35%**. Same as [[TIME-C](#kix.nqh4mp4cd7f2)] and [[RTOG 04-18](#kix.n1e5fah4ao76)].
    - Rectum: V45 < 60%. Compare to V30 ≤ 60% in [[RTOG 04-18](#kix.n1e5fah4ao76)], or V40 ≤ 80% in [[TIME-C](#kix.nqh4mp4cd7f2)].
    - Kidney: V18 < 67% each.
    - Cord: V45 < 0.03cc.
  + CCRT CDDP 40 q1w→ Carboplatin AUC 5 and palitaxel 135. Also allowed to enroll on [[TIME-C](#kix.nqh4mp4cd7f2)].

* **OUTBACK** / **ANZGOG 0902 / GOG 0274 / RTOG 1174** [[Protocol](https://www.rtog.org/clinicaltrials/protocoltable/studydetails.aspx?action=openFile&FileID=10105), [Background](https://ascopubs.org/doi/abs/10.1200/jco.2014.32.15_suppl.tps5632)]: Phase III. **CCRT/B→ ± CarboP x4c**.

See [[Future Directions](#_xgw4qyr3grr8)] section for more.

* + IB1 and positive nodes, IB2, II, IIIB or IVA. Definitive CCRT.
  + CCRT CDDP 40 q1w→ Carboplatin AUC 5 and palitaxel 155.

## 

## [Recurrent disease](#_npqfvkgpavlm)

See the [[Relapsed Gynecologic Malignancies](#_hhogskebb6ms)] section.

* If further RT or surgery is being planned, no more than 2-4c of combination chemo should be given to avoid unnecessary delay before definitive salvage.
* **Recurrent SqCC of cervix after definitive RT** [[Hong IJROBP '04]](http://www.redjournal.org/article/S0360-3016(04)00363-3/fulltext):
  + 375 (29%) of 1292 pts had either local or distant failure.
  + In the 162 pts with LF, 44% (n=71) had PD and 56% (n=91) had relapse after complete tumor regression.
    - Salvage surgery in 29% (n=47).
    - 5y OS for ± salvage surgery for local relapse of 3→ 29%.
    - 5y OS for confined to cervix / extending to adjacent tissues / beyond adjacent tissues of 22→ 9→ 4%
  + In the 213 pts with DM, 22% (n=46) had isolated pAO mets, and 76% (n=35) treated with CCRT.
    - 3y OS for ipAO / SCN ± pAO / other relapse of 34→ 28→ 5%.
    - Isolated pAO relapse treated with CCRT have a 3y OS of 34% with 27% surviving greater than 5y.
* **KEYNOTE 158** [[Chung JCO '19](https://www.ncbi.nlm.nih.gov/pubmed/30943124)]: Phase II. **Pembro 200 q2w for up to 2y**.
  + 98 pts. 82% had PD-L1 CPS ≥ 1. MFU 10 mo.
  + ORR 12% with three CR and 9 PR. All 12 responses were in PD-L1 positive tumors, with an ORR of 15%.
  + Median duration of response was not reached.
  + Treatment-related AE in 65%. G3-4 AE in 12%.
* Newer data for 40-45/5 SBRT to isolated pelvic or pAO recurrences suggests around half of patients will still be alive at 3 years. Around half of patients were alive without evidence of disease at MFU of 2.5 years [[Ling PRO '19](#ggzffy340rb6)].
* MRI and PET guided IS-BT for post-surgical vaginal recurrences of cervical cancer [[Chopra IJROBP '19](https://www.ncbi.nlm.nih.gov/pubmed/31682968)]: Phase II.
  + 50 pts. 2011-2016. Residual or recurrent dz after TAH. MFU 5y.
    - RT: 50/25 with CDDP 40 q1w.
    - BT: 16-20/4-5 for Parametrial disease while vaginal disease received 12-14/2-4.
  + 5y LC / DFS / OS of 84→ 73→ 75%.
  + G3-4 proctitis 4%, G3-4 cystitis 2%.

## 

## [Metastatic disease](#_npqfvkgpavlm)

* Carboplatin/paclitaxel and cisplatin/paclitaxel preferred.
* Cisplatin/Paclitaxel + Bevacizumab improves overall survival [NEJM '14].
  + Add bevacizumab if good performance status and risk of significant GI/GU toxicity has been carefully assessed.
* For SCV node only as DM, consider CCRT with curative intent ± adjuvant chemo.
* Around HALF of isolated pelvic or pAO failures will still be alive at 3y after treatment with SBRT [[2019 data](#ggzffy340rb6)]!
* **Stage IVB cervical cancer** [[Perkins Gyn Onc '19](https://www.ncbi.nlm.nih.gov/pubmed/31810653)]: Retro. **Chemo ± WPRT**.
  + 126 pts. 2005-2015. Nearly 3/4 SqCC. Median age 53y.
    - Details concerning the sequence of chemo and RT, and the dose and type of RT were unable to be collected.
  + MS 18→ 42 mo.

### 

## [Toxicity](#_npqfvkgpavlm)

See [general [Gyn toxicity](#_kwb29p841dr6)] section and [[EMBRACE I](#_efhwb1dgreff)] in the brachytherapy section for more on toxicity.

* The addition of concurrent chemo appears to increase G2+ heme toxicity in the setting of BM V40 > 37% [[RTOG 04-18](#kix.n1e5fah4ao76)].
* IMRT appears to demonstrate less frequent/almost constant diarrhea and antidiarrheal use in the acute setting [[TIME C](#qysq804xhro6)].
  + Patient reported diarrhea at 1 year and late GU effects at 3 years were improved with IMRT.
* There appears to be less bowel obstruction at 5 years with IMRT [[MSKCC](#kix.gn0w00l4s3l9)].

* **EMBRACE: Sexual activity and sexual functioning** [[Kirchheiner ASTRO '19](https://www.eventscribe.com/2019/ASTRO/fsPopup.asp?Mode=presInfo&PresentationID=559308)]: Baseline vs. 3y complaints.

Sexual functioning problems are reported in around 1/3 of patients and sexual enjoyment is compromised in almost half of sexually active patients.

* + 1416 patients. EBRT ± chemo with IGBT. MFU 3y.
  + After a cancer diagnosis, but prior to treatment, 22% of patients were sexually active to some degree.
  + 3y no sexual activity / occasional / frequent sexual activity of 38→ 12→ 46%.
  + Vaginal dryness of 7→ 38%.
  + Pain during intercourse of 11→ 33%.
  + Vaginal shortening of 3→ 36%.
  + Vaginal tightening of 5→ 34%.
  + Over half of patients reported enjoyment with sex. Between 1/3 and 1/2 reported no or little sexual enjoyment.

* **EMBRACE Rectal toxicity** [[Mazeron RTO '16]](https://www.sciencedirect.com/science/article/pii/S0167814016311549?via%3Dihub): Similar dosimetric constraint is used for vaginal toxicity.  
  **Late G2+ rectal morbidity for D2cc < 65 Gy of < 5%**, or 10% for D2cc ≤ 69.5 Gy.
  + 960 pts. 2y follow up.
  + G2+ Rectal proctitis/bleeding for D2cc ± 65 Gy of 10→ 4%.
  + Fistula for D2cc ± 75 Gy of 12→ 2%.
  + G2+ rectal morbidity of 10% for D2cc ≤ 69.5 Gy.
  + **V55 > 11 cc** may also be predictive of rectal morbidity [[Ujaimi BT '17]](https://www.sciencedirect.com/science/article/pii/S1538472117303938?via%3Dihub).

* **EMBRACE Vaginal stenosis** [[Kirchheiner RTO '16]](https://www.sciencedirect.com/science/article/pii/S0167814016000025?via%3Dihub): Similar endpoint for rectal toxicity.

**Proposed to limit D2cc to 65 Gy EQD2 to rectovaginal point**.

Keeping the rectovaginal point to < 65 Gy will be difficult with many applicators, therefore, it may be necessary to give this point a higher dose.

* + 630 pts. Measured doses at rectovaginal point. MFU 2y.
    - Recto-vaginal point: 5 mm dorsal of post vaginal wall at intersection between tandem and mid-source position, resembles rectum and upper vagina (previously thought upper vagina could tolerate 120 Gy, now we limit this point to < 65 Gy).
  + G2+ vaginal stenosis for 65 / 75 / 85 Gy of 20→ 27→ 34%... Is the vagina really radioresistant?
  + May be beneficial in new vaginal dose reporting [[1](https://www.sciencedirect.com/science/article/pii/S0167814013001849?via%3Dihub),[2](https://www.sciencedirect.com/science/article/pii/S0167814016310908?via%3Dihub)].
    - There are currently large differences in the definition of lower field border of EBRT. Reporting dose at the Posterior–Inferior Border of Symphysis (**PIBS**) vaginal dose point and PIBS ± 2 cm, corresponding to the mid and lower vagina, should reduce dose to lower and mid vagina.

* **EMBRACE Bladder toxicity** [[Jensen RTO '17]](https://www.thegreenjournal.com/article/S0167-8140(17)30500-5/pdf): Preliminary data under evaluation.

**Suggested advantage in limiting D2cc bladder < 80 Gy EQD2**.

* **EMBRACE Bladder toxicity after CCRT and IGBT** [[Fokdal RTO '18](https://www.ncbi.nlm.nih.gov/pubmed/29784450)]:  
  G3+ urinary toxicity is quite rare.
  + 1176 patients. MFU 2y.
  + 3y G2+ frequency-urgency / incontinence / cystitis 4→ 5→ 2%.
  + 3y G3-4 GU 5%.
  + 3y G3-4 fistula, bleeding, spasm and cystitis < 1%.
* BT: < 3% perforation, < 1% vaginal laceration, < 1% DVT.
* Late: 1-3% urethral stricture, < 2% vesico/rectovaginal fistula, < 5% obstruction/perforation, < 5% femoral neck fracture.
* Surgical mortality 1%.

## 

## [Brachytherapy](#_npqfvkgpavlm)

Return to the [[Overview of Brachytherapy](#_qxjzzedoyoxn)] section.

[[RetroEMBRACE](#_oz5ykvjkls6u)] demonstrated improved LC and reduced late toxicity for patients with large tumors treated by IGABT.

[[EMBRACE I](#_efhwb1dgreff)] identified improved DVH thresholds for urinary and rectovaginal toxicity.

See [[EMBRACE II](#_pik419qibug)], [[Dosing regimens](#_tfoawe58l2ux)], [[Target definitions](#kix.8yrje68n0x79)] and [[Coverage recommendations and Constraints](#_6xguu6v0w1a2)].

Cervical cancer EBRT [[Zaorsky](https://twitter.com/NicholasZaorsky/status/1222649051235127296?s=20)] and brachytherapy [[Zaorsky](https://twitter.com/NicholasZaorsky/status/1222648780903849986?s=20)].

* Co-60 half life 5.27 years, Ir-192 half life 73 days. LDR is between 0.4-2 Gy/h and HDR >12 Gy/h.
* **NCDB** [[Gill IJROBP '14](https://www.ncbi.nlm.nih.gov/pubmed/25216857)]:**Suggests detriment when IMRT utilized in place of BT**.
  + 7,654 pts, stage IIB-IVA. 90.3% received BT. From 2004-2011, BT decreased from 96.7→ 86.1% and IMRT and SBRT use increased from 3.3→ 13.9% in the same period. IMRT or SBRT boost resulted in inferior overall survival.
* **LDR vs. HDR no different**: No RCT compared HDR vs. LDR for cervical cancer subpopulations (NCIC data suggests no difference; meta-analysis suggests HDR less toxicity).
  + LDR: Manual afterloading Cs-137. PDR: Remote afterloading Ir-192 ~4 kU (1 Ci) vs ~42 kU (10 Ci) as for HDR.
  + Whereas LDR < 2 Gy/h (usu 0.4-0.8 Gy/h), HDR > 12 Gy/h.
* **Technique**:[ABS I[Viswanathan BT '12]](https://www.sciencedirect.com/science/article/pii/S1538472111003527)

Selecting for IS BT: Detailed exam at diagnosis looking for bulky tumors > 5 cm, asymmetrical tumor in the A/P or lateral dimension, thick upper vaginal involvement. Consider interim MRI is necessary, or may assess HR-CTV volume and above features at the time of the first IC-BT application.

* + First insertion 4-6 weeks after initiation of RT with completion of therapy by 8 weeks.
    - Trying to give enough time for tumor response, but minimize contraction of the upper vagina.
    - Start treatments based on tumor response (often at) week 4 once per week, then two fractions the last week, however, other fractionation of twice weekly or all after beam possible.
  + In OR, anesthesia. **Dorsal lithotomy**.
  + **EUA**, bimanual noting residual nodularity, cervix size, and size of fornices.
  + Place **foley**, balloon filled with 7cc 30% renograffin, empty bladder.
  + **Sound uterus**. Select tandem (60 degree most common, or 30, 45 based on sounding).
    - If the sound does not insert uterus easily, ultrasound may help guide and confirm correct placement.
    - Dilate os. Suture in **smit sleeve**, based on sounding.
    - No need to dilate os if a smit sleeve is in place.
  + Place flange on tandem, **insert tandem** with flange flush against os/sleeve. Tenaculum on cervix for countertraction.
    - Perforation usu occurs in the posterior cervix but may also occur at the fundus.
    - Be sure to **inspect flexion of the uterus** (anteversion, retroflexion) to help prevent perforation.
    - If perforation occurs, reposition the applicator before treatment and give TMP/SMZ.
    - The less angled the tandem, the more likely there will be a higher dose to sigmoid above rectal packing.
  + Remove speculum. **Select ovoids** with largest/snug fit.
  + Lock all 3 into place, maximize ovoid separation, and tighten screws to fix geometry.
    - **External fixation** devices: Fixation to table, a perineal bar or a "brachy board" (base plate and clamp).
  + **Place packing** ant and post, impregnated with diluted KY contrast.
    - Consider starting with packing posteriorly, as the anterior rectum wall has lower tolerance.
  + Take fluoro, AP-lat to **verify adequate implant**:
    - **Tandem bisects ovoids on AP and lateral** and points away from sacrum, > 3 cm away from sacrum.
      * Avoid tandem too close to sacrum, as could lead to increased sigmoid toxicity.
    - **Ovoids overlap on lateral film** and not be displaced from the flange.
      * Flange flush with cervix (< 1 cm from marker seeds).
    - Tandem ½ to ⅓ of the distance between the symphysis and sacral promontory, no packing sup to ovoids.
      * No superior packing so ovoids flush in high fornices.
  + **Implant quality matters** [[Viswanathan IJGC '12]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3246394/):
    - MFU 2y. Reviewed BT records. Higher LR with unacceptable geometry:
      * Displacement of ovoids relative to os (HR 2.67).
      * Unacceptable symmetry of ovoids and tandem (HR 2.50).
      * Inappropriate packing placement (HR 2.06).
  + Bring the patient to the CT simulation suite, also get MRI if available and fuse.

### [Point based planning](#_1nf811u0hkfi)

* **Point A** (where the uterine artery and ureter cross): In the plane of tandem, 2 cm superior and 2 cm lateral to external os.
* **Point B** (parametrium/obturator): 5 cm lat to midline. Receives ~25-33% of Point A dose.
* **Point C** (sidewall): 6 cm lat to midline. Receives 20% of Point A dose.
* **Bladder point**: Posterior surface of Foley on lat and center of balloon on AP. Fill w 7cm3, pull down against the urethra.
  + Without 3D, a point located 1.5 cm above the ICRU bladder may be more representative of bladder dose.
* **Recto-vaginal point**: 5 mm dorsal of post vaginal wall at intersection between tandem and mid-source position, resembles rectum and upper vagina (previously thought upper vagina to tolerate 120 Gy, now we limit this point to < 65 Gy).
* **Vaginal point**: Lateral edge of ovoid/ring on AP film and mid-ovoid/ring on lateral film (Vs) and 5mm deep (Vd).
  + Vd is the same as recto-vaginal point, while Vs is surface vaginal dose.
* Tandem loading: usually **15-10-10** mgRaeq to ensure dose to lower uterine segment.
  + Small ovoids typically 10-15 mg Raeq.
  + Mini ovoids with 5-7.5 mg Raeq because they lack internal shielding.
* **ABS review** [Brachy '17]: **Point based planning inferior to 3D**. Literature review of HDR BT. Pts treated w CCRT and 3D HDR BT had improved pelvic control and DFS compared to pts treated w Point A specifications.
* **French STIC study** [[Charra-Brunaud RTO '12]](https://www.sciencedirect.com/science/article/pii/S0167814012002095?via%3Dihub): Prospective. **Point A vs. CT-based planning**.  
  3D-BT is feasible and safe, with improved OS and toxicity compared to point based planning.
  + 705 pts. Stage IB-IIIB.
    - Group I: BT→ Surgery.
    - Group II: CCRT/BT→ Surgery.
    - Group III: CCRT/BT.
  + 2y local RFS for group 1 of c 3
  + 92→ 100%, group 2 of 85→ 93%, and group 3 for 74→ 79%.
  + G3-4 toxicity for group 1 of 15→ 9%, group 2 of 13→ 9%, and group 3 of 23→ 3%.

### [Volume based (3D) planning](#_1nf811u0hkfi)

Comparison and CTV consensus for CT and MR-based BT in L-A Cervical Cancer [[Viswanathan IJROBP '14](https://www.redjournal.org/article/S0360-3016(14)03328-8/fulltext)] [RoR](#kix.8yrje68n0x79)

Prescribing, Recording, and Reporting Brachytherapy for Cancer of the Cervix [[ICRU 89](https://icru.org/content/reports/prescribing-recording-and-reporting-brachytherapy-for-cancer-of-the-cervix-report-no-89)].

* **GEC-ESTRO Working Group I** [[Haie-Meder RTO '05](https://www.ncbi.nlm.nih.gov/pubmed/15763303)]: **Concepts and terms in 3D cervix brachytherapy**.
  + No PTV is required as the implant moves with the patient.
* [**GEC-ESTRO Working Group II** [Pötter RTO '06]](http://www.thegreenjournal.com/article/S0167-8140(05)00546-3/fulltext): **3D volume parameters**.

Coverage of a 80-90 Gy area and a 60 Gy area is important.

This laid the groundwork for prescribing [[HRCTV and IRCTV volumes](#kix.8yrje68n0x79)].

* + Report V150 and V200 for overall assessment of hot spots.
  + **D90 HRCTV** **≥ 85-95 Gy** EQD2. Previously, ≥ 80-90 Gy.
    - Previously, > 80 Gy recommended for < 4 cm residual (5 x 5.5 Gy). Now, > 85 for all (5 x 6 Gy).
    - New evidence that D90 HR-CTV ≥ 85 Gy EQD2 has 3y LC > 94% for HR-CTV < 20cc [[Tanderup '16]](https://www.sciencedirect.com/science/article/pii/S0167814016311173?via%3Dihub):
    - [Meta-regression analysis[Mazerno BT '16]](https://www.sciencedirect.com/science/article/pii/S1538472116304846?via%3Dihub): D90 of 81.4 / 90 Gy with 90→ 95% LC.
    - May need to employ interstitial needles, e.g. if parametrial involvement or tumor > 30cc.
    - If using interstitials, avoid 6 and 12 o'clock positions unless bladder or rectal involved.
  + **D98 IRCTV ≥ 60 Gy** EQD2.

* **ABS Consensus Guidelines** [[Viswanathan BT '12]](https://www.sciencedirect.com/science/article/pii/S1538472111003527): **Part I: General principles**.

See [[EMBRACE II](#_pik419qibug)] [[Target definitions](#kix.8yrje68n0x79)] and [[Coverage recommendations and Constraints](#_6xguu6v0w1a2)].

* + 45 Gy EBRT with 60-70 Gy to enlarged lymph nodes.
  + MRI: Cervix dz low T1, high T2 (dark). Cervix low/low, Parametrium high/high. Use T2 STIR or FS MRI.
    - Uterine junctional zone: low (bright) T2 inner myometrium, if high (dark), think uterine invlmt.
  + Deliver CDDP 40 q1w, give 1 hour prior to RT [[Pearcey '02]](http://ascopubs.org/doi/abs/10.1200/JCO.2002.20.4.966?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed).

* **ABS Consensus Guidelines** [[Viswanathan BT '12]](https://www.sciencedirect.com/science/article/pii/S1538472111003515): **Part II: HDR BT**.

Guidelines for after 45 Gy EBRT with CDDP with nodal boosts to 60-70 Gy.

See [[EMBRACE II](#_pik419qibug)] [[Target definitions](#kix.8yrje68n0x79)] and [[Coverage recommendations and Constraints](#_6xguu6v0w1a2)].

Loosely speaking, new EQD2 recommendations are for HR-CTV D90 ≥ 85-87 Gy EQD2.

* + Brachytherapy alone for IA1/IB1 < 1 cm: LDR 65-75 Gy or HDR 5-6 x 7 Gy.
  + Adjuvant BT: LDR 35-45 Gy at dose rate of 0.4-0.6 Gy/h, or LDR 15-20 Gy x 2.
  + Consider combined EQD2 of 80 Gy for tumors with complete response after EBRT (e.g., 27.5/5 BT after 45 Gy).
  + Consider combined EQD2 of 85-90 Gy for tumors > 4 cm at diagnosis (e.g., 30/5 BT after 45 Gy).

* **ABS Consensus Guidelines** [[Lee BT '12](https://www.ncbi.nlm.nih.gov/pubmed/22265438)]: **Part III: LDR and PDR BT.**
  + Target dose of 80-90 Gy total. After EBRT of 45 Gy, 35-45 Gy IC or IS BT should be added.
  + Dose and dose rate at Point A should be recorded.
  + Typical LDR BT source is Cs-137. LDR 35-45 Gy at dose rate of 0.4-0.6 Gy/h, or LDR 15-20 Gy x 2.
  + First BT application should be around 4-6 weeks after EBRT to allow for shrinkage. The second should be around 1-2 weeks later so that RT will be completed within 8 weeks of initiation.
* **Meta** [[Mazeron BT '16](https://www.ncbi.nlm.nih.gov/pubmed/27371991)]: **Tumor DVH in IGBT for cervical cancer.**
  + 13 studies with 1,299 patients.
  + D90 HR CTV ranged from 70.9-93.1 Gy.
  + HR CTV D90 of 81.4 Gy was associated with 90% local control.
    - The planning aim of 90 Gy corresponded to a 95% probability.
  + IR CTV D90 ranged from 61.7-69.1 Gy.
  + IR CTV D90 of 60 Gy was associated with a 79% local control probability.

### [RetroEMBRACE](#_1nf811u0hkfi)

RetroEMBRACE is an effort to standardize image-based volumetric BT endpoints instead of Point A.

RetroEMBRACE demonstrated improved LC and reduced late toxicity for patients with large tumors treated by IGABT.

See the goals of [[EMBRACE II](#n9hc7b9umqu)] for an overview of the results of this series of studies.

See [[Nomogram](#kix.xhdlngjj9zol)] for IGABT and overall survival based on RetroEMBRACE.

Failures are shifting distantly as we keep improving local therapy. There are more distant failures than locoregional failures. LRR and pAO failures are equal at about 10% of failures. Don't omit VBT for stage III+ patients, as there are double-digit rates of local failure in this subset [[Tan IJROBP '19](#rn7spp450d1n)].

* **Correlation of LC, dose, volume and OTT** [[Tanderup RTO '16]](https://www.sciencedirect.com/science/article/pii/S0167814016311173?via%3Dihub): Retro, multi-institutional.   
  Consider an additional 5 Gy to HR-CTV for > 30 cc or 1 week delay.
  + 488 pts RetroEMBRACE pts EBRT ± chemo. 4y follow up. OTT = overall tx time.
  + 4y LF 10% (n=43).
  + D90 HR-CTV affects LC, while increased HR-CTV volume and longer OTT a/w worse LC.
  + Histology, chemo, and dose rate did not have a significant impact on LC.
  + **D90 HR-CTV ≥ 85 Gy EQD2 delivered in 7 weeks** with 3y LC > 94% for < 20 cc HR-CTV.
    - 3y LC > 93% for 30cc HR-CTV, 3y LC > 85% for 70cc HR-CTV.
    - **D98 GTVB ≥ 95 Gy** and **D98 IR-CTV ≥ 60 Gy** EQD2 leads to similar LC as above.
    - An additional 5 Gy to HR-CTV req'd to compensate for increasing OTT by one week.
    - Increased HR-CTV volume by 10cc req's addnl 5 Gy for equivalent LC.
* **Improved pelvic control and survival with IGRT** [[Sturdza RTO '16]](https://www.sciencedirect.com/science/article/pii/S0167814016310180?via%3Dihub): Retro, multi-institutional. Aim for HR-CTV D90 > 87 Gy. Previously, goal was 80 Gy. Even with 87 Gy, toxicity is acceptable!

Improved LC and PC associated with OS benefit ~10% compared with historical cohorts

* + 731 pts. 1998-2012. IGBT. MRI at least one fraction (80%), CT (20%). Mean HR-CTV volume 37cc (20-30cc is common size) with mean **HR-CTV D90 87 Gy**.
    - RT 46 Gy WPRT with weekly cisplatin.
  + Mean D2cc bladder 81 Gy, Rectum 64 Gy, Sigmoid 66 Gy, bowel 64 Gy (all EQD23).
  + 3/5y LC for up to IIB / IIIB of > 90→ 75%.
    - For advanced adaptive BT (combined interstitial/cavitary) 3y LC 95→ 85% for ≥ 5 cm.
  + 3/5y PC for up to IIB / IIIB of > 90→ 70%.
  + There is a role for dose escalation from 85-95 Gy, regardless of tumor size.
    - D90 HRCTV > 85 Gy (87 Gy), D90 IR-CTV > 60 Gy, Subclinical dz 45-50 Gy.
    - D90 HRCTV for stage IB / IIB / IIIB of 93→ 88→ 83 Gy EQD2.
  + 5y G3+ bladder, GIT, and vagina ~5%.
* **IC+IS BT increases LC without increasing morbidity** [[Fokdal RTO '16]](https://www.sciencedirect.com/science/article/pii/S0167814016310271?via%3Dihub): Retro, multi-institutional. **IC ± IS BT**.

Consider IC/IS BT for > 30 cc tumors (or parametrial dz). Equivalent LC for < 30 cc, regardless of addition of IS.

* + 610 pts.
  + D90 HR-CTV 83→ 92 Gy EQD2. No significant difference in late morbidity.
  + 3y LC 10% higher for HR-CTV volume > 30 cc.

### [EMBRACE I](#_1nf811u0hkfi)

EMBRACE I is a prospective study looking into IGABT toxicity endpoints due to insufficient evidence.

See the goals of [[EMBRACE II](#n9hc7b9umqu)] for an overview of the results of this series of studies.

See EMBRACE I in the [[toxicity section](#_ud351cf7in4a)] for more details.

* IMRT (27%) and 3D CRT (83%) typically have 8-10 mm PTV. With daily imaging, PTV may be reduced to 5 mm.
* There appears to be less OAR morbidity with IC/IS BT when tumors have parametrial involvement [[Fortin BT '16]](https://www.brachyjournal.com/article/S1538-4721(16)30054-X/fulltext).
* Limit the rectal D2cc to ≤ 69.5 Gy EQD2 for around 10% late G2+ rectal morbidity, or 65 Gy EQD2 for late G2+ rectal morbidity of < 5% [[Mazeron RTO '16](#hi7c3wdz8bwq)]. Limiting 55 Gy to < 11 cc may also be wise [[Ujaimi BT '17]](https://www.sciencedirect.com/science/article/pii/S1538472117303938?via%3Dihub).
* Limit the **rectovaginal D2cc to ≤ 65 Gy EQD2**, although this is difficult to do with may applicators therefore it may be necessary to give this point a higher dose. G2+ vaginal stenosis only increases from 20% to 27% when increasing dose to this point from 65 Gy to 75 Gy, still remaining 34% with doses of 85 Gy [[Kircheiner RTO '16](#kix.lb7csgs1k37)].
* Suggestion to limit the **bladder D2cc** **< 80 Gy EQD2** (preliminary data under evaluation) [[Jensen RTO '17](#rn92zdko5mc4)]. G3+ bladder toxicity is quite rate, only occurring 5% of the time [[Fokdal RTO '18](#8huih63prie1)].
* **Sexual functioning** problems are reported in around 1/3 of patients and sexual enjoyment is compromised in almost half of sexually active patients [[Kirchheiner ASTRO '19](#im08jgwzdxvm)].
* Most failures are in the HR-CTV, while only 20% of failures are in the IR-CTV alone [[Schmid RTO '17](#12zm6xulg7q1)].
* pAO failure is a major challenge for nodal control, with nearly half of failures marginal to irradiated volume [[Beadle IJROBP '10](https://www.sciencedirect.com/science/article/pii/S0360301609005653?via%3Dihub)].
* There is around 40% OOF failure after CCRT and IGBT, most of which is in the pAO region [[Nomden RT '19](#vlt0o9isqkmc)].
* There appears to be more systemic relapses when ≤ 4c chemo is given [[Fortin IJROBP '15](#c1zpo34pwxa8)].

### 

### [EMBRACE II](#_1nf811u0hkfi)

See [[Target definitions](#kix.8yrje68n0x79)] and [[Coverage recommendations and Constraints](#_6xguu6v0w1a2)] for more.

**EMBRACE II** [[Pötter CTRO '18]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5862686/) **aims to benchmark high levels of local, nodal, and systemic control with IGABT**.

IGABT w excellent LC in limited, well responding dz. Challenges: LRC in advanced dz, tx-rel morbidity, and DM.

Overall G3+ major morbidity 3-6% per organ per RetroEMBRACE and EMBRACE data.

* OARs not meeting tolerance: 1) Check packing 2) Replan 3) Use more fractions, lower dose per fraction.
* **LR patients**: ≤ 4 cm tumor (up to IIA1), SqCC histology.
  + "Small pelvis": Internal iliac, External iliac, obturator, presacral.
* **IR patients**: Not LR or HR.
  + "Large pelvis": Include up to aortic bifurcation. Add inguinals with distal vagina. Entire mesorectal space with mesorectal nodes.
* **HR patients** (based on nodal path): **≥ 1 pathologic node at common iliac OR ≥ 3 pathologic nodes**:
  + **Upper border to renal veins** (e.g. L2) **OR if pAO+, cover ≥ 3 cm above the highest node**.

* **Goals**: See [[RetroEMBRACE](#_oz5ykvjkls6u)] and [[EMBRACE I](#_efhwb1dgreff)] for more information on the data backing these goals up.
  + **Utilize IC/IS for > 30 cc or parametrial involvement** [[Fortin BT '16]](https://www.brachyjournal.com/article/S1538-4721(16)30054-X/fulltext).
    - Common sizes are 20-30 cc. For every 10cc inc, you may need to give addn'l 5 Gy for equivalent LC.
    - For every 1 week delay, consider an additional 5 Gy to D90 HR-CTV [[Tanderup RTO '16]](https://www.sciencedirect.com/science/article/pii/S0167814016311173?via%3Dihub).
  + **Vaginal dose de-escalation**: **Recto-vaginal D2cc < 65 Gy EQD2**, & dec relative vaginal loading from 50→ 33%.
    - Limit the **rectovaginal D2cc to ≤ 65 Gy**, although this is difficult to do with may applicators therefore it may be necessary to give this point a higher dose. G2+ vaginal stenosis only increases from 20% to 27% when increasing dose to this point from 65 Gy to 75 Gy, still remaining 34% with doses of 85 Gy [[Kircheiner RTO '16](#kix.lb7csgs1k37)].
    - There are currently large differences in the definition of lower field border of EBRT. Reporting dose at the Posterior–Inferior Border of Symphysis (PIBS) vaginal dose point and PIBS ± 2 cm, corresponding to the mid and lower vagina, should reduce dose to lower and mid vagina.
  + Utilize IMRT w daily cone beam/5 mm PTV expansion (old PTV 8-10 mm).
  + **Utilize SIB in pts w LN involvement to avoid OTT > 50 days**.
    - Give an additional 5 Gy to compensate for every week OTT is extended.
    - 55/25 (2.2 Gy) or 57.5/25 (2.3 Gy) for EQD2 of 55.9 Gy and 58.9 Gy, respectively.
    - Add 5 mm for CTV. For non-retroperitoneal small bowel, limit the bag V55 to 5 - 10 cc.
  + **Take pAO chimney higher if concerned**, as nearly half of failures are marginal (read: cranial) to pelvic fields.
    - See HR patients above (e.g. ≥ 1 pathologic node at common iliac OR ≥ 3 pathologic nodes.

* + **Ensure ≥ 5 doses of chemo for high risk patients** [[Fortin IJROBP '15]](https://www.redjournal.org/article/S0360-3016(15)00757-9/fulltext).
    - Less than or equal to 4c of chemotherapy is associated with a high risk of DM.

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| **Volume-based Brachytherapy**  Cervical Brachytherapy Atlas [[RTOG Contouring Atlases](https://www.nrgoncology.org/ciro-gynecologic)]  Return to the [[Overview of Brachytherapy](#_qxjzzedoyoxn)] section. See [[RetroEMBRACE](#_oz5ykvjkls6u)], [[EMBRACE I](#_efhwb1dgreff)] and [[EMBRACE II](#_pik419qibug)].   * **GTVB** = **GTV at time of BT**, GTVD at diagnosis. * **HR-CTVB = GTVB + cervix + presumed extracervical extension at time of BT**.   + Superior border of cervix ≥ 1 cm above uterine vessels or where the uterus begins to enlarge.   + If CT alone, may use height ~3 cm for cervix with caveat that CT planned cases should treat the entire length of tandem, as difficult to determine superior extent of dz [[Viswanathan IJROBP '14](https://www.redjournal.org/article/S0360-3016(14)03328-8/fulltext)]. * **IR-CTVB** = HR-CTVB + initial extent of disease, minimal margins of 5-15 mm.  [Dosing regimens](#_1nf811u0hkfi) For boards, reasonable to give 45 Gy followed by 30/5 (6 Gy - EQD2 84.3) in almost all\* cases. Also acceptable to Rx to Point A ( > 65 Gy) with DVH analysis (i.e. account for OAR D2cc).   * **Point A based**: Use as a starting point to achieve D90 ≥ 100% to the HR-CTV for volume-based planning.   + 28/4 (7 Gy - EQD2 83.9 Gy): Over 2 implants - used in Europe for template-based HDR as well.   + **30/5** (6 Gy **-** EQD2 84.3 Gy).   + **30/5** (6 Gy **-** EQD2 84.3 Gy).   + 27.5/5 (5.5 Gy - EQD2 79.8 Gy): Used to be more common, but D90 HR-CTV goal now > 87 Gy EQD2\*.   + 25/5 (5 Gy - CTV EQD2 75.5 Gy). *27.5-30/5 for cases recommended D90 between 85-95 Gy, but respect OARs.*   + 30/6 (5 Gy - EQD2 81.8 Gy). * Templated-based HDR after 45 Gy, treatment with a single application BID.   + 31.5/9 (3.5 Gy - CTV EQD2 80 Gy).   + 29.75/7 (4.25 Gy - CTV EQD2 80 Gy).   + 25/5 (5 Gy - CTV EQD2 75.5 Gy). *27.5-30/5 for cases recommended D90 between 85-95 Gy, but respect OARs.* * Templated-based HDR after 50.4 Gy, treatment with a single application BID.   + 27/3 (9 Gy - CTV EQD2 78.8 Gy).   + 22.5/5 (4.5 Gy - CTV EQD2 77 Gy).   \*Cases which might require > 87 Gy include large tumors > 30cc or tx delays one week beyond 50 days. Cases which might only require an EQD2 of 80 Gy (e.g., 27.5/5 after 45 Gy EBRT) are those with [[complete response](#1vb7u8jdcrdy)] to EBRT.  For interstitial, there is a paucity of publications and number of fractions/fractionation is not standardized.  Interstitials: If using needles with tandem/ring, no more than 10% of dwell should go to needle positions. |

### [Volume-based Treatment Planning](#_1nf811u0hkfi)

See summary box above.

Cervical cancer EBRT [[Zaorsky](https://twitter.com/NicholasZaorsky/status/1222649051235127296?s=20)] and brachytherapy [[Zaorsky](https://twitter.com/NicholasZaorsky/status/1222648780903849986?s=20)].

* **OAR planning goals**: From [[EMBRACE II](#n9hc7b9umqu)].
  + **EQD2 = D (d + α/β) / (2 Gy + α/β)**, where α/β is 3 for OAR and 10 for tumor.
  + With 45/25 EBRT (EQD2 43.2) and 5 or 4 fraction brachy regimens, bladder and rectal doses per fraction:
    - 5 x 3.5 Gy (or 4 x 3.9 Gy) = 65 Gy. *Recall: Rectovaginal D2cc < 65 Gy based on [*[*EMBRACE*](#owgrc82n097r)*].*
    - 5 x 3.9 Gy (or 4 x 4.5 Gy) = 70 Gy. *Recall: Sigmoid D2cc < 70 Gy.*
    - 5 x 4.3 Gy (or 4 x 5 Gy) = 75 Gy.
    - 5 x 4.75 Gy (or 4 x 5.4 Gy) = 80 Gy. *Recall: Bladder D2cc < 80 Gy.*
    - 5 x 5.1 Gy (or 4 x 5.8 Gy) = 85 Gy.
    - 5 x 5.5 Gy (or 4 x 6.3 Gy) = 90 Gy.

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| **HDR Planning goals**:   * **D90 HRCTV** **85-95 Gy** EQD2\*. * **D98 HRCTV ≥ 75 Gy** EQD2. * **D98 GTVB ≥** 90-**95 Gy** * **D98 IR-CTV ≥ 60 Gy**   \*D90 HRCTV > 87 Gy preferred | **HDR Organ constraints**:   * **D2cc bladder < 80**-90 Gy EQD2. * **D2cc rectum/rectovaginal < 65**-75 Gy EQD2. * **D2cc sigmoid**\* **< 70-**75 Gy. * **D2cc bowel**\* **< 70**-75 Gy.   \*Sigmoid and bowel constraints are only valid if non-mobile. |
| Historically would limit **upper / mid / lower vagina** to 120→ 80→ 60 Gy.  G2+ vaginal stenosis for 65 / 75 / 85 Gy of 20→ 27→ 34%... *Is the vagina really radioresistant?* [[Kirchheiner '16]](https://www.sciencedirect.com/science/article/pii/S0167814016000025?via%3Dihub)  Recto-vaginal point: 5 mm dorsal of post vaginal wall at intersection between tandem and mid-source position, resembles rectum and upper vagina (previously thought upper vagina to tolerate 120 Gy, now we limit this point to < 65 Gy). | |

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| **This Summary Box was made possible by the ACRO Resident Committee.**  **A more comprehensive collection of resources for all disease sites may be found at** [**http://www.acro.org/**](http://www.acro.org/)  Zaorsky: [[Gyn staging](https://twitter.com/NicholasZaorsky/status/1219773291528884229?s=20)], [[Comparison of surgeries](https://twitter.com/NicholasZaorsky/status/1221824856834158592?s=20)], [[Gyn nodes AP](https://twitter.com/NicholasZaorsky/status/1221823861978693632?s=20), [Lat](https://twitter.com/NicholasZaorsky/status/1221824276740956162?s=20)], [[Cervical staging](https://twitter.com/NicholasZaorsky/status/1221828307068604417?s=20)], [[Cervical EBRT](https://twitter.com/NicholasZaorsky/status/1222649051235127296?s=20)], [[Cervical BT](https://twitter.com/NicholasZaorsky/status/1222648780903849986?s=20)].  ARRO: [[Cervical cancer](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/CervicalCancer.pdf)].  Contouring:   * eContour: [[AVARO cervix](http://econtour.org/cases/84)], [[post op cervix](http://econtour.org/cases/55)], [[EMBRACE 2 cervix](http://econtour.org/cases/111)] and [[NRG cervix](http://econtour.org/cases/38)]. * Female Normal Pelvis Atlas [[RTOG Contouring Atlases](https://www.nrgoncology.org/ciro-gynecologic)] * Improving target volume delineation in intact cervical cancer [[Eminowicz PRO '16](https://www.ncbi.nlm.nih.gov/pubmed/27032573)]. * Consensus guidelines for delineation of CTV for IMRT for definitive tx of cervix cancer [[Lim IJROBP '11]](https://www.ncbi.nlm.nih.gov/pubmed/20472347). * Consensus guidelines for delineation of CTV in Endo/Cervical PORT [[RTOG Gyn Atlas](http://www.rtog.org/corelab/contouringatlases/gyn.aspx), [Small IJROBP '09](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2752724/)]. [RoR](#8tjrn056kqnl) * Comparison and CTV consensus for CT and MR-based BT in L-A Cervical Ca [[RTOG Atlas](https://www.nrgoncology.org/ciro-gynecologic), [Viswanathan IJROBP '14](https://www.redjournal.org/article/S0360-3016(14)03328-8/fulltext)] [RoR](#kix.8yrje68n0x79)   Review Articles   * Gynecologic Malignancies [[Suneja and Viswanathan Heme/Onc Clin N. Amer '20](https://www.sciencedirect.com/science/article/pii/S088985881930111X?via%3Dihub)] [RoR](#_t4kv4aacj9qi)   Society Guidelines   * ASCO Guideline: Mgmt [and Care of Women with Invasive Cervical Ca Resource-Stratified Guideline](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/gynecologic-cancer#/11801) *May 25, 2016* * Society of Gynecologic Oncology (SGO) [[Guidelines]](https://www.sgo.org/clinical-practice/guidelines/) * FIGO Report: Cancer of the cervix uteri [[Bhatla IJGO '18](https://www.ncbi.nlm.nih.gov/pubmed/30306584)] * [[ESMO Guidelines](https://www.esmo.org/guidelines/gynaecological-cancers)] for Gynecological Cancers. * ESGO-ESTRO-ESP guidelines for the management of patients with cervical cancer [[June '18]](https://link.springer.com/article/10.1007%2Fs00428-018-2362-9) [RoR](#_a6plw395yelu) * ABS:   + ABS Consensus Guidelines [[Viswanathan BT '12]](https://www.sciencedirect.com/science/article/pii/S1538472111003527): Part I: General principles. [RoR](#l14oefxoqiz)   + ABS Consensus Guidelines [[Viswanathan BT '12]](https://www.sciencedirect.com/science/article/pii/S1538472111003515): Part II: HDR BT. [RoR](#1vb7u8jdcrdy)   + ABS Consensus Guidelines [[Lee BT '12](https://www.ncbi.nlm.nih.gov/pubmed/22265438)]: Part III: LDR and PDR BT. [RoR](#cj81a18qu433)   + ABS Task Group [[Albuquerque BT '19](https://www.sciencedirect.com/science/article/pii/S1538472118306305?via%3Dihub)] Compendium of fractionation schedules for Gyn HDR BT. [RoR](#hs48ru8dcnxy)   Relevant Accessible Radiation Protocols:   * TIME-C/RTOG 1203 [[Protocol (Supplement) Klopp JCO '18](http://ascopubs.org/doi/full/10.1200/JCO.2017.77.4273)]: Cervix/Endo (M)RH→ WPRT vs. IMRT. [RoR](#kix.nqh4mp4cd7f2) * RTOG 0418 [[Protocol](https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0418)] for post-operative cervical and endometrial. [RoR](#kix.n1e5fah4ao76) * OUTBACK / ANZGOG 0902 / GOG 0274 / RTOG 1174 [[Protocol](https://www.rtog.org/clinicaltrials/protocoltable/studydetails.aspx?action=openFile&FileID=10105)]: Phase III. (WPRT/EFRT)/B→ ± CarboP x4c. [RoR](#tgrkocfn51fu) * RTOG 0116 [[Protocol](https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileID=7534)]: Phase I/II. EFRT/B/CDDP ± amifostine. *Extended field with 3D is too toxic.* [RoR](#2s9lxocmlkr1) * RTOG 0417 [[Protocol](https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileId=4625)]: Phase II→ CCRT/B + Bevacizumab. *1/3 fail above WPRT field in pAO nodes.*  [RoR](#gsbf2k20udq7)   + RTOG 09-21 [[Viswanathan Cancer '15](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4685031/), ['16](https://www.redjournal.org/article/S0360-3016(16)30456-4/fulltext)][RoR](#eshihl13t11t) demonstrated IMRT high nodal boosts are safe. * EMBRACE II [[Pötter CTRO '18]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5862686/) aims to benchmark high level of local, nodal, and systemic control with IGABT. [RoR](#n9hc7b9umqu)   Quality of Life/Toxicity:   * TIME-C/RTOG 1203 [[Yeung JCO '20](https://www.ncbi.nlm.nih.gov/pubmed/32073955)]: (M)RH→ 3D-WPRT vs. IMRT. [RoR](#kix.nqh4mp4cd7f2) * RTOG 9001 [[Eifel JCO '04](http://ascopubs.org/doi/abs/10.1200/JCO.2004.07.197?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed)]: EFRT/B vs. CCWPRT/B. *Acute toxicity with CCRT worse initially, evens out in long run.* [RoR](#tasa0vnpp4s2) * RTOG 0116 [[Small IJROBP '07](https://www.ncbi.nlm.nih.gov/pubmed/17398031), [IJCG '11](https://www.ncbi.nlm.nih.gov/pubmed/21892091)]: Phase I/II. EFRT/B/CDDP ± amifostine. *40% late G3/4 toxicity.* [RoR](#2s9lxocmlkr1) * EMBRACE I [[Fortin BT '16]](https://www.brachyjournal.com/article/S1538-4721(16)30054-X/fulltext): IS/IC BT for parametrial involvement [RoR](#_efhwb1dgreff) * EMBRACE I [[Mazeron RTO '16](#hi7c3wdz8bwq)]: Limit the rectal D2cc to ≤ 69.5 Gy EQD2 for around 10% late G2+ rectal morbidity. [RoR](#_efhwb1dgreff) * EMBRACE I [[Ujaimi BT '17]](https://www.sciencedirect.com/science/article/pii/S1538472117303938?via%3Dihub): Limit the rectal V55 < 11 cc to minimize late G2+ rectal morbidity. [RoR](#_efhwb1dgreff) * EMBRACE I [[Kircheiner RTO '16](#kix.lb7csgs1k37)]: Limit the rectovaginal D2cc to ≤ 65 Gy EQD2. [RoR](#_efhwb1dgreff) |

## [Treatment Planning](#_npqfvkgpavlm)

See the Summary Box above.

See [[EMBRACE II](#_pik419qibug)] [[Target definitions](#kix.8yrje68n0x79)] and [[Coverage recommendations and Constraints](#_6xguu6v0w1a2)] and [[General Cervix Brachytherapy](#_5aol7dp7fnvi)].

* **ESGO-ESTRO-ESP guidelines for the management of patients with cervical cancer** [[June '18]](https://link.springer.com/article/10.1007%2Fs00428-018-2362-9).
* Consider ovarian transposition in women < 45y before pelvic RT.
* **Complete RT in 56 days!** [[Song Cancer '13](https://www.ncbi.nlm.nih.gov/pubmed/22806897)]:Prolonged RT = worse outcomes. Extending beyond 6-8 weeks results in ~0.5-1% decrease in LC and CSS for each extra day of overall treatment time. Based on RT alone data.
* Hypofx not advantageous b/c cervical CA relatively fast-growing.
* CT simulation: IV and small bowel contrast, anal marker, gyn marker (vaginal contrast or marker, gold seeds if intact cervix), mark inferior extent of vaginal disease. Full bladder, empty rectum.
* Special considerations:
  + Treat initially to 45-50.4 Gy to shrink the tumor.
    - Cervix shrinks 62% during tx, median change in 20 days, *Beadle et al.*
    - For < 20% shrinkage during treatment, significantly lower LC and DSS [[1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2958238/)].
  + Goal 80 Gy EQD2 (e.g. 5.5 Gy x 5) for < 4 cm residual, 85Gy EQD2 (e.g. 6 Gy x 5) for larger tumors.
  + Aim for 60-66 Gy if not resectable, 60 Gy to unresected nodes.
  + AP/PA for thin pts or uterosacral ligament. Consider MBB to avoid excess dose next to implant at 40 Gy.

### [3D Field Borders/Technique](#_a6plw395yelu)

See the [[WPRT Fields](#_rdqhiroqx6vu)] section for more.

* Borders:
  + Ant: posterior wall of bladder or external iliac vessel.
  + Post: uterosacral ligaments and mesorectal fascia.
  + Lat: Medial edge of internal edge of internal obturator.
  + Sup: Top of fallopian/broad ligament, which may also form ant boundary of parametrial tissue.
    - If PLN+: L1/L2 superiorly (renal veins).
    - If pAO+: T11/12 superiorly or 4 cm above the highest node.
  + Inf: Urogenital diaphragm.
* Caveats:
  + If distal third of vagina (stage IIIA), then flash to introitus and cover inguinal nodes.
  + If posterior vaginal wall or uterosacral involvement, then include mesorectum.
* MBB: For IIB, IIIB or LN+, consider a parametrial boost of 5.4-9 Gy (to 54 Gy) depending on response.
  + Reduces dose to bladder and rectum, but may underdose sacrum.
  + Block out middle 4 cm (Corresponds to matching point A).
    - If concerned about toxicity, may widen to 5 cm or put at 50% IDL.
    - Blocks narrower than 5 cm may include ureters.
    - Can go narrower if concerned about tumor.
  + With 3D, prescribe to the middle of the unblocked field - point A gets 50%, point B gets 100%.
  + Ideally, it is customized based on the implant.
    - Sup: Bottom of SI.
    - Inf/Lat: Same as pelvic field.
* **CTV** = GTV + entire cervix + uterus + parametria and ovaries, entire mesorectum if uterosacral involvement.
  + CTV1: GTV/Cervix/Uterus. *Add 1.5 cm for PTV1.*
  + CTV2: Parametria and sup vagina (3 cm below disease). *Add 1 cm for PTV2.*
    - **Vagina**: Upper ½ if minimal/no vaginal extension, upper ⅔ if upper involved, entire if extensive.
    - Vaginal CTV: Vagina and paravaginal tissues. Utilize full/empty bladder scan. The inf limit of the vaginal ITV is approximately the level of the upper third of the symphysis pubis. Identify the vaginal marker and add an additional 0.5-2 cm superiorly. Inf extend to 3 cm below vaginal marker or 1 cm above bottom of obturator foramen (whichever is lower).
  + CTV3: Common/II/EI and presacrals + 7 mm. *Add 7mm for PTV3.*
    - Contour presacrals up to S2/S3 (1-2 cm of tissue ant to S1-3), start external iliac above FH.
    - Contour commons up to 7 mm inf to L4/L5 interspace (aortic bifurcation) to account for PTV.
    - Consider EFRT if common iliacs involved: L1/L2 (renal veins), T11/12 if pAO+, or 4 cm above the node.
      * Most **pAO nodes** are to the left or right of the pAO, only 4% to the right of the IVC. Around ⅔ of these are in the low pAO, as compared to >2/3 above IMA for endometrial.
    - Gross nodal disease receives 60-70 Gy. See [[Lymph node Boosts](#_y9l1m6e7xjg3)] for more.

### [IMRT Technique](#_a6plw395yelu)

See [[Post-Operative IMRT](#_eb93f2h9mmw)], [[IMRT Trials](#_voic7ljxmng9)] and [[Lymph node Boosts](#_y9l1m6e7xjg3)] for more.

* **Consensus guidelines for delineation of CTV for IMRT for definitive treatment of cervix cancer** [**[**Lim IJROBP '11]](https://www.ncbi.nlm.nih.gov/pubmed/20472347).
  + CTV = GTV (Intermediate/High signal on T2 MRI) + Cervix + Uterus + parametrium (includes ovaries, includes entire mesorectum if uterosacral ligament involvement) + vagina (upper half if minimal or no vaginal extension, upper 2/3 if upper vaginal involvement, entire vagina if extensive involvement).
* **PTV margins**
  + CTVp: PTV margins for primary CTV 1.5 - 2 cm.
  + ITV: PTV margins for primary ITV: 0.7 - 1.0 cm.
  + CTV: PTV margins for nodal 7 mm [[Khan IJROBP '12](https://www.sciencedirect.com/science/article/pii/S036030161103389X?via%3Dihub)].
* Daily soft tissue IGRT may need replanning at short notice, as the motion of the cervix can exceed 2 cm in some situations.

### [SBRT boost?](#_6xguu6v0w1a2)

* **UTSW** [[Albuquerque IJROBP '19](https://www.sciencedirect.com/science/article/pii/S0360301619339665?via%3Dihub)]: Phase II. **50/25→ 28/4 SBRT** PTV boost.  
  Suboptimal outcomes probably related to patient selection and very large tumor volume. This approach may still be warranted in patients with smaller tumor volumes unable to undergo standard BT for cervical cancer.   
  TBL [QS](http://www.quadshotnews.com/2019/11/inside-job.html#more): Let’s be honest, using SBRT in place of brachytherapy for cervical cancer remains highly investigational with relatively high rates of late grade 3+ GI toxicity.
  + Study closed after 15 of 21 patients due to concern for toxicity. MFU 1.5y.
    - Over half with stage III/IV disease. Median PTV size of 139cc.
    - RT: 45/25 CCRT ± SIB of 10 Gy to any involved lymph nodes.
  + 2y LC 70%, 2y PFS 47%, 2y OS 53%.
  + 2y G3+ toxicity 27%, mostly rectal ulcer/fistula. MTTG3+ of 8 mo.
  + Median PTV for ± G3 toxicity of 95→ 225 cc.
  + Only the percentage of rectal circumference receiving 15 Gy was associated with G3+ toxicity.
    - PRC15 > 62.7% was the strongest predictor of toxicity (AUC 0.93, Sn 100%, Sp 90%).

## [Follow up](#_npqfvkgpavlm)

* 75% of recurrences occur within the first 2-3 years.

* **Nomograms predicting OS in LACC treated by IGBT** [[Sturdza ASTRO '19](https://www.eventscribe.com/2019/ASTRO/fsPopup.asp?Mode=presInfo&PresentationID=559307)]:  
  This is the first nomogram to predict OS in LACC patients treated with IGABT! In addition to previously reported factors such as age, FIGO stage, corpus involvement, chemotherapy delivery, overall treatment time (OTT) and lymph node involvement, response to EBRT and chemotherapy (volume of CTVHR at first BT) seems to be an essential outcome predictor.
  + 720 patients. 248 deaths occurred during the observation period. MFU 4.5y.
  + Size of tumor at brachytherapy is an important risk factor.

* **EMBRACE Local failures** [[Schmid RTO '17]](https://www.sciencedirect.com/science/article/pii/S0167814017304991?via%3Dihub): **98% of LF within HR-CTVB and IR-CTVB**.

Most failures are in the HR-CTV, while only 20% of failures are isolated in the IR-CTV.

* + 1419 pts. LF defined as incomplete remission 3 mos after tx which did not resolve at 6 mo.
  + LF 5%, half had synchronous nodal or distant mets.
    - 80% had LF within HR-CTV (50% HR-CTV alone), 50% IR-CTV (20% IR-CTV alone).
  + Median time to LR 12 mo. Nearly 90% LF occurred within 24 months.
  + Synchronous nodal or distant failure in half of patients with local failure.

* **RetroEMBRACE Patterns of failure at time of first relapse after IGBT** [[Tan IJROBP '19](https://www.redjournal.org/article/S0360-3016(19)30565-6/abstract)]:   
  Failures are shifting towards distant failures as we keep getting better at local therapy.

LRR and pAO failures are equal at about 10% of failures.

Don't omit VBT for stage III+ patients given double-digit rates of local failure in this subset.

* + 713 pts from 12 institutions.
  + Failures in 30% of patients (n=325). Local failures in 9%, regional failures in 6%.
    - Of failures, locoregional / pAO / pAO + DM / DM alone of 13→ 9→ 24→ 21%.
  + Pelvic only / Pelvic + DM / DM failures of 21→ 23→ 57%.
  + Failures within 1 year / 2 years of 40-50→ 20-30%.
  + Local, regional and pAO failure plateaued after 3y, while systemic failures can occur up to 10y.
  + Regional failures for node negative / node positive of 3→ 8%.
  + pAO failures for node negative / node positive of 6→ 10%.
  + Distant failures for node negative / node positive of 15→ 27%.
  + Local failures for ± stage III+ of 4→ 14%.
  + Regional failures for ± stage III+ of 2→ 9%.
  + pAO failures for ± stage III+ of 5→ 12%.
  + Distant failures for ± stage III+ of 11→ 29%.

* **EMBRACE Patterns of failure after CCRT and IGBT** [[Nomden RTO '19](https://www.ncbi.nlm.nih.gov/pubmed/31005214)]:

There is around 40% OOF failure, most of which is in the pAO region.

* + 1,416 pts. At diagnosis, 99% were PLN(+) with 14% pAO(+). MFU nearly 3y.
    - Lymph nodes could be boosted up to 60-65 Gy (2-2.2 Gy/fraction).
  + Nodal failure occurs within 2y in over 80% of patients.
  + 3y nodal failure for N(-) / N(+) of 7→ 16%. Of these, PLN / pAO failures of 55→ 68%.
  + OOF failures in 40%, with nearly all pAO.
  + 12% of patients who received a nodal boost had IFF.
  + PLN+ and pAO- patients (not common iliac) had less than 10% pAO failure when receiving pAO RT.
* H&P q3-6mo x2y→ q6-12mo up to year 5, yearly thereafter.

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## [Future Directions](#_npqfvkgpavlm)

See NCTN Trial Portfolios by Disease Site: [[Gyn](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_GYNE_Trials.pdf)]

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### Organ Confined, High risk

* See [[**GOG 0263**](#jq4ldzxzuxcj)]: Phase III. **RH/PLND→ WPRT ± CDDP qwk**.
  + Stage I-IIA. Role of CCRT in intermediate risk disease (2+ Sedlis criteria).
* See [[**RTOG 0724**](#vyhja2y0cn37)]: Phase III. **RH→ CCRT(B) ± CarboP** **x4c**.

This trial investigates the use of adjuvant chemo in high risk, early stage cervical cancer. Primary endpoint DFS.

* + IA2, IB, IIA→ RH with Peters Postop criteria. Strat by VBT, 3D/IMRT, and WPRT dose (45 vs. 50.4 Gy).
  + CDDP 40 q1w w RT→ Carboplatin AUC 5 and palitaxel 135. Also allowed to enroll on [[TIME-C](#kix.nqh4mp4cd7f2)].
  + Notable constraints: Bowel: V40 < 30% and Bladder: V45 < 35%.
* See [[**OUTBACK** / **ANZGOG 0902 / GOG 0274 / RTOG 1174**](#tgrkocfn51fu)]: Phase III. **CCRT/B→ ± CarboP x4c**.
  + IB1 and positive nodes, IB2, II, IIIB or IVA. Definitive CCRT/B.
  + CCRT CDDP 40 q1w→ Carboplatin AUC 5 and palitaxel 155.

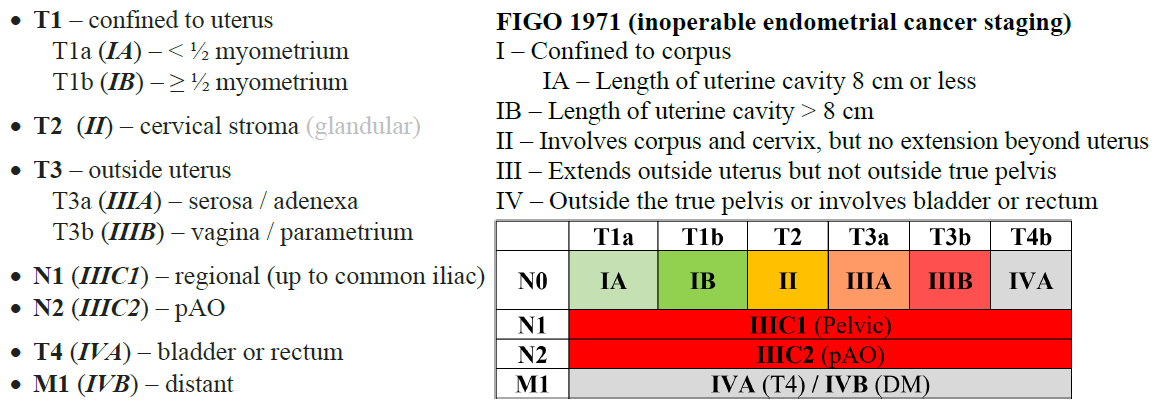
### Newly diagnosed, Locally advanced

* **NRG-GY017** [[NCT03738228](https://clinicaltrials.gov/ct2/show/NCT03738228)]: Phase I. **CCRT ± Atezolizumab before and or concurrently**.
  + Node positive IB2, II, IIIB or IVA cervical cancer.
* **NRG-GY006** [[NCT02466971](https://clinicaltrials.gov/ct2/show/NCT02466971)]: Phase II. **CCRT ± Triapine** (new anti-cancer drug).

See [[Future Directions](#_ppa831wuylrl)] in the Vaginal cancer section.

* + Advanced stage cervical and vaginal cancer.
* **EMPOWER-Cervical 1 / GOG 3016** [[NCT03257267](https://clinicaltrials.gov/ct2/show/NCT03257267)]: Phase III. **Investigators choice vs. Cemiplimab** q3w.
  + Metastatic cervical cancer resistant to Plt-based chemo, ≥ 2nd line.
  + Cemiplimab 350 q3w up to 2 years unless PD or unacceptable irAE.

# [Endometrial Cancer](#_nz4p8uik7qem)



IA: Endo or < 50% myometrium (old IB).

IB: ≥ 50% myometrium (old IC).

Cervical glandular epithelial involvement previously IIA, now IA or IB.

See [[Endometrial Cancer](#_83m96wfmlocl)] in the Introduction to Gynecologic Malignancies section.

**Zaorsky**: [[Comparison of hysterectomy subtypes and trachelectomy](https://twitter.com/NicholasZaorsky/status/1221824856834158592?s=20)], [[Gyn nodes AP](https://twitter.com/NicholasZaorsky/status/1221823861978693632?s=20), [Gyn nodes Lat](https://twitter.com/NicholasZaorsky/status/1221824276740956162?s=20)], [[Endometrial staging](https://twitter.com/NicholasZaorsky/status/1221829707450195975?s=20)].

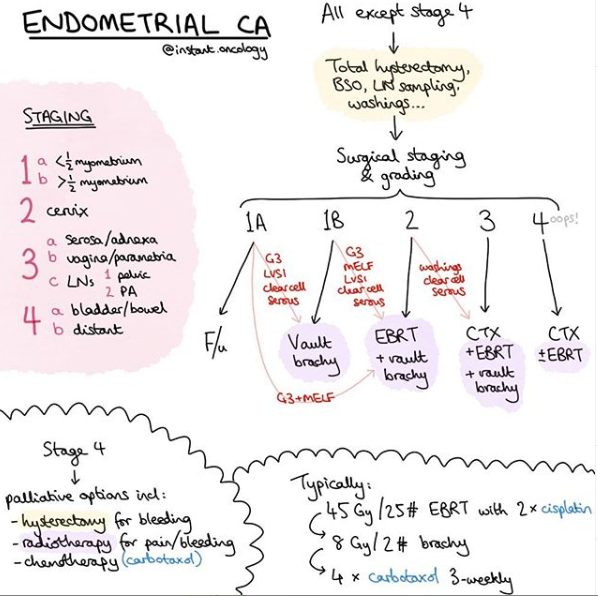
**ARRO**: [[Early-stage Endometrial Cancer](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/EarlyStageEndometrial.pdf)], [[Endometrial Cancer](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/Endometrial_Vu.pdf)]

**eContour**: [[AVARO endometrium](http://econtour.org/cases/85)], [[post op endometrial (pelvis)](http://econtour.org/cases/53)], [[post-op endometrial (VBT)](http://econtour.org/cases/57)].

[**StatPearls: Endometrial**](https://www.ncbi.nlm.nih.gov/books/NBK525981/)*Last update: 7/22/2019*

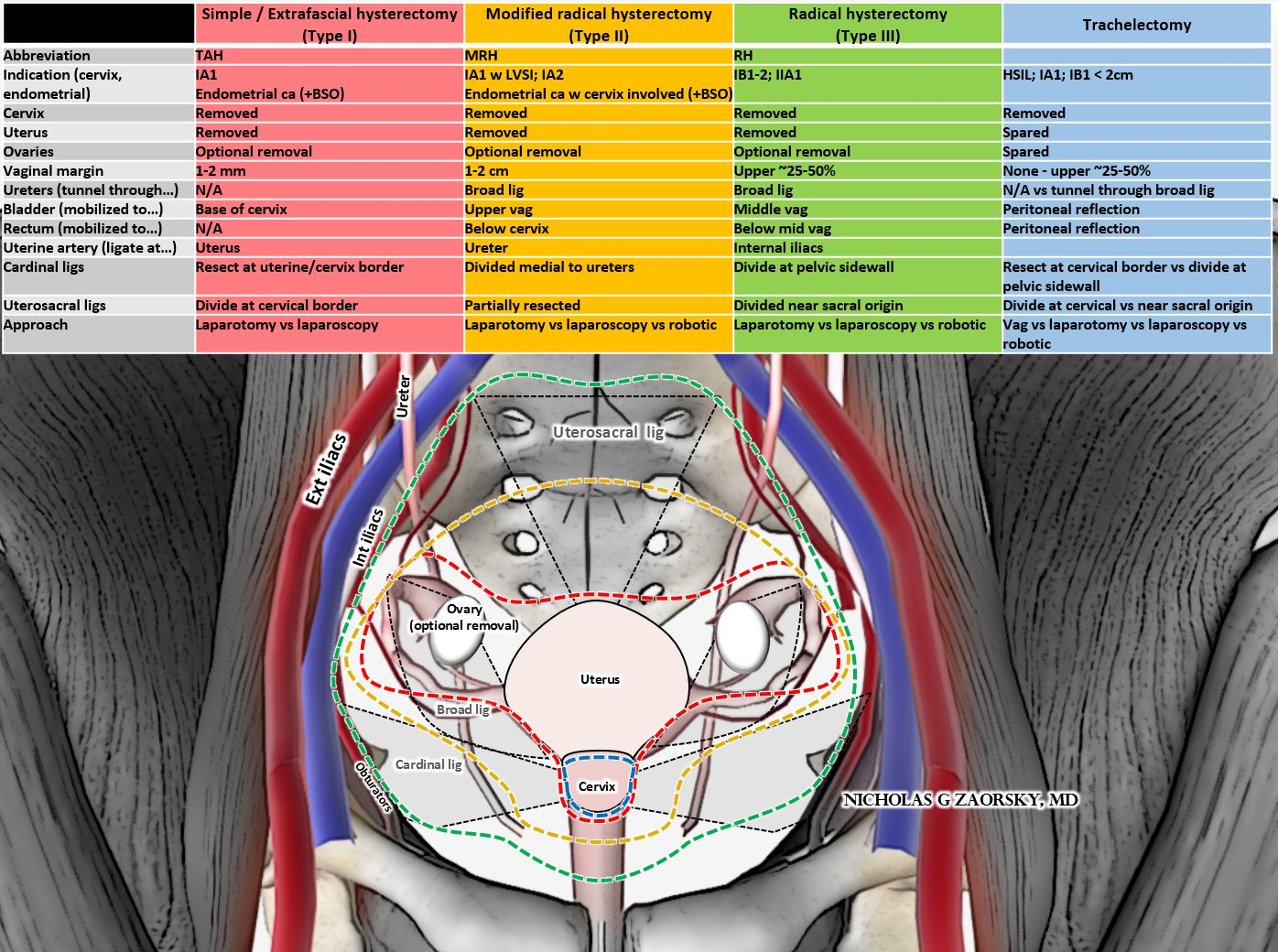
FIGO Summary Article: Cancer of the corpus uteri [[Amant IJGO '18](https://www.ncbi.nlm.nih.gov/pubmed/30306580)] *Note: Pre-PORTEC-3 final results.*

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| **ASCO/ASTRO Guideline: PORT** [**for Endometrial Cancer Endorsement**](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/gynecologic-cancer#/10256)*July 6, 2015*  See the Bayta.us [[nomogram](#_m811c6vihx23)] which is newly available as of 2020! See the [[Treatment Planning](#_ce97gipx12r6)] section.   * Surveillance appropriate for G1-2 and < 50% myometrial invasion, especially without other HR features. * VBT ≅ WPRT for G1-2 and > 50% myometrial invasion or G3 and < 50% myometrial invasion. * IBG3 may benefit from pelvic radiation. There is limited evidence for benefit to VBT to WPRT. |

[](https://www.instagram.com/p/B8PhfrkgHcf/?utm_source=ig_web_copy_link)

* MC gyn malignancy with 50k new cases per year with 8,000 deaths in 2013. 2nd MCC of gyn cancer deaths.
  + 4th MCC overall.
  + Decreasing trend with less hormone replacement, but increasing due to obesity.
    - A study of early stage G1 endometrial CA demonstrated 7% CSM, whereas 42% died from CV disease.
* 85% of new cases are stage I-II.
  + **Megestrol acetate**: Give for fertility preservation for G1 endometrioid histology, stage IA on MRI, no prior stroke or embolisms. Durable complete response occurs in only 50% of patients, requiring endometrial sampling q3-6mo.
    - PR positive tumors may respond to continuous PR-based agents such as megace.
    - **Could consider megace in IAG1**. If CR at 6 mo on megace, childbearing→ TAH/BSO.
    - Tamoxifen and arimidex may also be used for medically inoperable endometrial cancer, but these agents are not fertility sparing.
    - C/I to megace: breast cancer, stroke, MI, PE, DVT, smoking.
    - Although 35% with negative EMB are able to get pregnant, their recurrence rate is high (~35%).
* 70% confined to the uterus. 90% have abnormal vaginal bleeding.
  + Only 5-20% of postmenopausal women w abnormal vaginal bleeding have endometrial cancer.
  + Menorrhagia: heavier bleeding.
  + Metrorrhagia: between menses bleeding.
  + Ligaments of uterus:
    - Broad: From uterus to lateral to pelvic sidewall.
    - Round: From fundus anterolateral to internal inguinal ring.
    - Uterosacral: From lower uterus to posterior to sacrum.
    - Cardinal: From pelvic sidewall to cervix.
* **Risk factors**: Unopposed estrogen, postmeno, nulliparity, early menarche, late menopause, obesity, tamoxifen (**7.5x**), OCP.
  + Protective factors: Breast feeding, smoking, physical activity.
* **Pathology**
  + 75% adenocarcinoma; 20% non endometrioid: UPSC (<10%), clear cell (<5%), mucinous; 5% sarcoma.
    - Up to 5% are sarcomas, including carcinosarcoma, leiomyosarcoma and ESS.
  + **Grade** 1 / 2 / 3 with a dedifferentiated solid growth pattern of **5**→**50**→ >50%*.*
  + Simple hyperplasia becomes invasive 2% of the time. Hyperplasia with atypia 30-40% of the time.
* **Type I** (70-85%): Endometrioid, estrogen-dependent. Often low grade, slow growing. ~⅓ MSI.
  + K-Ras, MLH1 methyl, PTEN.
  + **Types**:
    - Papillary.
    - Villoglandular.
    - Squamous.
    - Adenosquamous (High grade).
    - Adenoacanthoma (benign appearing squamous component).
* **Type II** (20%): UPSC / CC / MMMT 2/2 mucosal atrophy, typically UPSC or CC, high grade, aggressive.
  + TP53, ERBB2 (HER2).
  + Responsible for half of EC deaths.
  + Subdiaphragmatic/abdominal failure is the most common failure site for UPSC, like ovarian.
  + **Types**:
    - Serous.
    - Clear Cell.
    - Carcinosarcoma (aka MMMT): *Increased LR/DM. Mets are usually epithelial components.*
* **Genetics**

See the Genetics section on [[SGO Website](https://www.sgo.org/clinical-practice/guidelines/)] for more.

* + **Cancer genome**: [[PORTEC-4a](#3niegyeqx8u5)] is investigating VBT vs. molecular profile-based tx for up to microscopic stage II.
    - POLE (Ultra mutated): 6% of low grade, 17% of high grade.
      * Best prognosis. PI3K, KRAS common. TP53 35%.
    - Microsatellite unstable (Hypermutated): 29% of low grade, 54% of high grade.
    - Copy number low (endometrioid): 60% low grade, 9% high grade. 2% serous. 25% mixed.
    - Copy number high (serous-like): Serous. > 90% p53 mutations.
      * Worst prognosis. Approximately 25% of patients are HER2+, with a potential PFS benefit by the addition of trastuzumab to chemo.
  + FDA has approved pembro + lenvatinib for endometrial carcinoma for the treatment of patients with advanced endometrial carcinoma who are not MSI-H or dMMR in patients who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation [[Arora Clinical Cancer Research '20](https://www.ncbi.nlm.nih.gov/pubmed/32295834)].
* **Workup**
  + **H&P**: Attention to postmenopausal bleeding, pain, bladder/bowel sx, Gyn hx, Tam, unopposed estrogen (tam RR 7x), fam hx (HNPCC/Lynch).
  + **PE**: Abd/pelvis, ascites, nodal exam. Speculum. Bimanual. Rectovaginal.
  + CA-125 elevated in 60% (normal <35).
  + Pap smear sensitivity 40%.
  + CXR, CT or MRI of A/P or TVUS.
    - TVUS: Thickened strip is >5 mm.
      * Risk of carcinoma is ~7% if >5 mm and 0.07% if the endometrial strip is < 5 mm [[1](https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1002/uog.1704)].
    - MRI for II+, PET/CT as indicated (sx or not doing surgical staging).
      * MRI: **Tumor usually low T1, high T2 (dark)** [[1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3336085/)].
      * Cervix low T1, low (bright) T2. Parametrium high T1, high (dark) T2.
      * Uterine junctional zone: low (bright) T2 inner myometrium, if high (dark), think uterine invlmt.
      * Take home: Tumor low/high, cervix low/low, parametrium high/high.
  + Endometrial biopsy:
    - EMB FN rate 3-10% ∴ follow w D&C (EMB may not be accurate for mesenchymal tumors).
    - D&C under anesthesia if initial biopsy is nondiagnostic.
  + Pathologic staging:
    - Ex-lap with inspection of omentum, liver, peritoneum, adnexa with peritoneal cytology and omental bx.
    - TAH and BSO w PA-PLND (>10 nodes – at least one from each of 5 stations bilat; PA, CI, EI, II, obturator).
    - Bisect uterus to determine the depth of invasion.
    - "LOLGD": Lower uterine segment, Ovary/fallopes, LVSI, Grade, DOI/total length, margins, nodes.
      * Interestingly, tumors arising in the lower uterine segment with higher incidence of Lynch syndrome.

## 

## [Surgery](#_3llouklhg1v3)

Comparison of hysterectomy subtypes and trachelectomy [[Zaorsky](https://twitter.com/NicholasZaorsky/status/1221824856834158592?s=20)].

* Lymph node dissection included PLN ± pAO dissection, especially for high risk histologies and advanced stage. pAO nodes dissected to the level of the IMA or higher. SLN mapping is considered for uterine confined lower grade cancers. Omental and peritoneal biopsy for serous and clear cell carcinoma.
* **Type I**: **TAH** (extrafascial). Uterus, cervix and small rim of vag cuff (outside pubocervical fascia).  
  See [[](#nwkpktpmw1xj)[Types of Hysterectomy](#_yrcjyvw6jf2d)] for MRH and RH details (i.e., 1-2 cm and upper 1/2 to 1/3 of vagina, respectively).
  + If TAH performed on stage II (cervical involvement), consider the addition of vaginal brachytherapy.
    - Gross cervical invasion requires preop RT or RH instead of TAH.
  + Indications for adjuvant: Type of surgery, LN assessment and # LN removed, cervical or lower uterine segment involvement, ovaries/fallopes, vaginal/parametrial extension, histology and tumor grade, LVSI, margin status, size.
* **Surgical guidelines at Mayo**: Omit LND if no disease beyond corpus and IA, G1-2, < 2 cm or confined to endometrium\*.

Periaortic disease occurs above the IMA around 75% of the time. This led to favoring of taking nodal dissection up to the renal hilum. LND to below the IMA missed up to nearly half of pAO positive cases. Isolated pAO involvement without PLNs is extremely rare.

\*These were defined from 2004-2006, and are now controversial. The [[LAP 2](#d0lhzkgi5r00)] trial demonstrated G1-2, IA and tumor size < 2 cm still harbor nodal metastases, supporting the use of SLNB in this population.

* + Mayo takes LND to renal hilum. 15% Pelvic and/or pAO.
    - Of those, pelvic only / pelvic + pAO / pAO only 50→ ~40→ ~15%.
  + In other words, isolated pAO involvement is only 2-3% [[Mariani Gyn Onc '04,](https://mayoclinic.pure.elsevier.com/en/publications/endometrial-carcinoma-paraaortic-dissemination) [Boronow Gyn Onc '08](https://www.gynecologiconcology-online.net/article/S0090-8258(08)00510-6/abstract), [LAP 2](#d0lhzkgi5r00)].
* **Mayo** [[Kumar Gyn Onc '13](https://www.gynecologiconcology-online.net/article/S0090-8258(13)00768-3/abstract)]: **Risk factors that mitigate the role of pAO LND in endometrial cancer**.

They had a pathologist in the OR with them, so this study is not really generalizable.

pAO positivity is correlated with PLN(+) (most importantly), but also associated with MI ≥ 50% and grade.

* + For patients with PLN(+) and MI ≥ 50%, around 20-25% will be pAO(+) if G2-3, while 10% if G1.
  + For patients with PLN(+) and MI ≤ 50%, at most 5% will be pAO(+) regardless of grade.
  + Of patients with pAO nodes, one third had nodes above the IMA only, half had nodes above and below the IMA, while only 12% had nodes below the IMA only (88% of positive pAOs are above the IMA).
  + Positive PLNs, LVSI and MMI > 50% are key factors to direct pAO LND. Omitting pAO LND for any grade endometrioid tumor with ≤ 50% MMI only missed 1% pAO metastasis or recurrence.
  + Using these criteria, pAO LND may be omitted in 77% of pts with endometrioid endometrial cancer.

### [Lymph Nodes](#_tswqoux8snp9)

*Old school:* Around 10% of all lymph nodes are palpable by the surgeon. Cannot reliably identify patients with nodal metastasis. Around 33% of PLN+ will be pAO+. Around 1/4 of patients will be upstaged with surgery. Therefore, nodal assessment is key. Morbidity of node dissection was low. Most patients did not need RT.

*New school:* Standard of care was to fully dissect the nodal basin and para aortics, but full lymphadenectomy is associated with [[greater morbidity](#kdnp5koag4dx)]. Isolated pAO lymph node involvement is only 2-3% [[Mariani Gyn Onc '04,](https://mayoclinic.pure.elsevier.com/en/publications/endometrial-carcinoma-paraaortic-dissemination) [Boronow Gyn Onc '08](https://www.gynecologiconcology-online.net/article/S0090-8258(08)00510-6/abstract), [LAP 2](#d0lhzkgi5r00)]. More than 90% of LNs are free of metastatic disease. Class III obsese women are difficult to resect up the hilum. As of 2020, pAO dissections are essentially dead in the USA. SLNB is key.

* Size cut off for lymph nodes 1 cm short axis has low Sn and high Sp, may be improved if 8 mm.
* Lymph nodes "USA ME LIES"
  + Upper uterine: Superficial inguinal and Aortic.
  + Middle portion (uterine body): External iliac nodes.
  + Lower portion (cervix): Internal iliac nodes, External iliac, Sacral nodes

* **GOG 33** [[Creasman Cancer ‘87](https://www.ncbi.nlm.nih.gov/pubmed/3652025)]: TAH/BSO, LND, peritoneal cytology.

**The “10-20-30” rule for deep invasion: For G1 / G2 / G3, positive pelvic LN of 10→ 20→ 30%.**

If PLN(+), then around 40% will have pAO LN(+), while if PLN(-) only 2% will have pAO LN(+).

Surgery upstages ~23% of cases.

Depth of myometrial invasion is proportional to the percentage of lymph node mets.

≤ 5% if endometrium alone, 10% for IA, from 10-35% for IB depending on grade. Think: G3, 33%.

* + 621 pts. Stage I endometrial cancer
  + G1, old IA (superficial) has ~5% chance of LNs. Inner ⅔, G1 has a 5-10% chance of LNs.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **GOG 33** | **Risk of PLN+** | | | **Risk of pAO+** | | |
| G1 | G2 | G3 | G1 | G2 | G3 |
| **Inner 1/3** | < 5% | 5% | 10% | < 5% | 5% | 5% |
| **Middle 1/3** | 5% | 10% | 10% | 5% | 5% | 5% |
| **Outer 1/3** | **10%** | **20%** | **35%** | 5% | 15% | 25% |

* **MRC ASTEC / EN.5** [[Lancet '09](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2646126/), [Lancet '09](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2646125/)]: TAH/BSO **±** LND ± EBRT if IR/HR for recurrence.

"The lymph node dissection trial": LND with no significant OS or PFS benefit.

Half of observation (and 5% EBRT) had VBT, so not reliable study (mushed together 2 somewhat discordant trials).

Adjuvant WPRT improved LC by a small amount compared to observation, but not OS or DSS.

* + 1408 pts with corpus confined disease. Int/high risk IAG3 or IB, old IIA, or UPSC/CC.
    - RT: median 45 Gy. Around 30% rec’d LND.
  + 5y OS ~84%, 5y DFS ~90%.
  + 5y LRR 7→ 4%, Isolated LRR 6→ 3%.
  + Severe acute toxicity for ± EBRT of 27→ 57%, moderate acute toxicity ± EBRT of 8→ 22%.
  + Late toxicity for ± EBRT of 3→ 7%.
  + Incidence of nodes: IAG1-2 2%. High-int: IB/G3 9%. ~RFS w LND.
  + LND toxicity: 12→ 17%.

* **Italy** [[Benedetti JNCI '08](https://www.ncbi.nlm.nih.gov/pubmed/19033573)]: **TAH/BSO ± LND**.
  + 514 pts. Stage I. Adjuvant chemo ± EBRT/BT in patients deemed high risk. MFU 4y.
  + More complications in the LND group. Median number of lymph nodes of 30.
  + There was no difference in 5y OS or DFS.
* Greater than 20 nodes on LND is associated with improved survival [[Chan Cancer '06](https://www.ncbi.nlm.nih.gov/pubmed/16977653)]
  + What is the adequacy of LND for staging? It depends on how pathologists examine the nodes. "If you want 10 lymph nodes I'll give you 10 lymph nodes" - Dr. R.J. Zaino.

* **LAP 2** [[Milam Ob and Gyn '12](https://www.ncbi.nlm.nih.gov/pubmed/22270280)]

Challenged the Mayo guidelines to omit assessment of LNs in women who were IA, G1-2, and < 2 cm, supporting the use of SLNB in this subgroup.

* + 971 pts with complete path data. Of whom, 7% (n=65) had positive nodes.
  + In the 65 node positive cases, 60% were G1-2. Nearly half had < 50% myoinvasion. 23% had tumor size < 2 cm.
  + Only 2% of pts had isolated pAO LN involvement, consistent with [[Mariani Gyn Onc '04](https://mayoclinic.pure.elsevier.com/en/publications/endometrial-carcinoma-paraaortic-dissemination), [Boronow Gyn Onc '08](https://www.gynecologiconcology-online.net/article/S0090-8258(08)00510-6/abstract)]
* Effect on nodal sampling [Kilgore Gyn Onc '95]

### [SLNB](#_tswqoux8snp9)

The number of SLNB have increased fivefold, while the number of para aortic dissections have decreased fivefold.

No nodal dissection is done in Europe. SLNB can help decide whether or not to dissect up to the renal hilum.

Sentinel nodes are found at the bifurcation of the common iliac around 90% of the time [Abu-Rustum Gyn Onc '09], while around 15% of patients had positive SLN in regions outside standard PLN volumes such as the presacrals or internal iliacs [[FIRES](#jxco7tbyfxq1)].

Lymphazurin blue or methylene blue is not obvious with Da Vinci. Indocyanine green is obvious.

* **Senti-Endo** [[Daraï Gyn Onc '15](https://www.ncbi.nlm.nih.gov/pubmed/25450151)]: Prospective. **SLN with cervical injection of patent blue and Tc-99→ PLND**.
  + 133 patients. Stage I-II, all grades. 15% type II. MFU 4y.
  + 88% mapped at least 1 SLN, with 17% positive nodes (n=19). 47% (n=9) only found on IHC ultrastaging.
  + NPV 97% and sensitivity of 84%. All 3 false negatives were in type II cancers.
* **SLN improves detection of metastasis** [[Khoury-Collado Gyn Onc '11](https://www.gynecologiconcology-online.net/article/S0090-8258(11)00329-5/abstract)]:

When using a cervical injection, metastatic cells are 3x more likely detected in the SLN vs. NSLN.

* + Positive nodes in NSLN / SLN of 1→ 3%.

* **FIRES SLNB trial** [[Rossi Lanc Onc '17](https://www.sciencedirect.com/science/article/pii/S1470204517300682)]: Prospective. **SLNB→ PLND** ± pAO.  
  SLNB is reasonable up to clinical stage IBG3. Interestingly, some nodes were found in the pAO region, the presacral region, and the deep obturator region (these are areas we do not commonly treat).
  + 385 pts. Clinical stage I EC undergoing RTAH with PLND. ~20% type II. ~10% G3. 66% IA, ~15% IB.
    - Dye with indocyanine green. Cervical injection 1 cm deep at 3 and 9 o'clock.
    - Ultra-staging of SLN (3 mm cuts).
    - Around 60% had pAO LND.
  + Successful mapping of at least one SLN in 86%, with 12% positive nodes on dissection (n=41).
    - ~50% had bilateral mapping.
  + Sensitivity 97%, NPV 99.6%.
  + Around 17% of patients had +SLN in regions outside of routine PLND (e.g. presacrals, internal iliacs).
  + Further LN+ for SLN micro (ITC or ultra-staging) / macromets of ~30→ 60%.
  + SLN represents the most distal level of metastatic disease in 80% of patients (n=28/35).
* **SLN ITCs** [[Plante Gyn Onc '17](https://www.ncbi.nlm.nih.gov/pubmed/28577885)]:Prospective. **SLNB→ PLND**.  
  This study said that ITCs didn't matter - but all received completion PLND!
  + 519 pts.
  + Of those with positive nodes, 36% were ITC.
    - All patients treated with completion PLND.
    - Around 33% of each received: Chemo ± WPRT, WPRT, or Obs ± VBT.
  + 3y PFS for macromet / micromet / node negative / ITC of 59→ 86→ 88→ 96%.
  + ITC patients received less chemo and WPRT than the macromets group.
* **SLN and NSLN metastasis** [[Kennard Gyn Onc '19](https://www.ncbi.nlm.nih.gov/pubmed/31027899)]: **SLNB→ PLND ± pAOLND for LR vs. IR vs. HR**.  
  There were no cases of isolated pAO mets in this study.
  + ITCs on SLN indicated a >10% risk of pAO positivity.
  + 414 pts. 19% IR. 14% HR.
    - **LR** (66%): Type I, IA. **IR** (20%): Type I, IB. **HR** (15%): Type II.
    - pAO LND performed in 25% of LR patients, while 84% of IR/HR patients.
  + PLN mets in 12→ 50→ 40%.
  + pAO LN mets in 3→ 11→ 17%.
  + ITC in 52→ 45→ 15%.
  + SLNB FNR of 0→ 2.5→ 5%.
  + NSLN(+) PLN in 32%, or 8% if ITC.
  + ITC with pAO(+) in 19→ 12→ 33%.
* **SLNB Treatment Recommendations** [[Barlin Gyn Onc '12](https://www.gynecologiconcology-online.net/article/S0090-8258(12)00147-3/abstract)]:

Evaluate any suspicious nodes in retroperitoneum regardless of mapping. If there is no mapping on a hemi-pelvis, a side-specific LND is performed. Para-aortic LND at attending discretion.

* + ITC approach differs if completion dissection is performed.
    - If dissection is performed→ VBT alone.
    - Without dissection→ Add EBRT if there are other higher risk intrauterine factors.
  + Macro/Micro-mets: Treated as node positive disease with CCRT [[PORTEC 3](#crqxu2jebdsq), [GOG 258](#kix.2wgy28yhajjf)].

## [Chemotherapy](#_3llouklhg1v3)

* **CCRT with CDDP. Adjuvant chemo: Carboplatin/Paclitaxel or CDDP with Doxorubicin or Docetaxel.**
  + Note: Adjuvant doxorubicin/cisplatin not seen in cervical cancer (CarboP preferred).
* Theory that CDDP is radiosensitizer by preventing sublethal damage repair.
* Lack of survival benefit to combine CCRT vs. RT vs. chemo alone in randomized studies.
* Greatest benefit with CRT in stage III: Give CRT followed by adjuvant chemo in IIIC, consider with other stage III.
* Limited rationale for CRT in HR stage I/II endometrioid, but trend towards improvement with CRT in serous histology.
  + IBG3 or stage II: Evidence is lacking.
  + Final results of [[PORTEC-3](#crqxu2jebdsq)] demonstrate a 10% OS benefit for stage III and/or serous histology treated with CCRT followed by four cycles of carboplatin and paclitaxel.
* Largest study of cervical stromal invasion w/o chemo had 5y RFS 77%, DSS 91% (similar to some stage I patients)
* Most early stage patients are excluded from chemo studies.
* NSGO/MaNGO pooled analysis of adjuvant chemo with CSS benefit.
* Japanese and Milan trials on EBRT vs. chemo with ~recurrence, DFS, and OS.

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| **Chemotherapy in Endometrial cancer**   * **CCRT**: Cisplatin **50** d1,28 + 45 Gy. Consider 50.4 Gy if no VBT to be delivered.   + There seems to be most benefit to add chemo to WPRT in stage III disease (FFS) and pts > 70y (OS benefit!) * **Adjuvant chemo**: Carbo AUC **5**, Paclitaxel **175** q3w x4c or CDDP + (Doxorubicin or Docetaxel [QS](http://www.quadshotnews.com/2019/03/chemo-kick.html)).   + According to new (2019) [[Japanese Phase III](#z4ti1zwvc1gx)] data [QS](http://www.quadshotnews.com/2019/03/chemo-kick.html), CDDP/Docetaxel seems like the best option, but it is rare to recommend adjuvant chemotherapy.   + Final results of [[PORTEC-3](#crqxu2jebdsq)] demonstrate a 10% OS benefit for stage III and/or serous histology treated with CCRT followed by four cycles of carboplatin and paclitaxel. |

## [Nomograms](#_3llouklhg1v3)

See the new [[Bayta.us](https://www.bayta.us/nomos/endometrial)] nomogram which obviates the need for manual risk score additions on the two pubs below.

TBL [QS](http://www.quadshotnews.com/2020/02/demystify.html): If your ouija board is on the fritz, you can now turn to a brand-new online calculator to help you decipher which treatment pathway to recommend for early-stage endometrial cancer by quantifying risk of outcomes per treatment modality. Granted, per PORTEC it treats [[LVSI](#iuwnoiy6bk4n)] as all or nothing, but it remains easily adaptable as new data rolls in.

* Pooled analysis of PORTEC 1 and PORTEC 2 [[Creutzberg IJROBP '15]](https://www.sciencedirect.com/science/article/pii/S0360301614044034?via%3Dihub):  
  Does not account for size, but AlHilli does.
  + Age, Grade, LVSI highly predictive for LRR, DR, OS, DFS and treatment given (EBRT vs. VBT).
    - LVSI does not influence LR, instead pelvic/DM (esp [[substantial](#iuwnoiy6bk4n)] LVSI).
    - Grade may be the most powerful predictor of vaginal recurrence.

* **AlHilli** [[Gyn Onc ’13 (LR)](https://www.sciencedirect.com/science/article/pii/S0090825813008706?via%3Dihub), ['14 (OS)]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4405150/): Predicts lymphoid dissemination and overall survival.  
  Includes tumor size > 2 cm as a risk factor for overall survival.
  + Lymphoid mets: Tumor >2 cm, Grade, Cervical stroma, LVSI predictive.
  + Overall survival based on high risk (G3, non-endometrioid) or low risk (G1-2 endometrioid).
    - Low risk: Age at surgery, stage, tumor >2 cm, post op issues, pelvic nodal status, CVD, COPD.
    - High risk: Age at surgery, ASA score, LVSI, cervical stroma, adjuvant tx, pAO status.

## 

## [Early Endometrial Cancer](#_3llouklhg1v3)

See the Treatment of Early Stage endometrial cancer summary box below.

See the new [[Bayta.us](https://www.bayta.us/nomos/endometrial)] nomogram which obviates the need for manual risk score additions on the two pubs above.

* **All patients get surgery! TAH/BSO + PAPLND→ RT**.
* Aim to start VBT within 12w of surgery.
* Observation acceptable in Stage I, unless IB G3, LVSI, or non-endometrioid histology.

|  |  |  |  |
| --- | --- | --- | --- |
|  | G1 | G2 | G3\*\* |
| < 50% no RF | Obs | Obs or VB | Obs or VB |
| < 50% + RF | Obs or VB | Obs or VB and/or WP | VB or WP, ± chemo |
| > 50% no RF | Obs or VB | Obs or VB and/or WP | VB and/or WP, ± chemo |
| > 50% + RF | Obs or VB and/or WP | VB and/or WP | WP and/or VB, ± chemo |

\*\* For high risk histologies, such as serous, clear cell, undifferentiated, and carcinosarcoma, may add chemotherapy.

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| **Treatment of Early Stage endometrial cancer**  See the new (2020) [[Bayta.us](https://www.bayta.us/nomos/endometrial)] nomogram to guide recommendations for intermediate risk endometrial cancer.  See the [[Uterine Brachytherapy](#_oc4dol5dwo1z)] or the [[Overview of Brachytherapy](#_qxjzzedoyoxn)] section for more.   * **Low Risk: G1-2, IA**. May omit VBT if ≤ 4 mm DOI unless high risk histology or LVSI.   + Netherlands [[Geels Gyn Onc '13]](https://www.sciencedirect.com/science/article/pii/S009082581300084X?via%3Dihub): **± 4 mm DOI** is predictive of PFS/OS. * **High intermediate risk**: Per NCCN: LVSI, LUSI, ≥ 60y, tumor size (e.g. > 2 cm), cervical/glandular involvement.   Hopelessly oversimplified: Consider WPRT for substantial LVSI. Consider VBT for cervical stromal involvement.  See [[High intermediate risk](#_gpdbaw92x9m0)] for an understanding of risk groups.   * + [[LVSI](#iuwnoiy6bk4n)] panned out as a risk factor on [[GOG 99](#4xfr7fwf372m)], as 20% of pts had LVSI, compared to 5% on [[PORTEC-1](#88qtqed5maf9)].   + “DGL” + age as risk factor: Either 50/70y or ± 60y on [[GOG 99](#4xfr7fwf372m)] and [[PORTEC-1](#88qtqed5maf9)], respectively. *Compare to “SDL” for cervical cancer per [*[*SeDLis*](#p8xcqpfzudaz)*].* * **“High Risk”**: **IBG3**. Excluded from many trials. The treatment of IBG3 is uncertain.   + The [[Norweigan trial](#iuyx48te4fxs)] demonstrated potential CSM benefit for EBRT + VBT in IBG3 disease.   + The [[Sorbe 2012](#s2si5ou0xt99)] paper demonstrated EBRT + VBT may be of benefit in IBG3 disease. * **Stage II** (Cervical involvement) is strongly recommended to receive BT in addition to EBRT. |

### [Low risk Endometrial cancer](#_x5yfx9juqx)

* **Sorbe** [[IJGC '09](https://journals.lww.com/ijgc/Fulltext/2009/07000/Intravaginal_Brachytherapy_in_FIGO_Stage_I.13.aspx)]: **± VBT**.

Safe to omit VBT if Low Risk: IA, G1-2, endometrioid, no LVSI.

* + 645 pts. **Low risk**: IA (old IA/IB), G1-2. Endometrioid. TAH/BSO, pelvic cytology, PLN sampling.
    - VBT 3-8 Gy x 3-6 fx.
  + Vaginal recurrences ~3.1→ 1.2% (p=0.11).
  + G1-2 toxicity 0.6→ 2.8%.

### [IBG3 disease](#_x5yfx9juqx)

EBRT is standard, especially with LVSI. Consider addition of VBT to EBRT for IBG3 disease (controversial), or potentially even adjuvant chemotherapy (controversial). The best indication for adding VBT to EBRT is cervical stromal involvement.

* **Norwegian** [[**Aalders** '80](https://www.ncbi.nlm.nih.gov/pubmed/6999399), [Osrund JCO '13](https://ascopubs.org/doi/full/10.1200/JCO.2013.48.8023)]: **TAH/BSO without PLND**→ **VBT ± EBRT**.   
  Poor design, but combined RT for ICG3 may have OS advantage.  
  Lack of well-defined risk groups in Aalders confounds interpretation.
  + 540 pts. IB-IC, 66% IB G1-2.
    - VBT 60 Gy LDR at surface: 40 Gy LDR at 5 mm or ~24 Gy HDR at 5 mm.
    - EBRT: 40 Gy EBRT, central shielding after 20 Gy.
  + 5y LRR 7→ 2% but DM 5→ 10%. 5y OS ~90%.No OS difference likely due to more DM in EBRT arm.
  + Higher rate of secondary cancers. There appears to be no difference in SMN with addition of RT [[Wiltlink](#lxc47lx11rb7)]
  + Subset analysis: ICG3 5y CSM 27→ 18% and 5y LR 20→ 5%, equivalent rates of DM.
  + Long term update: 20y OS with no difference in OS, except decreased OS in patients < 60y due to increased SMN (HR 2.0). Most common secondary malignancy was skin cancer. Recall: Cobalt and betastron have extra scatter.

* **ICG3 outcomes from PORTEC-1** [[Creutzberg JCO '04]](http://ascopubs.org/doi/abs/10.1200/JCO.2004.08.159?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): **TAH/BSO/LND for suspicious LNs only**→ **+ EBRT**.  
  Grade 3 is more prognostic than depth of invasion. Around 1/3 of ICG3 patients will have DM at 5 years.  
  Risk for LVSI increases with increasing depth of invasion. LVSI is associated with increased DM, but not LRR (note: all patients received WPRT on this study).
  + 104 pts ICG3 were registered but not randomized on PORTEC-1.
    - PORT from 40-50.4, the 16 pts who rec'd 40 Gy got brachytherapy boost.
  + LVSI risk for IBG2-3 / ICG1-2 / ICG3 of 3→ 9→ 17%.
    - 5y OS for ± LVSI of 82→ 57%.
  + 5y LRR for < ICG3 / ICG3 of 1-3→ 14%.
  + **5y DM for** G1-2 / IBG3 / **ICG3** of 3-8→ 20→ **31%**.
  + 5y OS for G1-2 / IBG3 / ICG3 of 84→ 74→ 58%.

* **Sorbe** [[Sorbe IJROBP '12]](https://www.sciencedirect.com/science/article/pii/S0360301611005311?via%3Dihub): TAH/BSO, selective LND, washings→ **VBT ± EBRT**.

Combined RT should be reserved for 2+ high risk factors (e.g. IBG3) due to cost, AE, and ~OS.

Pelvic recurrence decreases over 90% with the addition of EBRT to VBT.

* + 512 IR pts: G1/2, endometrioid, stage I with 1 of: IB, G3 or DNA aneuploidy.
    - VBT: 18/6, 17.7/3, 20/1 LDR to 5 mm. Upper 2/3 of vagina treated.
    - EBRT: 46 Gy WPRT.
  + Overall recurrence 10→ 6%, 5y LRF 5→ 1.5%.
  + 5y OS ~90%.
  + G3 toxicity < 2% although VBT significantly more well tolerated.
    - Late G1-3 3→ 14.5%.
* See [[ENGOT-EN2-DGCG](#2n66d7de4kf2)] in the Future Directions section.

### [High intermediate risk](#_x5yfx9juqx)

See the [[Summary of Uterine Cancer](#_83m96wfmlocl)] in the Introductory section and the PORTEC vs. GOG in a nutshell Summary Box below.

[[GOG 99](#4xfr7fwf372m)] and [[PORTEC-1](#88qtqed5maf9)] identified age as an additional risk factor.  
There were 4x as many LVSI+ patients on GOG 99 (20%), therefore LVSI panned out as a risk factor.

* **GOG 99**: **Women < 50y need DGL to be considered HIR; 50-70 if 2 histologic RF, > 70y w one RF**.
* **PORTEC 1**: **Needed 2 of 3 risk factors for HIR (>60 y, deep invasion, G3)**.
* **NCCN**: LVSI, LUSI, ≥ 60y, tumor size, cervical/glandular involvement.

|  |  |  |  |
| --- | --- | --- | --- |
| [PORTEC vs. GOG in a nutshell](#_x5yfx9juqx) See the [[Summary of Uterine Cancer](#_83m96wfmlocl)] in the Introductory section and High Intermediate Risk above for more information.    Fig 2 from **Gynecologic Malignancies** [[Suneja and Viswanathan Heme/Onc Clin N. Amer '20](https://www.sciencedirect.com/science/article/pii/S088985881930111X?via%3Dihub)]. See summary [[here](#_t4kv4aacj9qi)]. | | | |
| **Arms** (Patients) | **PORTEC** | **GOG** |  |
| **± EBRT** Up to IBG3  Old IIA in GOG. | [**PORTEC-1**](#88qtqed5maf9) 46 Gy WPRT.  L5-S1 superior border. | [**GOG 99**](#4xfr7fwf372m)  50.4 Gy WPRT.  L4-L5 superior border. | There were 4x as many LVSI patients in GOG 99.  Around 2/3 of recurrences in vaginal vault.  2y LRR 15-25→ ≤ 5% with EBRT. |
| **EBRT vs. VBT** New stage II and UPSC/CC in GOG. | [**PORTEC-2**](#y035jmu41jo8) 46 Gy WPRT vs.  VBT to upper half. | [**GOG 249**](#6rmy0whpf4lt) **•**  45-50.4 Gy WPRT vs.  VBT to 3-5 cm→ CarboP x3c\* | \*In order to affect DM, at least 6c is recommended. Toxicity is much worse when adding adjuvant chemo to VBT. Keep in mind GOG 249 has higher risk patients (including IBG3), asking an entirely different question. Around 1 in 8 patients have long term "Bowel bother" after WPRT alone. |
| **WART vs. Chemo** Stage III-IV | - | [**GOG 122**](#z85f2pta95ic) WART vs. DoxoCDDP x8c | Practice changing: Chemo is superior to WART for adjuvant tx of stage III/IV endometrial cancer. Critique: Stage-adjusted PFS and OS due to more “unfavorable” stages in chemo arm, which suggests inappropriate stratification in the first place.  Inadequate RT dose of 30 Gy WART→ 15 Gy boost. |
| **WPRT ± CCRT**  Lower stages in PORTEC-3. | [**PORTEC-3**](#crqxu2jebdsq) **•** WPRT(B) ±  CDDP→ CarboP x4c. | [**GOG 258**](#kix.2wgy28yhajjf) **•**  CarboP x6c vs. WPRT(B)/CDDP→ CarboP x4c. | There were many more node positive patients in GOG 258. No difference in RFS or distant failure, but LR can be cut in half with CCRT vs. chemo alone. The greatest benefit for CCRT appears to be in elderly and/or stage III or serous carcinoma.  Late sensory neuropathy < 10% due to carboplatin. |
| **General themes to keep in mind:**  GOG studies typically have higher risk patients than the corresponding PORTEC study.  GOG studies eventually worked towards the omission of radiation therapy.   * Only 2 RCTs looking at ± EBRT for early stage, IR: PORTEC 1 and GOG 99.   + Each study excluded 1988 FIGO IC and G3 dz (2008 FIGO IB, G3).   + Demonstrated 2/3 of LR occurs in vagina, prompting increased use of VBT!   + These studies discovered Age was as an additional [[risk factor](#_gpdbaw92x9m0)]! * [[GOG 122](#z85f2pta95ic)], [GOG [258](#kix.2wgy28yhajjf)], and PORTEC-3 included stage III patients. * [[**PORTEC-3**](#crqxu2jebdsq)] included IBG3, IAG3 with LVSI, stage II-III, or any stage I-III UPSC/CC (>25%)   Old (2018) TBL[QS](http://www.quadshotnews.com/2018/02/the-portec-trilogy.html): The addition of chemo to adjuvant pelvic radiation probably isn’t worth the toxicity for patients < 70 years old with stage I-II disease (supported by [GOG 249](#6rmy0whpf4lt)) and probably is worth it for patients ≥ 70y and/or stage III disease (supported by [GOG 258](#kix.2wgy28yhajjf)). And we’ll channel every trial designer of the last decade to completely ignore [PORTEC-2](#y035jmu41jo8). Will someone please draw us a Venn diagram?  New (2019) TBL [QS](http://www.quadshotnews.com/2019/07/time-will-tell.html): There’s now a good argument to be made that post-op chemoradiation is the new standard of care for women with high-risk endometrial cancer, particularly those with stage III disease or serous histology.   * [[**GOG 258**](#kix.2wgy28yhajjf)] included more advanced nodal disease but comparable proportions of non-endometrioid histology.   TBL [QS](http://www.quadshotnews.com/2019/06/vintage-asco.html#more): The addition of pelvis radiation to chemo alone doesn’t appear to improve recurrence-free survival among women with high-risk (read: high nodal burden) endometrial cancer. | | | |

**GOG 99** [[Keys Gyn Onc '04](https://www.sciencedirect.com/science/article/pii/S0090825803008631?via%3Dihub)]: **TAH/BSO**/**PLND mandated** ± pAO**→ ± 50.4/28 WPRT**.

**Identified age as additional risk factor** (**Depth, Grade, LVSI**). 20% improvement in recurrence for HIR at 2y with EBRT.

Women < 50y need “DGL” to be considered HIR; 50-70 if 2 histologic RF, >70y with one RF.

See [[PORTEC vs. GOG in a nutshell](#_pqcmr8kiuidd)] for more information.

Vaginal vault accounts for around two thirds of failures. Equivalent OS but 50% deaths not cancer related.

WPRT reduces LR, especially in the HIR subgroup.

* 448 pts. Stage IB, IC and IIA/B (occult), no UPSC or CC. Only 33% HIR.  
  Issue: G2 grouped with G3 even though G2 tends to behave like G1.
  + RT: 50.4 Gy WPRT. Superior border L4-L5*.* GOG 99: Higher border, higher WPRT dose.Superior border was L5-S1 in [[PORTEC 1](#88qtqed5maf9)].
  + Very low risk: Only 10% stage II, < 18% outer third, 81.5% G1/2 although 20% LVSI.  
    Higher risk patients than [[PORTEC 1](#88qtqed5maf9)], which had only 5% LVSI.
* **2y LRR 12→ 3%**, although HIR 26→ 6% vs LIR 6→ 2%. Vaginal recurrences 8.7→ 1.1% (ITT).
  + 4y LRR for HIR of 27→ 13%.
* Most recurrences occur within 18 months.
* 4y death incidence 22→ 13%. OS ~86→ 92% [NS]. Half of deaths not due to endometrial cancer.
* 4y G3-4 toxicity 6→ 14%.

**PORTEC 1** [[Creutzberg Lancet '00](https://www.sciencedirect.com/science/article/pii/S0140673600021395?via%3Dihub), [IJROBP '05](https://www.sciencedirect.com/science/article/pii/S0360301605004190?via%3Dihub)]: **TAH/BSO/LND for *suspicious* LNs→ ± 46/23 WPRT**.

**Identified age as an additional risk factor**: **> 60y, G3, new IB**. 20% improvement in LRR for HIR at 10y with EBRT.

Women need 2 of 3 risk factors for HIR (>60 y, deep invasion, G3).

See [[PORTEC vs. GOG in a nutshell](#_pqcmr8kiuidd)] for more information.Long term G2 GI/GU 25%, so utilize EBRT only for HIR.

PORTEC-2 later demonstrated VBT is acceptable for HIR, although perhaps ~3% worse pelvic relapses.

Consider addition of EBRT to VBT for [[IBG3](#s2si5ou0xt99)] disease and/or [[LVSI](#iuwnoiy6bk4n)].

Vaginal vault accounts for around two thirds of failures. Around 50% of deaths are not cancer related.

There is around a 1/8 chance of SBO in the long term with EBRT, but this appears to be ~1% for IMRT [[MSKCC](#kix.gn0w00l4s3l9)].

See [[Creutzberg nomogram](#ed493x3uzz7k)], which demonstrates grade as a significant factor for LR.

* 714 pts. IB G2-3, IC G1-2, any histo (unlike GOG 99). UPSC or CC < 1% of pts study.
  + RT: 46 Gy WPRT. Sup border L5-S1. Lower border, lower WPRT dose.
  + Only sampled suspicious lymph nodes. Lower risk than GOG 99: Only 5% LVSI.
  + Central path review, 40% downgraded from G2→ G1. 134 pts would not have met criteria.
* **5y LRR 14→ 4%**, although HIR 18→ 5%. 5y vaginal relapse 10→ 2%.
  + 10y LRR 15→ 4%. *Results remain significant even after excluding old IB G1 patients.*
  + 10y LRR for G1 / 2 / 3 of 7→ 11→ 18% [SS]. *Grade seems to be the most significant hazard.*
  + 10y LRR for old IB / IC of ~6→ 12% (p=0.07)
  + 10y LRR for age < 60 / 60-70 / > 70 of ~4→ 11→ 13% (p=0.07). *Patients < 60y tend to fare best.*
  + **10y HIR LRR 23→ 5%** for pts with **2 of 3 HIR factors**:**> 60y, G3, new IB***.*
  + 15y LRR 16→ 6%.
* 8y DM ~8%.
* OS at 5 / 10 / 15y of ~85→ ~70→ ~55%.
  + 10y OS ~66→ 74% (p=0.09). 10y CSM ~10%.
    - 10y CSM for G1 / 2 / 3 of 5→ 12→ 31%. Grade seems to be a more significant hazard.
* Long-term G2 of 4→ 26% (Mostly GI, 18% SBO), Late G3+ GI/GU 0→ 3% (all GI).
* Long term QoL [[Nout JCO '11](https://www.ncbi.nlm.nih.gov/pubmed/21444867)]:
  + GU: More urinary urgency, urinary incontinence, need to remain close to the toilet, and more limitations in ADL due to bladder symptoms.
  + GI: More diarrhea, fecal leakage, and more limitations in ADLs due to bowel symptoms.
  + Day and night usage of incontinence materials of 15→ 43%.
* Secondary cancers in ~12%: ~5% GIT, ~3% breast. GIT cancers well established connection with endometrial ca.
  + Majority of cancers CRC in RT group (RIR 2.72) and breast in control group (RIR 1.73, NS).
  + There appears to be no difference in SMN with the addition of RT [[Wiltlink](#lxc47lx11rb7)].
* See [[**Recurrence Outcomes**](#bvyfrjhrrd66)] from PORTEC-1.

75% of failures occur in the vaginal vault. Vaginal recurrences and no prior RT have much better prognosis. After failures, ~80% of patients will have complete response in the long term, and are more likely to have DM after receiving RT while vaginal recurrences if on observation arm. Patients in the observation arm are more likely to have CR to salvage therapy and are more likely to receive salvage therapy. Overall, only around 4 of 10 patients with pelvic relapses were treated with curative intent. Suggestion of 50% of patients alive at 10y with vaginal relapse and no prior RT, while 3y survival after pelvic nodal relapse is less than 10%. We now have [[2019 data](#ggzffy340rb6)] to suggest 3y OS is 50% for isolated pelvic or pAO relapse treated with SBRT.

* See [[**ICG3 outcomes**](#y66bpst2um71)] from PORTEC-1.   
  Grade 3 is more prognostic than depth of invasion. Around 1/3 of ICG3 patients will have DM at 5 years.  
  Risk for LVSI increases with increasing depth of invasion. LVSI is associated with increased DM, but not LRR.

**PORTEC 2** [[QoL JCO '08](http://ascopubs.org/doi/abs/10.1200/JCO.2008.20.2424?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed), [Nout Lancet '10](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)62163-2/fulltext), [Wortman BJC '18](https://www.nature.com/articles/s41416-018-0310-8)]: **TAH/BSO/LND for *suspicious* LNs→ 46/23 WPRT vs VBT**.

Includes patients who were HIR from PORTEC-1. Women need 2 of 3 risk factors for HIR (>60 y, deep invasion, G3).

See [[PORTEC vs. GOG in a nutshell](#_pqcmr8kiuidd)] for more information.  
VBT noninferior to EBRT for vag recurrence for less than IBG3 or old IIA with better QoL.

There are fewer acute toxic GI effects with VBT.

There is around a 1 in 8 chance of "bowel bother" after WPRT [[PORTEC 2 QoL](#lnko79pxk5ba)].

See [[Creutzberg nomogram](#ed493x3uzz7k)], which demonstrates grade as a significant factor for vaginal recurrence. Consider VBT for IBG3 / II.

* 427 pts. Age > 60y with IAG3-IBG2, any age old IIA (10%). No IBG3. MFU 10y.
  + 46 Gy WPRT. LDR 30 Gy or **HDR 21/3 to 5 mm** (dose equiv of 45-50Gy) to the **upper half of vagina**.
  + No UPSC/CC subtypes in this study. Unlike PORTEC 1, but PORTEC 1 only had < 1% of these types.
  + Like PORTEC-1, no LND, but suspicious LNs removed. ~10% LVSI (focal LVSI not allowed).
  + Central pathology review: 30% downgraded from G2→ G1. Result = 79% with G1 disease.
* 5y Vaginal relapse ~1.7%, 5y LRR ~2→ 5% (p=0.17), 5y pelvic relapse\* 0.5→ 3.8% (NNT = 333).
  + \*When adjusted to remove G1 patients, 5y pelvic recurrence ~0.5→ 3.3% (p=0.06).

* + Almost all pelvic recurrences after VBT were associated with widespread distant recurrence.
* 10y VR ~3%. 10y Pelvic recurrence 1→ 6% in the context of DM. 10y DM ~9%.

VBT was only statistically significant for pelvic recurrence.

* + MVA for Pelvic recurrence: Substantial LVSI / VBT with HR of 8.7→ 4.6.
  + MVA for DM: Substantial LVSI / L1CAM / TP53mt with HR of 5.4→ 4.2→ 3.4.
  + MVA for CSS: Substantial LVSI / L1CAM / TP53mt with HR of 7.2→ 5.1→ 3.3.
* DM ~7%. 5y DM for HIR and old stage IIA 6→ 27%.
* 5y OS ~82%. 10y OS ~68%.
* Acute G1-2 GI 54→ 13% but equivalent at 2y. Late G3 2→ < 1% [NS].
* QoL at 2y demonstrated worse social fxn, more diarrhea and fecal leakage with EBRT.

Note: Difference of 5-10% is considered clinically relevant.

Limitation of activities due to bowel symptoms in one of eight patients who received WPRT.

* + After RT need to remain close to the toilet 21→ 9%. 2y 13→ 8%. *Difference 5%.*
  + After RT limitation of daily activities due to bowel sx 22→ 6%, 2y 14→ 3%. *Difference >10%.*
  + After RT diarrhea 31→ 9%; 2y diarrhea 13→ 6%. *Difference >5%.*
  + After RT fecal leakage 9→ 4%, 2y 9→ 2%. *Difference >5%.*
  + After RT rectal blood loss 2→ 1%, 2y 2→ 1%.

**LVSI in PORTEC 1-2** [[Bosse EJC '15](https://www.sciencedirect.com/science/article/pii/S0959804915004463?via%3Dihub)]: **No LVSI vs. Focal LVSI vs. Substantial LVSI**.

Substantial LVSI should receive WPRT. Substantial LVSI predicts pelvic relapse, DM and OS.

Recall: PLND was not mandated in PORTEC 1 and 2, only sampling if *suspicious* LNs were noted.

One foci involving up to two vessels is focal, while multiple foci is substantial LVSI.

* Any degree of LVSI in 13.9% (only 7% before review). Substantial LVSI 5% (n=44).
* LVSI strongest independent predictive factor for pelvic relapse (HR 6.2), DM (HR 3.6) and OS (HR 2.0).
* Only EBRT (HR 0.3) reduced risk of pelvic regional recurrence.
* 5y pelvic relapse for no LVSI / focal / substantial LVSI of 1.7→ 2.5→ 15%.
* 5y pelvic relapse for substantial LVSI receiving obs / VBT / EBRT of 31→ 27→ 4%.
* Table 3 demonstrates focal LVSI one foci involves a median of nearly two vessels (1.8) per the three tiered approach.

**GOG 249** [[ASTRO '17](https://www.redjournal.org/article/S0360-3016(17)33873-7/fulltext), [Randall JCO '19](https://ascopubs.org/doi/full/10.1200/JCO.18.01575)]: **TAH/BSO/PLND** (90%)**→** **46/23 WPRT alone vs. VBT→ carboP x3**.

See [[PORTEC vs. GOG in a nutshell](#_pqcmr8kiuidd)] for more information.High intermediate risk per GOG 99 or Stage II serous or Clear Cell.

WPRT is acceptable with less pelvic failure and six times less acute toxicity than VBT with chemotherapy. Late toxicity is similar.TBL [QS](http://www.quadshotnews.com/2017/09/a-puff-to-cuff-just-isnt-enough.html): Perhaps most surprising, among the pelvic radiation alone arm, IMRT techniques resulted in numerically higher rates of acute toxicity than with the Joe Blow 4-field box approach. Turns out, when it comes to HIR endometrial cancer, a puff to the cuff isn’t up to snuff...and the 4-field box still rocks.  
Critique: 3c of chemo didn’t affect DM, but traditionally 6c given especially for HR histology. Allowed 12w for the start of RT, historically 8w as LR known to increase if 9w delay.

The addition of adjuvant chemo to adjuvant pelvic radiation probably isn’t worth the toxicity for patients < 70 years old with stage I-II disease (supported by [PORTEC-3](#crqxu2jebdsq)).

* 601 pts. HIR stage I (74%), stage II or I-II UPSC (15%) / CC (5%). 90% PLND. MFU 4.5y.  
  HIR per GOG 99: Women < 50y need DGL to be considered HIR; 50-70 if 2 histologic RF, > 70y with one RF.
  + WPRT: 45-50.4/25-28.
  + BT boost encouraged for stage II or UPSC/CC in WPRT arm (35% of WPRT arm rec’d VBT).
  + BT + chemo: 3-5 HDR or 2 LDR to **3-5 cm** Rx→ carboplatin AUC **6** / paclitaxel **175** mg/m2 q3w x3c.
* **5y Pelvic/pAO failure 4→ 9%**, largely driven by pelvic failure 2→ 7% .
* 3y ~OS 91→ 88% and 3y RFS ~83%.
  + Comorbidity correlates to OS.
* 5y OS ~86%. 5y RFS ~76%. DM ~18%.
* Acute G3+ toxicity 11→ 64%; Equivalent late G3+ ~12.5%.
  + Early G3+ with 3D / IMRT of 10→ 14%.
* QoL [[ASCO '18]](http://abstracts.asco.org/214/AbstView_214_224087.html): Fatigue and neurotoxicity significantly worse in VBT/chemo arm, WPRT more GI sx.

### [Historical Adjuvant Chemo](#_x5yfx9juqx)

These studies do not matter as much now that mature results of [[PORTEC-3](#crqxu2jebdsq)] have been released, which demonstrates 10% OS advantage for CCRT→ CarboP for Stage III and 20% OS advantage for UPSC/CC Stage I-III.

You'd pretty much never be wrong to recommend carboplatin and paclitaxel in a Gyn tumor board.

There is [[2019 Japanese data](#z4ti1zwvc1gx)] which suggests docetaxel and cisplatin may be superior to carboplatin and paclitaxel.

* **GOG 34** [[Morrow Gyn Onc ‘90]](https://www.gynecologiconcology-online.net/article/0090-8258(90)90166-I/pdf): TAH→ **RT→ ± doxorubicin**.   
  There appears to be no benefit with adjuvant chemotherapy in up to stage II cervical cancer treated with surgery and RT.
  + 181 pts. I-II (occult) with 1+ RF: >50% myometrium, pN+, stage II, adnexal metastasis.
    - WPRT 50 Gy, if pAO+ then PA field to top of T12 45/30.
    - Doxorubicin 45 mg/m2 q3w, could be escalated to 60 mg/m2.
  + ~5y PFS/OS.
  + Toxicity: 7% SBO in RT arm, treatment related deaths 2→ 25%.
  + Study underpowered. Around ⅓ of patients in the chemo arm received no chemo.
* **NSGO-EC-9501/EORTC 55991 and MaNGO** combined analysis [[Hogberg EJC '10]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3552301/): **RT ± 4c Plt-based adj chemo**.CSS benefit is seen with adjuvant chemo.

This study does not matter as much now that mature results of [[PORTEC-3](#crqxu2jebdsq)] have been released, which demonstrates 10% OS advantage for CCRT→ CarboP for Stage III and 20% OS advantage for UPSC/CC Stage I-III.

* + 534 pts. FIGO I-III w no residual tumor after TAH/BSO/optional LND. 71% endometrioid, 79% FIGO I-II.
    - RT to 45 Gy. EFRT and VBT allowed.
  + NSGO-EORTC: 383 pts. Surgical stage I-II, IIIA +cytology or IIIC1. RT ± Chemo (various regimens).
    - Most ≥ 2 RF: G3, IB, DNA non-diploid. UPSC, CC, or anaplastic eligible regardless of risk.
      * EBRT (> 44 Gy) ± VBT (~40% on each arm).
  + MaNGO-ILIADE: 156 pts. IIB, IIIA (+cytology only excluded), IIIC (included pAO nodes)
    - No high risk histology. AP Chemo: Doxorubicin 60, CDDP 50 q3w x3c.
    - Pelvic RT + PA field if N+ to 45 Gy, VBT only for cervical stromal involvement.
  + 5y PFS 69→ 78%, 5y CSS 75→ 82%, HR 0.55 and 5y OS ~75→ 82%, HR 0.69 (p=0.07).

## 

## [Advanced Endometrial Cancer](#_3llouklhg1v3)

* TH/BSO + debulking→ chemo→ RT→ chemo (sandwich chemoRT).
  + Chemo: Paclitaxel **175** and carbo **350** q3w x3-4c→ RT→ Paclitaxel/carbo x2-3c (total of 6 cycles planned).
* Or TH/BSO/debulking→ carbo/taxol x 4-6 cycles→ WPRT.
* Debulking surgery: Reduce gross disease as much as possible (prefer < 2 cm).
* If PA involved, EFRT with boost to involved nodes to 60 Gy (IMRT for boost).
* VBT for vaginal involvement/consider boost if cervical involvement.
* **RT Alone**
  + Retrospective reviews available but highly variable groups of patients.
  + Most common mode of relapse is systemic, a single treatment modality is not adequate to prevent recurrences.
* **High risk histology** 
  + **Canadian HR endometrial cancer consortium (CHREC)** [[Bernardini Gyn Onc '16](http://www.gynecologiconcology-online.net/article/S0090-8258(16)30028-2/fulltext)]:   
    Caution when combining high risk subtypes together.
    - G3 endometrioid (EC3), clear cell (CCC), serous (ESC), carcinosarcoma (CS - aka MMMT).
    - CC and EC3 demonstrate OS advantage with adjuvant RT.
    - ESC or CS (MMMT) have OS advantage with adjuvant chemo.
      * Recurrence in comprehensively staged stage IA serous and carcinosarcoma cancers is high: ~20%.
  + **GOG 94**: TAH/BSO/PLND/+washings. WART 30/20→ pelvic boost 19.8/11 ± pAO boost (15 Gy).   
    Authors concluded CTX is likely necessary for these radioresistant tumors, even though RT was sub-par.
    - Phase I-II. 21 pts UPSC or CCC or stage III-IV any histo, 180 stage II-IV pts.
    - At 5y, > 50% failures within RT field, and 5-yr PFS 38% for UPSC and 54% for CCC.
  + **Treat as high risk endometrial**:
    - I: Surgery→ Chemo + VB.
    - II-IV: Surgery→ Chemo + Tumor directed RT.

### [RT ± Adjuvant chemo versus chemo](#_70muvcsfz1v8)

Pretty much all of these trials used doxorubicin and cisplatin - remember this for 122! This is outdated chemo.

You'd pretty much never be wrong to recommend carboplatin and paclitaxel in a Gyn tumor board.

There is [[2019 Japanese data](#z4ti1zwvc1gx)] which suggests docetaxel and cisplatin may be superior to carboplatin and paclitaxel.

* **GOG 122** [[Randall JCO '06]](http://ascopubs.org/doi/abs/10.1200/JCO.2004.00.7617?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): **RH→** **30/20 WART vs. AP** x8c.

Practice changing: Chemo is superior to WART for adjuvant treatment of stage III/IV endometrial cancer.  
Critique: Stage-adjusted PFS and OS due to more “unfavorable” stages in chemo arm, which suggests inappropriate stratification in the first place. Inadequate RT dose of 30 Gy WART→ 15 Gy boost, especially in the context of residual.

The use of RT in advanced stage endometrial cancer is being tested in [[GOG 258](#kix.2wgy28yhajjf)].

* + 388 pts. Optimally debulked (< 2 cm residual) stage III and intra-abdominal IV. LND optional. 21% UPSC.
    - WART 30/20 AP/PA + 15 Gy boost to PLN ± pAO vs. AC chemo. No VBT.
    - AP: **Doxorubicin** 60, **CDDP** 50 q3w x8c. Only 63% able to tolerate all chemo.
  + Pelvis relapse 13→ 18%.
  + Overall relapse ~50%, predominantly in pelvis and abdomen.
  + **Stage-adjusted 5y OS 42→ 55%**, 5y PFS 38→ 50%, G3-4 heme 14→ 88% and inc GI, CV, and neuro tox.
  + Note: Only 50% alive at 5y, so TI needs to be improved. CCRT may be promising.
* **JGOG 2033** [[Susumu Gyn Onc ‘08]](http://ma6ek2jh6s.scholar.serialssolutions.com/?sid=google&auinit=N&aulast=Susumu&atitle=Randomized+phase+III+trial+of+pelvic+radiotherapy+versus+cisplatin-based+combined+chemotherapy+in+patients+with+intermediate-and+high-risk+endometrial+cancer:+a+Japanese+Gynecologic+Oncology+Group+study&id=pmid:17996926): **RH→ EBRT vs.** C**AP**.

HIR might benefit more from adjuvant chemo (unplanned subset).   
Critique: Only 25% of pts had pAO dissection, and this chemo is uncommon.

* + 385 pts. IB-III with >50% myometrial invasion. TAH/BSO/PLND. Only 3% got VBT.
    - 40-50 Gy AP/PA vs. CAP: Cyclophosphamide 333 /Adriamycin 40 / Cisplatin **50** q4w x3c
  + Unplanned subset analysis defined LIR and HIR:
    - LIR: < 70y G1/2 endometrioid. Equivalent PFS between arms.
    - HIR: 1) IBG3 or IB age >70y or 2) Stage II or IIIA from +cytology.
      * In this subset, PFS 66→ 84% and OS 74→ 90%.
    - 5y PFS ~83%, 5y OS ~86%, and toxicity.
  + 7% pelvic failures in each arm, but fewer vaginal recurrences in RT arm.
* **Italian** [[**Maggi** BJC '06]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2360651/):C**AP vs. WPRT ± pAO→ chemo.**Equivalent PFS/OS but RT delays LF, while chemo delays DM.
  + 345 pts. IBG3-III (65% stage III). TA/RH/BSO w selective LND.
    - CAP: Cyclophosphamide 600 / Adriamycin 45 / Cisplatin 50 q4w x5c.
    - WPRT 45-50 Gy→ ACC x5.
  + 7y OS ~62%, 7y PFS ~58%.
  + Different patterns of failure. RT delayed LF (~11→ 7%), chemo delayed DM (~21→ 16%) but neither SS.
* **JGOG 2043** [[Nomura JAMA Onc '19](#z4ti1zwvc1gx)]: **Doxorubicin/CDDP vs. Carboplatin/Paclitaxel vs. Docetaxel/CDDP**.  
  Recall that GOG 122 and MaNGO-ILIADE utilized the first regimen, while GOG 249, 258 and PORTEC-3 utilized CarboP.
  + 788 patients. Stage I-II endometrial cancer at high risk or stage III-IVA.
  + 5y PFS ~73→ 74→ 79% (p=0.12).
  + 5y OS ~83→ 86→ 88% (p=0.37).
  + There appears to be a trend to superiority for Docetaxel/CDDP over standard carboplatin and paclitaxel.

### [CCRT](#_70muvcsfz1v8)

* [**RTOG 9708** [Greven Gyn Onc '06]](https://www.sciencedirect.com/science/article/pii/S0090825806001715?via%3Dihub): Phase II. **WPRT 45 Gy + CDDP→ CisplatinP x4**.   
  Toxicity reasonable, basis for PORTEC-3 chemo. RTOG attempted to design a study similar to PORTEC-3, but [[GOG 122](#z85f2pta95ic)] was open, meaning Stage III patients would be lost to GOG 122, so the RTOG concept withered.
  + 46 pts. G2-3 and IB, II or IIIC1.
    - CDDP **50** d1,28 + 45 Gy + VBT→ CDDP **50**/Pacli **175** q4w x4c.
  + 4y pelvic, regional, distant recurrence of 2%, 2%, and 19%, respectively.
  + 5y OS 85% and 5y DFS 79%.
    - Stage IIIC1 pts: 4y OS 77%, 4y DFS 72%.
  + No recurrences for stages IC, IIA or IIB.
  + Toxicity: G3 (16%) and G4 (5%) reasonable.

[](https://www.instagram.com/p/B7EVmZiJDeD/?utm_source=ig_web_copy_link)

*Note: This Instant.Oncology concerns the 2018 publication, hence the comment on a "non-significant" OS benefit.*

**PORTEC 3** [[Protocol](https://www.msbi.nl/promise/Projects/PORTEC3.aspx),[DeBoer Lancet '18,](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30079-2/fulltext) [Lanc Onc '19](https://www.sciencedirect.com/science/article/pii/S147020451930395X?via%3Dihub)]: **TAH/selective LND**→ **48.6/27 ± CDDP→ CarboP** q3w **x4c**.

See [[PORTEC vs. GOG in a nutshell](#_pqcmr8kiuidd)] for more information.  
The 2019 results are the first to demonstrate an OS advantage with CCRT/adjuvant chemo for Stage III and stage I-III serous!

Although acute toxicity is higher with CCRT, these differences wash out at one year of followup with the most significant and clinically relevant side effect of late G2+ neuropathy 0→ 6%.

Old (2018) TBL[QS](http://www.quadshotnews.com/2018/02/the-portec-trilogy.html): The addition of chemo to adjuvant pelvic radiation probably isn’t worth the toxicity for patients < 70 years old with stage I-II disease (supported by [GOG 249](#6rmy0whpf4lt)) and probably is worth it for patients ≥ 70y and/or stage III disease (supported by [GOG 258](#kix.2wgy28yhajjf)). And we’ll channel every trial designer of the last decade to completely ignore [PORTEC-2](#y035jmu41jo8). Will someone please draw us a Venn diagram?

New (2019) TBL [QS](http://www.quadshotnews.com/2019/07/time-will-tell.html): There’s now a good argument to be made that post-op chemoradiation is the new standard of care for women with high-risk endometrial cancer, particularly those with stage III disease or serous histology.

* 660 pts. TAH/BSO/selective LND. High risk: G3IA/LVSI, G3IB, II-III, UPSC/CC I-III (>25%). LVSI nearly 2/3. R2 not allowed. Only 71% Stage III (compared to nearly 100% Stage III on [[258](#9yn5t41lh8m)]). MFU 6y.
  + RT 48.6 ± CDDP **50** d1,28→ Carbo AUC **5**, paclitaxel **175** q3w x4c.
  + BT (50% each arm): 10/2 to 5mm strongly encouraged for stage II.  
    Note: 15/3 or 12/2 to surface after 45 Gy or 50.4 Gy, respectively, standard per ABS [[Albuquerque BT '19](https://www.sciencedirect.com/science/article/pii/S1538472118306305?via%3Dihub)]
* Equivalent outcomes ± cisplatin/adjuvant carboP.
* **5y OS 76→ 81%**, **5y FFS 69→ 76%**, 5y DM 29→ 22%.

*Most deaths (85%) in this higher risk population were due to endometrial cancer.*

* + Survival after recurrence ~1.3y.
* Isolated vaginal relapse as first site of recurrence ~0.3%, Isolated pelvic relapse as first site of recurrence of ~1%.
* For Stage III subset: 5y FFS 58→ 71%, 5y OS 69→ 79%.
  + There appeared to be a larger OS advantage for patients ≥ 70y.
* For Stage I-III serous subset (n=105): 5y FFS 48→ 60%, 5y OS 53→ 71%.
* There was no subset analysis for IBG3.
* Recurrences for IIIB (vagina/parametrium) / IIIC (lymph nodes) of 45→ 38%.
* Recurrences for serous / clear cell / endometrioid grade 3 of 45→ 27→ 27%.
* Molecular analysis [[Creutzberg ESMO '19](https://oncologypro.esmo.org/meeting-resources/esmo-2019-congress/Molecular-classification-of-the-PORTEC-3-trial-for-high-risk-endometrial-cancer-impact-on-adjuvant-therapy)]: p53mt (22%), POLEmt (13%), MMRd (33%), no specific profile (32%).
  + 5y RFS for RFS for p53mt / POLEmt / MMRd / NSMP of 50→ 98→ 74→ 76%.
  + 5y RFS for p53mt of 61→ 37%. *There is a significant benefit for CCRT and adjuvant chemo in p53mt.*
* Acute G2+ 44→ 94%
* Acute G3-4 13→ 61%. *Quality of life differs up to 6 months, becoming insignificant at 12 months.*
* Late G3 ~5→ 8% (p=0.24). Most commonly hypertension in 2% of both groups.
* Late G2 23→ 38%.%.
* Toxicity and QoL [[de Boer Lanc Onc '16](https://www.ncbi.nlm.nih.gov/pubmed/27397040)]:
  + There was worse functioning and symptoms in the CCRT arm at the completion of RT and at 6 mo.
  + The most significant and clinically relevant side effect was late G2+ neuropathy 0→ 10

**GOG 258** [[ASCO](http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.5505), [Protocol (Supplement) Matei NEJM '19](https://www.nejm.org/doi/full/10.1056/NEJMoa1813181)]: RH/selective LND→ **CarboP** x6c **vs. WPRT-(B)/CDDP→ CarboP** x4c

Protocol available in supplementary material. See [[PORTEC vs. GOG in a nutshell](#_pqcmr8kiuidd)] for more information.  
Compared to [[PORTEC-3](#crqxu2jebdsq)], 258 included more advanced nodal disease but comparable proportions of non-endometrioid histology. Meaning the “high-risk” in this trial was higher than the “high-risk” in PORTEC-3. In that context, 258 shows that even though radiation reduces nodal and vaginal failures, that reduction isn’t enough to negate high rates of distant failure. However, acute G4+ toxicity is cut in half, as are local recurrences, in the WPRT-(B)/CDDP→ CarboP arm.   
TBL [QS](http://www.quadshotnews.com/2019/06/vintage-asco.html#more): The addition of pelvis radiation to chemo alone doesn’t appear to improve recurrence-free survival among women with high-risk (read: high nodal burden) endometrial cancer.

If your friendly neighborhood med onc believes chemo should go first, then try to deliver RT after all six cycles of chemotherapy or chemo x3→ RT→ chemo x3.

* 813 pts. Surgical stage III (97%) or IVA (< 2 cm residual, selective LND) or stage I/II CC (18%) or Serous (3%). MFU 4y.
  + Chemo: Carbo AUC **6** + Paclitaxel **175** q3w x6c.
  + CCRT: Cisplatin **50** d1,28 + 45 Gy ± VBT ± boost→ Carbo AUC **5**, Paclitaxel **175** q3w x4c.

Only 75% completed adjuvant chemo in CCRT, while 85% completed CTX alone.

* + RT: 45/25 (3D/IMRT). Encouraged BT for LUSI or extension to cervix.   
    Tumor extension into vagina should be covered with a 2 cm inferior margin. Distal 1/3 of vagina should have inguino-femoral node coverage.
  + HDR 6 Gy x2-3 to surface, treating 4 cm length minimum. Around 50% received it.
* 5y RFS ~58%. OS results are not yet mature.
* 5y vaginal recurrence 7→ 2%. 5y pelvic/pAO recurrences 20→ 11%. 5y Distance recurrences 21→ 27%.
* Toxicity G3+ ~60% in each arm: G3+ GI 4→ 13%, metabolic 19→ 15%, neuro 6→ 7%, myelosuppression 40→ 52%, infection 4→ 5%. There were no G5 events in the CCRT arm vs. 3 in the chemo arm.
* Acute G4+ toxicity 30→ 14%.
* [[QoL ASCO '18]](http://abstracts.asco.org/214/AbstView_214_218875.html): Assessed at baseline, and 6/18/70 wks after tx starts.
  + Scores ~4 pts lower with CCRT at 18/70w, but none exceeded 6 pt difference of "clinically meaningful".
  + CCRT with worse GI sx at all assessments.
  + Both groups reported neuropathy which did not return to baseline by 1 year.

|  |
| --- |
| **Management of high-risk endometrial cancer: Are we there yet?** [[Randall Lance Onc '19](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30416-4/fulltext)]:  "Endometrial cancer is a diverse disease that includes varying stages and histologies. As a result, the design, completion, and interpretation of large randomised trials comparing adjuvant therapies for this disease, even when well conducted and well analysed, is problematic."   * The OS advantage in [[PORTEC-3](#crqxu2jebdsq)] appears to only apply to the Stage III and serous carcinomas of all stages. * Chemotherapy alone does not appear to be sufficient despite the lack of OS or RFS benefit, as the incidence of nodal failure is higher when omitting WPRT [[GOG 249](#6rmy0whpf4lt), [GOG 258](#kix.2wgy28yhajjf)]. * The preferred way of combining chemo and radiotherapy is still in the air. RTOG 97-08 was a phase II trial which set the standard for WPRT→ VBT→ adjuvant chemo x4c. However, there was a heated debate in the creation of GOG 258 protocol where some providers felt strongly about a "sandwich" regimen with up-front chemotherapy followed by IFRT followed by more chemotherapy which suggests a maximization of both local and distant control. |

**Chemotherapy Alone**

* **Japan Phase III** [[Nomura JAMA Onc '19](https://jamanetwork.com/journals/jamaoncology/fullarticle/2728809)]: **CDDP/Doxorubicin vs. CarboP vs. CDDP/Docetaxel** q3w x6c.

CDDP/Docetaxel appears superior in regards to PFS if adjuvant chemo is recommended.

TBL QS: If you’re going to use post-op chemo for high-risk endometrial cancer—which remains a big IF (until results of [[PORTEC-3](#crqxu2jebdsq)] clarified this)—docetaxel / cisplatin may be the most effective regimen.

* + 788 pts. G2-3 Stage IB-II, and stage III-IV without extra-abdominal mets. Age 20-74. MFU 7y.
    - Optimal debulking (< 2cm residual after TAH/BSO/PLND). Median 24 PLN, 13 pAO.
    - CDDP **60**, docetaxel **70** q3w x6c.
    - Carbo AUC **6**, paclitaxel **180** q3w x6c.
    - CDDP **50**, doxorubicin **60** q3w x6c.
  + Around 20% of patients did not complete 6c of chemotherapy, regardless of arm.
  + 5y PFS 73→ 74→ 79% (p=0.12).
  + 5y OS 83→ 86→ 88% (p=0.67)
  + Planned subgroup with PFS advantage for CDDP/Docetaxel over CDDP/Doxorubicin for < 70y, no residual tumor, low grade disease, and lymph node metastasis, while CDDP/Docetaxel is superior to CarboP for patients with no lymph node metastasis.
  + Toxicity: More cytopenias with doxorubicin, more GI issues w CDDP, and more neuropathy w carboplatin.
* GOG 184: Chemo “intensification”. AC ± P with limited RT (PLN ± pAO). More chemo, more toxicity, ~OS.
* **GOG 209** [[2012 Abstract](https://www.gynecologiconcology-online.net/article/S0090-8258(12)00228-4/fulltext)]: **TAP vs. TC**. CarboP is more tolerable than Doxo/CDDP/Pacli with ~ outcomes.
  + 1381 pts. **Metastatic or recurrent** endometrial carcinoma.
    - TC: Paclitaxel **175** mg/m2, Carboplatin AUC **6** q3w x7c.
    - TAP: Doxorubicin **45** mg/m2, CDDP **50** mg/m2 d1; paclitaxel **160** mg/m2 d2 q3w x7c.
      * In 2008, initial doses of TC were reduced (135 mg/m2, AUC 5) for h/o pelvic/spine RT.
  + ~7% neutropenic fever. G2+ sensory neuropathy 26→ 19%.
    - G3+ Thrombocytopenia 32→ 12%, G3+ other hematologic 30→ 22%, G3+ vomiting 7→ 4%, G3+ diarrhea 6→ 2%, G3+ metabolic 14→ 8%, but more G3+ neutropenia 52→ 79% w TC.
  + Study tx discontinued due to toxicity 18→ 12%.
  + ~67% received the 7 planned cycles.

## Recurrent Endometrial Cancer

* 10-15% of early stage pts will have recurrence.
  + Most within the first two years (60%) with 76% within 3 years, although >15y recurrences noted.
* WPRT to 45 Gy, if residual:
  + < 5 mm: VC 5.5 Gy x 5 to 5mm depth.
  + > 5 mm: Syed.
* PET is the way to go: Meta of 500 pts with 95.8% Sn and 92.5% Sp.
* < 2 cm and longer time to development correlates with better tumor control.
* Histo at time of Dx (IA, G1-2) significant OS predictors.
* 5y OS can be 55-85% and > 90% for pts with early stage dz at the time of diagnosis.
* No prior RT has best outcomes.
* See [[**Recurrence Outcomes**](#bvyfrjhrrd66)] from PORTEC-1.

75% of failures occur in the vaginal vault. Vaginal recurrences and no prior RT have much better prognosis. After failures, ~80% of patients will have complete response in the long term, and are more likely to have DM after receiving RT while vaginal recurrences if on observation arm. Patients in the observation arm are more likely to have CR to salvage therapy and are more likely to receive salvage therapy. Overall, only around 4 of 10 patients with pelvic relapses were treated with curative intent. Suggestion of 50% of patients alive at 10y with vaginal relapse and no prior RT, while 3y survival after pelvic nodal relapse is less than 10%. We now have [[2019 data](#ggzffy340rb6)] to suggest 3y OS is 50% for isolated pelvic or pAO relapse treated with SBRT.

* **Interstitial BT for salvage of vaginal recurrences in previously unirradiated EC pts** [[Nag IJROBP '02]](https://www.redjournal.org/article/S0360-3016(02)03019-5/pdf):
  + 13 previously unirradiated pts. Sept 1989-Sept 2000. Median age 70. VBT ± EBRT (n=11).
    - 10 at apex, 3 at lower ⅔ vagina.
  + 11 originally FIGO 1, 2 originally FIGO 2.
  + Vaginal recurrences occurred at a median of 28 months. Followed for median 60 mo.
  + All tumors were locally controlled. 3/13 pts had distant relapse.
  + 8y DSS 77%. MS 39 mo.
  + G3+ chronic in 13% (n=2), including G3 vaginal ulceration in 1 pt, G4 colovesical fistula in 1 pt.
* Dose-escalated IMRT for nonvaginal pelvic or pAO w/o prior RT: 2y OS 71%, late G3+ GI 8%.
* Two GOG RCTs for more effective chemo in advanced or recurrent.
  + GOG 177: AC ± P in intact setting with ↑ response rate, PFS and OS a/w increased toxicity.
  + GOG: adjuvant treatment after surgery and EBRT, AC ± P ~OS. 3y alive and recurrence free 64→ 62%.

* **GOG 0238** [[NCT00492778](https://clinicaltrials.gov/ct2/show/NCT00492778)]: Phase III. Pelvic-only recurrence. **Definitive RT ± weekly cisplatin**. 45 Gy→ 7x3 to 5 mm.

See NCTN Trial Portfolios by Disease Site: [[Gyn](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_GYNE_Trials.pdf)] and [[Future Directions](#_e9e7oz6ftgla)] section for more.

* + IMRT boost is allowed for patients who are not candidates for brachytherapy.
  + 18% G3-4 GI toxicity, 50% grade 3 vaginal sequelae.

**Alternative treatment regimens**Includes split course, sandwich therapy, and adding Bevacizumab to WPRT/CDDP.

* **Ontario group** [[Lupe Gyn Onc ‘09](https://www.gynecologiconcology-online.net/article/S0090-8258(09)00202-9/abstract)]: Prospective. **CarboP x4c→ WPRT→ CarboP x2c**.   
  Reasonable outcomes with sandwich regimen.
  + 33 pts. Stage III/IV. UPSC 50%. MFU 2.5y.
    - RT: 45 Gy WPRT. pAO RT and VBT optional.
    - Carbo/pacli q3w x4c→ WPRT 45 Gy→ same chemo x2c.
  + 3y DFS 53%, 3y OS 68%, with only 3% pelvic relapse.
* **Duke U** [[Secord Gyn Onc ‘09](https://www.ncbi.nlm.nih.gov/pubmed/19560193)]: Retro. TAH/BSO/selective LND→ (**RT→ Chemo vs. Chemo→ RT vs. ChemoRTChemo**).  
  Sandwich regimen is associated with improved OS in this retrospective analysis.
  + 109 pts. 1993-2007. Surgical stage III-IV. UPSC 20%. CC 5%.
  + 3y OS 54→ 57→ 88%.
  + 3y PFS 47→ 52→ 69%.
  + OS benefit with ChemoRTChemo maintained after adjustment for stage, age, grade, race, histology & cytoreduction.
* **Albert Einstein** [[Einstein Gyn Onc ‘12](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3787514/)]: Phase II. **CarboP x3c→ WPRT/B→ CarboP x3c**.   
  Sandwich regimen has favorable outcomes and toxicity for UPSC.
  + 81 pts. UPSC, Stage I-IV.
    - RT: 45 Gy WPRT, VBT 15/3 to 0.5 cm. RT to pAO if ≥ 2 PLN or PA nodes.
  + Stage I-II MS 6.5y, MPFS 5.5y. 3y OS 84%.
  + Stage III-IV MS 3y, MPFS 2y. 3y OS 50%.
  + G3-4 heme 2.5%.
* **Finland** [[Kuoppala Gyn Onc ‘08](https://www.gynecologiconcology-online.net/article/S0090-8258(08)00253-9/abstract)]: **Split course RT ± interdigitated chemo**.Atypical treatment paradigms include split-cour se therapy. Split course RT is associated with a detriment across disease sites.
  + 156 pts. IAG3-IIIA. TAH/BSO (PLND 80%)→ split course pelvic EBRT vs. interdigitated CRT.
    - 28 Gy x 2 w 3-wk break vs. 28 Gy→ CTX→ 28 Gy→ CTX (cisplatin/epirubicin/cyclophosphamide).
  + ~5y DFS, LR, and DM.
  + Chemotherapy was associated with a low rate of acute toxicity but appeared to increase bowel complications

* **RTOG 0417** [[Protocol](https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileId=4625), [Schefter IJROBP '14](https://www.ncbi.nlm.nih.gov/pubmed/24331655)]: Phase II**→ CCRT/B + Bevacizumab**.

The 31% overall rate of pAO failures was the impetus to use nodal boosts in [[RTOG 0921](#eshihl13t11t)] (below).

* + 49 pts. IIB-IIIB or IIIC1 and/or size ≥ 5 cm. AC, SqCC or adenosquamous carcinoma of cervix. MFU 4y.

Mostly IIB (62%), SqCC (80%).

* + - CCRT: 45/25→ LDR x2 or HDR x5→ parametrial boost (if indicated).
    - Concurrent chemo: Cisplatin 40 q1w x6c, Bevacizumab 10 IV q2w x3c.
  + 3y OS 91%. 3y DFS 69%. 3y LRF 23%.
  + Total pAO failures 31%, Isolated pAO failure 8%, DM without pAO failure 15%, DM with pAO failure 23%.

* **RTOG 0921** [[Viswanathan Cancer '15](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4685031/), ['16](https://www.redjournal.org/article/S0360-3016(16)30456-4/fulltext)]: **IMRT + CDDP/bevacizumab→ ± VBT→ CarboP x4c**.  
  Adding postop bev to chemo and pelvic IMRT is well tolerated and without pelvic recurrences.
  + 34 pts. TAH + PLND. IBG3, IIG2-3, IIIC1. MFU 4y.
    - Vaginal and nodal PTV 45/25. 14.4 Gy to enlarged/involved LNs.
    - IMRT based on the [RTOG consensus guidelines].
  + 7 pts G3 nonhematologic within 90 days, 6 pts G3 nonhematologic 90-365 days.
  + 4y follow up: 5 pts G3+ >1y from treatment start.
  + 4y OS 87%, 4y DFS 73%, pAO failure 7%, DM 23.5%. No patients with recurrent disease in the pelvis.

## Toxicity

* Toxicity: Perioperative issues wound healing, vaginal stenosis, bowel bladder frequency.
* Acute: Dermatitis, N/V/D, cystitis.
* Long term: Small bowel obstruction, reduced bladder volume, femoral head fractures, lower extremity edema, vaginal narrowing.
* Complication rates: PLND + pelvic RT 5-12%, WPRT 3-5%, VBT 0-1%.
* HDR side effects: Vaginal stenosis, telangiectasia, bowel and bladder.
* The addition of concurrent chemo appears to increase G2+ heme toxicity in the setting of BM V40 > 37% [[RTOG 04-18](#kix.n1e5fah4ao76)].
* IMRT appears to demonstrate less frequent/almost constant diarrhea and antidiarrheal use in the acute setting [[TIME C](#kix.nqh4mp4cd7f2)].
  + Patient reported diarrhea at 1 year and late GU effects at 3 years were improved with IMRT.
* There appears to be less bowel obstruction at 5 years with IMRT [[MSKCC](#kix.gn0w00l4s3l9)].

## [Brachytherapy](#_3llouklhg1v3)

Return to the [[Overview of Brachytherapy](#_qxjzzedoyoxn)] section.

See the new (2020) [[Bayta.us](https://www.bayta.us/nomos/endometrial)] nomogram to guide recommendations for intermediate risk endometrial cancer.

See the [[Treatment of Early Stage endometrial cancer](#f362ka102v2f)] summary box.

ABS Task Group [[Albuquerque BT '19](https://www.sciencedirect.com/science/article/pii/S1538472118306305?via%3Dihub)] Compendium of fractionation schedules for Gyn HDR BT. [RoR](#hs48ru8dcnxy)

ABS consensus guidelines for adjuvant vaginal cuff BT after hysterectomy [[Small BT '12](https://www.sciencedirect.com/science/article/pii/S1538472111003874?via%3Dihub)] [RoR](#_oc4dol5dwo1z)

ABS statement for BT in the treatment of medically inoperable endometrial cancer [[Schwarz BT '15](https://www.ncbi.nlm.nih.gov/pubmed/26186975)]. [RoR](#h7y4krhnstic)

* Given 6-8 weeks post-op (not more than 12 weeks - NCCN) or 1 week after EBRT.
  + Be sure to check for wound healing first!
* Critical to perform pelvic exam and inspect vaginal cuff prior to treatment to rule out early disease and ensure adequate healing of vaginal cuff prior to brachytherapy. Also need to estimate the diameter of the vaginal cylinder. May consider fiducial marker placement at apex.
  + Place the patient in stirrups. Speculum. 2 gold seed markers at vaginal cuff at the suture line. Estimate vaginal length (average 7 cm). Largest comfortable cylinder (1.5-4 cm diameter), typically **3 cm**. Visual and manual inspection of vaginal cuff. Selection of appropriate diameter applicator based on physical exam. Lubrication of applicator prior to insertion. Slow insertion of applicator, observing patient for discomfort. Method for external immobilization (secure with mesh stocking or other means of immobilization). Pretreatment imaging to confirm applicator placement.
* Treat proximal **4 cm** of vagina, consider the length **of vagina** for stage IIIB.
  + What length to treat?
    - Upper 1/2 in PORTEC 2.
    - Upper 2/3 in [[Sorbe](#sud9bzz86n32)] dose escalation.
    - Most common Rx length to upper 1/2 or upper 4 cm of vagina, ABS recommends **upper 3-5 cm**.
    - Can treat the whole vagina if extensive LVSI, clear cell/serous, or IIIB (uncommon).
* **The vaginal cylinder: Misunderstood, misused, or trivial? An in depth dosimetric and multi institutional outcome investigation** [[Guy BT '19](https://www.brachyjournal.com/article/S1538-4721(19)30087-X/fulltext)]

"Dramatic differences in dose distributions arise by small variations of plan parameters, with large impact on rates of vaginal stenosis, but no clear relation with local recurrence. To help radiation oncologists interpret the magnitude of these effects for their patients, we created a tool that allows comparison between dose and fractionation parameters."

* + There is a wide variation when changing the diameter of the cylinder, which varies by whether dose is prescribed to 5 mm or to the surface.
  + Deeper prescription point and longer treatment length correlate to increased stenosis rate.
* **Dose can be prescribed to the vaginal surface or to a depth**.
  + 95% of vaginal lymphatics lie within 3 mm of the vaginal surface.
  + **ABS Survey of VBT in postoperative endometrial cancer** [[Harkenrider BT '16](https://www.sciencedirect.com/science/article/pii/S1538472115005632?via%3Dihub)]:   
    Most physicians prescribe to 5 mm depth.
    - **2/3 Rx to 5 mm** and ~20% to surface. 7x3 to 5 mm, 6x5 to surface, 5.5x4 to 5 mm.
    - May Rx to surface as representative of Dmax to normal tissue.
    - Note: If Rx to 5 mm depth, dose at surface will change with cylinder size.

* + **ABS Survey of BT in postoperative endometrial cancer** [[Martell BT '19](https://www.sciencedirect.com/science/article/pii/S1538472119304386)]:

Most common for monotherapy: 21/3 to 0.5 cm depth. Second most common: 30/5 to surface (Figure 1).

* + - Around 80% of respondents recommend adjuvant VBT alone for IB, G2, SM (-), LVSI (-) disease.
    - Respondents are split over the addition of VBT to EBRT for IB, G3, LVSI (+) disease.
    - Around 75% of respondents recommend VBT + EBRT for IIIC1, SM(+) disease.
    - Only half of respondents utilize an ITV when planning adjuvant EBRT, with 75% recommending 45/25.
    - Around half of respondents determine applicator size at the time of BT.

* + **Sorbe** [[IJROBP '05]](https://www.sciencedirect.com/science/article/pii/S0360301605000416?via%3Dihub): Ir-192 **5 Gy vs. 2.5 Gy x 6 at 5mm**   
    Equivalent LC but increased vaginal foreshortening with 5 Gy x 6.
    - Stage IA-IB, G1-2. TAH/BSO/Pelvic sampling + washings.
    - Vaginal cylinders 2.0, 2.5 and 3.0 cm. Proximal 2/3 of vaginal length treated.
    - 5y vaginal foreshortening 25→ 3% (2.1→ 0.3).
  + [[PORTEC-4](#1ysyu0brf2hr)] is investigating observation vs. two HDR regimens (21/3 vs. 15/3 to 5 mm) for HIR up to IBG3.
  + [[PORTEC-4a](#3niegyeqx8u5)] is investigating VBT vs. molecular profile-based treatments for up to microscopic stage II.
* **VBT monotherapy**: See the [[Treatment of Early Stage endometrial cancer](#f362ka102v2f)] summary box.

See the new (2020) [[Bayta.us](https://www.bayta.us/nomos/endometrial)] nomogram to guide recommendations for intermediate risk endometrial cancer.

See the [[Uterine Brachytherapy](#_oc4dol5dwo1z)] or the [[Overview of Brachytherapy](#_qxjzzedoyoxn)] section for more.

* + LDR if monotherapy: 60-65 Gy to vaginal surface. If combined, 65-70 Gy. If recurrent, > 75 Gy.
    - PORTEC-2: HDR 21/3 or LDR 30 to 5mm (dose equivalent of 45-50Gy).
  + HDR alone:
    - **21/3 to 5mm** (7 Gy - PORTEC 2): Most common scheme based on [[most recent survey](#vvscrycdosny)].

*Around 60 Gy to the vaginal surface and 30 Gy EQD210 to 5 mm with 3 cm cylinder.*

* + - * May be associated with late morbidity.
      * May adjust based on size. For 2.5 cm cylinder, consider **18/3** **to 5mm** to reduce surface dose.
    - **22/4 to 5mm** (5.5 Gy - ABS survey).Equivalent to 38/4 to surface.

*Around 55 Gy to the vaginal surface and 28 Gy EQD210 to 5 mm with 3 cm cylinder.*

* + - 25/5 to 5mm (5 Gy - Michigan).
    - 15/6 to 5mm (2.5 Gy - Sorbe).
    - 31.5/3 to surface (10.5 Gy - UCSF).
    - 38/4 to surface (8.5 Gy - Australian series). Equivalent to 22/4 to 5 mm.
    - 30/5 to surface (6 Gy - MDACC): Second most common scheme based on [[most recent survey](#vvscrycdosny)].

*Around 40 Gy to the vaginal surface and 15 Gy EQD210 to 5 mm with 3 cm cylinder.*

* + - 24/6 to surface (4 Gy - DFCI/Harvard).
* **Adjuvant VBT after EBRT**:Consider for IBG3 (controversial), cervical (II), vaginal (IIIB) or in the recurrent setting.

See the new (2020) [[Bayta.us](https://www.bayta.us/nomos/endometrial)] nomogram to guide recommendations for intermediate risk endometrial cancer.

See the [[Uterine Brachytherapy](#_oc4dol5dwo1z)] or the [[Overview of Brachytherapy](#_qxjzzedoyoxn)] section for more.

* + LDR 20 Gy at vaginal surface.
  + HDR, after 45 Gy EBRT: 65-70 Gy. If superficial SM+, 70-75 Gy.
    - 15-18/3 to surface after 45 Gy, 12/2 after 50.4/28 WPRT. *One less 6 Gy fraction after 50.4/28 WPRT.*
    - 15/3 to 5 mm after 45 Gy, 10/2 after 50.4/28 WPRT. *One less 5 Gy fraction after 50.4/28 WPRT.*
  + HDR for recurrence after 45 Gy EBRT: ≥ 75 Gy.
    - 21/3 to 5 mm (7 Gy - EQD210 74 Gy).
    - 24/4 to 5 mm (6 Gy - EQD210 76 Gy).
    - 30/5 to surface (5 Gy - EQD210 84 Gy).
    - 28/4 to surface (4 Gy - EQD210 84 Gy).

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| **Inoperable Endometrial cancer**  **ABS statement for BT in the treatment of medically inoperable endometrial cancer** [[Schwarz BT '15](https://www.ncbi.nlm.nih.gov/pubmed/26186975)].   * Make sure to get an MRI! * IA, G1-2: brachy alone For early stage uterine treated with brachy alone, LC upwards of 80-90%. * IA G3, IB-II: WPRT + BT * III-IV: ChemoRT (WP) + interstitial brachy * Consider progestin-based hormone therapy if ER/PR positive and not candidate for RT.   + Hormone therapy: Megace, tamoxifen, aromatase inhibitor.   + **Could consider megace in IAG1**. If CR at 6 mo on megace, childbearing→ TAH/BSO.   + C/I to megace: breast cancer, stroke, MI, PE, DVT, smoking.   + Although 35% with negative EMB are able to get pregnant, their recurrence rate is high (~35%). * OS 20% less. If using hormone therapy, q3-6 mo endo biopsies.   **Intact IA**: **VBT alone for stage IA G1-2**. Rx to D90 CTV, goal 48-62.5 Gy EQD210. GTV to 80-90 Gy EQD210.  **Take home: 36/6 VBT (EQD210 48 Gy) is adequate for intact IA.**   * 34/4 (8.5 Gy - EQD2 52.4 Gy). * 36.5/5 (7.3 Gy - EQD2 52.6 Gy). * 38.4/6 (6.4 Gy - EQD2 52.5 Gy). * **36/6** (6 Gy - EQD2 48 Gy). * 39.9/7 (5.7 Gy - EQD2 52.5 Gy). * 45/9 (5 Gy- EQD2 50 Gy). * 50/10 (5 Gy - EQD2 62.5 Gy)   **Intact > IA**: Rx to D90 CTV. Goal 65-70 Gy (stage IA) or 70-75 Gy (stage II+). GTV to 80-90 Gy EQD210.  **Take home: After 45 Gy, 25/5 VBT (EQD210 75 Gy) is adequate for intact > 1A.**   * After 45 Gy EBRT:   + 17/2 (8.5 Gy - EQD2 70.5 Gy)   + 19.5/3 (6.5 Gy - EQD2 71 Gy)   + 18.9/3 (6.3 Gy - EQD2 70 Gy)   + 20.8/4 (5.2 Gy - EQD2 70.6 Gy)   + **25/5** (5 Gy - EQD2 75 Gy) * After 50.4 Gy EBRT:   + 12/2 (6 Gy - EQD2 66 Gy)   + 22.5/6 (3.75 Gy - EQD2 75 Gy) |

### [Intact uterus](#_oc4dol5dwo1z)

See the Summary Box for inoperable endometrial cancer above. Most patients are surgical candidates.

TL;DR - VBT alone may be used for stage IA G1-2 (no EBRT required). Rx to D90 CTV, goal as low as 48 Gy EQD2.

Return to the [[Uterine Brachytherapy](#_oc4dol5dwo1z)] or the [[Overview of Brachytherapy](#_qxjzzedoyoxn)] section.

* Utilize Martinez-Y applicator or combo of tandem and cylinder ± interstitials.
* **Canada** [[Niazi IJROBP ‘05](https://www.redjournal.org/article/S0360-3016(05)00803-5/abstract)]: Retro. **Inoperable candidates. HDR** (24/3) **± EBRT** (42 Gy).  
  Single modality HDR demonstrated favorable results for Stage I endometrial cancer.
  + 38 pts. Clinical stage I-II endometrial AC. HDR alone in 80%, CMT in 20%.
  + 15y DSS 78% for all stages.
  + DSS for Stage I / II of 90→ 42%.
  + If Stage I by MRI and at least 30 Gy HDR, then 10y DSS 100%.
* **Definition of volumes**
  + **HRCTV = entire uterus to serosa, cervix, and 1-2 cm of proximal vagina**.
    - May exclude cervix and proximal vagina if G1-2 stage IA.
    - CTV D90 EQD2 65-70 Gy for stage IA, 70-75 Gy for stage II and up.
  + HRGTV by MRI with a goal of 80-90 EQD2 no matter what stage.
  + D2cc to rectosigmoid < **70**-75 Gy (EQD2).
  + D2cc to bladder < **80**-100 Gy (EQD2).
* Point based prescription is also acceptable (2 cm points or Madison system). Similar to cervical cancer.
  + 5 mg RaEq/cm of uterine tandem.
  + 10 mg RaEq/cm in the upper 2 cm of tandem.
  + Specify dose at 2 cm from central axis at midpoint along Y-shaped applicator, optimized to 0.5 cm depth within vaginal mucosa.
  + **"Superior" Point S**: ⅔ thickness of fundus, superior to tip of tandem.
  + **"Wall" Point W**: 2 cm inferior to tip of tandem and 2-3 thickness of the uterine wall, lateral to tandem.
  + Point M, similar to Point A but lies at the lateral extent of the cervical wall.
  + **Bladder point**: Posterior surface of Foley on lat and center of 7 cc balloon on AP. Pull down against the urethra.
  + **Rectal point**: 5mm behind posterior vaginal wall at midvaginal source.
  + **Vaginal point**: Lateral edge of ovoid/ring on AP film and mid-ovoid/ring on lateral film.
  + Keep rectum and bladder to < 75% of Rx dose. Anterior surface of rectum received the full dose.
  + Limit **upper vagina** to **120** Gy, **mid vagina** to **80** Gy, and **lower vagina** to **60** Gy.
    - Doses >50-60 Gy can cause significant fibrosis and stenosis.

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| **This Summary Box was made possible by the ACRO Resident Committee.**  **A more comprehensive collection of resources for all disease sites may be found at** [**http://www.acro.org/**](http://www.acro.org/)  Zaorsky: [[Gyn staging](https://twitter.com/NicholasZaorsky/status/1219773291528884229?s=20)], [[Comparison of surgeries](https://twitter.com/NicholasZaorsky/status/1221824856834158592?s=20)], [[Gyn nodes AP](https://twitter.com/NicholasZaorsky/status/1221823861978693632?s=20), [Lat](https://twitter.com/NicholasZaorsky/status/1221824276740956162?s=20)], [[Cervical staging](https://twitter.com/NicholasZaorsky/status/1221828307068604417?s=20)], [[Cervical EBRT](https://twitter.com/NicholasZaorsky/status/1222649051235127296?s=20)], [[Cervical BT](https://twitter.com/NicholasZaorsky/status/1222648780903849986?s=20)].  ARRO: [[Cervical cancer](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/CervicalCancer.pdf)].  Contouring:   * eContour: [[AVARO cervix](http://econtour.org/cases/84)], [[post op cervix](http://econtour.org/cases/55)], [[EMBRACE 2 cervix](http://econtour.org/cases/111)] and [[NRG cervix](http://econtour.org/cases/38)]. * Female Normal Pelvis Atlas [[RTOG Contouring Atlases](https://www.nrgoncology.org/ciro-gynecologic)] * Improving target volume delineation in intact cervical cancer [[Eminowicz PRO '16](https://www.ncbi.nlm.nih.gov/pubmed/27032573)]. * Consensus guidelines for delineation of CTV for IMRT for definitive tx of cervix cancer [[Lim IJROBP '11]](https://www.ncbi.nlm.nih.gov/pubmed/20472347). * Consensus guidelines for delineation of CTV in Endo/Cervical PORT [[RTOG Gyn Atlas](http://www.rtog.org/corelab/contouringatlases/gyn.aspx), [Small IJROBP '09](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2752724/)]. [RoR](#8tjrn056kqnl) * Comparison and CTV consensus for CT and MR-based BT in L-A Cervical Ca [[RTOG Atlas](https://www.nrgoncology.org/ciro-gynecologic), [Viswanathan IJROBP '14](https://www.redjournal.org/article/S0360-3016(14)03328-8/fulltext)] [RoR](#kix.8yrje68n0x79)   Review Articles   * Gynecologic Malignancies [[Suneja and Viswanathan Heme/Onc Clin N. Amer '20](https://www.sciencedirect.com/science/article/pii/S088985881930111X?via%3Dihub)] [RoR](#_t4kv4aacj9qi)   Society Guidelines   * ASCO Guideline: Mgmt [and Care of Women with Invasive Cervical Ca Resource-Stratified Guideline](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/gynecologic-cancer#/11801) *May 25, 2016* * Society of Gynecologic Oncology (SGO) [[Guidelines]](https://www.sgo.org/clinical-practice/guidelines/) * FIGO Report: Cancer of the cervix uteri [[Bhatla IJGO '18](https://www.ncbi.nlm.nih.gov/pubmed/30306584)] * [[ESMO Guidelines](https://www.esmo.org/guidelines/gynaecological-cancers)] for Gynecological Cancers. * ESGO-ESTRO-ESP guidelines for the management of patients with cervical cancer [[June '18]](https://link.springer.com/article/10.1007%2Fs00428-018-2362-9) [RoR](#_a6plw395yelu) * ABS:   + ABS Consensus Guidelines [[Viswanathan BT '12]](https://www.sciencedirect.com/science/article/pii/S1538472111003527): Part I: General principles. [RoR](#l14oefxoqiz)   + ABS Consensus Guidelines [[Viswanathan BT '12]](https://www.sciencedirect.com/science/article/pii/S1538472111003515): Part II: HDR BT. [RoR](#1vb7u8jdcrdy)   + ABS Consensus Guidelines [[Lee BT '12](https://www.ncbi.nlm.nih.gov/pubmed/22265438)]: Part III: LDR and PDR BT. [RoR](#cj81a18qu433)   + ABS Task Group [[Albuquerque BT '19](https://www.sciencedirect.com/science/article/pii/S1538472118306305?via%3Dihub)] Compendium of fractionation schedules for Gyn HDR BT. [RoR](#hs48ru8dcnxy)   Relevant Accessible Radiation Protocols:   * TIME-C/RTOG 1203 [[Protocol (Supplement) Klopp JCO '18](http://ascopubs.org/doi/full/10.1200/JCO.2017.77.4273)]: Cervix/Endo (M)RH→ WPRT vs. IMRT. [RoR](#kix.nqh4mp4cd7f2) * RTOG 0418 [[Protocol](https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0418)] for post-operative cervical and endometrial. [RoR](#kix.n1e5fah4ao76) * OUTBACK / ANZGOG 0902 / GOG 0274 / RTOG 1174 [[Protocol](https://www.rtog.org/clinicaltrials/protocoltable/studydetails.aspx?action=openFile&FileID=10105)]: Phase III. (WPRT/EFRT)/B→ ± CarboP x4c. [RoR](#tgrkocfn51fu) * RTOG 0116 [[Protocol](https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileID=7534)]: Phase I/II. EFRT/B/CDDP ± amifostine. *Extended field with 3D is too toxic.* [RoR](#2s9lxocmlkr1) * RTOG 0417 [[Protocol](https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileId=4625)]: Phase II→ CCRT/B + Bevacizumab. *1/3 fail above WPRT field in pAO nodes.*  [RoR](#gsbf2k20udq7)   + RTOG 09-21 [[Viswanathan Cancer '15](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4685031/), ['16](https://www.redjournal.org/article/S0360-3016(16)30456-4/fulltext)][RoR](#eshihl13t11t) demonstrated IMRT high nodal boosts are safe. * EMBRACE II [[Pötter CTRO '18]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5862686/) aims to benchmark high level of local, nodal, and systemic control with IGABT. [RoR](#n9hc7b9umqu)   Quality of Life/Toxicity:   * TIME-C/RTOG 1203 [[Yeung JCO '20](https://www.ncbi.nlm.nih.gov/pubmed/32073955)]: (M)RH→ 3D-WPRT vs. IMRT. [RoR](#kix.nqh4mp4cd7f2) * RTOG 9001 [[Eifel JCO '04](http://ascopubs.org/doi/abs/10.1200/JCO.2004.07.197?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed)]: EFRT/B vs. CCWPRT/B. *Acute toxicity with CCRT worse initially, evens out in long run.* [RoR](#tasa0vnpp4s2) * RTOG 0116 [[Small IJROBP '07](https://www.ncbi.nlm.nih.gov/pubmed/17398031), [IJCG '11](https://www.ncbi.nlm.nih.gov/pubmed/21892091)]: Phase I/II. EFRT/B/CDDP ± amifostine. *40% late G3/4 toxicity.* [RoR](#2s9lxocmlkr1) * EMBRACE I [[Fortin BT '16]](https://www.brachyjournal.com/article/S1538-4721(16)30054-X/fulltext): IS/IC BT for parametrial involvement [RoR](#_efhwb1dgreff) * EMBRACE I [[Mazeron RTO '16](#hi7c3wdz8bwq)]: Limit the rectal D2cc to ≤ 69.5 Gy EQD2 for around 10% late G2+ rectal morbidity. [RoR](#_efhwb1dgreff) * EMBRACE I [[Ujaimi BT '17]](https://www.sciencedirect.com/science/article/pii/S1538472117303938?via%3Dihub): Limit the rectal V55 < 11 cc to minimize late G2+ rectal morbidity. [RoR](#_efhwb1dgreff) * EMBRACE I [[Kircheiner RTO '16](#kix.lb7csgs1k37)]: Limit the rectovaginal D2cc to ≤ 65 Gy EQD2. [RoR](#_efhwb1dgreff) |

## 

## [Treatment planning](#_3llouklhg1v3)

See the ACRO Summary Box above.

See the [[WPRT Fields](#_rdqhiroqx6vu)] and [[General IMRT](#_voic7ljxmng9)] section for information on nodal boosts, post-operative RT and more.

* Dose
  + WPRT 45 Gy (50.4 if EBRT alone).
  + 4 field vs. IMRT: IMRT spares small bowel, bladder, and rectum. If using IMRT, sim w bladder full and bladder empty. Plan and daily treatment with full bladder.
  + Sequential boost up to 65 Gy or SIB to 54/25.

### [3D Field borders/Technique](#_pu52d22rkch6)

See the [[WPRT Fields](#_rdqhiroqx6vu)] section and Protocols above for more.

* WART: Automatic fail on boards. Only say WART if stage III and no chemo unless you want to fail boards, even then, IMRT with consideration of higher chimney would be standard.
  + Sup above diaphragm.
  + Inf at obturator foramen.
  + Laterally at peritoneal stripe.
  + Block kidneys after 15 Gy, liver after 25.5 Gy.
  + Then drop the border to L5/S1 and treat 4 field WP to 45 Gy.

### [IMRT planning](#_pu52d22rkch6)

See [[Post-Operative IMRT](#_eb93f2h9mmw)], [[IMRT Trials](#_voic7ljxmng9)] and [[Lymph node Boosts](#_y9l1m6e7xjg3)] for more.

* General information:
* CTV = Int iliac, obturator, and ext iliac. Presacrals if cervix involvement.
  + 7 mm margin on vessels excluding muscle, bowel, bone.
* ITV = Vaginal cuff, 3 cm vagina, and paravagina on bladder full and empty.
* PTV nodes = CTV + 7 mm.
* PTV vagina ITV + 1-1.5 cm (make sure it extends laterally to obturator muscles).
* Isolated pAO involvement without pelvic lymph node involvement is only 3% (fundal involvement?).

## [Follow up](#_3llouklhg1v3)

* For < IBG3, [[focal vs. substantial LVSI](#iuwnoiy6bk4n)] means the difference between single and double digit rates of pelvic relapse at 5y.

* PORTEC 1 Recurrence paper: [[Creutzberg Gyn Onc '03]](https://www.sciencedirect.com/science/article/pii/S0090825803001264?via%3Dihub): TAH/BSO **no PLND** (sampled suspicious LNs)**→ ± EBRT**.  
  75% of failures occur in vaginal vault. Vaginal recurrences and no prior RT have much better prognosis.

After failures, around 80% of patients will have complete response in the long term, and are more likely to have DM after receiving RT while vaginal recurrences if on observation arm.

Patients in the observation arm are more likely to have CR to salvage therapy and are more likely to receive salvage therapy. Overall, only around 4 of 10 patients with pelvic relapse are treated with curative intent.

Suggestion of 50% of patients alive at 10y with vaginal relapse and no prior RT, while 3y survival after pelvic nodal relapse is less than 10%. We now have [[2019 data](#ggzffy340rb6)] to suggest 3y OS is 50% for isolated pelvic or pAO relapse treated with SBRT.

* + 8y actuarial LR 15→ 4%. First failure of DM in 8% of RT group, vaginal in 10% of the control group.
  + Median time to relapse 21 mo, with 60% within 2y, 76% within 3y.
  + 2y OS after vaginal / pelvic or distant recurrence 79→ 21%, 3y OS 69→ 13%.
  + 3y OS after first relapse for no prior / prior RT arms 51→ 19%.
  + 3y OS after vaginal / pelvic nodal / distant recurrence 73→ 8→ 14%.
  + 5y OS after vaginal recurrence for no prior / prior RT 65→ 43%.
    - 10y OS after vaginal recurrence for no prior / prior RT 51→ 25%.
  + CR to salvage therapy 89% in observation arm, with 77% in CR long term.
    - Only 4 of 10 pts w pelvic relapse were treated with curative intent.
* **UPSC: Patterns of Failure and Survival** [[Wang Aust NZ J Obs Gyn '09](https://www.ncbi.nlm.nih.gov/pubmed/19694700)]: Retro. TAH/BSO/LND → Plt based chemo + RT.

Optimal cytoreductive surgery leaving no macroscopic disease is recommended. VBT should be delivered to all patients, along with EBRT. Sub-diaphragmatic failure is the most common mode of failure.

* + 1995-2006.
  + OS at 2 / 5y of 65→ 43%. MS 39 mo.
  + PFS at 2 / 5y of 60→ 35%.
  + MVA demonstrated macroscopic residual disease at the completion of surgery was significant for OS. MS 11 mos with macroscopic disease, and all patients died within 18 mo despite adjuvant therapy.
  + Only 1/16 pts who rec'd VBT failed in the vagina, while 3/7 who received EBRT failed in the vagina.
* Overall survival: IA/B, II, III 90→ 80→ 70→ 60%.
  + 5y OS 70% PLN, 40% pAO.
* H&P + pelvic exam q3-6 mo x2-3y, then q6mo or annually.
* Imaging as clinically indicated (except routine chest for sarcoma).
* CA-125 if initially elevated.
* Lifestyle modification (obesity, exercise, nutrition).

## [Future Directions](#_3llouklhg1v3)

See NCTN Trial Portfolios by Disease Site: [[Gyn](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_GYNE_Trials.pdf)]

* **NRG-GY020** [[NCT04214067](https://clinicaltrials.gov/ct2/show/NCT04214067)]: Phase III. Newly diagnosed, Stage I/II. HIR, dMMR. **RT ± Pembrolizumab**.
* See [[**GOG 0238**](#g86ppyi9d02)]: Phase III. Pelvic-only recurrence. **Definitive RT ± weekly cisplatin**. 45 Gy→ 7x3 to 5 mm.
  + IMRT boost is allowed for patients who are not candidates for brachytherapy.
  + 18% G3-4 GI toxicity, 50% grade 3 vaginal sequelae.
* **NRG-GY018** [[NCT03914612](https://clinicaltrials.gov/ct2/show/NCT03914612)]: Phase III. Stage III/IV or recurrent. **CarboP ± Pembrolizumab**.
* **NRG-GY012** [[NCT03660826](https://clinicaltrials.gov/ct2/show/NCT03660826)]: Phase II. Recurrent. Any histology. **Cediranib/Olaparib vs. Cediranib vs. Olaparib**.
* **NRG-GY014** [[NCT03348631](https://clinicaltrials.gov/ct2/show/NCT03348631)]: Phase II. Recurrent. Endometrioid or ovarian clear cell.

See [[Future Directions](#_b0dcq0tt2tp3)] in the ovarian cancer section.

* + Tazemetostat.

* **ENGOT-EN2-DGCG** [[NCT01244789](https://clinicaltrials.gov/ct2/show/NCT01244789), [Background](https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.TPS5613)]: Phase II. **TAH/PLND**→ ± VBT **± CarboP x6c**.
  + Stage I-II serous, clear cell; Stage I G3 endometrioid; Stage II endometrioid with negative nodes after hysterectomy.

* **PORTEC-4** [[Nout and Creutzberg Protocol](https://www.msbi.nl/promise/LinkClick.aspx?fileticket=hhxkNW1k6xI=)]: Phase III. **TAH/BSO→ Obs vs. HDR (21/3 or 15/3 to 5 mm)**.
  + HIR: Any age IAG3 without LVSI or IBG1-2 with LVSI. If older than 60y, then may be IB G1-2.
  + 500 planned patients. Endometrioid carcinoma. No UPSC or CC. VBT: 21/3 or 15/3 to 5 mm.

* **PORTEC-4a** [[Nout and Creutzberg Protocol](https://www.msbi.nl/promise/LinkClick.aspx?fileticket=ze9k6rHS-bE%3d&tabid=125&portalid=0&mid=581)]: **TAH/BSO→ 21/3 vs. molecular-risk based Obs / VBT/ EBRT**.  
  Molecular profile vs. standard recommendations. Primary endpoint vaginal recurrence at 5y.
  + Early Stage: Any age stage IAG3 ± LVSI, IBG3 without LVSI, II (micro) G1, IBG1-2 + (LVSI or age ≥ 60y).
  + 500 planned patients.
  + Low risk (POLEmt without MSI or CTNNB1mt - ~50%): Observation.
  + Intermediate risk: VBT.
  + Unfavorable risk (p53mt, >10% L1CAM or substantial LVSI - ~10%): EBRT.

## 

# [Uterine Sarcoma](#_nz4p8uik7qem)

## 

* Uterine sarcomas account for 3% of all uterine cancers (1600 anticipated uterine sarcoma cases in 2015).
* **Types of Malignant Mesenchymal (sarcoma) uterine neoplasms**:
  + Low-grade endometrial stromal sarcoma (**ESS**).
  + High-grade endometrial stromal sarcoma (ESS).
  + Undifferentiated uterine sarcoma (**UUS**).
  + Uterine leiomyosarcoma (**uLMS**).
* Treatment = Surgery (LND not indicated).
  + ESS: Adjuvant hormone therapy (megestrol, NOT tamoxifen).
  + Leiomyosarcoma or undifferentiated: Adjuvant chemotherapy
    - Chemotherapy: Docetaxel/Gemcitabine; doxorubicin.

* **EORTC 55874** [[Reed EJC ‘08](https://www.ncbi.nlm.nih.gov/pubmed/18378136)]: TAH/BSO/LND recommended **± WPRT**.

Use caution when combining high risk subtypes together: WPRT appears to benefit carcinosarcomas the most.

WPRT appears to have little benefit for LC in LMS, as they tend to fail distantly.

WPRT appears to cut LR in half for carcinosarcomas.

* + 224 pts. I/II uterine sarcoma (LMS, carcinosarcoma, ESS).
    - WPRT: 51/28 in 5-6 weeks.
  + LR 40→ 21% with 50% PFS/OS.
  + On subset analysis, LC benefit only seen for carcinosarcomas, not leiomyosarcomas.
    - LR for carcinosarcomas of 47→ 24%.
    - LR for LMS of 24→ 20%.
    - DM for carcinosarcomas of ~30%.
    - DM for LMS of 33→ 54%. This suggests WPRT might increase local control, leading to more DM.
* **GOG 150** [[Wolfson Gyn Onc '07](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2752331/)]: **WART vs. Chemo**.

Equivalent recurrence and survival with chemo.

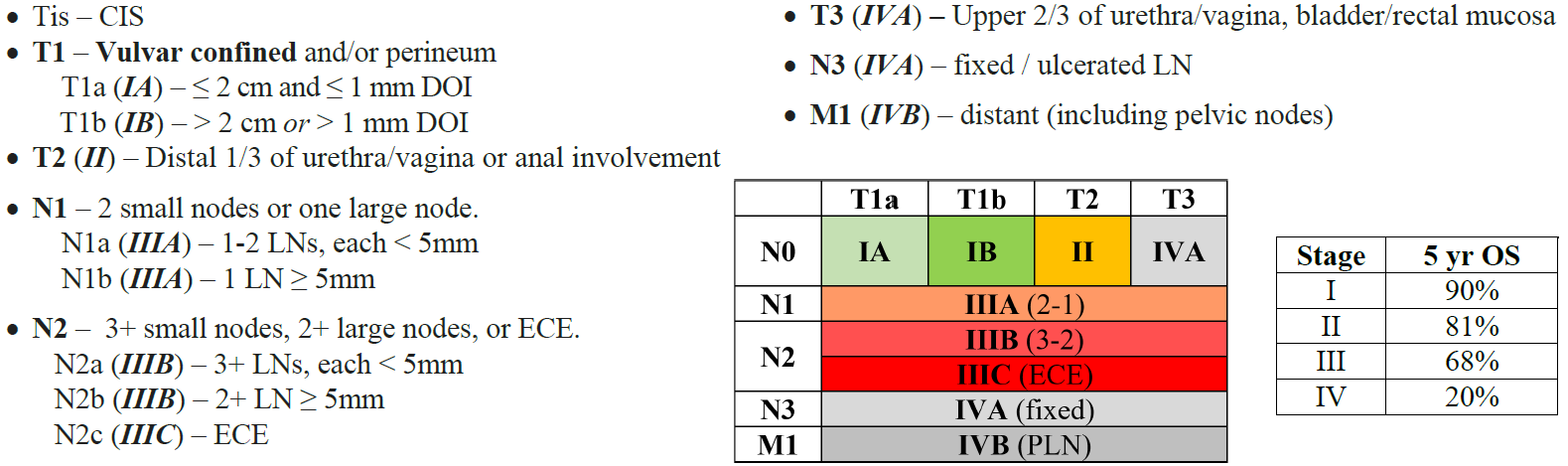
* + 232 pts. I-IV uterine carcinosarcoma with ≤ 1 cm residual.
    - WART 30/WPRT 50 Gy at 1 Gy BID or 1.5 Gy qday vs. chemotherapy
      * Cisplatin/Ifosfamide/Mesna x3c
    - Equivalent recurrence rate and survival between arms.
* Sampath [[IJROBP '10](https://www.ncbi.nlm.nih.gov/pubmed/19700247)]: Retro.

RT with 50% reduction in LRF, but no OS difference.

* + 3,650 pts. Uterine sarcomas (ESS, uLMS and carcinosarcoma). National oncology database. MFU 5y.
  + 5y OS 37%. Adjuvant RT is not predictive of survival.
  + RT with 53% reduction in risk of 5y LRF.
* **GOG 261** [Pending]: **Paclitaxel + Carboplatin vs. Ifosfamide + Paclitaxel**.
  + Chemo-naive patients with newly diagnosed I-IV persistent or recurrent carcinosarcoma of uterus or ovary.

## 

# [Vulvar Cancer](#_nz4p8uik7qem)



T1b >1 mm DOI or > 2 cm; T2 lower; T3 upper.

Most tumors > 2 cm (T1b+) or with fixed lymph nodes (N3) are not surgically resectable with good functional outcomes.

N1 does not include 2 lymph nodes unless both are under 5 mm. N2 disease was likely influenced by the results of [[GOG37](#8jvpsgbv0nv6)].

N3 disease is stage IVA (fixed/ulcerated LN), while **pelvic nodes are M1** and stage IVB.

See [[Vulvar Cancer](#_k19a41x9sid8)] in the Introduction to Gynecologic Malignancies section.

FIGO Report: Cancer of the Vulva [[Rogers and Cuello IJGO '18](https://www.ncbi.nlm.nih.gov/pubmed/30306583)]

Zaorsky: [[Gyn staging](https://twitter.com/NicholasZaorsky/status/1219773291528884229?s=20)], [[Gyn nodes AP](https://twitter.com/NicholasZaorsky/status/1221823861978693632?s=20), [Gyn nodes Lat](https://twitter.com/NicholasZaorsky/status/1221824276740956162?s=20)], [[Vulvar cancer staging](https://twitter.com/NicholasZaorsky/status/1222649476386578438?s=20)].

ARRO: [[Operable Vulvar Cancer](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/Vulvar.pdf)]

Consensus Recommendations for RT Contouring and Treatment of Vulvar Carcinoma [[Gaffney IJROBP '16](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5189987/)]

Vulvar Cancer Atlas [[RTOG Contouring Atlases](https://www.rtog.org/CoreLab/ContouringAtlases.aspx)]

* 3,500 new cases and 1,000 deaths in the US in 2015, or 1/100k ppl.
  + Less than 5% of all gyn malignancies (4th most common), 1-2% of all cancers in women.
  + Over the past 25 years, incidence has slightly increased.
* **Seven subsites of vulva**: Majora/minora (70%), mons pubis, clitoris, vaginal vestibule, perineal body, posterior fourchette.
* 1/3 LN+ (stage III/IV); 80% early stage confined.
* ~40% of patients will have a local recurrence at 10y. Around 30% of patients will die from their cancer at 10y if they develop a local recurrence [[GROINS V I](#gapq6vf7kmp7)]
* **Etiology**: **HPV** and **vulvar dystrophy** (e.g. lichen sclerosus). Synchronous cervical cancer in ~20%. Synchronous lesions in 5-10%
  + Median age **68**, Bimodal.
  + **Type I**: **younger** women, smoking, HPV. *HPV is associated with VIN.*
    - 33% of vulvar cancer will be in the background of VIN.
    - VIN will progress < 5% of the time, while ~80% of VIN III progress.
  + **Type II**: **older** women. Lichen sclerosus.
    - 30-60% of vulvar cancer will be in the background of lichen sclerosus.
    - Lichen sclerosus will progress ~5% of the time.
  + Basaloid carcinoma associated with HPV.
  + Keratinizing carcinoma associated with vulvar dystrophy.
* **Histology**: SqCC 90%, Melanoma 5-10%, others < 5% such as BCC, merkel cell, sarcoma, AC of bartholin glands.
  + Verrucous carcinoma is a squamous variant that rarely metastasizes.
  + Squamous carcinoma with **spray** or **diffuse** variant is more likely to recur after surgery.
    - Spray pattern: associated with "fingers" into dermis.
    - Diffuse: Connected tumor >1 mm in any dimension, often deeply invasive with stromal desmoplasia.
* **Risk factors**: Age, HPV (multifocal - 5%), VIN, Bowen Disease (Sq CIS), Paget's (arising from Bartholin, urethra, rectum), smoking, immune deficiency, lichen sclerosus, deep stromal invasion.
  + Extramammary Paget's disease is associated with invasive carcinoma in ~80%.
* **Workup**
  + H&P with attention to symptom onset and duration, bleeding, RF: HPV, HIV, HSV, prior lesions, smoking hx, lichen sclerosus
  + Physical exam focused on the extent of disease, synchronous lesions. DRE.
  + Pap smear, EUA with bx and FNA of inguinal LN, biopsy of primary. HPV testing.
  + PET/CT (consider if T2+) or MRI. CXR.
    - FIGO: only need chest imaging to complete metastatic workup of vulvar cancer.
  + Clinical exam unreliable for inguinal mets:
    - U/S with FNA have high Sn and Sp for inguinal nodes.
    - PET/CT 95% Sp, 67% Sn, 86% PPV, 86% NPV.
      * Kamran: 100% Sp, 50% Sn, 100% PPV, 57% NPV.
    - MRI: Group of 22 pts using ≥ 10 mm in short axis for nodes has 40% Sn and 97% Sp.
      * For 39 pts s/p LND, 86% Sn , 82% Sp , 64% PPV, 94% NPV.
    - Clinical examination: 94% Sp, 70% PPV, 80% NPV. *~20-25% false negative rate.*
    - NPV is not high enough with non-invasive modalities
* **Management**
  + **Radical vulvectomy**: Removal of vulva to deep fascia of thigh with removal of periosteum of pubis with 2 cm margin. Can be combined with uni or bilateral LND.
    - In stage I or II, RV does not change recurrence rates vs. WLE (7% in both).
  + **VIN**: Local excision, skinning vulvectomy, imiquimod, topical 5-FU, laser ablation.
  + **IA**: WLE with 1 cm margin without LND for < 1 mm invasion.
  + **IB/II**: Radial local resection or modified radical vulvectomy + inguinal SLNB.
    - Consider SLNB for lesions < 4 cm and cN0. May be unilateral if well-lateralized, or > 2 cm from midline.
    - **RT to vulva**: SM < 8 mm, consider for LVSI, DOI > 5mm, tumor size, diffuse or spray histology.
    - **RT to inguinal and pelvis**: ≥ 2 positive nodes, ECE, or 1 PLN with < 12 nodes resected without SLNB. CCRT can be considered based on risk factors, with no clear indications described.
    - 3 incision technique.
      * Sup vs. deep inguinofemoral dissection: separated by cribriform fascia. Do deep if superficial +.
  + **Locally advanced** has no formal definition but includes III/IVA or extension to adjacent GU system, anorectum or fixation to bones. Also stage II (⅓ lower urethra, ⅓ lower vagina, anus), as radical vulvectomy does not cure them.
    - **Preop CCRT**: Biopsy or groin dissection for confirmation of CR. Surgical excision of residual disease.
      * CDDP 40 mg q1w x6c, RT to **57.6 Gy**.
        + pPR→ Resect if possible, otherwise additional CRT.
        + cCR→ Bx, if neg, observe. If pos, resection or CRT.
    - **Definitive CCRT**: CDDP 40 mg q1w with RT to **64.8 Gy**.
    - Radical vulvectomy - May require pelvic exenteration.
  + For positive pelvic nodes, treated with curative intent.

## [Surgical margins](#_jvy8eyvc333a)

Current recommendations for no adjuvant for SM < 8 mm, but some use 5 mm. 2019 data suggests 40% of pts will have local recurrence at 10y, with no relation to SM clearance. It appears as if dVIN with or without lichen sclerosis at the cut edge of the surgical specimen has higher local recurrence [[Grootenhuis '19](#lnsp2bntimc4)]. Surgery seems most beneficial for SM+ or very close SM (< 3 mm) [[Franco Gyn '19](#vz1hugs0vy1n)]

* **UK Definition of Margins in Vulvar Cancer** [[Kortekaas IJ Gyn Path '19](https://journals.lww.com/intjgynpathology/Abstract/publishahead/Practical_Guidance_for_Measuring_and_Reporting.99077.aspx)]:  
  Margins = the minimum distance from the peripheral edge of the invasive tumor nests toward the inked peripheral surgical margin reported in millimeters. This measurement should run through tissue and preferably be measured in a straight line.
  + In general, re-excision is recommended for SM < 8 mm.
  + DOI, tumor thickness and distance to deep margins should be reported.

* **UCLA** [[**Heaps** Gyn Onc '90](http://www.gynecologiconcology-online.net/article/0090-8258(90)90064-R/pdf)]: Retro. **Surgery only. No adjuvant treatment**.  
  SM < 8 mm have a LR rate of approximately 50%. Give vulvar PORT for SM < 5/**8** mm, LVSI, DOI > 5/**9** mm.

LR is a significant predictor of death, with 2y actuarial survival of 25% following relapse.

There is an approximate 25% shrinkage of tissue on formaldehyde fixed vs. fresh tissue.

* + 135 pts. 1957-1985. 21 vulvar recurrences.
  + All 21 vulvar recurrences have SM < 8 mm on formaldehyde fixed (corresponds to 1 cm in fresh tissue).
  + Factors include: SM < 8 mm, LVSI, DOI > 9mm. Also infiltrative, increasing keratin, >10 mitoses/HPF.
    - LR for SM < 8 mm / ≥ 8 mm of 48→ 0%. LR for SM < 4.8 mm / ≥ 4.8 mm of 57→ 7%.
    - LR for ± LVSI of 12→ 39%.
    - LR for DOI < 2.5 mm of 0%.
    - LR for DOI 2.5-5 mm of 17% (n=6/36).
    - LR for DOI 5.1-7.5 mm of 30% (n=6/20).
    - LR for DOI > 9mm of 39%.
  + SM using 4.8 mm as a cutoff identified 91% of pts who did not have recurrence and 62% who did.
  + LR for close and positive SM ± adjuvant RT of 58→ 16% [[Faul IJROBP '97](https://www.ncbi.nlm.nih.gov/pubmed/9226327)]

* **BWH/DFCI** [[**Viswanathan** Gyn Onc '13]](https://www.sciencedirect.com/science/article/pii/S0090825813007695?via%3Dihub): SM status, radiation dose and LR.   
  SM < 1 cm had nearly 40% local recurrence. Aim to deliver > 54-56 Gy for close margins.

SM ≥ 5 mm is associated with significantly reduced risk of vaginal relapse.

* + 205 pts. Vulvar recurrences in up to SM of 9mm. SM < 5 mm w significant risk of vulvar recurrence.
    - SM+ 10%, over 50% SM < 1 cm (n=116), 33% SM-.
    - Median dose to vulva of 45 Gy for those with recurrence, 50.4 Gy without.
  + LR for ≥ 56 Gy of 20% (n=4/19), LR for ≤ 50.4 Gy of 34% (n=11/32).
  + LR for SM+ / SM < 1 cm / SM- who did not receive vulvar RT of 56→ 37→ 14%.
  + Median time to recurrence 1.5y.
  + Lymph node positivity, stage, and margins predicted for RFS, while LN+ and stage predicted for OS.
  + Magins were only significant for vulvar recurrence on UVA, and were not predictive of OS.

* Grootenhuis [[Gyn Onc '19](https://www.gynecologiconcology-online.net/article/S0090-8258(19)31235-1/abstract)]: Margin status evaluation from [[GROINS-VI](#gapq6vf7kmp7)].   
  LR occurs in approximately 40% of patients within 10y after treatment.

Pathologic tumor free margin distance had no effect on the local recurrence rate.

Patients with dVIN ± LS in the margin have higher local recurrence rates.

* + 287 patients. 2000-2010. MFU nearly 7y.
  + Margin status was not associated with local recurrence on MVA.
  + SM+ for dVIN and LS present with HR 2.76, SM+ for dVIN alone HR 2.14, and FIGO stage II+ HR 1.62.

* **Surgical re-excision for negative SM appears to be a reasonable alternative to RT** [[Bedell Gyn Onc '19](https://www.gynecologiconcology-online.net/article/S0090-8258(19)31272-7/abstract)]
  + 150 pts, of whom 31% (n=47) had close or positive margins. Stage I. Primary surgical management. 1995-2017.
  + 31% of patients with stage I vulvar SqCC had close or positive margins.
  + There was no difference in RFS or OS for patients who received adjuvant surgery or RT for close/SM+.

* **FrancoGyn Vulvar Study** [[Raimond EJS Onc '19](https://www.ejso.com/article/S0748-7983(19)30542-6/fulltext)]: Retro.   
  There was no difference in OS or DFS according to margin status (analyzed at 3, 5 and 8 mm).

Moreover, the benefit of re-excision seems stronger when tumor free margins are positive or very close (< 3 mm).

* + 112 pts. 2005-2012. MFU 2y.
  + 2y LR for SM < 3 mm / 3-8 mm / ≥ 8 mm of 23→ 21→ 35%.
  + Extracapsular lymph node disease appears to be a severe risk factor.
* PNI study [Needs reference]:
  + 5y DFS for ± PNI of 72→ 18%.
  + 5y OS for ± PNI of 75→ 35%.

|  |
| --- |
| **Nodal Rules of thumb**: Palpable nodes have ~50% false positive rate.   * 25% cN0 will be pN+. Clinical exams have a 25% false negative rate. * 25% of the pts w ipsi groin will have contra disease. * 25% groin LN+ will have pelvic LN+ dz. * If the ipsilateral inguinals are negative with full dissection, there is < 3% chance of contralateral nodes. * DOI ≤ 1 mm→ 3 mm→ 5 mm→ >5 mm: < 5→ < 10→ < 25→ 40% (if >2 cm).   + Compared to oral cavity DOI and risk of LN.   + Add LND if DOI >1mm. * Risk of LN involvement for stage I / II / III / IV of 20→ 40→ ~60→ 80-100%. |

## [Lymph Node Management](#_jvy8eyvc333a)

* Superficial inguinofemoral→ deep inguinofemoral (separated by cribriform fascia)→ EI.
  + Cloquet node: Most superior deep inguinal/femoral node.
* Clitoris/urethra→ deep femoral or EI/obturators (**Clitoris = direct drainage to pelvis**).

* **GOG 36** [[Sedlis '87](https://www.sciencedirect.com/science/article/pii/0002937887901323?via%3Dihub), [Homesley Gyn Onc '93](https://www.sciencedirect.com/science/article/pii/S0090825883711273)]: **Radical vulvectomy with bilateral inguinofemoral LND**.   
  There is around 1/4 risk of a positive lymph node in the cN0 groin.

There is around 1/4 risk of lymphedema with bilateral inguinofemoral LND.

There is < 10% risk of contralateral groin metastasis if the ipsilateral groin has been fully resected and is positive.

There is a 3% risk of contralateral groin metastasis if the ipsilateral groin has been fully resected and is negative.

* + 588 pts. 50% ≤ 5 mm thick. 33% ≤ 2 cm.
  + Groin mets ± 2 cm of 19→ 42%, or ≤ 1/2 cm of 18→ 19%.
  + Groin mets ± LVSI of 27→ 75%.
  + Groin mets G1/2/3 of 27→ 36→ 55%.
  + Groin mets age < 64 / 74 / 75+ of 25→ 36→ 46%.
  + **Unilateral lesions: 8% contra groin mets if ipsi groin pN+, 2.5% contra groin if ipsi groin pN0.**
  + cN0 groins were 24% pN+. *25% cN0 will be pN+.*
  + Groin mets by tumor thickness/invasion for ≤ 1/2/3/4/5/5+ mm of 2.6→ 9→ 19→ 31→ 33→ 34%.
    - 3 mm thick tumors have nearly 20% groin involvement.
  + Toxicity: Chronic lymphedema 27%, wound breakdown 49%.
  + For tumors ≤ 5 mm thick, groin LN mets predicted by grade, LVSI, clitoral/perineal location, cN+.
  + For other tumors, grade, cN+, LVSI, older age, thickness predictive. Tumor size and location not.
* Old school recs for LN
  + Inguinals: Lat fem head to 3 cm from midline; 1 cm below upper head of fem and 2.5 cm below ischial tuberosity. [1-2 cm addnl margin important\*]
* **Old dogma that adjuvant RT only needed if < 12 LN on dissection or 2+ LN positive**:
  + **SEER** [[Gyn Onc '06]](https://www.sciencedirect.com/science/article/pii/S009082580600518X?via%3Dihub): 208 pts, single inguinal LN→ 92% vulvectomy **± RT**.   
    Adj RT hasOS benefit for < 12 nodes resected.
    - Median nodes resected = 13. 50/50 got RT.
    - 5y OS 55→ 77% for < 12 nodes. 5y OS ~67→ 77% for > 12 nodes.
    - 5y DSS 61→ 77%.
  + **AGO-CaRE-1** [[JNCI '15]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4356703/): Multi retro. All got at least SLNB.   
    Adjuvant RT has PFS benefit for 2+ LN positive.
    - 1249 pts, 447 N+, 244 adj RT. Most 1-2 nodes. Average nodes harvested = 15 (adequate).
      * Only 40% had RT directed at the groins ± other fields. 13% CCRT.
        + Of those, 50% groins/pelvis, ~25% groins ± vulva.
      * cN0 got at least SLNB, uni if ≤ 2 cm, 1 cm from midline.
    - 3y PFS 35→ 75% and 3y OS 56→ 90% for node negative.
    - 3y PFS 26→ 40% and ~3y OS ~54% for node positive receiving adjuvant groin RT.
      * This only holds true for 2+ nodes, not SS for one node! *But, only 77 pts w one node.*
    - ↑ PFS, trend to OS. 3y PFS for N+/N- 35→ 75% and 3y OS for N+/N- 56→ 90%. PFS w RT for N+ 26→ 40%. Benefit consistent regardless of # nodes, grade, DOI.
  + **Woelber** [IJGC '12]: **All except < 1 cm and < 1 mm DOI got SLNB**.   
    Adjuvant RT is beneficial for 1 LN positive.
    - Retro 157 pts. 49 N+, w nearly half 1 node (n=21). 36 got pelvis/groins RT, 14 of those w 1 node.
      * For 1+ node, 14 (67%) rec'd adj RT, of which half were bc >10 mm or ECE.
    - 2y OS for 0 / 1 / 2 / 2+ nodes of 88→ 60→ 43→ 29%.
      * Subset: Adjuvant RT eliminates differences in OS. Most pronounced in 1 node.
    - Certain pathologic features may be worse: ECE, >50% involvement of lymph nodes.

* **GOG 37** [[Homesley '86](https://www.ncbi.nlm.nih.gov/pubmed/?term=3785783), [Kunos '09](https://www.ncbi.nlm.nih.gov/pubmed/?term=19701032)]: **Groin pN+→** **Ipsi PLND vs. groin/pelvic RT** (no vulvar RT).   
  Study closed early due to the superiority of PORT over ipsilateral PLND.

However, OS benefit was only in the short term for clinically palpable or matted LN, 2+ nodes, or ECE.   
Notes: No vulvar irradiation. Remains controversial to cover vulva... Is surgery enough for vulva?

* + 114 pts. I-IV. RV and sup/deep b/l inguinal LND→ if pN+, ipsi PLND vs. groin/pelvic RT. 50% cN0.
    - RT 40-50 Gy to 3 cm depth - inadequate (groin/obturator/iliac). **MBB to central vulva.**
  + 2y groin recurrence 24→ 5%. **2y OS 54→ 68%**.
  + OS benefit in the short term only for clinically palpable or matted LN, 2+ pN+, or ECE.
    - cN2-3 2y OS 31→ 59%, ≥ 2 inguinal nodes 2y OS 37→ 63%.
  + PLN+ in 28% of dissected patients. Pelvic failure rate ~1.8→ 6.8% [NS].
  + 6y RFS 48→ 59%, 6y CSM 51→ 29%, 6y OS ~42→ 52% [NS]. CSM correlated with inguinal relapse.
    - **6y vulvar recurrence ~8%**, a little greater for PLND than groin/pelvic RT arm.
    - Ratio ≥ 20% ipsi LN+: contra groin LN 50→ 30%, recurrence 58→ 36% and CRD 58→ 33%.
  + Lymphedema ~22→ 16% [NS].

* **GOG 88** [[Stehman IJROBP '92]](https://www.sciencedirect.com/science/article/pii/036030169290699I?via%3Dihub): **cN0→ RV + b/l inguinofemoral LND vs. b/l inguinal RT**.   
   Inferior OS with inguinal RT versus inguinofemoral LND. Study closed early due to groin recurrences in RT arm.

Several follow up trials have demonstrated equivalent RFS in LND vs. RT.  
Issues: 3 cm depth is not enough! Most patients have groin nodes at 5-6 cm depth.

There is a 20% false negative rate with cN0 inguinal lymph nodes.

* + Planned for 400 pts T1-T3. Closed early with 58 pts due to more groin recurrences and worse OS in no IFLND arm.
  + Excluded T1 unless LVSI or DOI > 5 mm. 66% 2-4 cm. Half G2. Half on labia. 20% of surgery arm pN+.
    - RT: 50 Gy Rx to **3 cm** depth with surgery only arm receiving RT if LN+.
      * No CT based planning in this study. Obese pts (50%) have groin nodes at 5-6 cm depth.
  + Groin recurrence 0→ 18%. Therefore, study closed early with only 58 pts. 3y OS 88→ 63%.
* **Washington** [[Koh IJROBP '93](https://www.sciencedirect.com/science/article/pii/036030169390476C?via%3Dihub)]: Depth matters for inguinal coverage. GOG 88 used inadequate energy electrons.
  + 50 pts eval by CT with depth of femoral vessels from 2-18.5 cm (6 cm).
  + 50% of pts in GOG 88 were obese and therefore had deep nodes. In the 5 pts with groin failures on RT only, failures were in regions with < 47 Gy. Three were underdosed by > 30%.

* **Dusenberry** [[IJROBP '94]](https://www.sciencedirect.com/science/article/pii/036030169490393X?via%3Dihub): Retro. **Adjuvant RT w midline block** in N+ vulvar cancer.Vulvar recurrence 50% if using midline block. Much higher than 8% in [[GOG 37](#8jvpsgbv0nv6)]. So, should we treat primary when treating nodes?
  + 27 pts. Stage III/IV with positive lymph nodes.
    - RT: Median dose 45 Gy. All but 1 pt had a midline block.
  + 17 relapsed (63%) with 13 vulvar recurrences (~50%) although unknown [[Heaps](#owjsvsmvfryg)] criteria.
* MDACC [[**Katz** IJROBP '03]](https://www.sciencedirect.com/science/article/pii/S0360301603005911?via%3Dihub): 1992-2014. Evaluation of treatment of inguinal nodes: **± LND ± RT**.
  + 227 pts w treatment of inguinals between 1990-1998. SqCC vulva. 67 with cN+ inguinals.
  + 5y inguinal recurrence 15%.
  + RT arms are significantly more likely than LND alone to have T3-4 tumor, >5 cm tumor, or lymph node involvement, however, INR (involved nodal ratio) was similar for all three groups!
    - PORT with increased INR when time from LND to RT was greater than 50 days.
  + LND only arm with risk of INR greater for tumors >2 cm or poorly differentiated.
  + 33 pts w grossly positive groin nodes. 50% PLN+. Median RT dose to nodes 66 Gy (60-70 Gy).
  + Majority of failures were patients 66 Gy to lymph nodes.

### [Role of SLNB](#_p6thujzfu6i0)

* **GOG 173** [[Levenback JCO '12]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3478573/): Phase II. **cN0 groin→ SLNB→ inguinofemoral LND** regardless of SLN status.  
  SLNB is a reasonable approach, with 8% false negative rate (FNR). Tumors < 4 cm have a 2% FNR.
  + 452 pts to undergo SLNB, 418 (92%) had at least one SLN. Vulvar SqCC, ≥ 1 mm DOI, 2-6 cm tumor.
  + 132 pN+, including 11 (8.3%) FN. Sn 92%, false NPV (1-NPV) 3.7%. If < 4 cm, FNPV < 3%.

* **GROINSS-V** [[JCO '07](http://ascopubs.org/doi/full/10.1200/JCO.2007.14.0566), [Groontenhuis Gyn Onc '16](https://www.sciencedirect.com/science/article/pii/S0090825815301384?via%3Dihub)]: **SLN(+)→ IFLND + Ipsi groin/pelvis RT. SLN(-) → Obs**.  
  Groningen International Study on Sentinel Nodes in Vulvar Cancer.

SLN+ requires further groin treatment irrespective of the size of LN mets. Potential exception = ITC.

There is an approximate 40% rate of local recurrence at 10y. Around 30% of patients will die from their cancer at 10y if they develop a local recurrence. Therefore, do not use a midline block. Treat the vulva!

Pathologic tumor free margin distance had no effect on the local recurrence rate [[2019 analysis](#lnsp2bntimc4)].

Patients with dVIN ± LS in the margin have higher local recurrence rates [[2019 analysis](#lnsp2bntimc4)].

* + - 403 cN0 pts w 623 SLN bx. 127 SLN+, 276 SLN-. T1-T2 < 4 cm with > 1 mm DOI. MFU 8y.
      * Dye + radiotracer. Surgeons needed 10 cases of experience.
      * RT: SLN+ 50 Gy PORT to Groin/Pelvis recommended.
    - **SLN-** Among 259 SLN- unifocal pts, 6 groin LR (**2.3%**), 3y OS 97%.
    - **SLN+**: **Lymphedema** 2→ **25%**, recurrent erysipelas 0.4→ 16%, wound breakdown 12→ 34%, cellulitis 5→ 21%, hospital stay 8→ 14 days.
      * NSLN+ for SLN with ITC / 2 / 5 / ±10 mm with 4→ 11→ 13→ 40→ 60%.

Interpretation: Even 1 mm SLN have > 10% chance of further NSLN.

* + - At MFU of nearly 5y, only 3 of 57 pts (5.2%) had groin recurrence.
    - 10y DSS for SLN(+) / SLN(-) of 65→ 91% with 10y LR 46→ 36%. 5y isolated groin recurrence 8→ 2.5%.
    - 10y DSS for patients without LR / with LR of 90→ 69%.
    - With each progressive recurrence, the incidence of DM increases.

* **GROINSS-V II / GOG 270** [[NCT01500512](https://clinicaltrials.gov/ct2/show/NCT01500512), [Zee SGO '20](https://sgo.confex.com/sgo/2020/meetingapp.cgi/Paper/17185)]: Phase II. **SLN(+)→ Ipsi groin/pelvis RT. SLN(-)→ Obs**.

See [[Future Directions](#_z0vfy1tc4nj6)] for more.

TBL [QS](http://www.quadshotnews.com/2020/04/groin-pains.html): Women with early-stage vulvar cancer with ≤ 0.2 cm sentinel node involvement without ECE can safely forgo full nodal dissection if receiving adjuvant ipsilateral groin radiation.

* + 1,552 pts. 2005-2016. Depth > 1 mm in all, T1B-2N0 < 4 cm. SLNBx in all, 21% positive (n=324).
    - Not encroaching urethra, vagina or anus. CT/MRI required to exclude bulky groin metastases.
  + Interim analysis: 9/45 failures with > 2 mm and 50 Gy, 1/46 failures with < 2 mm and 50 Gy.   
    *Protocol was modified to mandate completion IFLND with adjuvant RT for > 1 mets or or ENE:*
    - SLN < 2 mm, no ECE: 50 Gy to ipsi groin/low pelvis.
    - SLN > 2 mm or ECE: Completion IFLND→ 56 Gy to groin/pelvis if > 1 met or ENE.
  + 2y isolated ipsilateral groin failure for micomets receiving RT to ipsi groin/low pelvis of 1.6% (n=2). Two additional patients had contralateral groin failure.
  + G3 toxicity for ipsi groin RT after SLNB of 4.2%. There were no G4-5 toxicities.

**Neoadjuvant therapy**

Daily RT 45 to 57 Gy with weekly CDDP is reasonable. 5-FU seems to add toxicity without proven benefit.

* Necessary because exenteration has 10% operative mortality and high complication rates.
* Neoadjuvant RT alone: Two studies, Boronow and Hacker demonstrated 42.5% and 50% pCR after moderate doses of RT, such as 45-54 Gy EBRT ± 24 Gy BT, and can downsize tumor in ¾ of patients.
* NAC alone: Bleo, MTX, CCNU response 64%. Retro eval: Bleo > pacli > Cis + 5-FU w response rate of 60/40/20.
* NACCRT heavily influenced by SqCC of anal canal which demonstrated ↑ LC and CFS, particularly w 5-FU/MMC.
  + Roughly speaking, cCR of up to ⅔ and pCR ⅓ (40%) with 5-FU + MMC.
  + Recent GCIG on patterns of care demonstrated differing indications for treatment, treatment fields and use of chemo even though RT doses were similar.
* [**GOG 101** [Moore IJROBP '98]](http://www.redjournal.org/article/S0360-3016(98)00193-X/fulltext): Phase II. **Split course RT BID/CDDP/5-FU→ Surgery**.  
  Planned two week break with lower dose, therefore lower response than [[GOG 205](#m5n52h1hwbif)].

cCR in 48%, pCR in 31% with pCR/cCR ratio of 65%.

* + 73 pts. Unresectable T3/4 with either N0/N1 (2/3) or N2/N3 (1/3), also to avoid more radical surgery.
    - **Split course** 23.8 Gy x2. Cis d1, 5-FU d1-4 w **BID** RT 1.7 Gy on days of chemo, qday otherwise.
    - 20 Gy boost for unresectable or 10-15 Gy boost for microscopically positive margins.
    - N2/N3 covered inguino-femoral lymph nodes, 1.5-2.5 wk break depending on vulvar reaction→ surgical excision of residual primary + bilateral inguinal-femoral LND.
  + **47% cCR**, only 2/71 (3%) had residual unresectable dz - **97% became resectable**! Among 50 pts who would have required exenteration, only 1 needed it and 2 required colostomy. At MFU, 1/3 developed recurrence and 1/2 were alive and NED.
    - 4y OS 55%.
  + Also included 46 pts w unresectable N2/N3 inguinofemoral nodes undergoing LND. 38/40 nodes became resectable (95%) and only one had radical vulvectomy w/o groin LND. LN were pN0 in 41%, only 1 with groin failure. Overall, 20 pts NED and 5 died w/o evidence of disease. LC primary 76%, LC nodal 97%.

* **GOG 205** [[Moore Gyn Onc '12](http://www.gynecologiconcology-online.net/article/S0090-8258(11)00884-5/fulltext)]: Phase II. **57.6/32/CDDP**→ Biopsy or surgical resection at 4-6 weeks.~50% of the entire series had pCR by biopsy although only 70% able to complete tx.

cCR in 64%, pCR in 50% with pCR/cCR ratio of 78%. *20% higher pCR in GOG 205.*

In general, be wary of series who define pCR by biopsy only. True total pCR requires the entire organ to be removed with lymph node dissection, and lymph nodes need to specifically be listed as negative in order for true representation of pCR.

* + 58 pts, unresectable T3/4, Nx.
    - CCRT: CDDP 40 q1w + 57.6/32 (20% ↑ over GOG 101 without planned break).
    - cPR→ resect if possible, otherwise additional CRT up to 65 Gy.
    - cCR→ biopsy→ if neg, observe. If pos, resection or CRT.
  + Only 40 (69%) completing all study treatment. Of these, 37 (**64%** of series) with cCR. Of these, 34 underwent bx and 29 (78%) had "pCR" (50% of the entire series).

* **GOG** **279** [[NCT01595061](https://clinicaltrials.gov/ct2/show/NCT01595061)]: Phase II. **IMRT/Gem/Cis**.   
  See [[Future Directions](#_z0vfy1tc4nj6)] for more.

GOG 279 builds off 205 in that NACCRT with IMRT, increased RT dose, and adding Gem to Cis to improve pCR.

* + Locally advanced vulvar T2-T3, N0-3, not amenable to resection.
    - RT: IMRT 64 Gy to gross disease, 45-50 Gy to groin and pelvis + Cis/Gem→ resection.
    - Goal: pCR 65% of greater. 10 Gy boost for 3+ LN, ECE, or positive margin.
  + If nodes become resectable, stop at 50 Gy and resect disease.
  + Assess 6-8w later with an exam and MRI.
    - If cCR, bx tumor bed to confirm "pCR" (not true pCR as the entire specimen is not removed).
    - If residual, salvage surgery.
  + IMRT to spare femoral heads, small bowels and skin.

## 

## [Toxicity](#_jvy8eyvc333a)

* TD 11/5 femoral neck = 50 Gy.
* Side effects:
  + Skin and vaginal stenosis
  + Early skin rxns (before 35Gy) is usually yeast – give diflucan and keep treating!
  + Sitz baths for prevention of infection during RT
  + Limit femoral head dose!
  + Try for < 40 since these pts are elderly
* Dose constraints:
  + Rectum V45 < 60%. Contour inferior margin 2 cm above the anal verge and sup at sigmoid.
  + Bladder V45 < 35%
  + Femoral heads V30 < 50%, V40 < 35%, V44 < 5%.

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| **This Summary Box was made possible by the ACRO Resident Committee.**  **A more comprehensive collection of resources for all disease sites may be found at** [**http://www.acro.org/**](http://www.acro.org/)  Zaorsky: [[Gyn staging](https://twitter.com/NicholasZaorsky/status/1219773291528884229?s=20)], [[Gyn nodes AP](https://twitter.com/NicholasZaorsky/status/1221823861978693632?s=20), [Gyn nodes Lat](https://twitter.com/NicholasZaorsky/status/1221824276740956162?s=20)], [[Vulvar cancer staging](https://twitter.com/NicholasZaorsky/status/1222649476386578438?s=20)].  ARRO: [[Operable Vulvar Cancer](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/Vulvar.pdf)]  **Contouring**   * Female Normal Pelvis Atlas [[RTOG Contouring Atlases](https://www.nrgoncology.org/ciro-gynecologic)] * Consensus Recommendations for RT Contouring and Treatment of Vulvar Carcinoma [[Gaffney IJROBP '16](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5189987/)] * Vulvar Cancer Atlas [[RTOG Contouring Atlases](https://www.rtog.org/CoreLab/ContouringAtlases.aspx)]   **Review Articles**   * Gynecologic Malignancies [[Suneja and Viswanathan Heme/Onc Clin N. Amer '20](https://www.sciencedirect.com/science/article/pii/S088985881930111X?via%3Dihub)] [RoR](#_t4kv4aacj9qi) * UK Definition of Margins in Vulvar Cancer [[Kortekaas IJ Gyn Path '19](https://journals.lww.com/intjgynpathology/Abstract/publishahead/Practical_Guidance_for_Measuring_and_Reporting.99077.aspx)] [RoR](#_dx362qpsjtbt)   **Society Guidelines**   * FIGO Report: Cancer of the Vulva [[Rogers and Cuello, IJGO '18](https://www.ncbi.nlm.nih.gov/pubmed/30306583)]   **Relevant Accessible Radiation Protocols**   * GOG 205 (methods) [[Moore Gyn Onc '12](http://www.gynecologiconcology-online.net/article/S0090-8258(11)00884-5/fulltext)]: Phase II. Locally advanced Vulvar. 57.6/32/CDDP. [RoR](#m5n52h1hwbif) * Washington University IMRT technique (methods) [[Rao ARO '17](https://www.ncbi.nlm.nih.gov/pubmed/28740926)]: Retro. * Pittsburgh vulvar IMRT technique (methods) [[Beriwal IJROBP '06](https://www.ncbi.nlm.nih.gov/pubmed/16442238)] |

## 

## [Treatment Planning](#_jvy8eyvc333a)

See the Summary Box above.

* CT simulation:
  + Oral contrast 30-60 min prior to scan.
  + If IMRT, perform simulation with a full and empty bladder.
  + Supine in the frog leg immobilized in a vac-lock to decrease inguinal skin fold.
  + Wire the tumor, scar, palpable nodes, and place a BB at the vaginal introitus.
  + Fiducials may be used to identify close or postoperative margin sites for a boost.
  + May place 5 mm bolus over operative bed and TLD measurements the first three days.
    - If you can see a tumor, you need bolus.
    - If you cannot see a tumor, it will likely auto-bolus (but still check TLDs).
* **Historic 3D**: Use wide AP and narrow PA, electrons supplement dose to inguinal region. Caution, as electron depth must be adequate and hot and cold spots are of concern. IMRT is more commonly used today. [RoR](#_xj0a5wng2iup)
  + **Wide AP field** (6 MV)
    - Sup: Mid SI joint for negative nodes. L5/S1 if + inguinal nodes, L4/5 if + pelvic nodes.
    - Inf: 3 cm below tumor.
    - Lat: Lat edge of greater trochanter or 2 cm on inguinal node.
  + **Narrow PA field** (18 MV): Same AP/PA but Lat 1.5 from pelvic brim to protect femoral heads.
  + **Electron supplementation of the inguinal nodes** (since PA field not contributing) if patient anatomy allows, and most inguinal nodes are 5-6 cm deep. Alternatively, you can use angled photon field aka monoisocentric modified segmental boost technique (Yale).
  + See Methods from [[GOG 205](#m5n52h1hwbif)].
    - Superior border: Inferior SI joint.
    - Inferior border: 2 cm below most inferior portion of the primary vulvar tumor.
    - Lateral border: Include groin nodes medial to ASIS. Patients with negative groin nodes were allowed to receive RT to only the primary tumor, with or without groin RT at discretion.
    - After 45 Gy, radiation fields were reduced from initial wide coverage to encompass only the primary vulvar tumor and any other sites of gross residual + 2 cm.
* **Nodal volumes**: Elective nodal: Bilateral inguinal, obturator, internal/external iliac.
  + No recurrences seen posterior or lateral to the femoral vessels, so no margin necessary there.
  + **Inguinal node anatomic boundaries** [[Kim PRO '12]](https://www.practicalradonc.org/article/S1879-8500(11)00381-X/fulltext): Anteromedial and anterior, not posterior or lateral.
    - 22 pts w 52 total positive inguinal nodes. Positive if bx, PET/CT avid or ≥ 1.5 cm of CT. Distance measured from the center of node to nearest femoral vessel.
    - Corresponding anatomic boundaries:
      * Lateral: Lateral inguinofemoral vessels or medial aspect of the iliopsoas.
      * **Medial**: lateral aspect of adductor longus or medial aspect of pectineus.
        + To pectineus muscle or **2.5-3 cm medially from vessels** per NCCN.
      * Posterior: iliopsoas muscle laterally and anterior aspect of the pectineus.
        + Posterior border is anterior vastus medialis per NCCN
      * **Anterior**: **Anterior edge of the sartorius muscle**. This is the most anterior muscle on the lateral inguinofemoral border.
      * **Inferior**: **Top of lesser trochanter of femur**.
    - Relative to the location of femoral vessels, nodes were 52% anteromedial, 21.2% anterior, 11.5% anterolateral, 9.6% medial, 1.9% posterior and 3.9% lateral.
    - To cover ≥ 90% disease, margins needed around the nearest femoral vessel were 3.5cm anteromedial, 2.3 cm anterior, 2.5 cm anterolateral, 2.2 cm medial, 0.9 cm posterior, 3.2 cm lateral.
    - Boards: 2.5-3 cm medially from vessels.
* Nodal coverage:
  + Sup border no lower than bottom of SI, no higher than L4/L5 unless PLN+.
  + If PLNs are involved, the upper border may be raised to **5 cm** above the most cephalad-positive node per NCCN.
  + Inferolateral border parallel to the inguinal crease, inferior to encompass inguinofemoral nodal bed to the intertrochanteric line of the femur or 1.5-2 cm distal to saphenofemoral junction.
  + The inferior vulvar border will be lower, at least 2 cm below most distal part of the vulva.

### IMRT

Consensus Recommendations for RT Contouring and Treatment of Vulvar Carcinoma [[Gaffney IJROBP '16](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5189987/)]

Potential disadvantages: steep learning curve, controversies about target delineation, daily setup.

* Replanning should be considered for vulvar edema or tumor shrinkage.
* Preoperative IMRT to spare femoral heads, small bowel, and skin outside PTV. Similar post op complication rates as primary surgery without neoadjuvant treatment [[Beriwal Gyn Onc '08](https://www.sciencedirect.com/science/article/pii/S0090825807008499?via%3Dihub)].
* **Locally advanced**: Unresectable 66-70 Gy with concurrent CDDP q1w ± 5-FU. *Chemo extrapolated from cervix data.*
* **RT to primary** (based on [[Heaps](#owjsvsmvfryg)] surgical review): Give vulvar PORT for SM < 5/8 mm, LVSI, or DOI > 9 mm.
  + Always treat primary - no central blocking. 50% recurrence in [[Dusenberry](#79d8ahvot8)] (27 pts). 8% in [[GOG 37](#8jvpsgbv0nv6)].
  + According to 2019 data, there is an approximate 40% rate of local recurrence at 10y, with no relation to SM clearance. Around 30% of patients will die from their cancer at 10y if they develop a local recurrence. Therefore, do not use a midline block. Treat the vulva! [[GROINSS-V](#gapq6vf7kmp7)]
  + Pathologic tumor free margin distance had no effect on the local recurrence rate [[2019 analysis](#lnsp2bntimc4)].
  + Patients with dVIN ± LS in the margin have higher local recurrence rates [[2019 analysis](#lnsp2bntimc4)].
  + No PORT at SM 8 mm (8mm fixed formaldehyde, 1 cm gross), but some use SM 5 mm.
    - Can treat primary alone if only indication is close/positive SM and full LND is negative.
    - If close/positive margin is only indication, re-resect.
    - Surgery seems most beneficial for SM+ or very close SM (< 3 mm) [[Franco Gyn '19](#vz1hugs0vy1n)]
    - Treat to 56 Gy with platinum based chemotherapy if SM < 5 mm.
  + GTVp\_54-70 (treat to at least 56 Gy). [[GOG 279](#obi3l3lyiz4c)] is treating the primary and nodes > 2 cm to 64-68 Gy.
  + CTVp\_45-50.4 = GTV, entire vulva and + **1 cm to areas extending outside of vulva**.
    - Include rim of muscle if involved.
    - In general, **for invasion to structures, add 2 cm except vagina which gets at least 3 cm** added.
      * Add 3 cm to vaginal involvement vs entire vagina (if LVSI).
      * Add 2 cm on anorectal, clitoral, urethral or bladder involvement.
  + PTVp = CTV + 0.7-1 cm. Consider 2 cm PTV margins in cases of edema and variability during treatment.
* **PORT**

TL;DR consider 56 Gy for margins < 1.0 cm, 63 Gy if SM+, and 65-70 Gy for gross disease.

* + CTVp\_45-50.4: CTV covers the entire **operative bed + 2 cm** around close/positive margin.
* **RT to LNs**: 1) SLN+ and NFT, irrespective to size of SLN mets; 2) Consider omission if < 5mm LN, no ECE, and fully dissected groin (>9 nodes, medial femoral nodes); 3) >1 LN positive, although in practice some treat any positive node due to prognostic implications of failure; and 4) imaging and FNA/biopsy of suspicious nodes.
  + GTVn\_60-70 Gy for gross residual.
  + CTVn: Treat symmetrically to 45-50 Gy if microscopic, 50-56 Gy if macro and no ECE, 60-66 Gy with ECE.
  + Nodal dissection or SLN-, give 45/25.
  + 1-2 nodes are positive on dissection, give 50/25.
  + 3+ nodes or ECE on dissection, give 60/30.
    - Involved nodal beds (and its contralateral counterpart).
    - Include inguinal nodes from top of pubic rami down to bottom of lesser trochanter.
    - Distal vagina: inguino fem, obturator, internal/external iliac.
    - Posterior proximal vagina: presacral.
    - Anus: inguino fem, obturator, I/E iliac, perirectal/mesorectal, presacral.
    - CTV should not come within 3 mm of skin surface in the absence of skin involvement.
    - Always treat bilateral inguinals unless bilateral dissection is all negative.
  + PTVn: CTV + 0.7-1 cm.

## 

## [Follow up](#_jvy8eyvc333a)

* Washington University IMRT technique [[Rao ARO '17](https://www.ncbi.nlm.nih.gov/pubmed/28740926)]: Retro.

Durable LRC after definitive IMRT remains challenging, and several refinements to our technique is suggested.

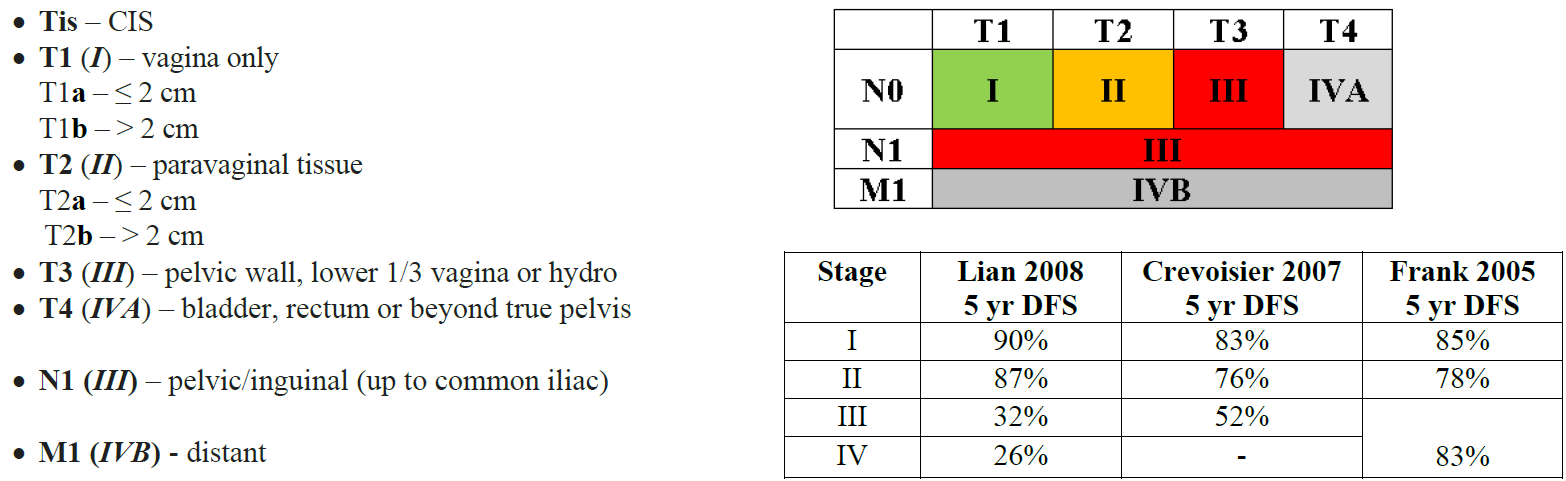
* + 39 patients. 21 PORT, 5 preop, 13 definitive IMRT. Brachy in 8 pts. CCRT 14 pts. 2005-2015. MFU nearly 3y.
  + Median pre/post op IMRT dose of 50.4 Gy.
  + Median definitive IMRT/BT dose of 70 Gy.
  + 3y LRC / OS for PORT of 89→ 67%.
  + 3y LRC / OS for definitive IMRT of 42→ 49%.
  + 3y cCR / pCR for IMRT of 69→ 44%.
  + 3y inguinal recurrence of 7%.
  + No acute G3-4 heme, GI or GU toxicities.
  + No late G3-4 GI or GU toxicities.
* 5y OS confined (no nodes) 86%, regional nodes 55%, pelvic nodes 45%, heme mets 20%.
  + Overall, 23% have recurrence at 5y. After recurrence, death at 1y is 60% and 3y is 70%.
* Predominal failure pattern is LOCAL.
* H&P every 3-6 months for 2 years, then every 6-12 months for 3-5 years.
* CXR q 5y.
* Follow up imaging based on symptoms or atypical exam findings.
* Cervical/vaginal cytology as indicated.

## 

## [Future Directions](#_jvy8eyvc333a)

* See [[**GROINSS-V II / GOG 270**](#fb8a7u304m1p)] which is evaluating the utility of completion IFLND versus adjuvant RT for women with early-stage vulvar cancer with a single positive lymph node after SLNB.
* See [[**GOG 279**](#obi3l3lyiz4c)] which is evaluating definitive CCRT/Gem/Cis to 64 Gy with reservation of surgery for patients with less than cCR or conversion of resectability after 50 Gy.
  + Locally advanced vulvar T2-T3, N0-3, not amenable to resection.
  + Assess 6-8w later with an exam and MRI.
  + If cCR, bx tumor bed to confirm "pCR" (not true pCR as the entire specimen is not removed).
  + If residual, salvage surgery.

# [Vaginal Cancer](#_nz4p8uik7qem)



III - pelvic wall, N+

Tumors that invade the vulva should be considered as vulvar cancer, while tumors invading the cervix should be considered cervical cancer.

Zaorsky: [[Gyn staging](https://twitter.com/NicholasZaorsky/status/1219773291528884229?s=20)], [[Gyn nodes AP](https://twitter.com/NicholasZaorsky/status/1221823861978693632?s=20), [Gyn nodes Lat](https://twitter.com/NicholasZaorsky/status/1221824276740956162?s=20)], [[Vulvar cancer staging](https://twitter.com/NicholasZaorsky/status/1222649476386578438?s=20)].

ARRO: [[Vaginal Cancer](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/VaginalCancer.pdf)]

eContour [[vaginal](https://econtour.org/cases/51)]

FIGO Report: Cancer of the Vagina [[Adams and Cuello IJGO '18](https://www.ncbi.nlm.nih.gov/pubmed/30306589)]

* Around 3% of all gyn cancers, ~4k a year (half of anal).
  + 70% of cases are in women ≥ 60y.
* Most evidence single institution, mgmt usually extrapolated from clinical experience and data from cervical/anal cancer.
* Standard of care for Stage I disease is surgery, but surgeries are typically extensive in order to obtain a tumor-free margin. This leads to severe morbidity in many cases.
* 50% of women diagnosed with primary vaginal carcinoma previously had TAH for benign, premalignant or malignant dz.
  + It is ok to continue paps in elderly women who underwent TAH for cervical cancer.
* Cancer free period of at least 5y = new diagnosis.
* **Pathology**
  + SqCC 90%, 5% melanoma, 5% AC. Also, sarcoma, lymphoma, clear cell adenocarcinoma.
    - Adenocarcinoma is typically considered to have a worse prognosis.
    - Clear cell AC a/w diethylstilbestrol. Younger age of onset ~19y.
    - Vaginal sarcoma
      * Adult: LMS
      * Children <6y: Embryonal RMS (sarcoma botryoides).
  + ~80% SqCC are associated with HPV.
  + Need to treat VAIN, as it progresses to invasive disease. 60% of VAIN is multifocal.
* **RF**: Number of partners, early intercourse, current smoking.
* **Sx**: Bleeding, discharge, pruritus, dyspareunia. Pain or changes in bladder or bowel habits.
* 50% located in the upper vagina. ~80% are metastatic from somewhere else.
  + Most lesions are located in the posterior wall, superior 1/3 of vagina.
* **Workup**
  + **H&P**: R/o prior Gyn malignancy. On the exam, be sure to rotate the speculum to see the posterior wall.
  + CXR, EUA, bimanual/rectovaginal, cystoscopy and/or proctoscopy, IVP
  + Remember to colpo w biopsies of cervix/vulva to rule out primary cervical or vulvar cancer.
    - If it touches cervix or vulva, then it is cervical or vulvar.
    - Colposcopy: Acetic acid (lesion appears white) and Lugol (stains normal mucosa) = Schiller's test.
  + MRI encouraged - T2 hyperintense. Consider placement of cylinder for RT planning.
    - Consider instillation of vaginal gel in order to separate the vaginal walls.
    - EBRT is preferred due to inaccurate assessment of DOI by MRI.
  + PET/CT may change patient management
* **Nodes**
  + Upper 1/3 to EI and pAO.
  + Middle 1/3 to II and CI.
  + Distal 1/3 to superficial inguinal, femoral, perirectal.
  + Nodal involvement from surgical series:
    - 6-14% stage I, 26-32% stage II (think: "Rule of 15s" as for cervical) but III 75%, IV 85%.
* **Management**
  + **VIS/VAIN**: WLE, topical 5-FU, laser vaporization.
  + **I**: Definitive RT alone (EBRT + BT) - very select cases may do surgery small, superficial, resectable locations.
  + **II+**: Definitive CRT. ERBT + BT. Concurrent CDDP 40 mg qw x6 - concurrent data extrapolated from cervix.
  + If after EBRT, disease is < 5 mm deep by exam and MRI, can do VC alone.
    - Otherwise do IS (Syed).
  + **IVA**: brachy can cause fistula! Consider exenteration.
* **Early stage - Vaginal and/or paravaginal**
  + Surgical options are morbid:
    - Radical upper vaginectomy + LND ± Rad Hys.
      * Upper vaginal lesions = conservative excision or upper vaginectomy.
    - Exenteration.
      * Distal vaginal lesions include total excision and inguinal LND.
  + NCDB 5y OS 63→ 90% favoring surgery over definitive RT, but likely biased.
  + SEER demonstrated increased risk of mortality in stage I with RT vs surgery, adjusted HR 1.5.
    - NS difference in stage II, but more extensive surgeries like total vaginectomy or exenteration required.
  + NAC with cis/paclitaxel with cCR 27% at time of RV and PLND.
  + Adjuvant RT after R1/2 or N+ with 5y OS 100% for stage I and 40-69% for stage II.
* **Locally advanced - pelvic sidewall or nodal involvement**
  + Definitive RT is choice!
    - CSS 23-58% for stage III and 0-25% for stage IV.
      * Pelvic control of 62-71% and 12-30%, respectively.
  + CCRT:
    - Based on locally advanced cervical cancer, but generally recommend CCRT for tumors >4 cm or stage III.
    - 5-FU ± CDDP or MMC (like anal).
* [**MDACC** [Frank IJROBP '05]](https://www.sciencedirect.com/science/article/pii/S0360301604026847?via%3Dihub): Retro. **Definitive RT** (~66% EBRT/BT, ~30% EBRT, ~5% BT alone).   
  Definitive RT leads to favorable outcomes for vaginal cancer. 5y pelvic control/ DSS >80% if no nodes/pelvic sidewall!
  + 193 pts vaginal SqCC. 76% stage I-II, 78% upper 2/3 vagina. 9% resected. 22% of the advanced stage got chemo.
  + 5y pelvic control for stage I / II / III-IVA of 86→ 84→ 71%. Pelvic control >80% if no nodes/pelvic sidewall!
    - 5y pelvic control for ± 4 cm 85→ 75%.
  + 5y vaginal control: Stage I-II 91%, stage III-IVA 83%.Vaginal control >90% if no nodes/pelvic sidewall!
    - 5y vaginal control for BT of 88%.
  + 5y CSS for stage I / II / III-IVA of 85→ 78→ 58%.
    - 5y CSS for ± 4 cm 82→ 60%.
* **NCDB** [[Rajagopalan Gyn Onc '14]](https://www.sciencedirect.com/science/article/pii/S0090825814013456?via%3Dihub): **Definitive RT vs. CCRT**. *CCRT w 6% 5y OS improvement over RT alone.*
  + NCDB report, 1998-2011, comparison of patients of all stages (I, II, III, IV) receiving RT alone vs CCRT.
  + Stage I MS 83→ 109 mo.
  + Stage II MS 42→ 86 mo.
  + Stage III MS 20→ 43 mo.
  + Stage IV MS 9→ 19 mo.
* **SEER** [[Orton Gyn Onc '16]](https://www.gynecologiconcology-online.net/article/S0090-8258(16)30068-3/fulltext): **EBRT ± BT**. *BT decreased the rate of death by 20% for all stages.*
  + 2,517 pts. 1988-2011. 75% SqCC.
  + All stages with decreased rate of death by 20%.
  + MS 3.6→ 6.1y.
  + >5 cm tumors benefit most w BT.

## 

## [Toxicity](#_ngxza69hnb07)

* Vaginal stenosis/fibrosis (~50%), cystitis (~50%), proctitis (~40%), rectovaginal/vesicovaginal fistula (<5%), vaginal necrosis (<5-15%), lymphedema, urethral stricture (rare).

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## 

## [Treatment Planning](#_ngxza69hnb07)

See Summary Box above.

* Cover external iliacs (L5/S1) if no nodes. Inferiorly cover the whole vagina.
* **ENI**: EI, II, Obturators.
  + If superior half of posterior vaginal wall, cover presacrals and perirectals
  + If inferior half of the posterior vaginal wall, cover inguinals.
* CTV = GTV + 1-2 cm.
* IMRT: Vaginal apex can be displaced by 1.5-2cm in AP direction with organ filling.
* **Dose**
  + 45 Gy AP-PA or 4-field.
  + Boost sidewall, parametria or nodes to 55-66 Gy - favor 60 Gy.
  + Boost primary to 64-70 Gy (Only give 70 EBRT instead of Syed if involving rectovaginal septum/bladder).
* **ABS Guidelines for interstitial brachytherapy for vaginal cancer** [[Beriwal BT ‘12](https://www.ncbi.nlm.nih.gov/pubmed/22265440)]
  + Patients with bulky disease (approximately > 0.5cm thick) should be considered for treatment with interstitial brachytherapy.
* **Clinical evaluation of ABS Consensus Guidelines for Bulky Vaginal Masses** [[Murofushi IJGC ‘18](https://www.ncbi.nlm.nih.gov/pubmed/30044320)]  
  IS-BT is favored over IC-BT for vaginal tumor thickness > 0.5 mm to maintain bladder and/or rectum D2cc.
  + 21 pts. 5y LC 90%.
* **MRI-based IS BT for vaginal tumors** [[Leung BT '19](https://www.ncbi.nlm.nih.gov/pubmed/31230941)]: Consensus concepts to define targets.
  + Highest contouring variability appears to be seen with small residual at BT.
  + Contouring is more consistent on pre-BT MRI.
  + Consensus definitions of CTVHR and CTVIR defined.
* **Definitive RT with IGABT for primary vaginal cancer** [[Westerveld Lanc Onc '20](https://www.ncbi.nlm.nih.gov/pubmed/32135119)]:
  + Much discussion is extrapolated from cervical cancer data.
  + Aim for a prescription EQD2 of at least 80 Gy, but may extrapolate to higher doses from cervical cancer data.
  + Send the patient to a high volume center.
  + Place markers at the time of diagnosis to assist with marking the extent of mucosal spread.
* **Brachytherapy**

ABS Task Group Report [[Albuquerque BT '19](https://www.sciencedirect.com/science/article/pii/S1538472118306305?via%3Dihub)] Compendium of fractionation schedules for Gynecologic HDR BT. [RoR](#_qxjzzedoyoxn)

See Table 8 for vaginal interstitial brachytherapy HDR fractionation schemes.

* + Be sure to place vaginal wall fiducials to delineate distal, proximal and lateral extent of disease.
  + One week prior to insertion, do CT/MRI sim w template in place.
  + EBRT 45 Gy + BT boost 25-35 Gy.
  + HDR boost after 45 Gy EBRT: 6-7 Gy x 3 (~30 Gy LDR equivalent).
  + Consider the whole vagina to 60 Gy, and conedown to the tumor for final boost.
  + Recommend treatment delivery within 8-9 weeks and transfusions needed to maintain hgb >10-11.
  + Give from 70-80 Gy. 85 Gy if large bulky remains.
  + **Intracavitary**: Only if < 5mm thick. Give full vagina 60-65 Gy. Boost tumor additional 10-20 Gy.
    - May be done w single/multi channel, or partially shielded vaginal cylinder applicators.
  + **Interstitial**: For >5 mm gross disease thickness.
    - Syed applicator, consider referral to tx center with specialist/expertise.
  + **Syed**: Single insertion; 5 Gy x 5 fraction BID (EQD2 75-80)
* Syed Brachytherapy technique
  + In OR, anesthesia. **Dorsal lithotomy**.
  + **EUA**, bimanual noting residual nodularity, cervix size, and size of fornices.
  + Rotate **speculum** 90 degrees to see the posterior wall.
  + Place **foley**, balloon filled w 7cc 30% renografin, empty bladder.
  + Place the obturatorin vagina.
  + Put **stitch through the apex** of vagina and feed through the middle of the obturator and tie to Syed to prevent displacement of Syed when pts legs come down.
  + **Insert needles** with flexiguide catheters in a template with 1 cm concentric circles to encompass the pretreatment palpable lesion, pathologic involvement of the uterus, disease on staging CT, and routinely the parametria.
  + **Suture template** to perineum.
  + Insert rectal tube.
  + CT simulation for treatment planning.
  + Dose distributions should be designed to achieve tumor dose uniformity and bladder and rectal maximum doses below 75% and 65% of the tumor dose.
  + Tumor dose calculated so that the 100% isodose distributions contiguously included all of the catheters with a 5mm to 1 cm margin. (ie finding the isodose line that doesn’t break up and weighing tumor and nl tissues)
  + Load the needles to treat the dz w a 1-2 cm margin.

## 

## [Follow up](#_ngxza69hnb07)

* 5y DFS 80% for stage I/II, 60% for stage III/IVA (Based on RT alone data from MDACC study above).
* Local failure is very similar to cervix. Of those that fail, ~75% fail locally.
* If asymptomatic, first 2y q3mo, then next 3y q6mo, then annually.
* Cytology and imaging as indicated.

## [Future Directions](#_ngxza69hnb07)

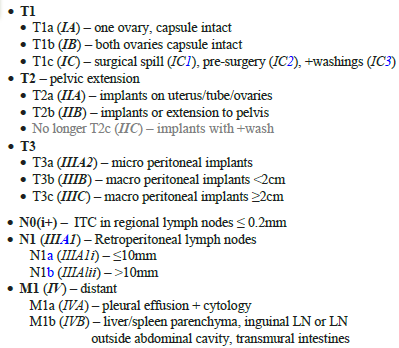
See NCTN Trial Portfolios by Disease Site: [[Gyn](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_GYNE_Trials.pdf)]

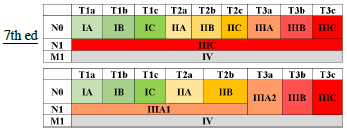
* **NRG-GY006** [[NCT02466971](https://clinicaltrials.gov/ct2/show/NCT02466971)]: Phase II. Advanced stage cervical and vaginal cancer.

See [[Future Directions](#_xgw4qyr3grr8)] in the Cervical cancer section.

* + CCRT ± Triapine (new anti-cancer drug).

# [Ovarian Cancer & Fallopian tube Cancer](#_nz4p8uik7qem)





I - Ovaries.

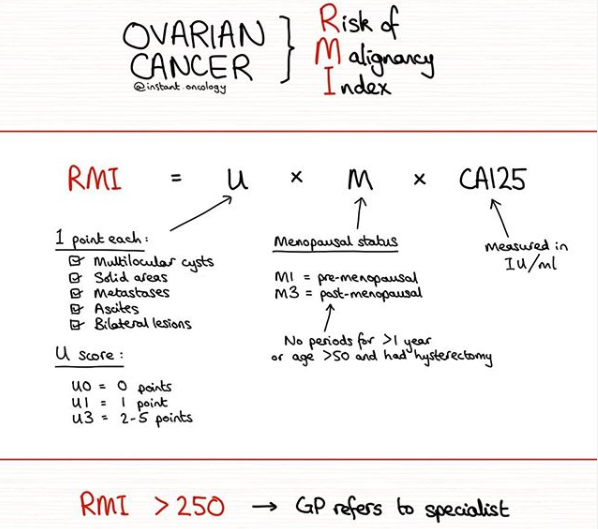
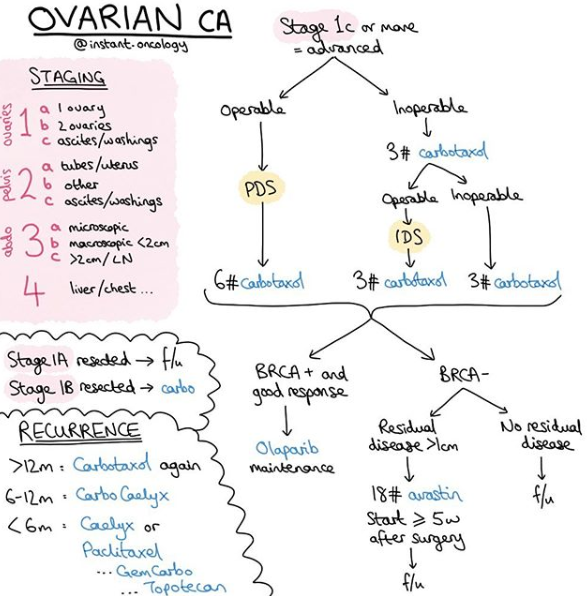
II - Pelvis.

III - Peritoneal.

IV - Mets.

See [[SGO Guidelines]](https://www.sgo.org/clinical-practice/guidelines/)

|  |
| --- |
| [**ASCO Guideline: Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer**](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/gynecologic-cancer#/142631) *Konstantinopoulos, Jan 27, 2020*   * All women with epithelial ovarian cancer should have germline genetic testing for BRCA1/2 and other ovarian cancer susceptibility genes. * Women with clear cell, endometrioid, or mucinous ovarian cancer should be offered somatic testing for dMMR. * First or second degree blood relatives of patients with ovarian cancer and a known germline pathogenic cancer gene variant should be offered individualized genetic risk evaluation, counseling, and genetic testing. * Variations of unknown significance (VUS) should not influence clinical decisions. |

[](https://www.instagram.com/p/B_7ST1SA3-b/?utm_source=ig_web_copy_link)[](https://www.instagram.com/p/B7rXJdIJz2e/?utm_source=ig_web_copy_link)

* 22k new cases and 14k deaths in 2016.
* 5th leading cause of cancer death in women; leading cause of gyn cancer death.
* Average lifetime risk 1/70, median age 63y.
* 75% present with stage III or IV disease or involvement of lymph nodes.
* **Pathology**: 85% epithelial, 10% germ cell, 5% sex cord stromal.
  + Epithelial types: Serous 50%, endometrioid 20%, mucinous 10%, clear cell 10%, transitional, mixed epithelial and undifferentiated.
* **Risk Factors**: family hx, nulliparity, first parity >35y, infertility, early menarche, late menopause, ovulation-inducing drugs, HRT, obesity, endometriosis, smoking.
  + Strongest RF is family history (20% familial), but only 5-10% from known genetic disposition. Lifetime risk 1.8%, one first degree relative 5%, two first degree relatives 25-50%.
  + **Familial** occurs earlier and has a more indolent course than sporadic.
    - **BRCA1** (45% lifetime risk), **BRCA2** (25% lifetime risk), **HNPCC**, **Peutz-Jager**.
* **Workup**: CA-125, AFP/hCG, CEA.
  + If < 35-40y, AFP and β hCG to rule out germ cell tumors.
  + TVUS, CT/MRI.
* Chemo-resistant non-serous histologies may benefit from adjuvant WART, but not yet prospectively evaluated.
* 90% of recurrences occur within 5 years. 85% of relapses are intra-abdominal (local failure most common).
* **Italy** [[Chiara AJCO '94](https://www.ncbi.nlm.nih.gov/pubmed/8311013)]: **CDDP/Cyclophosphamide vs. WART** (43.2 Gy to pelvis, 30.2 Gy upper abdomen).

There is a trend to worsened OS and RFS with WART. Critique: RT technique is outdated.

* + 70 pts. FIGO stage I-II.
  + No difference in 5y RFS or OS.
  + 5y OS 71→ 53% (p=0.16).
  + 5y RFS 74→ 50% (p=0.07).
  + Chemo toxicity: G3 emesis 71%.
  + WART toxicity: G2-4 diarrhea 28%, severe enteritis (n=2).
* **IFRT for locoregionally recurrent ovarian cancer** [[Brown, Gyn Onc '13]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4308098/): Retro.   
  Definitive IFRT can yield excellent local control, protracted DFS in select pts.
  + 102 epithelial ovarian cancer pts treated with definitive IFRT directed to localized nodal and extranodal recurrences.
  + 5 yr OS and PFS were 40% and 24%. 35% were NED at a median of 38 mo after IFRT. 8 clear cell patients had higher 5-yr OS and PFS (88% and 75%).
* **MITO RT1 Study**: MITO, AIRO GYN, MaNGO [[Macchia Oncologist '20](https://www.ncbi.nlm.nih.gov/pubmed/32043791)]: Retro. SBRT for oligometastatic ovarian cancer.
  + Patients aged < 60y, PTV < 18 cc, lymph node disease, and BED10 > 70 Gy were associated with a higher chance of complete response. Achievement of CR and total dose > 25 Gy were associated with better LC rate.
* **Prospective study** [[Lou JAMA Onc '19](https://jamanetwork.com/journals/jamaoncology/fullarticle/2735099#full-text-tab)]: Prospective observational. **Tumor stroma proportion ≥ 50%**.  
  **Only 15-30% of pts are primary plt-resistant**. **Tumor stroma is an easy tell for platinum resistance**.  
  TBL [QS](http://www.quadshotnews.com/2019/06/the-real-mvp.html): Reporting tumor-stroma proportion on simple H&E eval of ovarian cancer may be a cheap and effective biomarker of platinum resistance.
  + 24 women with newly diagnosed ovarian carcinoma enrolled prospectively.
  + Of 5 women who recurred within 6 months of platinum chemo, 4 (80%) had high tumor-stroma proportion.
  + Conversely, only 5/19 (26%) of those who did not experience early recurrence had a high tumor stroma proportion.

* **GOG 218** [[Tewari JCO '19](https://ascopubs.org/doi/full/10.1200/JCO.19.01009)]: **Carbo/Taxol q3w x6c ± concurrent ± maintenance Bevacizumab**.  
  TBL QS: You’re still never wrong in GYN tumor board with an answer of carbo/Taxol, the real MVP since circa 2000.

Carboplatin and paclitaxel q3w should be standard over q1w chemotherapy per the ICON8 trial [[Clamp Lancet '19](https://www.ncbi.nlm.nih.gov/pubmed/31791688)].

* + 1800 pts with incompletely resected Stage III-IV ovarian cancer. MFU 8.5y.
  + MS ~42 mo, although for stage IV maintenance and concurrent bev improved MS 33→ 44 mo.
* **LION** [[Harter NEJM '19](https://www.nejm.org/doi/pdf/10.1056/NEJMoa1808424)]: **Macroscopic CR ± PLN and pAO LND**.

Lymphadenectomy did not provide a survival benefit despite positive nodes in over half of patients.

* + 647 patients. 80% present with lymph node metastases. Stage IIB-IV with normal appearing lymph nodes.
  + MPFS ~25 mo.
  + MS ~ 5.5y.
  + Serious postoperative complications 7→ 12%. 60 day mortality 1→ 3%.
* **GOG 213** [[Coleman NEJM '19](http://www.quadshotnews.com/2019/11/zero-help.html)]: **Platinum-based chemotherapy ± R0/1 of oligometastases**.

TBL [QS](http://www.quadshotnews.com/2019/11/zero-help.html): Having 0 resection is better than having an R0 resection for recurrent ovarian cancer.

* + 485 pts. One previous therapy, then platinum-free interval of 6+ mo. MFU 4y.
    - Adjuvant CarboP or gem-carbo and bevacizumab at discretion. Concurrent and adjuvant bev in 87%.
  + Complete gross resection was achieved in 2/3 of patients assigned to surgery who underwent the procedure.
  + MS for no surgery / surgery of 65→ 51 mo.
  + Surgical morbidity at 30 days of 9%.
* **DESKTOP III/ENGOT-ov20** [[Du Bois ASCO '20](https://meetinglibrary.asco.org/record/185438/abstract)]: Phase III. **Recurrent ovarian cancer→ ± 2nd cytoreductive surgery**.

Patients who are highly likely to achieve R0 resections may have a survival benefit with 2nd cytoreductive surgery.

* + 407 pts. 2010-2014. Required ECOG 0, ascites < 0.5L, and R0 at initial surgery. PFI ≥ 6 mo.
    - PFI exceeded 12 mo in 75% of patients. *These are highly selected patients!*
  + CR was achieved in 75%, with almost 90% in both arms receiving Plt-containing second line chemo.
  + MS 46→ 54 mo. MTT first subsequent therapy of 14→ 18 mo.
  + MS among R0 resections of 46→ 61 mo. R1+ resections with MS of 29 mo.
* **GOG 172** [[Armstrong NEJM '06](https://www.ncbi.nlm.nih.gov/pubmed/16394300)]: **IV vs. Intraperitoneal (IP) Cisplatin and Paclitaxel**.

Although reduced QoL and toxicity are observed with IP chemo, MPFS and OS may be improved.

* + 429 pts. Optimally debulked stage III ovarian carcinoma.
  + MPFS 18→ 28 mo.
  + MS 50→ 66 mo.
* **Dose-dense early postoperative intraperitoneal chemotherapy** [[Shi BJC '19](https://www.ncbi.nlm.nih.gov/pubmed/31383985)]: Phase II. **IV-Chemo ± DD-EPIC**.  
  DD-EPIC is associated with a longer OS than IV chemotherapy alone.
  + 218 pts. FIGO IIIC-IV. MFU 6.5y.
  + MS 46→ 68 mo.
  + 5y OS 38→ 61%.
  + 5y PFS 9→ 26%.
* **GOG 252** [[Walker JCO '19](https://www.ncbi.nlm.nih.gov/pubmed/31002578)] (**IV CarboP vs**. **IV Paclitaxel/IP Carbo vs**. **IV Paclitaxel/IP CDDP-Paclitaxel**) + **IV Avastin**

This trial actually concluded that GOG 172 intraperitoneal chemo (without avastin) should be used for select optimally debulked tumors.

* + 1,560 women.
  + MPFS ~25 mo.
  + MS ~77 mo.
  + G3-4 toxic effects are more common in the IP cisplatin arm, but there were no increase in GI perforations, fistulas, or necrosis.
* **ENGOT-OV16/NOVA** [[Matulonis JCO '19](https://ascopubs.org/doi/full/10.1200/JCO.19.00917)]: **Metastatic ≥ PR to chemo ± Niraparib** (PARPi).

TBL [QS](http://www.quadshotnews.com/2019/09/outcomes-with-twist.html): Lookout for TWiST as the newest surrogate endpoint in oncology clinical trials.

* + 533 pts. Predominantly high grade serous features with CR or PR 6 mo after 2+ plt-based chemos.
  + MPFS for BRCAmt of 6→ 12 mo.
  + MPFS for no BRCAmt of 4→ 9 mo.
  + Time without symptoms or toxicity (TWiST): Mean PFS benefits were 39 mo for BRCAmt, while 16 mo for no BRCAmt. TWiST benefit was roughly 3y for BRCAmt, while 1y for no BRCAmt.
* **NRG GY004** (2016-2017)[[Liu ASCO '20](https://meetinglibrary.asco.org/record/185456/abstract)]: Phase III. **Platinum-based vs. Olaparib ± Cediranib**.

This trial did not select for BRCA mutants, which likely contributed to this being a negative study.

* + 656 pts. PFI > 6 mo. No prior antiangiogenics or PARPi allowed. 24% BRCAmt. MFU 2.5y.
  + 1/3 of patients on the standard of care arm received PARPi maintenance.
  + MPFS ~10 mo.
  + Arms with olaparib and BRCAmt appeared to benefit the most, although not statistically significant.
* **SOLO2/ENGOT-ov21** [[Poveda ASCO '20](https://meetinglibrary.asco.org/record/185419/abstract)]: Phase III. **BRCAmt. Ongoing Plt response→ ± Olaparib (PARPi)**

When appropriately selecting for platinum sensitive relapsed ovarian cancer, BRCA mutants may see over a year of a survival benefit when given PARPi maintenance.

* + Platinum sensitive recurrent ovarian cancer with ≥ 2 lines of prior tx. MFU 5.5y.
  + MPFS improved 14 months.
  + 5y OS 33→ 42%. MS 39→ 52 mo.
  + 5y alive and without subsequent treatment of 33→ 42%.
* **PAOLA-1** [[Ray-Coquard NEJM '19](https://www.ncbi.nlm.nih.gov/pubmed/31851799)]: **Metastatic ≥ PR to chemo→ maintenance Bev ± Olaparib** (PARPi).  
  Patients with advanced ovarian cancer benefit from maintenance PARPi if homologous recombination deficiency (HRD) is present, regardless of if the HRD is a BRCAmt. See the concept of [[synthetic lethality](https://docs.google.com/document/d/1WGO0ms-uutSies98CoG31NpD2aBpzX8ffUS5auOgYW4/edit#bookmark=id.wisgerfvt7s3)] with PARPi in the Rad Bio section.

TBL [QS](http://www.quadshotnews.com/2019/10/decisions-decisions-decisions.html): Maintenance olaparib, when added to a bevacizumab containing regimen, improves PFS for advanced ovarian cancer mainly by benefiting those with HRD.

* + 806 pts. Newly diagnosed ovarian cancer with response to first-line [[Plt-Taxane](#xc5bo29ot26s)] chemo and Bev. MFU 2y.
    - Olaparib 300 mg BID up to 2y. All patients received maintenance bevacizumab q3w up to 15 mo in total.
  + MPFS 17→ 22 mo.
  + Patients with homologous recombination deficiencies were at lower risk of death, regardless of BRCA mutation.
  + G3-5 in 51→ 57%. Most commonly hypertension and anemia.
* **VELIA** [[Coleman NEJM '19](https://www.nejm.org/doi/10.1056/NEJMoa1909707)]: **Metastatic first line Carboplatin/Paclitaxel ± Velaparib** (PARPi) ± maintenance Velaparib.

TBL [QS](http://www.quadshotnews.com/2019/10/decisions-decisions-decisions.html): Veliparib given with chemo and then in maintenance improves PFS for advanced ovarian cancer mainly by benefiting those with HRD.

* + 1140 pts. Previously untreated stage III-IV high grade serous ovarian carcinoma.
    - Cytoreductive surgery could be performed initially or after 3c of trial treatment.
    - Combination chemo was 6c, maintenance therapy was 30 additional cycles.
  + MPFS for BRCAmt of 22→ 35 mo.
  + MPFS for HRD of 21→ 32 mo.
* **PRIMA** [[Gonzalez-Martin NEJM '19](https://www.ncbi.nlm.nih.gov/m/pubmed/31562799/)]: **Metastatic ≥ PR to plt-based chemo→ ± Niraparib** (PARPi).

TBL [QS](http://www.quadshotnews.com/2019/10/decisions-decisions-decisions.html): Maintenance niraparib following platinum-based chemotherapy improves PFS among all subsets of patients with advanced ovarian cancer.

* + 733 pts. Stage III-IV with response after frontline chemotherapy. Half had homologous repair deficiency (HRD).
  + MPFS for HRD of 10→ 22 mo.
  + MPFS in overall population of 8→ 14 mo.
  + 2y OS 77→ 84%.
  + G3+ anemia (31%), thrombocytopenia (29%), neutropenia (13%).
* **NRG GY003** [[Zamarin JCO '20](https://www.ncbi.nlm.nih.gov/pubmed/32275468)]: Phase II. **Nivo ± Ipi**.
  + 100 patients. Measurable disease, 1-3 prior regimens, platinum free interval (PFI) < 12 mo. PFI < 6 mo in 62%.
    - Nivo 3 q2w vs. Nivo 3 /Ipi 1 x4c q3w→ Nivo q2w up to 42 doses.
  + ORR 12→ 31%. Including stable disease, ORR 41→ 70%.
  + MPFS 2→ 4 mo.
  + G3+ 33→ 49%.
* **KEYNOTE-100** [[Matulonis ASCO '20](https://meetinglibrary.asco.org/record/189536/abstract)]: **Pembro** inCohort A (≤ 2 prior lines of chemo) vs. Cohort B (3-5 prior chemo).

There is a modest ORR with Pembro which appears to correlate with higher PD-L1 expression.

* + 376 pts. Epithelial ovarian, fallopian tube, or primary peritoneal cancer with confirmed recurrence following platinum-based therapy. Progression free interval of 3 mo. MFU 1.5y.
  + ORR for CPS ≥ 1 / ≥ 10 of ~9→ 15%.
  + Median DOR 8→ 24 mo.
  + MPFS 2 mo.
* **Management**
  + I/II: TAH/BSO→ Carbo/Taxol x3-6c.
    - Goal of surgery is to cyto reduce to < 1 cm gross disease
  + III: Surgery→ Carbo/Taxol x6-8c. WART if not chemo candidate or refuses chemo.
  + Recurrence: Chemo. RT for palliation.
* **Treatment Planning**
  + If IFRT for locoregionally recurrent disease: 45-60 Gy
    - Primary GTV = gross disease
    - Primary CTV = post op bed or pre chemo extent of dz + 1-1.5 cm margin, exclude uninvolved clinical structures \*Technical note: patients may have had multiple regional recurrences at the same or nearby regions. Therefore, for CTV delineation, it is important to critically examine all previous imaging studies to ensure adequate coverage of regions at risk
    - Nodal CTV: include grossly involved nodes, may extend to cover adjacent uninvolved regions.

## [Future Directions](#_2y4nw0w64v2o)

See NCTN Trial Portfolios by Disease Site: [[Gyn](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_GYNE_Trials.pdf)]

### Epithelial

* **NRG-GY019** [[NCT04095364](https://clinicaltrials.gov/ct2/show/NCT04095364)]: Phase III. Newly diagnosed. Low grade serous.
  + CarboP→ Letrozole maintenance vs. Letrozole monotherapy.
* **NRG-GY021** [[NCT04034927](https://clinicaltrials.gov/ct2/show/NCT04034927)]: Phase II. Recurrent. Plt sensitive. All HGS/EOC and others with BRCAmt.
  + Olaparib ± Tremelimumab.
* **NRG-GY009** [[NCT02839707](https://clinicaltrials.gov/ct2/show/NCT02839707)]: Phase II/III. Recurrent. Plt resistant. All histology.
  + Pegylated doxorubicin ± bevacizumab ± Atezolizumab.
* **NRG-GY005 / COCS** [[NCT02502266](https://clinicaltrials.gov/ct2/show/NCT02502266)]: Phase II/III. Recurrent. Plt resistant ovarian, fallopes, primary peritoneal. HGSOC.
  + Cediranib/Olaparib vs. Cediranib vs. Olaparib vs. Standard chemotherapy.
* **NRG-GY016** [[NCT03602586](https://clinicaltrials.gov/ct2/show/NCT03602586)]: Phase II. Recurrent or progressive. Clear cell.
  + Pembrolizumab + Epacadostat.
* **NRG-GY014** [[NCT03348631](https://clinicaltrials.gov/ct2/show/NCT03348631)]: Phase II. Recurrent. Endometrioid or clear cell.

See [[Future Directions](#_e9e7oz6ftgla)] in the endometrial cancer section.

* + Tazemetostat.

### Non-epithelial

* **GOG 0264** [[NCT01042522](https://clinicaltrials.gov/ct2/show/NCT01042522)]: Phase II. Newly diagnosed, stromal, advanced stage/recurrent chemonaive.
  + CarboP vs. BEP.

### Germ cell

See Future Directions in the [[Peds](https://docs.google.com/document/d/17O0LOemBhckXGuuPBCh6u8vqBfc6lg88r46B8YctMXU/edit#heading=h.4ub44tk80n2c)] and [[GU](https://docs.google.com/document/d/1j15zXLBPWwqty60Slm2jnHEiqaoT2iw5Gapp4iMWJsw/edit#heading=h.yntl3awv37k7)] Germ Cell tumors section for more.

* **AGCT1531** [[NCT03067181](https://clinicaltrials.gov/ct2/show/NCT03067181)]: Phase III. **AS vs. Bleomycin vs. Carboplatin vs. Etoposide vs. CDDP**.
  + Low-standard risk.
* **AGCT1532** [[NCT02582697](https://clinicaltrials.gov/ct2/show/NCT02582697)]: Phase III. **Accelerated vs. standard BEP**.
  + Intermediate and poor risk metastatic.