Role of Radiotherapy in type1 early stage Endometrial Cancer

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Who benefit from RT in type1 early stage Endometrial Cancer?

Early Stage Endometrial Cancer

Stage	FIGO and the American Joint Committee on Cancer (AJCC) 2010	
I	IA	Limited to endometrium or invades less than one-half of the myometrium
	IB	Invades one-half or more of the myometrium
II	II	Invades stromal connective tissue of the cervix
III	IIIA	Tumor involves serosa and/or adenexa
	IIIB	Vaginal or parametrial involvement
	IIIC	Metastases to pelvic and/or para-aortic lymph nodes
IV	IVA	Invades bladder mucosa and/or bowel
	IVB	Distant metastases

Early Stage Endometrial Cancer

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Early Stage Endometrial Cancer

- What is the role of adjuvant radiotherapy in women with endometrial cancer?
- Specifically, are there subgroups of patients with stage I endometrial cancer who benefit from adjuvant radiotherapy?
- If so, which radiotherapy treatment is recommended?
- When is VCBT indicated?

Early Stage Endometrial Cancer

- Surgery (with or without adjuvant therapy) is recommended for medically operable patients
- Complete Staging Procedure?
- Adequate surgical staging provides important information to assist in selection of adjuvant therapy for endometrial tumors

Early Stage Endometrial Cancer

- Patients with stage I endometrial cancer, who are completely surgically staged, are stratified by adverse risk factors :

  - grade of tumors
  - myometrial invasion
  - LVSI
  - patient age

  - papillary serous or clear cell histologies

  - tumor volume
  - involvement of the lower uterine segment

Randomized Clinical Trials of RT

- Aalders et al. (1980)
  - **Aalders J, et al. *Obstet Gynecol. 1980;56(4):419-427.***
- PORTEC 1 (2000)
  - Creutzberg CL, et al. Lancet 2000;355:1404-1411.
- GOG 99 (2004)
  - **Keys HM, et al. *Gynecol Oncol. 2004;92(3):744-751. 2.***
- ASTEC (2007)
  - **Orton J, et al. *J Clin Oncol. 2007;25(18S): Abstract 5504.***
- PORTEC 2 (2008)
  - Nout RA,, et al. *J Clin Oncol* 2008;26: LBA5503
- Sorbe et al. (2009)
  - Sorbe B, et al. Int J Gynecol Cancer. 2009 Jul;19(5):873-8. doi: 10.1111/IGC.0b013e3181a6c9df
- Sorbe et al. (2011)
  - Int J Radiat Oncol Biol Phys. 2012 Mar 1;82(3):1249-55. doi: 10.1016/j.ijrobp.2011.04.014. Epub 2011 Jun 14.

Meta-analysis of RT

- SEER EBRT Overview (Lee JAMA 2006)[1]
- Cochrane Analysis (Kong Ann Oncol 2007)[2]
- Meta-analysis Johnson N (BJOG 2007)[3]
- Cochrane update Kong A, et al (2012)[4]

1- Lee CM, Szabo A, Shrieve DC, et al. Frequency and effect of adjuvant radiation therapy among women with stage I endometrial adenocarcinoma. *JAMA* 2006;295:389-397.[PMID: 16434629]

2- Kong A, Johnson N, Cornes P, et al. Adjuvant radiotherapy for stage I endometrial cancer. *Cochrane Database Syst Rev* 2007:CD00391

3- Johnson N, Cornes P. Survival and recurrent disease after postoperative radiotherapy for early endometrial cancer: Systematic review and meta-analysis. *BJOG* 2007;114:1313-1320.[PMID: 17803718]

4- Kong A, Johnson N, Kitchener HC, Lawrie TA. Adjuvant radiotherapy for stage I endometrial cancer. JNCI.J , Volume 104 (21) Oxford University Press – Nov 7, 2012.

Early Stage Endometrial Cancer

- the use of adjuvant RT improves pelvic control in patients with selected risk factors (and in some patients, RT also improves progression-free survival), but RT did not improve overall survival in any of the trials.
- many of these trials had limitations because most of the patients were low risk.
- the trials were underpowered for patients with high-risk factors.

Early Stage Endometrial Cancer

Aalders Trial :

- 540 St I pts, all received ICBT, 6000 rads
- Randomized to no vs 4000 rads pelvic RT
- No difference in overall survival or overall relapse
- Pelvic RT decreased pelvic failure, but altered pattern of failure
- benefit in patients with grade 3 and > 50% DMI

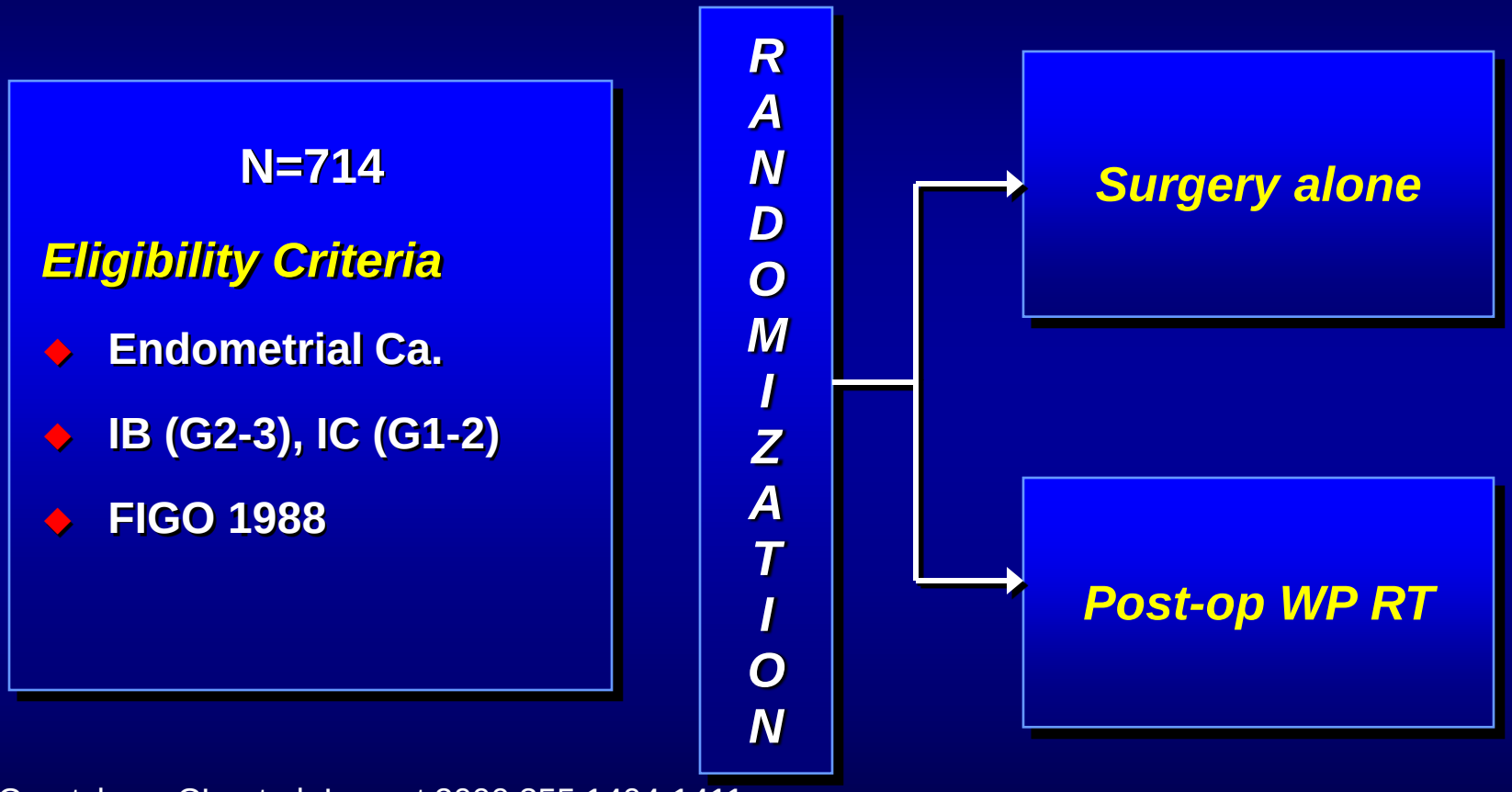
Aalders J, et al. *Obstet Gynecol. 1980;56(4):419-427.*

PORTEC-1

- PORTEC-1 trial :
  - suggested that RT provides a therapeutic benefit in selected patients with uterine-confined disease.

Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, et al. ***Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group.*** Lancet 2000 Apr 22;355(9213):1404-11

PORTEC-1



Creutzberg CL, et al. Lancet 2000;355:1404-1411.

*with 5 yr f/u, WP radiotherapy decreased LRR (14 → 4%) (P < 0.001)

75% of failures occuring in the vaginal vault

PORTEC-1

- First step to identification of risk categories
  - G3
  - IC
  - age > 60
- 2 out of 3 this risk factors, adopted as indication for EBRT in early endometrial cancer

PORTEC-1

- No difference in OS (81 vs. 85%; P=0.31) or DM (8 vs. 7%)

- Update with 10-year f/u and central pathology review for 80% of patients confirmed WP RT continued to reduce LRR (14 → 5%) ($p < 0.001$) without an OS benefit (66 vs. 73%), even after excluding IB grade 1 patients (134 cases).

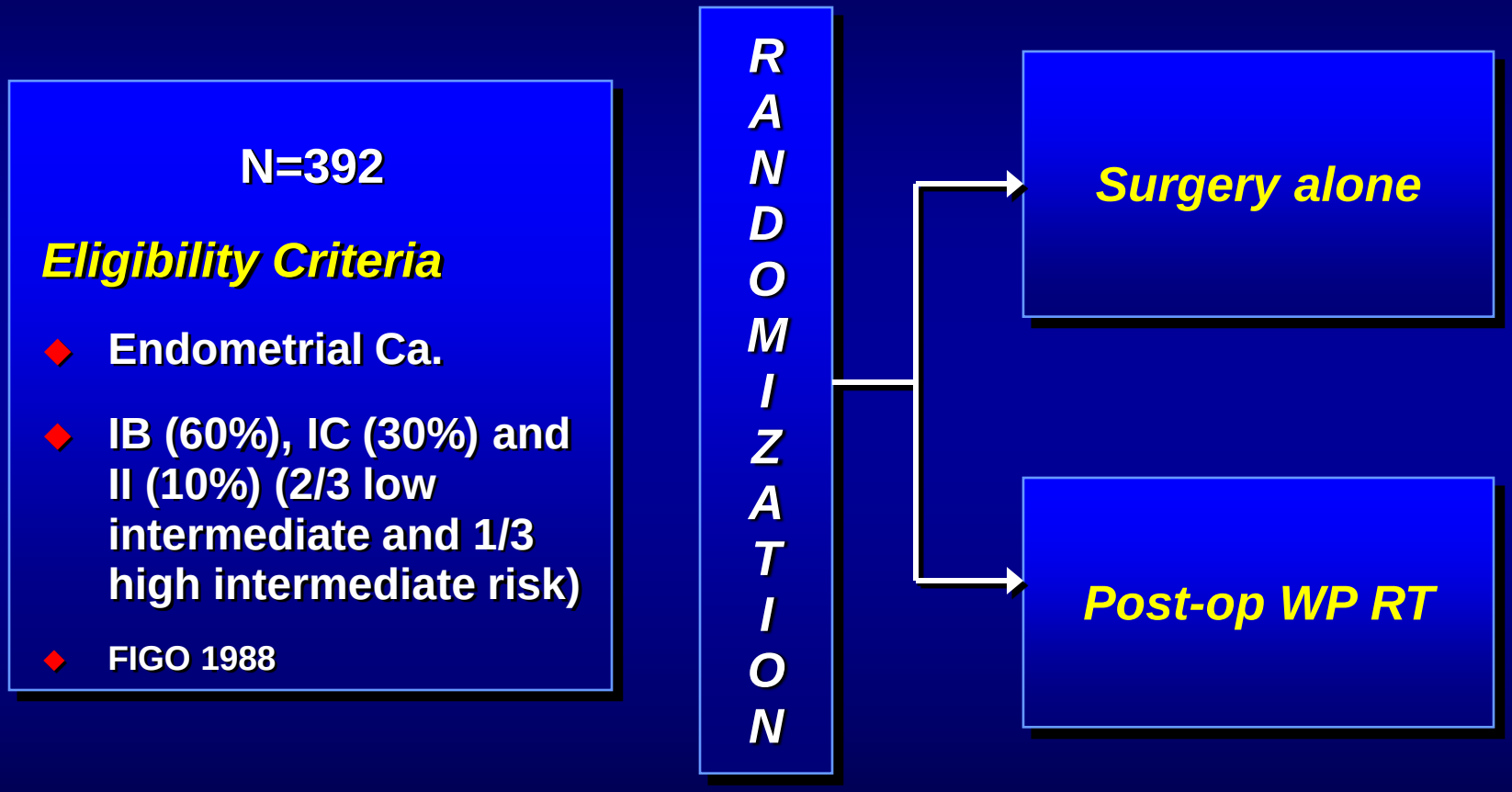
Scholten AN, van Putten WL, Beerman H, et al. Postoperative radiotherapy for stage 1 endometrial carcinoma: Long-term outcome of the randomized PORTEC trial with central pathology review. *Int J Radiat Oncol Biol Phys* 2005;63:834-838.[PMID: 15927414]

PORTEC-1

- Patients with 2 or more risk factors (age > 60 years, grade 3, and > 50% myometrial invasion) had greatest 10 yr LRR benefit with RT (23.1 → 4.6%)

Scholten AN, van Putten WL, Beerman H, et al. Postoperative radiotherapy for stage 1 endometrial carcinoma: Long-term outcome of the randomized PORTEC trial with central pathology review. *Int J Radiat Oncol Biol Phys* 2005;63:834-838.[PMID: 15927414]

GOG-99 (keys Trial-2004)



Keys HM, et al. *Gynecol Oncol. 2004;92(3):744-751. 2.*

*with 6 yr follow-up, improved LRR (12 → 3%; P=0.07) mostly among high-intermediate risk patients (26 → 6%) compared to low intermediate risk (6 → 2%)

OS no differece (86 → 92) but not powered to detect OS change

GOG-99 (keys Trial-2004)

- Complete surgical staging
- EBRT ➔ 50.4 Gy
- Risk Grouping :

  - G2-3
  - Outer 1/3 involvement
  - LVSI

Age < 50 + 3 factors
age > 50 <= 70 years + 2 factors
or age >70 years + 1 factor

} High Intermediate

GOG-99 (keys Trial-2004)

- WPRT improved LRR (12 → 3%), mostly among high-intermediate risk patients (26 → 6%) compared to low–intermediate risk patients (6 → 2%)

- No difference in OS (86→92%), but not powered to detect OS change. Majority of pelvic recurrences were in the vaginal cuff

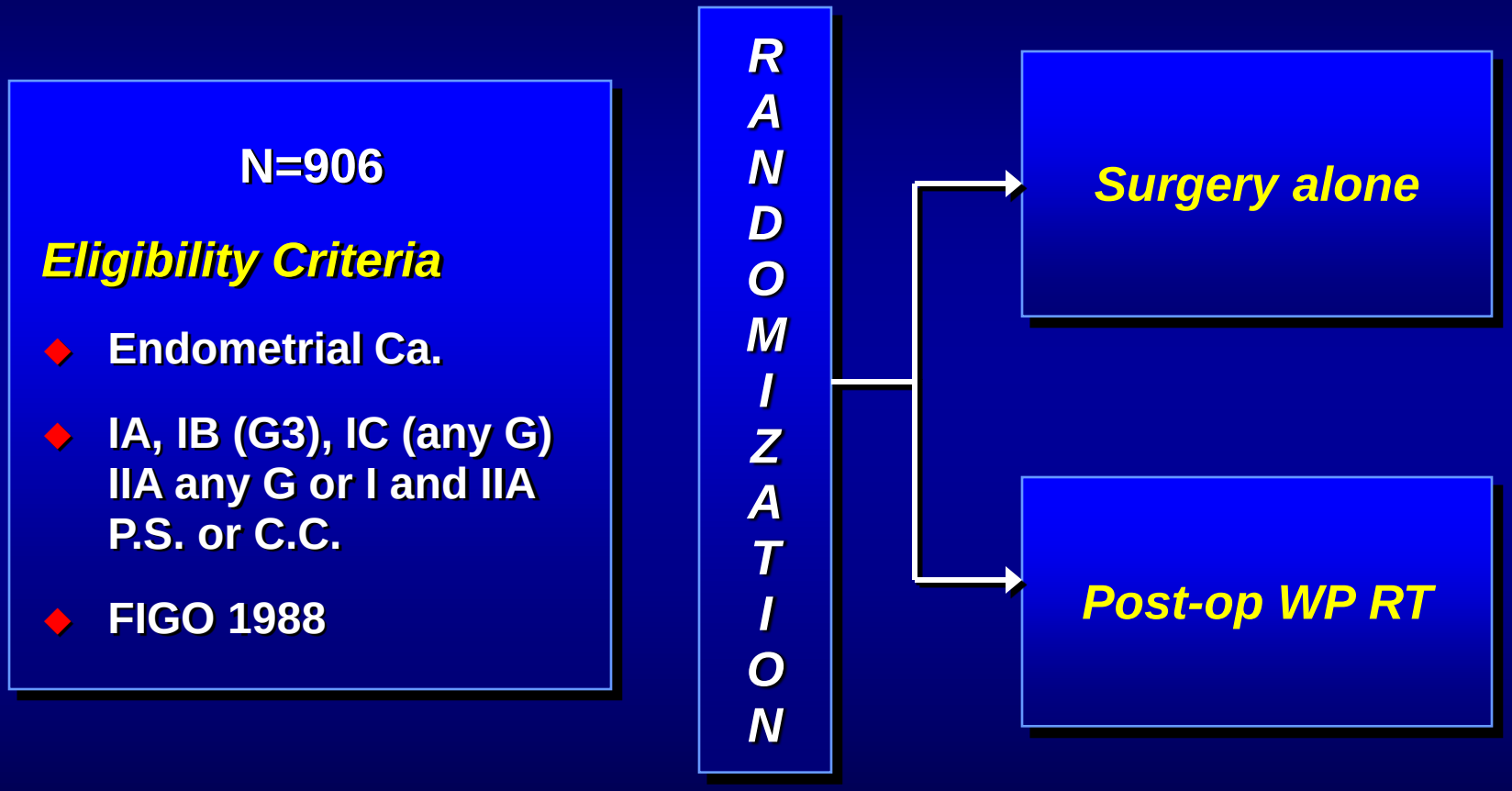
ASTEC-EN5 (2007)

- ASTEC trial :

  - ASTEC/EN.5 suggested that adjuvant pelvic RT alone did not improve either relapse-free survival (i.e., progression-free survival) or overall survival in patients with intermediate-risk or high-risk early stage endometrial cancer, but there was a small improvement in pelvic control.

  - However, the ASTEC/EN.5 study is very controversial; 51% of the patients in the ASTEC observation group received vaginal brachytherapy.

ASTEC-EN5 (2007)



Orton J, et al. *J Clin Oncol. 2007;25(18S): Abstract 5504.*

***51% of observation arm, recived vaginal cuf brachytherapy**

WP RT reduced isolated pelvic or vaginal recurrences (6.1 → 3.2%; P=0.02) and increased toxicity

ASTEC-EN5 (2007)

- EBRT ➔ 40– 46 Gy??
- vaginal cuff brachytherapy was used in 51% of patients randomized to the observation arm??

ASTEC-EN5 (2007)

- There was no difference in 5-year OS (84%) or DSS (89–90%)

- WP RT :
  - reduced isolated pelvic or vaginal recurrences (6.1→3.2%)
  - increased acute toxicity (27→ 57%) and late severe toxicity (3 → 7%)

PORTEC-2 (2008)

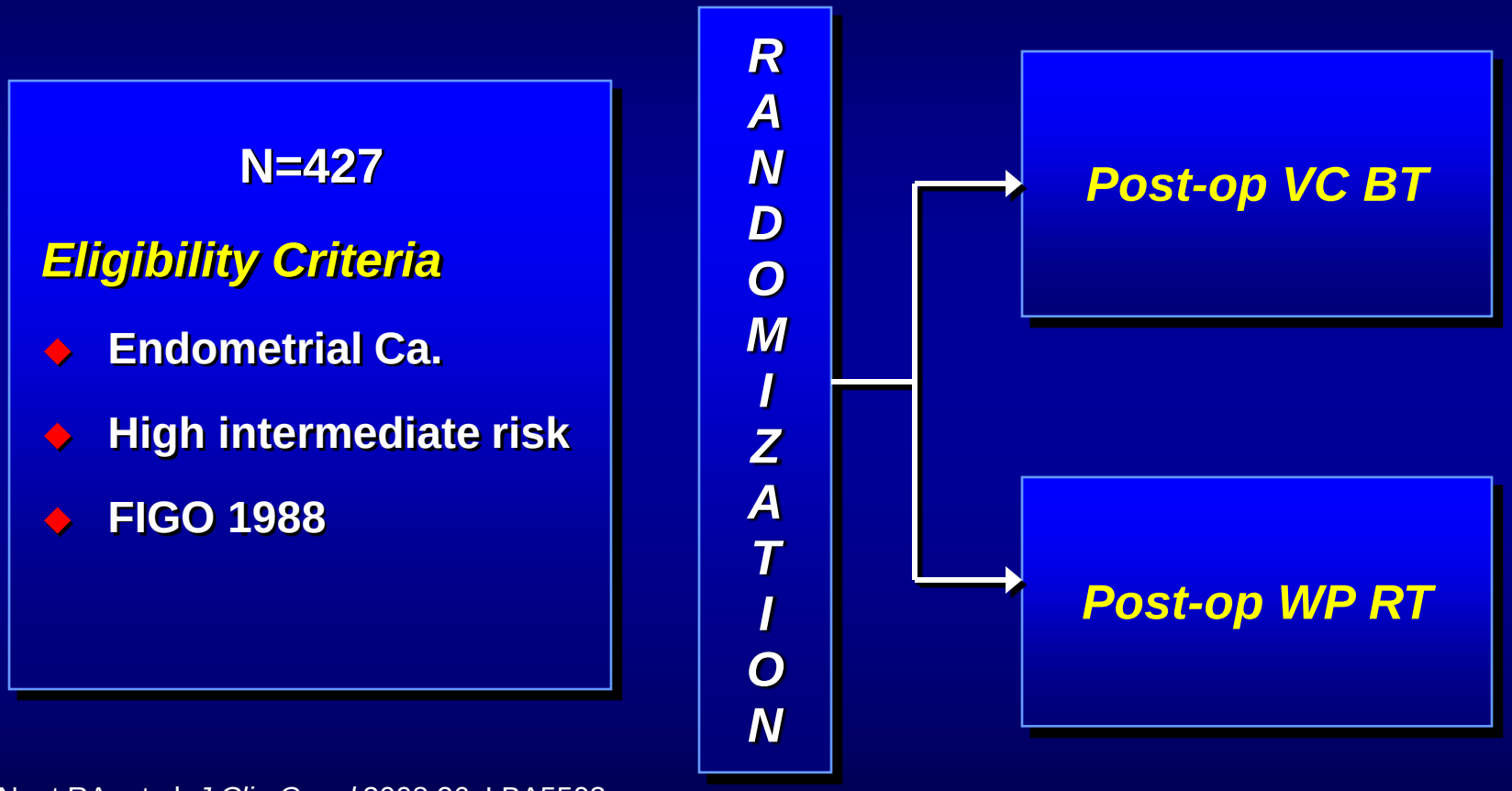
- Both the GOG 99 and PORTEC-1 trials revealed that most of the initial recurrences for patients with initial uterine-confined tumors were limited to the vagina, prompting the increasing use of vaginal brachytherapy alone as adjunctive treatment.

PORTEC-2 (2008)

- PORTEC-2 trial :
  - To further assess the relative benefits of whole pelvic RT versus vaginal brachytherapy alone in uterine-confined disease, PORTEC-2 randomly assigned patients to these 2 modalities.
  - PORTEC-2 showed excellent and equivalent vaginal and pelvic control rates with both adjuvant radiation approaches, and no difference in overall survival.

Nout RA, Putter, H., Jürgenliemk-Schulz IM, et al. Vaginal brachytherapy versus external beam pelvic radiotherapy for high-intermediate risk endometrial cancer: Results of the randomized PORTEC-2 trial [abstract]. *J Clin Oncol* 2008;26: LBA5503.

PORTEC-2 (2008)



Nout RA, et al. *J Clin Oncol* 2008;26: LBA5503.

*There was no significant difference in 3yr VC relapse (0.9% VC; 2% WP), OS (90 → 91%) or RFS (89 → 90%).

Quality of life was better with VCBT

PORTEC-2 (2008)

- high-intermediate risk ➔
  - age >60 years ➔ stage IC grade 1–2 or IB grade 3
  - any age ➔ stage IIA grade 1–2 or grade 3 with <50% invasion

- randomized to WPRT (46 Gy) or VC brachytherapy (21 Gy HDR in 3 fx or 30 Gy LDR)

PORTEC-2 (2008)

- Although WP RT reduced pelvic relapse (3.6 → 0.7%), there was no significant difference in 3-year:

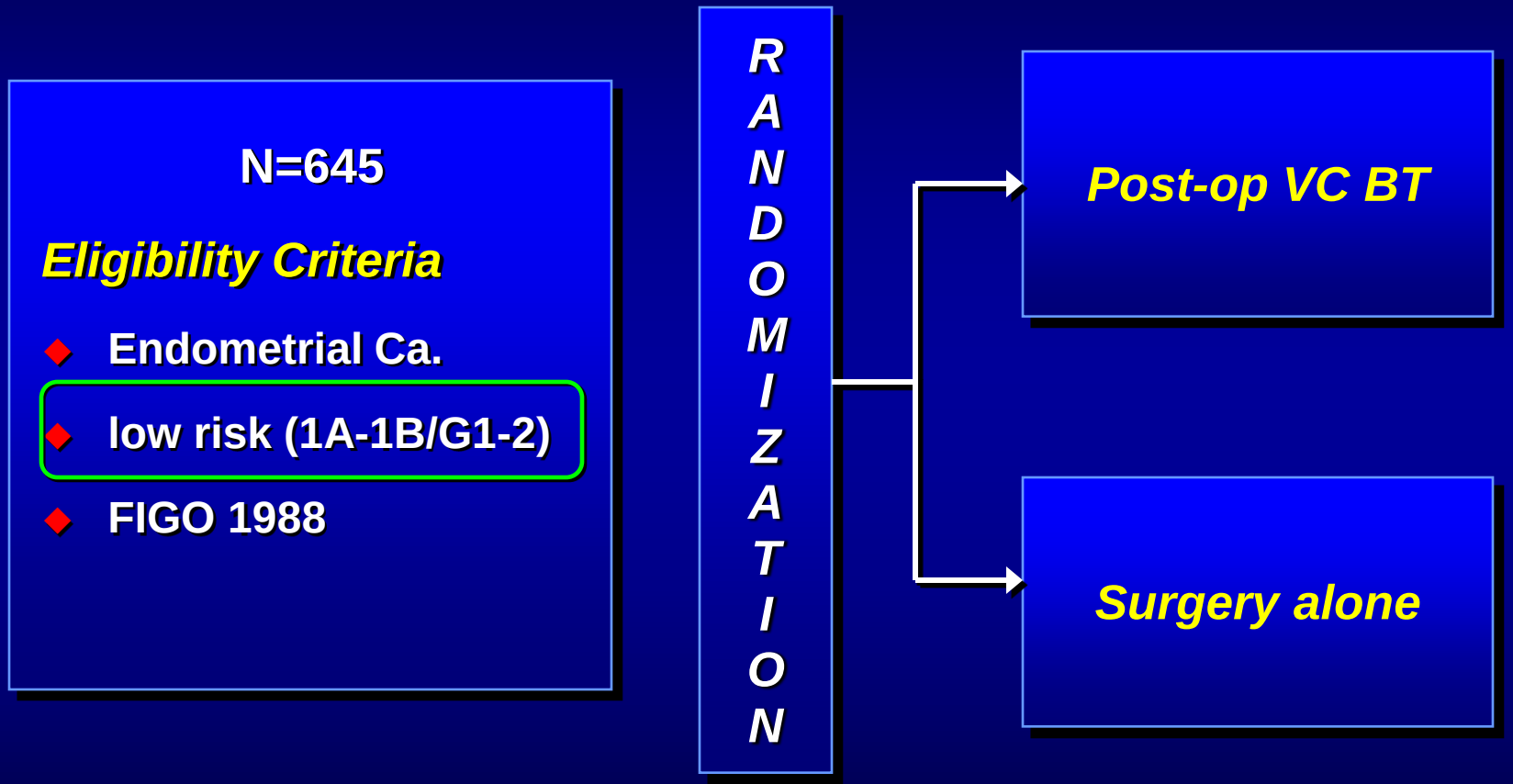
VC relapse (0.9% VC vs. 2% WP)

OS (90–91%)

RFS (89–90%)

Patient-reported quality of life was better with VC brachytherapy

Swedish (Sorbe2009)



Sorbe B, et al. Int J Gynecol Cancer. 2009 Jul;19(5):873-8. doi: 10.1111/IGC.0b013e3181a6c9df.

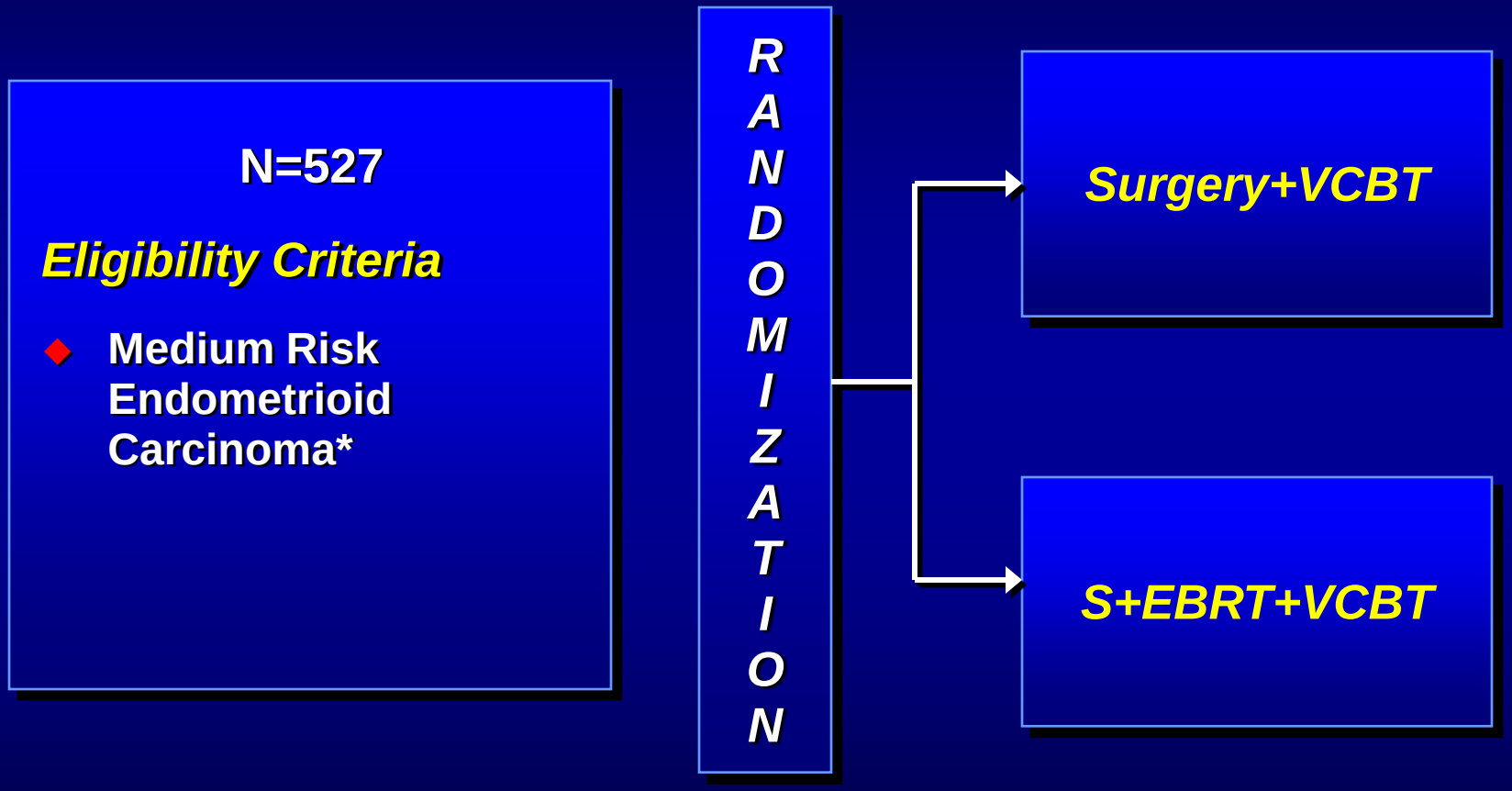
* The rate of vaginal recurrences was 1.2% in the treatment group versus 3.1% in the control group (*P* = 0.114).

The overall recurrence rate and survival were similar in the 2 groups.

Sorbe (2009)

- Side effects were few and mild (grade 1-2).
  - Dysuria, frequency, and incontinence were slightly more common after vaginal irradiation (2.8% vs 0.6%, respectively).
  - Late intestinal problems were few and similar in the 2 groups.

Sorbe (2011)



Int J Radiat Oncol Biol Phys. 2012 Mar 1;82(3):1249-55. doi: 10.1016/j.ijrobp.2011.04.014. Epub 2011 Jun 14.

***1- Stage1 2- Endometrioid Histology 3- Presence one of the following risk factors: G3/DMI/DNA aneuploidy 4- Nuclear G1-2 5- Negative LN 6- negative cytology**

Sorbe (2011)

- **Median follow-up 62 mo =>**

  Five-year LRR were:

  1.5% after EBRT plus VBT

  5% after vaginal irradiation alone

  (p = 0.013)

- 5-year overall survival rates were 89% and 90%, respectively (p = 0.548)

- Endometrial cancer-related death rates were 3.8% after EBRT plus VBT and 6.8% after VBT (p = 0.118)

Sorbe (2011)

- Combined radiotherapy was well tolerated, with serious (Grade 3) late side effects of less than 2%

However, there was a significant difference in favor of VBT alone

Sorbe (2011)

- Authors Conclusion:
  - EBRT should probably be reserved for high-risk cases with two or more high-risk factors (G3/DMI/DNA aneuploidy)
  - VBT alone should be the adjuvant treatment option for purely medium-risk cases

Early Stage Endometrial Cancer

- stage IC, deeply invasive, grade 3, uterine-confined disease have a relatively poor prognosis
- Despite adjuvant therapy with pelvic RT, a significant number of patients continue to have an appreciable risk of distant metastases
- Therefore, some clinicians suggested that adding chemotherapy to adjuvant RT may provide added therapeutic benefit (i.e., decrease distant metastases).
- Progression-free survival is improved with adjuvant sequential chemoRT.
- The role of adjuvant chemotherapy in invasive high-grade, uterine-confined disease is being further studied (e.g., GOG 249, PORTEC-3)

Meta-analysis of EBRT

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Identification of High Risk

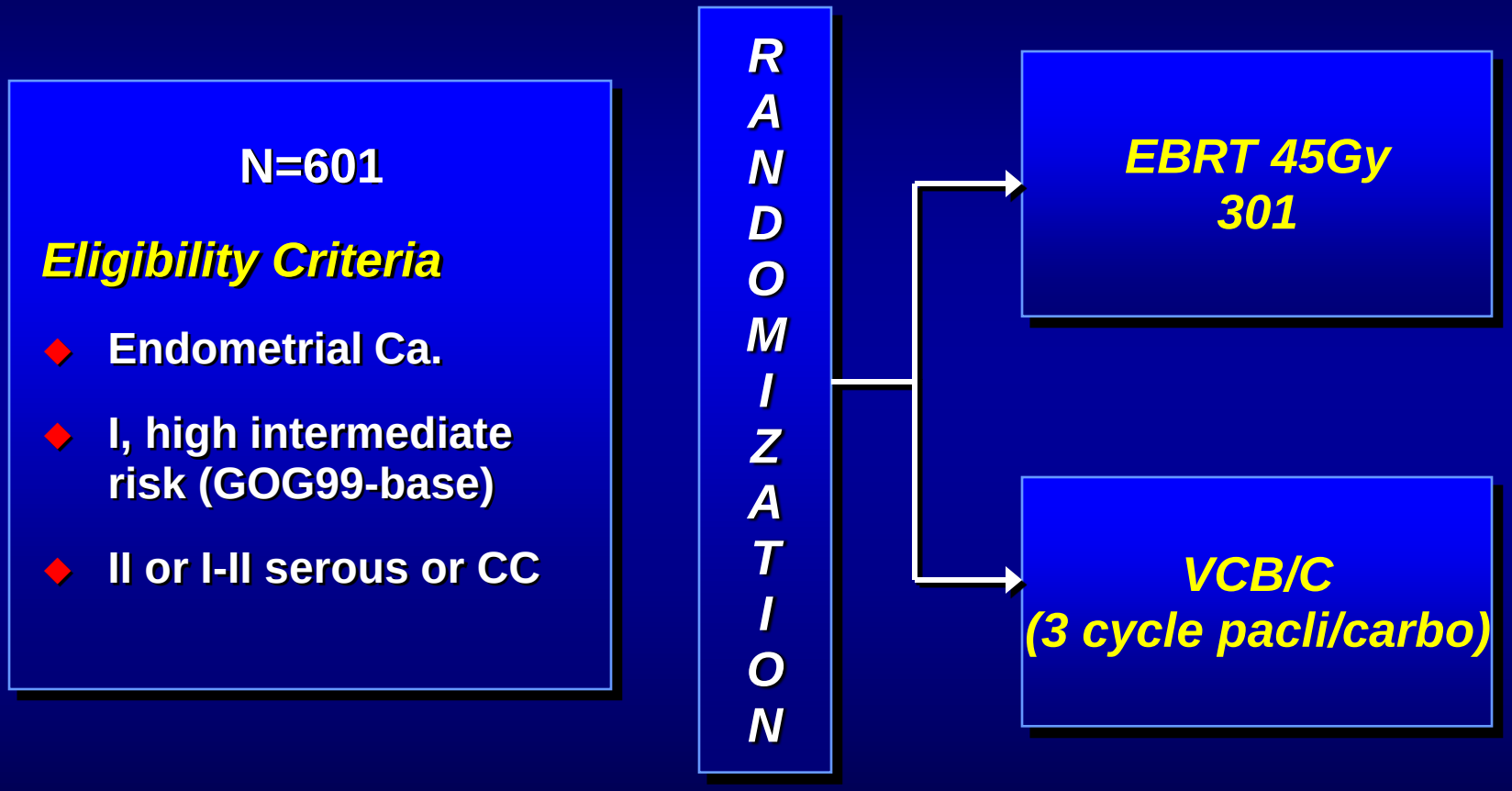
Estimated Hazard Ratios of Radiation vs No Radiation for All Patients and Patients With Surgical Lymph Node Examinations*

	All Patients		Patients With Surgical Lymph Node Examination	
Stage/ Grade	Hazard Ration (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
IA/1	0.73 (0.34-1.57)	.42	0.80 (0.44-1.45)	.46
IB/1	0.89 (0.62-1.27)	.51	0.75 (0.49-1.16)	.20
IC/1	0.44 (0.31-0.63)	<.001	0.59 (0.39-0.90)	.01
IA/2	1.42 (0.84-2.37)	.19	1.15 (0.68-1.94)	.59
IB/2	1.02 (0.81-1.28)	.88	1.08 (0.80-1.45)	.62
IC/2	0.93 (0.73-1.19)	.56	0.84 (0.62-1.14)	.26
IA/3-4	1.01 (0.65-1.56)	.96	1.03 (0.64-1.66)	.90
IB/3-4	0.94 (0.77-1.16)	.58	0.95 (0.74-1.21)	.66
IC/3-4	0.72 (0.57-0.92)	.009	0.73 (0.55-0.96)	.02

*Estimates are averaged over the observed race, lymph node examination status, and age at diagnosis specific for each stage/grade combination.

Lee CM, et al. *JAMA*. 2006;295(4):389-397.

GOG 249



Orton J, et al. *J Clin Oncol. 2007;25(18S): Abstract 5504.*

- Acute toxicity was more common and more severe with VCB/C. Grade 3 or higher adverse events were reported in 32 patients on the PXRT arm versus 187 patients on the VCB/C arm. Grade 3 or higher late effects were seen in 37 and 35 patients on the PXRT and VCB/C arms, respectively.

GOG 249

- With a median follow-up of 53 months, the 36 month RFS was 82% for both PXRT and VCB/C.
- The 36-month OS was 91% versus 88% for PXRT and VCB/C, respectively.
- No significant differences were noted between the two arms in terms of vaginal or distant failure.
- However, pelvic or para-aortic nodal recurrences were significantly more common in the VCB/C arm (25 vs 12), largely driven by the difference in pelvic nodal failure (20 vs 6 patients).

GOG 249

- Conclusion:

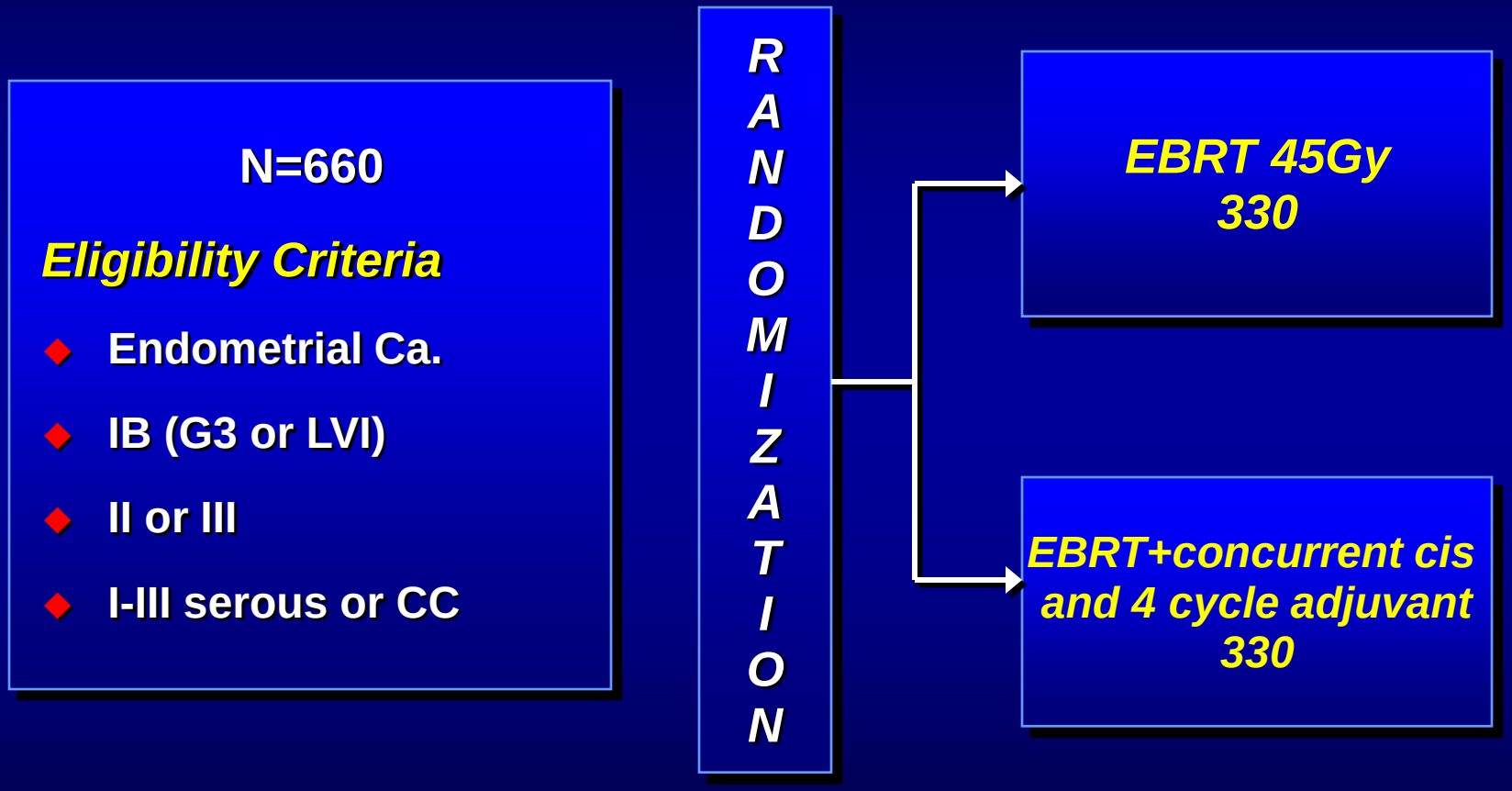
This study did not demonstrate a superiority of VCB/C to PXRT in women with HR endometrial cancer.

Acute and late toxicity

and pelvic and para-aortic nodal failure were more frequent in the VCB/C arm.

- Both arms appeared to be well tolerated with high completion rates.
- PXRT remains an effective, well-tolerated, and acceptable adjuvant treatment in patients with high risk, early-stage endometrial carcinoma.

PORTEC3



Lancet Oncol. 2018 Mar; 19(3): 295–309. doi: 10.1016/S1470-2045(18)30079-2

PORTEC3

- 5-yr OS was 81·8% (95% CI 77·5–86·2) with chemoradiotherapy versus 76·7% (72·1–81·6) with radiotherapy (adjusted hazard ratio [HR] 0·76, 95% CI 0·54–1·06; p=0·11);

- 5-year failure-free survival was 75·5% (95% CI 70·3–79·9) versus 68·6% (63·1–73·4; HR 0·71, 95% CI 0·53–0·95; p=0·022).

- Grade 3 or worse adverse events during treatment occurred in 198 (60%) of 330 who received chemoradiotherapy versus 41 (12%) of 330 patients who received radiotherapy (p<0·0001).

- Neuropathy (grade 2 or worse) persisted significantly more often after chemoradiotherapy than after radiotherapy (20 [8%] women vs one [1%] at 3 years; p<0·0001).

Risk Stratification

- Low risk ➔ Stage IA, grade1 and 2

- Intermediate risk
  (Stage IB, IC, G3)
  - Low intermediate
  - High intermediate

Risk Stratification

- Low risk ➔ Stage IA, grade1 and 2

- Intermediate risk
  (Stage IB, IC, G3)

Low

- Age < 50 + 1 or 2 factors
- age > 50 = < 70 years + 1 factor
- Any age without risk factors

High

- Age < 50 + 3 factors
- age > 50 = < 70 years + 2 factors
- or age >70 years + 1 factor

Risk factors

- G2-3
- Outer 1/3
- LVSI

Recommendation

- Low risk ➔ Relapse =< 5% ➔ Observation
- Intermediate risk
  - Low ➔ Observation or VCBT
  - High ➔ VCBT or EBRT
- Stage II ➔
  - grade 1/stromal invasion < 50% ➔ VCBT
    else ➔ EBRT
  - I-II SC/CC ➔ EBRT

Recommendation

- Low risk ➔ Relapse =< 5% ➔ Observation
- Intermediate risk
  - Low ➔ if G3 + Stage IC ➔ VCBT
    else ➔ observation
  - High ➔ if G3 + Stage IC ➔ EBRT
    else ➔ VCBT

NCCN 2/2020

Surgically staged: Stage I[d]

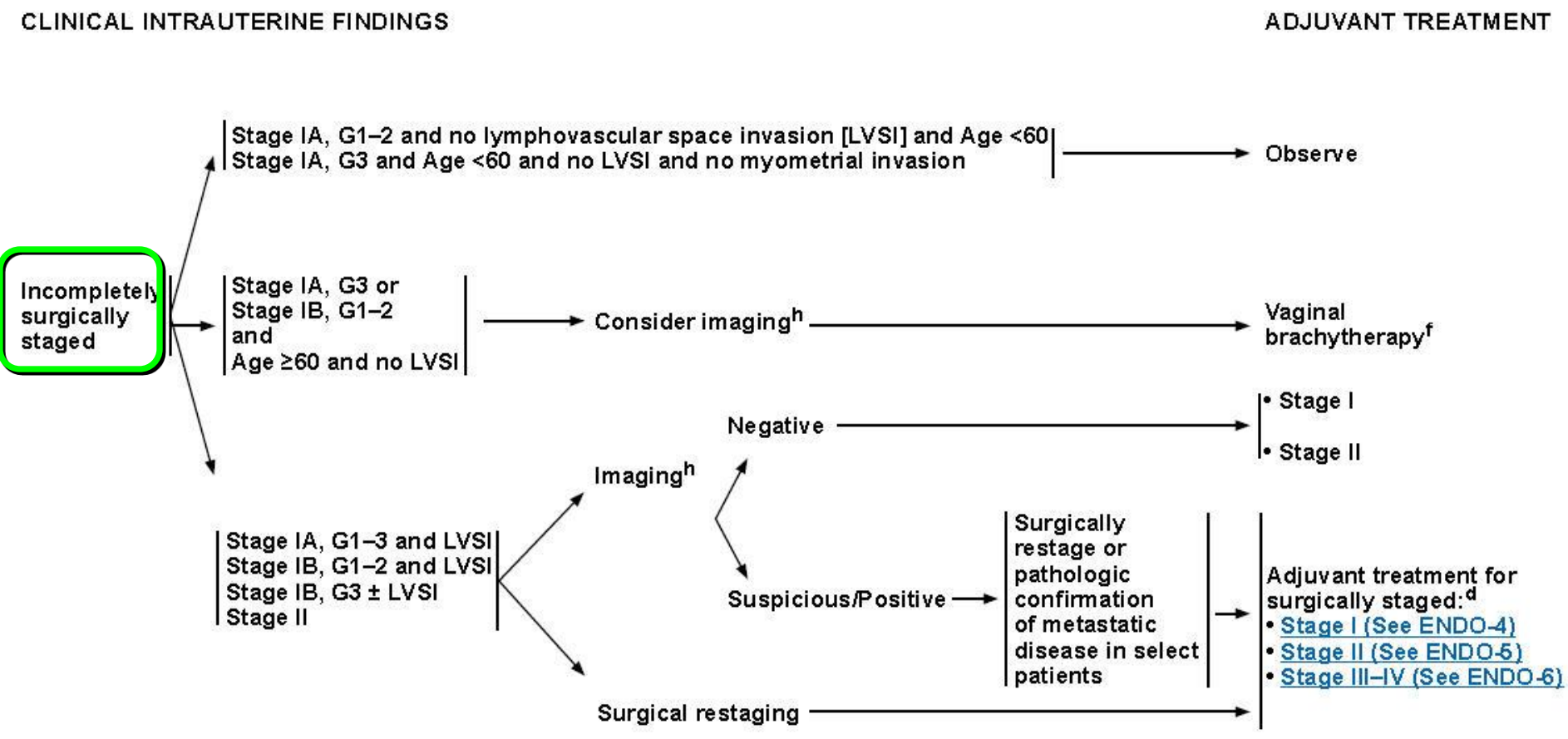
FIGO Stage	Histologic Grade	Adjuvant Treatment
IA	G1, G2	Observation preferred or Consider vaginal brachytherapy if lymphovascular space invasion (LVSI) and/or age ≥60 y[m]
	G3	Vaginal brachytherapy preferred or Consider observation if no myoinvasion or Consider EBRT if high-intermediate risk (HIR)[n] (category 2B)
IB	G1	Vaginal brachytherapy preferred[n] or Consider observation if no other adverse risk factors[n,o]
	G2	Vaginal brachytherapy preferred or Consider EBRT if HIR[n] or Consider observation if no other adverse risk factors[p]
	G3	RT (EBRT and/or vaginal brachytherapy) ± systemic therapy[p] (category 2B for systemic therapy)

Surgically staged:[d] Stage II[q,r]

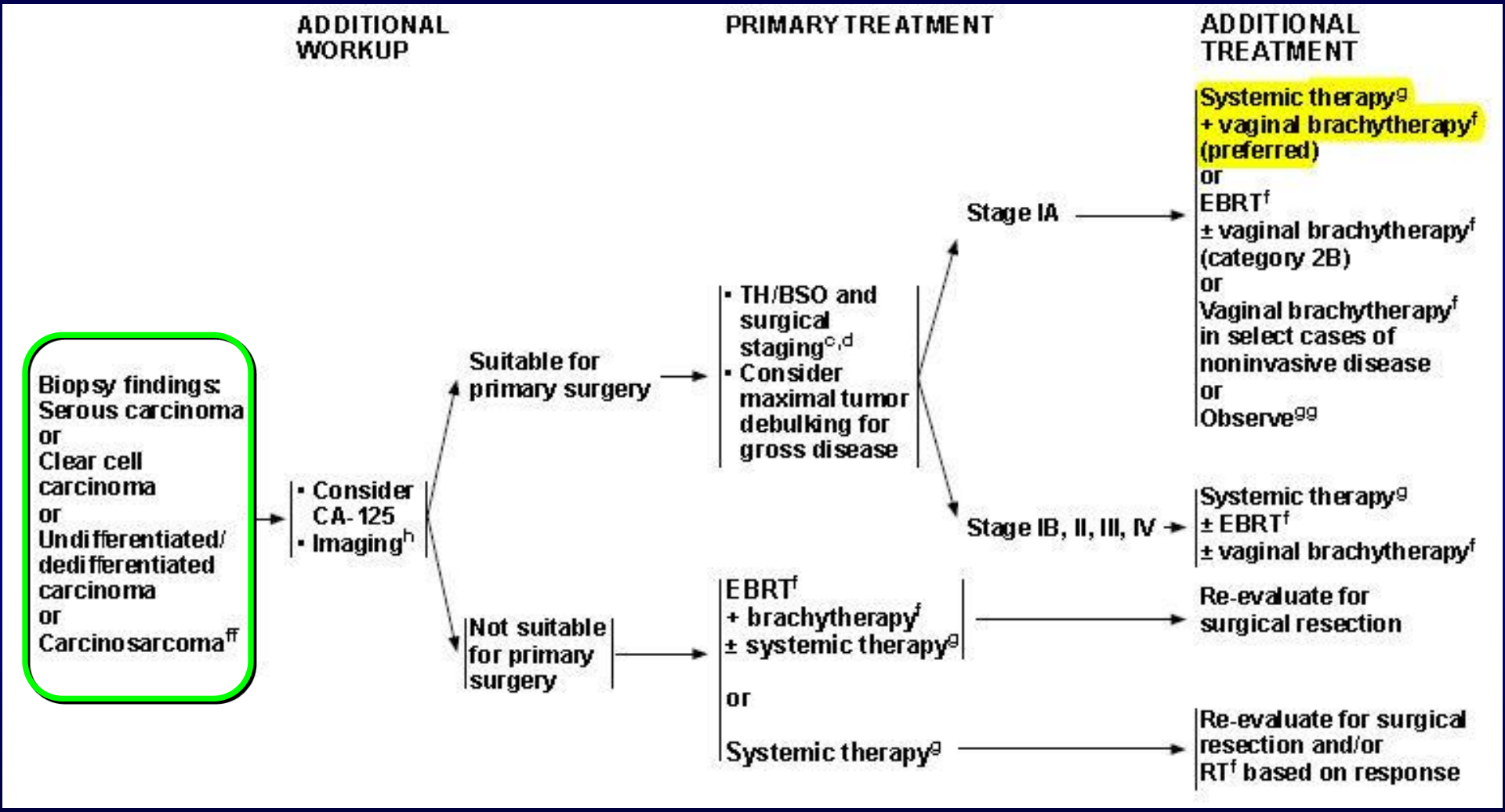
FIGO Stage	Histologic Grade	Adjuvant Treatment
II	G1–G3	EBRT (preferred) and/or vaginal brachytherapy[s] ± systemic therapy (category 2B for systemic therapy)

sVaginal brachytherapy is also an option for low-grade disease with negative surgical staging or minimal invasion. Observation is an option for those patients who have had a radical hysterectomy with negative surgical margins.

NCCN 2/2020


CLINICAL INTRAUTERINE FINDINGS
ADJUVANT TREATMENT
Incompletely surgically staged
Stage IA, G1–2 and no lymphovascular space invasion [LVSI] and Age <60
Stage IA, G3 and Age <60 and no LVSI and no myometrial invasion
Observe
Stage IA, G3 or
Stage IB, G1–2
and
Age ≥60 and no LVSI
Consider imaging[h]
Vaginal brachytherapy[f]
Stage IA, G1–3 and LVSI
Stage IB, G1–2 and LVSI
Stage IB, G3 ± LVSI
Stage II
Imaging[h]
Negative
• Stage I
• Stage II
Suspicious/Positive
Surgically restage or pathologic confirmation of metastatic disease in select patients
Surgical restaging
Adjuvant treatment for surgically staged:[d]
• Stage I (See ENDO-4)
• Stage II (See ENDO-5)
• Stage III–IV (See ENDO-6)

NCCN 2/2020



ggObservation only for select patients with no residual serous or clear cell carcinoma in the hysterectomy specimen.

NCCN 2/2020

- Stage IA ➔
  - G1, G2 ➔ Observe (preferred)
    - If LVI or age > 60 ➔ consider BRT
  - G3 ➔ BRT (Preferred)
    - If < 60yr, No LVI → Consider observation
- Stage IB ➔
  - G1, G2 ➔ BRT (preferred)
    - Consider observation if there is no risk factor
    - For grade2 consider EBRT if HIR
  - G3 ➔ EBRT and/or BRT
- Stage II ➔
  - **Prefered ➔ EBRT and/or BRT**
  - G1 & minimal invasion ➔ BRT

Risk
- age >= 60
- Outer 1/3
- LVSI

Molecular subtypes

- the Cancer Genome Atlas (TCGA) consortium10 defined 4 prognostic EC subgroups:

1- polymerase ε exonuclease (POLE) ultramutated ➔ favorable prognoses

2- hypermutated MSI ➔ intermediate prognoses (MMR protein)

3- copy number low (CNL) ➔ intermediate prognoses (TP53-wild-type)

4- copy number high (CNH) (serous-like) ➔ unfavorable prognoses (highTP53-mutant)

Molecular subtypes

- The TCGA applied methods that are too costly and cumbersome for widespread implementation into routine clinical practice

- Several other groups have attempted to identify these categories by using immunohistochemical biomarkers rather than molecular studies

Molecular subtypes

- With regard to the TP53-mutated tumors, even with endometrioid histology, were still found to have worse outcomes

- Molecular subtyping can be incorporated into clinical practice through the implementation of diagnostic algorithms ➔

Molecular subtypes

- POLE hotspot mutation analysis ➔ If patients test positive, they fall within the POLE-mutated molecular subtype, while negative testing would indicate the need to look at the DNA mismatch repair IHC.

- If deficient mismatch repair is observed, the tumor would be categorized as MSI-high.

- However, if the IHC is intact, this would indicate the addition of another IHC, which is P53, a commonly available and easy to biomarker to perform

Molecular subtypes

- From there, if aberrant staining is observed, then the tumor would be categorized as copy-number high or TP53-abnormal molecular subgroup.

- Finally, if the tumor shows normal or wild-type staining, that puts it into the copy-number low group.

- With the exception of the POLE hotspot mutation analysis, most of this would be pretty easy to incorporate into regular clinical practice

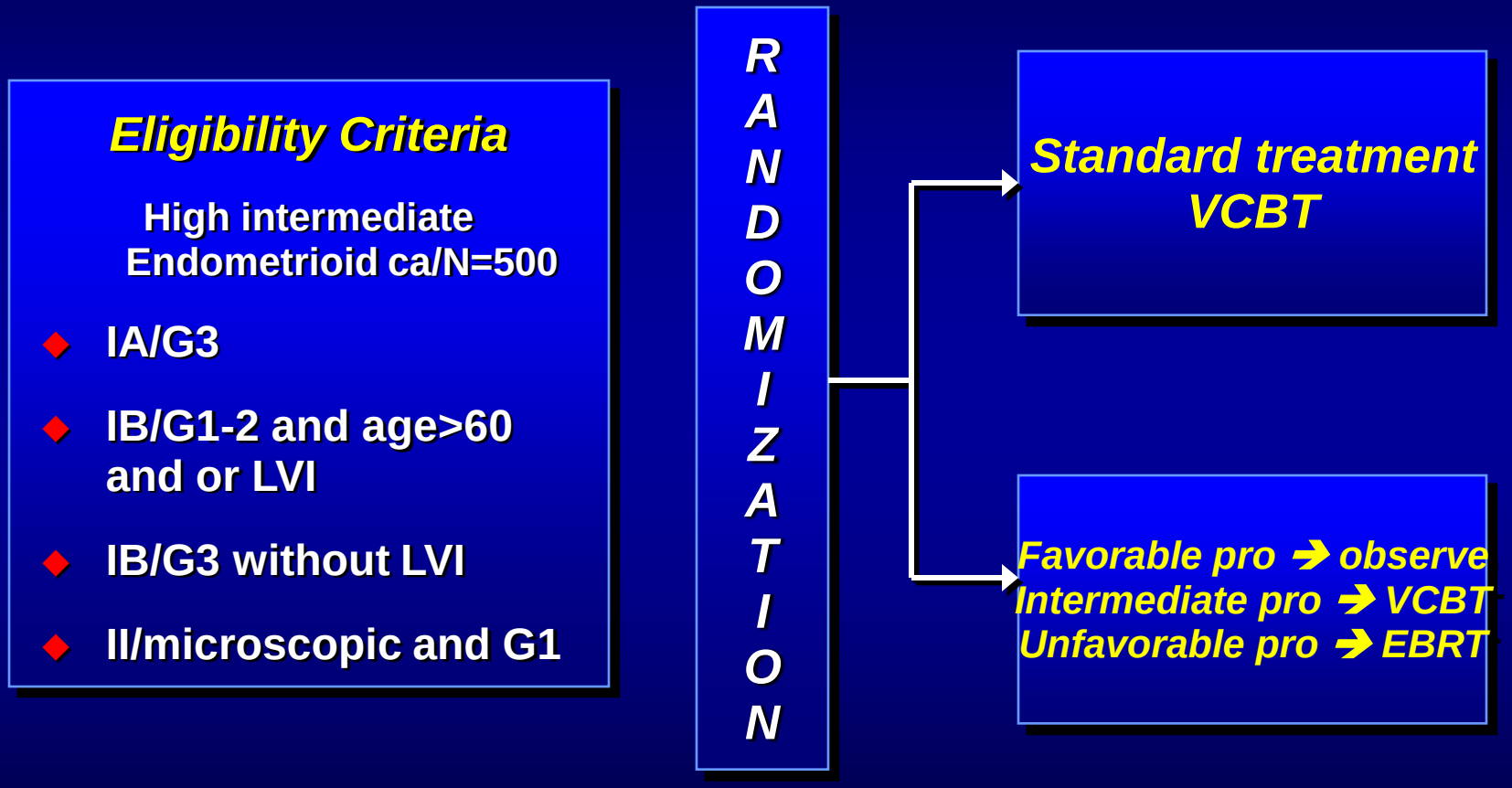
Molecular subtypes

- Similar diagnostic algorithms have been tested in trials such as the PORTEC-4a study

- Much like the aforementioned algorithm, patients with a POLE mutation were found to have favorable outcomes. Another molecular subtype found to fall into this favorable category were patients who did not have a mismatch repair deficiency; these patients were put into the category of CTNNB1 wild-type. Those who were found to have mismatch repair deficiency were categorized as having a CTNNB1 mutation, which indicated an intermediate prognosis. However, patients who were noted as having substantial LVSI, a TP53 mutation, or a >10% L1CAM expression, were ranked as having the most unfavorable prognosis.

- there is potential to change practice

PORTEC4a



The trial is registered at clinicaltrials.gov (NCT03469674) and ISRCTN (11659025).

Estimated date for presentation of (first) results is expected in 2023.

PORTEC4a

- prospective, multicenter, randomised phase III trial with high-intermediate risk features:

  - to investigate the role of an integrated:

    Clinicopathological risk profile

    molecular risk profile

PORTEC4a

- The primary endpoint is vaginal recurrence.

- Secondary endpoints are recurrence-free and overall survival; pelvic and distant recurrence; 5-year vaginal control (including treatment for relapse); adverse events and patient-reported symptoms and quality of life; and endometrial cancer-related healthcare costs.

Molecular subgrouping

- Stello et al. used IHC for p53 and MMR protein assessment and Sanger sequencing for POLE hotspots genotyping as surrogate of the EC TCGA subgroups

- was to develop a method based on the genotyping of only 12 genes with the definition and implementation of a reproducible RF model (12g-algorithm) to classify EC into the four prognostic groups.

- We designed a small NGS gene panel with data from the EC TCGA dataset consisting of 13 of the most discriminant genes which presented the highest absolute and differential mutational frequency among the groups.