RANZCR PHASE II · RADIATION ONCOLOGY VIVA

Endometrial Carcinoma

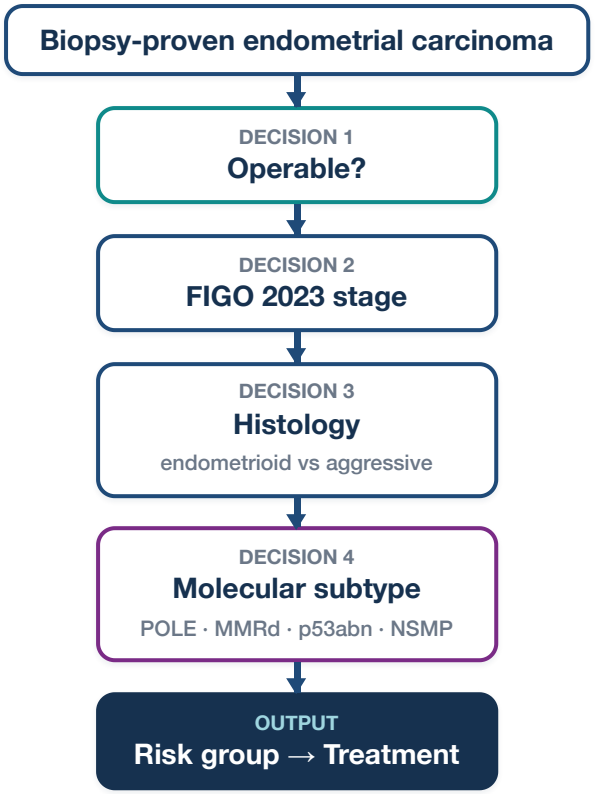
A premium rapid-revision handbook — flowcharts, decision trees, dose anchors, molecular logic and viva-grade reasoning for the advanced trainee.

STAGING	PRACTICE	FORMAT	LEVEL
FIGO 2023	**Australian / RANZCR**	**13 high-yield sections**	**Exam viva**

CONTENTS

1 Master Management Flowchart

BIOPSY → OPERABILITY → STAGE → HISTOLOGY → MOLECULAR → RISK → TREATMENT



★ VIVA PEARL — OPEN EVERY ENDOMETRIAL CASE

"Is she **operable**? Then I stage by **FIGO 2023**, define **histology** and the **molecular subtype**, and only then place her in a **risk group**. Molecular can **up- or down-stage my intent** — POLE rescues, p53abn escalates."

IF OPERABLE → ADJUVANT BY ESGO/ESTRO/ESP RISK GROUP

● LOW RISK

Stage IA endometrioid G1–2, no/focal LVSI, NSMP/MMRd · **or any POLEmut Stage I–II**

→ **Observation (no adjuvant RT)**

● INTERMEDIATE RISK

Stage IB endometrioid G1–2 · or IA G3 · no substantial LVSI

→ **Vaginal brachytherapy (VBT)**

● HIGH–INTERMEDIATE RISK

Substantial LVSI, Stage II, G3 with deep invasion (node-negative)

→ **EBRT ± VBT (VBT alone if surgically node-staged & node-negative)**

● HIGH RISK

Stage III, aggressive histology (serous/clear cell/carcinosarcoma), p53abn, Stage II G3 LVSI+

→ **EBRT + chemotherapy ± VBT**

● STAGE III–IVA / ADVANCED

Gross nodal / serosal / vaginal / parametrial / mucosal disease

→ **Combined-modality (chemo + RT) ± immunotherapy (esp. dMMR)**

? WHY THIS SPINE WORKS

Risk group is a **composite of local-recurrence risk (drives RT intensity: nil → VBT → EBRT)** and **distant-relapse risk (drives systemic therapy)**. VBT controls the vaginal vault; EBRT adds pelvic nodal/parametrial coverage; chemo addresses occult micrometastatic disease; IO is reserved for advanced/recurrent disease, transformative in dMMR.

FIGO 2023 Staging

TWO PATHWAYS: NON-AGGRESSIVE (ENDOMETRIOID) VS AGGRESSIVE HISTOLOGY

ENDOMETRIOID / NON-AGGRESSIVE PATHWAY

STAGE	DEFINING FEATURE
IA1	Limited to a polyp or confined to endometrium — **no myometrial invasion**
IA2	**<50%** myometrial invasion, no/focal LVSI
IA3	**Low-grade endometrioid involving uterus AND ovary** only (synchronous, good-prognosis criteria) → still Stage I, not III
IB	**≥50%** myometrial invasion, no/focal LVSI
IIA	Cervical **stromal** invasion
IIB	**Substantial LVSI** (≥focal extensive) — new in 2023

PEARL

For endometrioid, **myometrial depth (IA2 vs IB)** and **substantial LVSI (IIB)** are the staging levers. **IA1/IA2/IB** all require non-aggressive histology — see trap opposite.

AGGRESSIVE HISTOLOGY PATHWAY

Serous · Clear cell · Carcinosarcoma · Undifferentiated · Dedifferentiated · (mixed)

STAGE	DEFINING FEATURE
IC	**Aggressive histology, no myometrial invasion** (confined to endometrium/polyp). Note: **no IA for aggressive types**
IIC	**Aggressive histology with ANY myometrial invasion** → automatically ≥ Stage II

Stages III–IV (both pathways)

STAGE	DEFINING FEATURE
IIIA1 / A2	Adnexa (ovary/tube) / uterine serosa
IIIB1 / B2	Vagina &/or parametria / pelvic peritoneum*
IIIC1 / C2	Pelvic nodes / para-aortic nodes (i = micro, ii = macro)
IVA	Bladder &/or bowel **mucosa**
IVB / IVC	Abdominal peritoneal mets / **distant metastases**

**Memory hook IIIB1 = vagina/parametria, IIIB2 = pelvic peritoneum. (IVB = intra-abdominal spread; IVC = distant.)*

FIGO 2009 → 2023: WHAT CHANGED

2023 STAGE	WHY IT'S NEW / DIFFERENT
IA3	Synchronous low-grade endometrioid endometrial+ovarian → **down-classified** from Stage III to good-prognosis Stage I
IC	Aggressive histology confined to endometrium — captured separately (would have been "IA" in 2009)
IIC	Aggressive histology + **any** myometrial invasion → escalates straight to Stage II
IIB	**Substantial LVSI** alone now defines Stage II (previously not stage-defining)
Molecular	**POLEmut** and **p53abn** modifiers: stage suffix $\mathbf{m}_{\mathbf{POLE}}$ / $\mathbf{m}_{\mathbf{p53abn}}$. POLEmut down-stages early disease; p53abn up-stages

CARDINAL TRAP

Histology gates which boxes you may tick. **Endometrioid can NEVER be IC or IIC. Clear cell/serous with any invasion = IIC,** not IB.

WHY 2023 CHANGED

2009 staging poorly predicted outcome once molecular data emerged: low-grade synchronous tumours behaved benignly while "early" serous relapsed. 2023 folds in **histology, LVSI and molecular class** to match biology.

3 Molecular Classification

TCGA / PROMISE — FOUR PROGNOSTIC GROUPS THAT NOW STEER THERAPY

SURROGATE IHC: POLE SEQ · MMR IHC
P53 IHC · (NSMP = NONE OF THE ABOVE)

SUBTYPE	TYPICAL PATHOLOGY	PROGNOSIS	MANAGEMENT IMPLICATIONS	VIVA PEARL
POLEmut POLE exonuclease-domain mutation	Often high-grade endometrioid, high TMB, prominent TILs & LVSI — but **biologically indolent**	**Excellent** ~recurrence rare in Stage I–II	**De-escalate.** In Stage I–II, POLEmut **overrides** adverse LVSI, grade and deep invasion → typically **observation**, omit adjuvant RT/chemo (RAINBO **POLE-BLUE** testing de-escalation)	"High-grade, LVSI+, deep invasion — looks terrible, but if **POLEmut** I de-escalate to observation in early stage."
MMRd Loss of MLH1/PMS2 or MSH2/MSH6 (MSI-high)	Endometrioid, often G2–3, LVSI common; MLH1 hypermethylation (sporadic) vs germline	**Intermediate**	**Conventional risk-based RT.** Screen for **Lynch syndrome** (reflex MLH1 methylation; germline testing). **Highly IO-sensitive** — checkpoint inhibitor in advanced/recurrent disease	"MMRd has two jobs: **Lynch referral** for the patient/family, and it flags **immunotherapy sensitivity** in advanced disease."
p53abn Aberrant p53 IHC / copy-number-high	Serous, carcinosarcoma, clear cell, high-grade endometrioid; deep invasion, LVSI, early spread	**Poor** highest relapse / distant failure	**Escalate.** Treat **like serous carcinoma** regardless of light microscopy: **chemotherapy + RT**, even in apparent Stage I. HER2-positive serous → consider trastuzumab. RAINBO **P53ABN-RED**	"**p53abn endometrioid is not low-grade disease** — it behaves like serous and gets systemic therapy."
NSMP No specific molecular profile (p53-wt, MMR-intact, POLE-wt)	Commonest group; low–intermediate-grade endometrioid, oestrogen-driven	**Intermediate** (heterogeneous)	**Default to classical risk stratification** (grade, depth, LVSI, stage). ER/PR-positive → endocrine options in advanced disease. RAINBO **NSMP-ORANGE** (de-escalation testing)	"NSMP is the only group where **old-school clinicopathological risk still rules** — the others rewrite the rules."

? WHY MOLECULAR CLASSIFICATION MATTERS

- **Prognosis:** four groups separate survival far better than grade/stage alone — POLEmut (best) → MMRd ≈ NSMP → p53abn (worst).
- **De-escalation:** POLEmut spares early-stage patients RT/chemo toxicity.
- **Escalation:** p53abn mandates systemic therapy even when "early".
- **Therapy selection:** MMRd predicts immunotherapy benefit; triggers Lynch testing.
- **Trial framework (RAINBO):** prospective molecular-directed adjuvant trials — one colour per subtype.

★ PRACTICAL IHC ALGORITHM (PROMISE ORDER)

- **1. POLE** sequencing → if mutant = **POLEmut** (stop).
- **2. MMR IHC** → if loss = **MMRd** (stop).
- **3. p53 IHC** → if aberrant = **p53abn**.
- **4. None** of the above = **NSMP**.

*Order matters: a tumour can be POLEmut and p53-aberrant — **POLE wins** (classified POLEmut, good prognosis). "Multiple-classifier" → resolve up the hierarchy.*

4 Operable Disease Algorithm

POST-HYSTERECTOMY ADJUVANT DECISION TREE

TH + BSO ± NODAL ASSESSMENT
THEN RISK-ADAPTED ADJUVANT

STEP 1 · RISK INPUTS AFTER SURGERY

- Histology (type)
- Grade (1–3)
- LVSI (focal vs substantial)
- Myometrial invasion (</≥50%)
- Cervical stromal invasion
- Nodal status (SLN/LND)
- **Molecular subtype** (POLE / MMRd / p53abn / NSMP)

Integrate → risk group

LOW → OBSERVATION

IA G1–2 NSMP/MMRd, no substantial LVSI · or any POLEmut St I–II

INTERMEDIATE → VBT

IB G1–2 · IA G3 · vault control with minimal toxicity

HIGH-INTERMEDIATE → EBRT ± VBT

Substantial LVSI · Stage II · deep G3. VBT alone acceptable if surgically node-negative

HIGH → EBRT + CHEMO ± VBT

Aggressive histology · p53abn · Stage II G3 LVSI+

STAGE III → COMBINED-MODALITY

Chemo + RT (sequential/sandwich) ± IO if dMMR

STAGE II ENDOMETRIOID

→ **EBRT ± VBT**, intensity titrated to vaginal/cervical risk factors (extent of stromal invasion, grade, LVSI). VBT boost added for close/positive vaginal margin or bulky cervical involvement.

AGGRESSIVE HISTOLOGIES (SEROUS / CLEAR CELL / CARCINOSARCOMA)

→ **Individualised by stage & risk factors**; low threshold for **chemotherapy + RT** even in apparent Stage I. Serous behaves like high-grade ovarian-type disease.

STAGE III

→ **Combined-modality treatment** — systemic chemotherapy is the backbone (controls distant failure), RT for locoregional control (PORTEC-3 / GOG-258 logic).

NODE-POSITIVE (IIIC)

→ **Chemo + EBRT with nodal SIB.** VBT not automatic — add only for vaginal/cervical risk factors.

MOLECULAR OVERLAY — MODIFIES THE ABOVE

P POLEMUT

De-escalate. Stage I–II: omit adjuvant therapy → **observation**, regardless of grade/LVSI/depth. (Outside trial, individualise Stage III.)

M MMRD

Standard risk-based RT + **Lynch testing**. Advanced/recurrent → add **checkpoint inhibitor** (dostarlimab/pembrolizumab).

53 P53ABN

Escalate. Add **chemotherapy** even if "early"; treat as serous. EBRT + chemo ± VBT. HER2+ serous → trastuzumab.

★ VIVA PEARL

State your tree as a **two-axis decision**: "**RT intensity** (nil → VBT → EBRT ± nodal SIB) tracks **local** recurrence risk; **systemic therapy** tracks **distant** risk (aggressive histology, p53abn, Stage III). Molecular subtype then **nudges me up or down** both axes."

? PRINCIPLE

Inoperable (comorbidity / obesity / patient choice). **Brachytherapy is the definitive workhorse** (covers the in-situ uterus & tumour); **EBRT is added to treat myometrial extension, cervix and at-risk nodes**. Dose escalates with stage to overcome larger tumour burden & nodal risk.

Medically inoperable endometrial carcinoma

↓

STRATIFY BY FIGO STAGE
Tumour extent + nodal risk

STAGE IA
HDR brachytherapy alone `7 Gy × 5`
Disease confined — brachy alone sufficient. **EQD2 ≈ 50 Gy**

STAGE IB
`45 Gy / 25#` **EBRT** + `7 Gy × 3` **brachy**
Deep myometrial invasion → add EBRT. **EQD2 ≈ 74 Gy**

STAGE II
`45 Gy / 25#` **EBRT** + `7 Gy × 4` **brachy**
Cervical involvement → higher brachy dose. **EQD2 ≈ 84 Gy**

STAGE III
`45 Gy / 25#` **EBRT** + `7 Gy × 4` **brachy**
+ nodal SIB & consider chemo. **EQD2 ≈ 84 Gy**

STAGE IVA
`45 Gy / 25#` **EBRT** + `7 Gy × 5` **brachy**
Highest tumour burden → maximal dose. **EQD2 ≈ 94 Gy**

★ THE MEMORY RULE

IA = 7 × 5

IB = 45 + 7 × 3

II–III = 45 + 7 × 4

IVA = 45 + 7 × 5

Brachy fraction count climbs 5→3→4→4→5 as EBRT carries more of the load. Reads as an EQD2 ladder: ≈50 → 74 → 84 → 84 → 94 Gy.

STAGE	EBRT	BRACHY	≈EQD2$_{10}$
IA	—	7×5	50 Gy
IB	45/25	7×3	74 Gy
II	45/25	7×4	84 Gy
III	45/25	7×4	84 Gy
IVA	45/25	7×5	94 Gy

! MANDATORY CAVEAT — SAY THIS ALOUD

"These are **memory-anchor schedules only**. Actual brachytherapy must be **individualised on image-guided (MRI/CT) planning** — target coverage of the whole uterus/tumour and **OAR dose constraints** — not delivered as a fixed prescription."

? WHY BRACHY-LED?

The uterus tolerates very high local dose; brachy delivers a steep gradient to the in-situ tumour while sparing bladder/rectum. EBRT alone can't safely reach tumoricidal uterine dose — hence the brachy boost dominates.

STANDARD ADJUVANT PRESCRIPTIONS

INDICATION	PRESCRIPTION	NOTES
Pelvic EBRT	**45 Gy / 25#** (1.8 Gy/#)	Whole-pelvis IMRT/VMAT; covers vault, parametria, pelvic nodes
Adjuvant VBT (alone)	**21 Gy / 3#** HDR	To 0.5 cm depth (PORTEC-2 schedule); upper vagina only
EBRT + VBT boost	**45 Gy/25#** + **10 Gy/2#**	Vault boost for cervical/vaginal risk or close margin
Pelvic nodal SIB	**55 Gy / 25#** (2.2 Gy/#)	Simultaneous boost to involved/at-risk pelvic node
Common iliac / para-aortic SIB	**57.5 Gy / 25#** (2.3 Gy/#)	Extended-field for IIIC2 / high common iliac nodes

★ **PEARL — VBT-ALONE VS EBRT**

45/25 is the universal pelvic spine; alternative VBT regimens include **7 Gy×3 to 5 mm** or **11 Gy×1** at surface. **SIB grammar:** 2.2 Gy/# → 55 Gy (pelvis), 2.3 Gy/# → 57.5 Gy (common iliac/PA), keeping elective nodes at 45 Gy in the same 25 fractions.

? **WHY THESE DOSES**

45 Gy sterilises microscopic nodal/parametrial disease at acceptable bowel toxicity. **VBT 21/3** escalates vault dose where recurrence concentrates, sparing pelvis (PORTEC-2). **Nodal SIB** escalates only the gross/high-risk node within one plan — better therapeutic ratio than sequential boost.

EQD2 EQUIVALENCE

REGIMEN	GY/#	$EQD2_{10}$ (tumour α/β10)	$EQD2_{3}$ (late α/β3)
45 Gy / 25#	1.8	44.3 Gy	43.2 Gy
VBT 21 Gy / 3#	7.0	29.8 Gy	42 Gy*
VBT boost 10 Gy / 2#	5.0	12.5 Gy	16 Gy*
Pelvic SIB 55 Gy / 25#	2.2	55.9 Gy	57.2 Gy
PA SIB 57.5 Gy / 25#	2.3	58.9 Gy	61.0 Gy
45/25 + VBT 7×3	—	**≈74 Gy**	—
45/25 + 7×4 (def. brachy)	—	**≈84 Gy**	—

*EQD2 = D × (d + α/β)/(2 + α/β). *VBT late-EQD2 quoted at prescription point; surface mucosa receives substantially more.*

QUICK CONVERSION REFERENCE

- Tumour **α/β = 10**, late-reacting OAR **α/β = 3**.
- Hypofractionated brachy (7 Gy/#) is **"hot" for late effects** (high dose/#) → why OAR D2cc limits dominate planning.
- Summing modalities: convert **each** to EQD2, then add — never add raw Gy across EBRT + HDR.

! **TRAP**

Don't quote "physical" combined dose. An examiner wants **"45 Gy EBRT plus brachy to a total ≈84 Gy EQD2"** — the radiobiological language, separated for tumour vs OAR.

TARGET DOSE CONCEPTS (D90 OF CTV, $EQD2_{10}$)

STAGE IB
≈ 75 Gy
whole uterus + tumour

STAGE II–III
≈ 85 Gy
+ cervix / lower segment

STAGE IVA
≈ 95 Gy
maximal local dose

OAR D2CC CONSTRAINTS ($EQD2_3$, TOTAL EBRT+BRACHY)

ORGAN AT RISK	D2CC LIMIT	COMMENT
Bladder	**< 90 Gy** EQD2	Highest tolerance; fill protocol for reproducibility
Rectum	**< 75 Gy** EQD2	Often dose-limiting posteriorly
Sigmoid	**< 75 Gy** EQD2	Mobile — verify position each fraction
Bowel (small)	**< 75 Gy** EQD2	Bladder filling to displace loops

? WHY IMAGE-GUIDED

The uterus is large, mobile and variably shaped — a fixed point-A/library plan under-doses fundal tumour or over-doses rectum. **Volumetric (MRI/CT) optimisation** shapes dose to the real CTV each insertion, the same paradigm that transformed cervix brachy (GEC-ESTRO / EMBRACE).

TECHNIQUE SELECTION

MODALITY	WHEN / HOW
Intracavitary (Heyman/Simon capsules or dual-tandem)	Workhorse for the **in-situ uterus**. Multiple sources/capsules pack the cavity to cover a bulky fundus. Tandem ± ovoids if cervix involved.
Interstitial	Add needles for **deep myometrial / cervical / parametrial** extension where intracavitary gradient can't cover the CTV (e.g. eccentric or thick-wall tumour). Hybrid intracavitary+interstitial.
Image-guided (IGABT)	**MRI (or CT) at each insertion**; contour uterus+tumour CTV & OARs; inverse-optimise dwell positions/times to hit D90 target within D2cc limits.
Applicator selection	Single tandem (small uterus) → **dual tandem / Heyman capsules** (bulky uterus) → **tandem-ring/ovoid + needles** (cervix/parametrial). Choose to fill the cavity & respect anteflexion/retroflexion.

★ VIVA PEARLS — BRACHYTHERAPY

- **Coverage drives applicator:** bulky fundus → multi-channel/Heyman; thick or eccentric wall → add **interstitial needles**.
- **Quote D90 (target) and D2cc (OAR)** in EQD2 — the volumetric language an examiner expects.
- **Bladder filling + rectal/vaginal packing** reproducibly push OARs off the high-dose region.
- **Uterine perforation** risk in atrophic/inoperable patients → image-guided insertion + post-insertion imaging before dwell.
- Always pair the dose with the caveat: **schedule individualised to coverage & OARs**, not fixed.

! TRAP

Don't conflate **adjuvant VBT** (post-hysterectomy vault, vagina-only target, 0.5 cm depth) with **definitive uterine brachy** (uterus in situ, whole-organ CTV, much higher dose). Different targets, applicators and intent.

REGIMENS & SEQUENCING STRATEGIES

STRATEGY	REGIMEN	USE
Standard chemo	**Carboplatin AUC 5 + Paclitaxel 175 mg/m²**, q3-weekly × 6	Backbone for high-risk / advanced / recurrent disease
PORTEC-3 (concurrent + adjuvant)	EBRT (48.6 Gy/27#) + **cisplatin 50 mg/m² wk 1 & 4**, then **carbo/paclitaxel × 4**	High-risk Stage I–III; benefit greatest in Stage III & p53abn
Sequential RT → chemo	Chemo follows completion of RT	Common modern pragmatic approach
Chemo → RT ("reverse PORTEC" / GOG-258 style)	Up-front chemo, then RT	Bulky nodal / high distant-risk; treat micromets first
"Sandwich"	Chemo → RT → chemo	Aggressive histology; locoregional + systemic both addressed

? WHY A SEQUENCE IS CHOSEN

Distant relapse dominates high-risk endometrial cancer (GOG-258), so systemic therapy is the priority. RT adds **locoregional control** (PORTEC-3 reduced pelvic/vaginal recurrence). The order balances **which failure you fear most** against **tolerability of concurrent treatment**.

★ REASONS TO FAVOUR CHEMOTHERAPY FIRST

- **Serous histology** — high distant-failure rate.
- **p53abn disease** — aggressive biology, systemic-driven.
- **Bulky nodal disease** — micromets need early systemic control.
- **High concern for distant relapse** over local.

DECODING THE TRIALS

PORTEC-3

High-risk early/Stage III. **Chemo-RT (concurrent cisplatin + adjuvant carbo/taxol) vs EBRT alone** → improved failure-free & overall survival, **driven by Stage III and p53abn/serous**. Established adding chemotherapy to RT in high-risk disease.

GOG-258 — THE COUNTERPOINT

Stage III/IVA. **Chemo-RT vs chemo alone → no PFS benefit** from adding RT, but **fewer locoregional (vaginal/pelvic nodal) recurrences**; **distant failure unchanged**. ⇒ chemo is the essential backbone; RT refines local control.

! VIVA DISCUSSION BOX

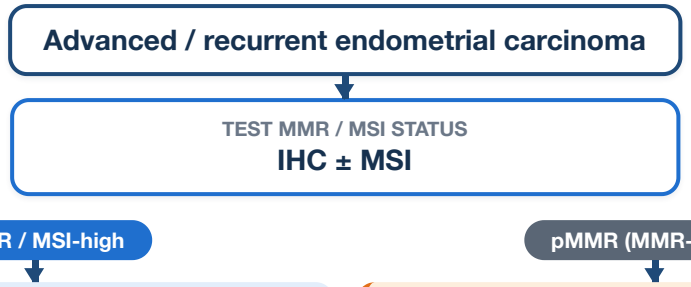
"Why might an MDT NOT follow PORTEC-3?"

- **GOG-258 logic:** distant failure dominates → chemo first/alone may suffice; concurrent cisplatin adds toxicity without clear survival gain in some Stage III.
- **Tolerability:** elderly/comorbid patient may not tolerate concurrent chemoradiation → sequential.
- **Histology/molecular:** p53abn/serous → prioritise systemic (chemo-first/sandwich); MMRd advanced → IO-containing regimen.
- **Pragmatism:** many ANZ units favour **sequential carbo/taxol then EBRT** over concurrent cisplatin — easier delivery, similar outcomes for many.

★ PEARL

Concurrent cisplatin is optional, not mandatory. The non-negotiable element of high-risk treatment is the **carboplatin/paclitaxel backbone**; the radiosensitiser and the sequence are MDT-individualised.

MANAGEMENT ALGORITHM



1 FIRST-LINE ADVANCED/RECURRENT

Dostarlimab + carboplatin/paclitaxel
→ followed by **maintenance dostarlimab**

Basis: **RUBY** trial — dramatic PFS/OS benefit in dMMR.

2 RECURRENCE AFTER PLATINUM

Pembrolizumab + lenvatinib

Basis: **KEYNOTE-775** — IO + TKI superior to chemotherapy in pMMR recurrence.

? WHY MMR STATUS FORKS THE PATHWAY

dMMR tumours are hypermutated → abundant neoantigens → **highly responsive to single-agent checkpoint blockade**. **pMMR** tumours are immunologically "cold" → need **lenvatinib (VEGFR TKI) to prime the microenvironment** for pembrolizumab to work.

FRONT-LINE CHEMO-IO (BOTH SUBTYPES)

NRG-GY018: pembrolizumab + carbo/paclitaxel improved PFS in **both dMMR and pMMR** advanced/recurrent disease. **RUBY**: dostarlimab + chemo, benefit greatest in dMMR (also OS in overall population). Establishes **chemo + checkpoint inhibitor as front-line standard** for advanced/recurrent disease.

SETTING	REGIMEN
dMMR advanced/recurrent, 1st line	Dostarlimab + carbo/taxol → maint. dostarlimab
pMMR advanced, 1st line	(Pembrolizumab +) carbo/taxol per protocol
pMMR recurrence post-platinum	Pembrolizumab + lenvatinib
HER2+ serous	Add trastuzumab to chemo
ER/PR+ low-grade	Endocrine ± CDK4/6 inhibitor

★ VIVA PEARLS — IMMUNOTHERAPY

- **Always test MMR/MSI** in advanced/recurrent disease — it is now a **treatment-selection biomarker**, not just prognostic.
- **dMMR = dostarlimab** (RUBY); **pMMR recurrence = pembro + lenvatinib** (KEYNOTE-775).
- **Lenvatinib toxicity** (hypertension, proteinuria, diarrhoea, fatigue) is significant — needs active management.
- dMMR also flags **Lynch syndrome** screening — a parallel duty.

! TRAP

IO is for **advanced/recurrent** disease (and trials in earlier stages, e.g. KEYNOTE-B21 / RAINBO). Don't offer routine adjuvant immunotherapy for resected early-stage disease off-trial.

10 Landmark Trials

WHO WAS STUDIED · BROAD RESULT · WHY WE STILL CARE

VIVA LEVEL — NARRATIVE, NOT NUMBERS

TRIAL	PATIENT COHORT	MAIN RESULT	PRACTICE-CHANGING MESSAGE
PORTEC-1	Stage I endometrioid, intermediate-risk; EBRT vs observation	EBRT **halved locoregional recurrence** but **no OS benefit**; most relapses are vaginal & salvageable	Don't irradiate everyone — **reserve EBRT for high-intermediate risk**; observation safe for low-risk
PORTEC-2	High-intermediate-risk Stage I–IIA; **VBT vs pelvic EBRT**	**Equivalent vaginal control**, fewer GI side-effects with VBT	**VBT is the standard** for high-intermediate-risk — same control, less toxicity than EBRT
PORTEC-3	High-risk Stage I–III (incl. serous); **chemo-RT vs EBRT alone**	Improved **failure-free & overall survival**, benefit concentrated in **Stage III & p53abn/serous**	**Add chemotherapy to RT in high-risk disease**; molecular subgroup defines who benefits most
GOG-249	High-intermediate / early high-risk; **VBT + chemo vs pelvic EBRT**	VBT+chemo **not superior**; pelvic EBRT gave **better nodal/pelvic control**	**Pelvic EBRT remains standard** for early high-risk — substituting VBT+chemo is not better
GOG-258	Stage III/IVA; **chemo-RT vs chemo alone**	**No RFS benefit** from adding RT; **fewer locoregional recurrences**; distant failure dominates	**Chemo is the essential backbone**; RT refines local control — sequence is individualised
RUBY	Primary advanced / recurrent; **dostarlimab + chemo vs chemo**	Marked **PFS/OS benefit, dramatic in dMMR**; benefit also in overall population	**Add a checkpoint inhibitor to front-line chemo** — transformative in dMMR disease
NRG-GY018	Advanced / recurrent; **pembrolizumab + chemo vs chemo**	Improved PFS in **both dMMR AND pMMR**	**Chemo-immunotherapy is front-line standard** across MMR status in advanced disease

★ **THE PORTEC STORY IN ONE LINE**

1: who needs RT (HIR, not all) → **2**: VBT is enough for HIR → **3**: add chemo for high-risk. A clean escalation narrative examiners love.

? **PORTEC-3 VS GOG-258**

Same question, opposite framing: PORTEC-3 (vs RT-alone) shows **chemo adds survival**; GOG-258 (vs chemo-alone) shows **RT adds local control, not survival**. Together: **both modalities, chemo-led**.

! **DON'T DROWN IN NUMBERS**

At viva, give **cohort → direction of effect → current relevance**. Reserve exact HRs only if pressed. Knowing *why* a trial still guides practice beats reciting figures.

11 Recurrent Disease

PATTERN OF RELAPSE DRIVES INTENT — CURATIVE VS PALLIATIVE

PRIOR RT STATUS IS DECISIVE

ISOLATED VAGINAL RECURRENCE

Intent: curative — best salvage outcomes of all relapse patterns.

RT-naïve: salvage EBRT + brachytherapy boost (≈high vaginal control, PORTEC-1 salvage data).
Prior RT: consider **surgery** (vaginectomy/exenteration) or **re-irradiation / interstitial brachy**.

PELVIC (NODAL / CENTRAL) RECURRENCE

Intent: curative where feasible.

RT-naïve: EBRT (± nodal SIB) ± brachy ± concurrent/sequential chemo.
Prior RT: surgery (incl. exenteration for central) or **re-irradiation** (SBRT/interstitial) in selected cases; otherwise systemic.

OLIGOMETASTATIC RECURRENCE

Intent: aggressive local + systemic.

SBRT to oligomets (lung/node/bone) or **metastasectomy**, plus **systemic therapy**. Defer/omit local ablation if rapidly progressive.

DISSEMINATED RECURRENCE

Intent: palliative / disease control.

Systemic therapy backbone (carbo/taxol ± IO). **MMR-directed:** dMMR → dostarlimab; pMMR → pembro+lenvatinib. ER/PR+ → endocrine. **Palliative RT** for bleeding/pain/obstruction.

STEP 1
Confirm + restage
imaging ± biopsy ± MMR/molecular

→

STEP 2
Prior pelvic RT?
naïve → re-RT possible · prior → surgery/SBRT

→

STEP 3
Pattern → intent
curative salvage vs palliative

→

STEP 4
Modality
RT · brachy · SBRT · surgery · systemic · IO

VIVA PEARL

The first two questions in any recurrence are **"pattern of relapse?"** and **"has she had pelvic RT before?"** — these two answers determine whether salvage is curative and which modality is even on the table.

WHY VAGINAL RELAPSE IS SPECIAL

Isolated vaginal recurrence in an **RT-naïve** patient has a **high curative salvage rate** with EBRT + brachytherapy — the main argument for **observing** low-risk patients up front (you keep RT in reserve).

! STAGING — HISTOLOGY GATES THE BOXES

Endometrioid can NEVER be IC or IIC. Those codes are reserved for **aggressive histology**. Endometrioid uses IA/IB (depth) and IIB (substantial LVSI).

! SUBSTANTIAL LVSI = IIB

Substantial LVSI alone upstages to Stage II (IIB) in 2023, even without cervical or myometrial criteria. Focal LVSI does not.

! POLEMUT + GRADE 3

High grade does **not** override POLE. **POLEmut Grade 3 early-stage = excellent prognosis → de-escalate.** Grade is trumped by molecular class.

! STAGE IA MEDICALLY INOPERABLE

Inoperable IA is treated with **brachytherapy ALONE (7 Gy × 5)** — no EBRT needed for confined disease. Adding EBRT is over-treatment.

! WHEN VBT IS NOT REQUIRED

Low-risk → observation (no VBT). POLEmut early-stage → observation. Node-positive disease on EBRT doesn't automatically need a VBT boost.

! NODE-POSITIVE ≠ AUTOMATIC VBT

IIIC needs chemo + EBRT (± nodal SIB); add VBT **only** if vaginal/cervical risk factors are present — not reflexively because nodes are positive.

! CLEAR CELL + ANY INVASION = IIC

Any aggressive histology (serous, clear cell, carcinosarcoma, undifferentiated) with **any myometrial invasion** jumps to **Stage IIC** — don't call it IB.

! POLEMUT + LVSI

Don't be lured into escalating. **POLEmut overrides adverse LVSI** in Stage I–II → still **observation**. The LVSI is a red herring once you know POLE.

! P53ABN ENDOMETRIOID

A "low-grade-looking" endometrioid that is **p53abn behaves like serous → escalate to chemo + RT**. Don't treat it as low-risk on light microscopy alone.

! WHEN VBT IS REQUIRED

Intermediate-risk (IB G1–2, IA G3) → VBT. Also as a **boost** with EBRT for cervical/vaginal involvement or close vault margin.

! CONCURRENT CISPLATIN IS OPTIONAL

The high-risk backbone is **carboplatin/paclitaxel**. **Concurrent cisplatin (PORTEC-3) is one option, not mandatory** — sequential chemo-RT is widely used.

! VBT VS DEFINITIVE BRACHY — DON'T CONFLATE

Adjuvant VBT = vault, 0.5 cm depth, post-hysterectomy. **Definitive uterine brachy** = whole uterus in situ, far higher dose, different applicator/intent.

★ MASTER PEARL TYING IT TOGETHER

Almost every trap reduces to **two reflexes**: (1) **histology gates staging** (endometrioid ≠ aggressive codes), and (2) **molecular trumps clinicopathology** (POLE de-escalates, p53abn escalates — regardless of grade/LVSI). Say both out loud and you defuse the majority of curveballs.

13 One-Page Exam Cram Sheet

TWO-MINUTE PRE-VIVA REVIEW — EVERYTHING THAT MATTERS, NO PROSE

PRINT THIS · REVIEW AT THE DOOR

FIGO 2023 — ESSENTIALS

IA1/2	no / <50% myo (endometrioid)
IA3	low-grade uterus+ovary (good px)
IB	≥50% myo
IC	aggressive, no invasion
IIA/B/C	cervix / subst.LVSI / aggressive+any invasion
III	A adnexa·serosa / B vagina·peritoneum / C nodes
IVA/B	bladder-bowel mucosa / distant

MOLECULAR — 4 GROUPS

POLEmut	excellent → **de-escalate** (observe St I–II)
MMRd	Lynch test · IO-sensitive
p53abn	poor → **treat as serous** (chemo+RT)
NSMP	classical risk stratification

! TOP TRAPS

Endometrioid ≠ IC/IIC · clear-cell+invasion=IIC · subst.LVSI=IIB · POLE beats LVSI & G3 · p53abn endometrioid=escalate · inoperable IA=brachy alone · cisplatin optional · node+ ≠ auto-VBT.

RISK GROUP → TREATMENT

Low	Observation
Intermediate	VBT
High-intermediate	EBRT ± VBT
High	EBRT + chemo ± VBT
Stage III–IVA	Chemo + RT ± IO

KEY DOSES

Pelvic EBRT	**45 Gy/25#**
VBT alone	**21 Gy/3#**
EBRT + VBT boost	**45/25 + 10/2#**
Pelvic nodal SIB	**55 Gy/25#**
Common iliac/PA SIB	**57.5 Gy/25#**

★ DEFINITIVE BRACHY MEMORY RULE

IA=7×5 · **IB**=45+7×3 · **II–III**=45+7×4 · **IVA**=45+7×5
EQD2 ladder ≈ 50 → 74 → 84 → 94 Gy. *Individualise to coverage + OAR.*

OAR D2CC ($EQD2_3$)

Bladder <90 · Rectum <75 · Sigmoid <75 · Bowel <75 Gy

SYSTEMIC THERAPY

Backbone	Carbo AUC5 + Paclitaxel 175 q3wk ×6
PORTEC-3	RT + cisplatin wk1&4 → carbo/taxol ×4
Sequence	sequential / sandwich / chemo-first (MDT)
Chemo first if	serous · p53abn · bulky nodes · distant risk

IMMUNOTHERAPY (ADVANCED/RECURRENT)

dMMR	Dostarlimab + carbo/taxol → maint. dostarlimab (RUBY)
pMMR recur.	Pembrolizumab + lenvatinib (KN-775)
Both	Pembro/dostarlimab + chemo front-line (GY018/RUBY)

TRIALS IN ONE LINE

P-1 EBRT↓LRR not OS · **P-2** VBT=EBRT (HIR) · **P-3** +chemo↑OS (St III/p53abn) · **GOG-249** EBRT>VBT+chemo · **GOG-258** chemo backbone, RT↑local · **RUBY** dostarlimab (dMMR) · **GY018** pembro both MMR.

? TWO REFLEXES TO WIN THE VIVA

1 · **Histology gates staging.**
2 · **Molecular trumps clinicopathology** — POLE de-escalates, p53abn escalates.