Classification moléculaire

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Classification bio-moléculaire née d'un nouveau paradigme bien identifié dans le TCGA :

Groupe1: Tumeurs ultra-mutées « POLE » (7%)	Groupe2: Tumeurs hyper-mutées avec MSI (28%)	Groupe3: Tumeurs à faible nombre de copies, MSS (39%)	Groupe 4: Tumeurs à nombre de copies élevé « serous-like »(26%)
• (90%) Carcinomes endométrioïdes de G3 • Mutation dans le domaine exonucléase du gène de la polymérase E (POLE) impliqué dans la réplication et la réparation de l'ADN • charge de mutations élevée • **Excellent pronostic** • **Survie sans maladie à 5 ans: >95%**	• 30 à 40% des carcinomes endométrioïdes • perte de protéines de la voie de réparation MMR • forte charge mutationnelle (PTEN, PIK3CA, KRAS) • **Bon pronostic** • **Survie sans maladie à 5 ans: 90%**	• Stabilité des micro satellites • Comprend la plupart des CE MSS (60% BG, 8% HG), 2,3% Ca séreux • Mutations CTNNB1 (β Caténine/52%), PTEN, PIK3CA, KRAS… • **Pronostic intermédiaire** • **Survie sans maladie à 5 ans: 52%**	• 98 % Ca séreux, 25% des CE HG, 5% des CE BG • Mutation *TP53+++* • **Mauvais pronostic** • **Survie sans maladie à 5 ans: 42%**

Profils évolutifs et pronostics distincts, non superposables à ceux identifiables via les critères classiques (histologie – grade – LVSI)

Historiquement (avant 2010) :

- RTE pelvienne = standard en adjuvant des CE haut risque

- Essais randomisés : CT versus RTE

→ Pas de différence en survie mais

+ de récidive à distance dans le bras RTE

+ de récidive locale/pelvienne dans le bras CT

DONC développement de la RT-CT

Maggi R, Lissoni A, Spina F, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. *Br J Cancer* 2006; **95:** 266–71.

Susumu N, Sagae S, Udagawa Y, et al. 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. *Gynecol Oncol* 2008; **108:** 226–33.

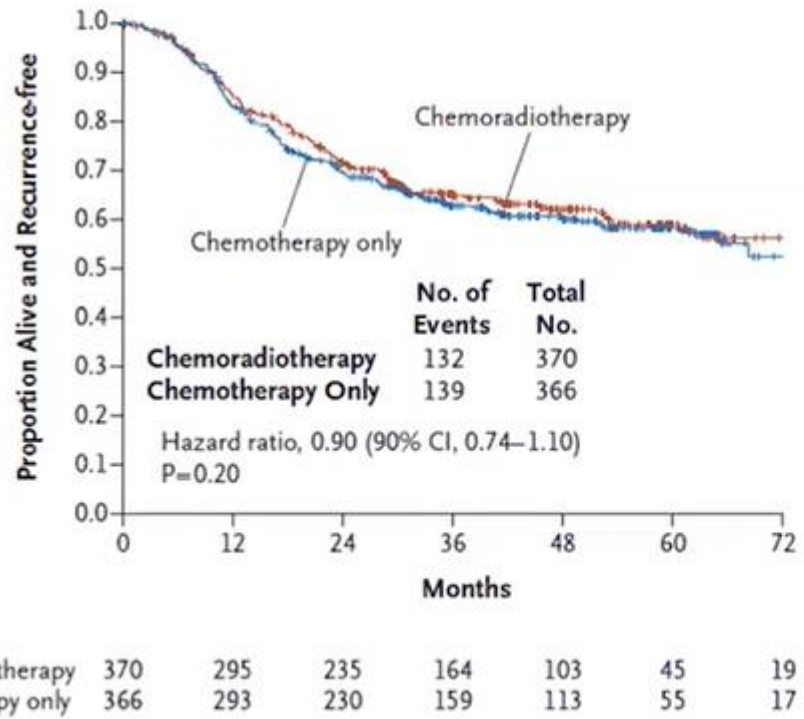
Klopp AH, Jhingran A, Ramondetta L, Lu K, Gershenson DM, Eifel PJ. Node-positive adenocarcinoma of the endometrium: outcome and patterns of recurrence with and without external beam irradiation. *Gynecol Oncol* 2009; **115:** 6–11.

Mundt AJ, McBride R, Rotmensch J, Waggoner SE, Yamada SD, Connell PP. Significant pelvic recurrence in high-risk pathologic stage I–IV endometrial carcinoma patients after adjuvant chemotherapy alone: implications for adjuvant radiation therapy. *Int J Radiat Oncol Biol Phys* 2001; **50:** 1145–53.

GOG 258

Stade III et IV
RT-CT concomitante puis 4 cures de Paclitaxel – Carboplatine versus
6 cures de Paclitaxel – Carboplatine

- Pas de différence en survie sans rechute



Dans le bras chimio seule:
Plus de récidives vaginales/ganglionnaires

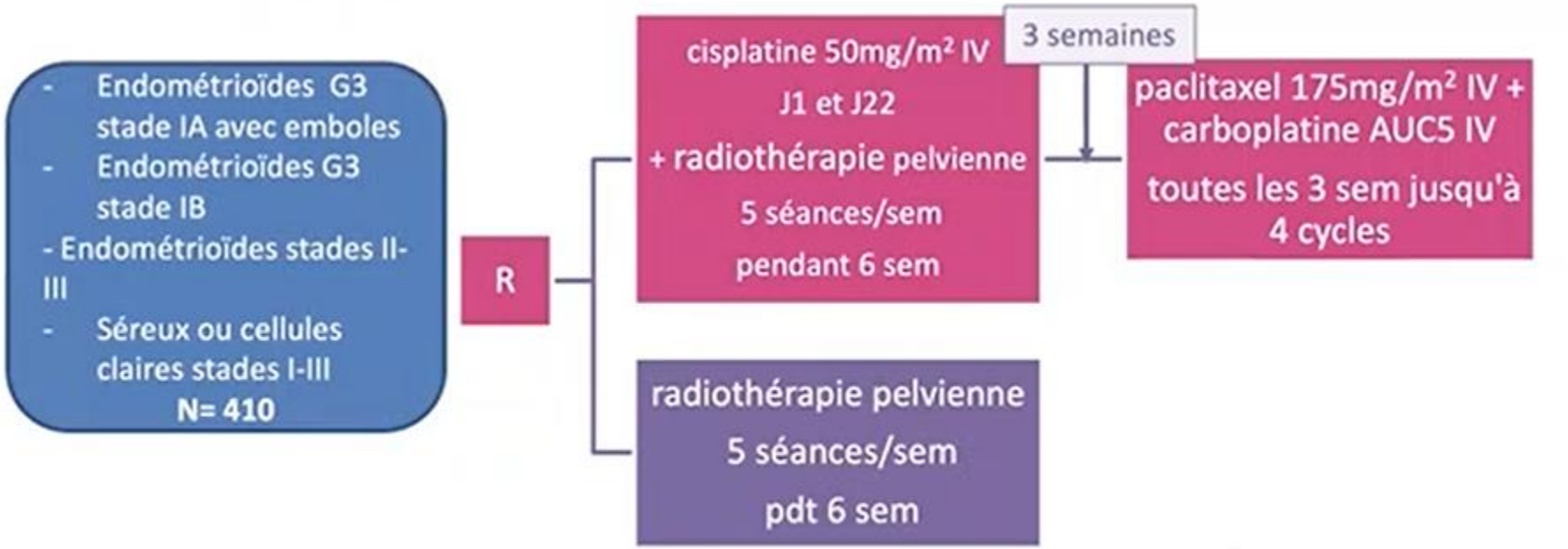
Matei et al N Engl J Med 2019

PORTEC 3: du TCGA à la vraie vie

Objectif principal : Comparer la survie globale et la survie sans récidive

Population: carcinomes à haut risque

686 patientes
Nov 2006 à déc 2013



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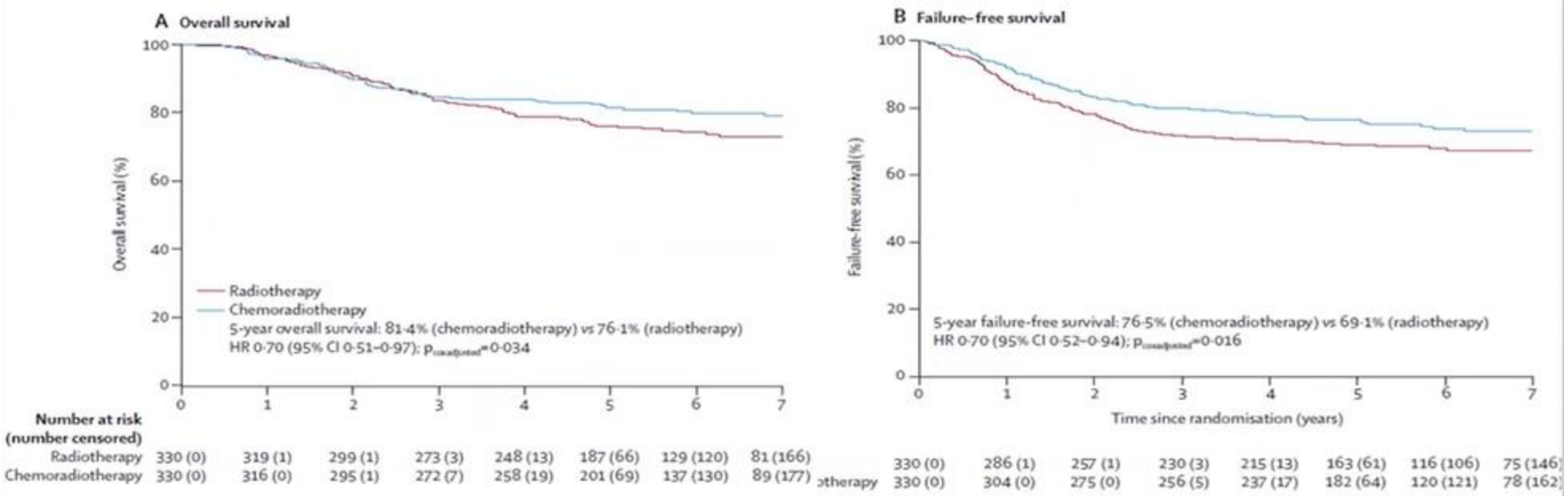
PORTEC 3: efficacité population globale

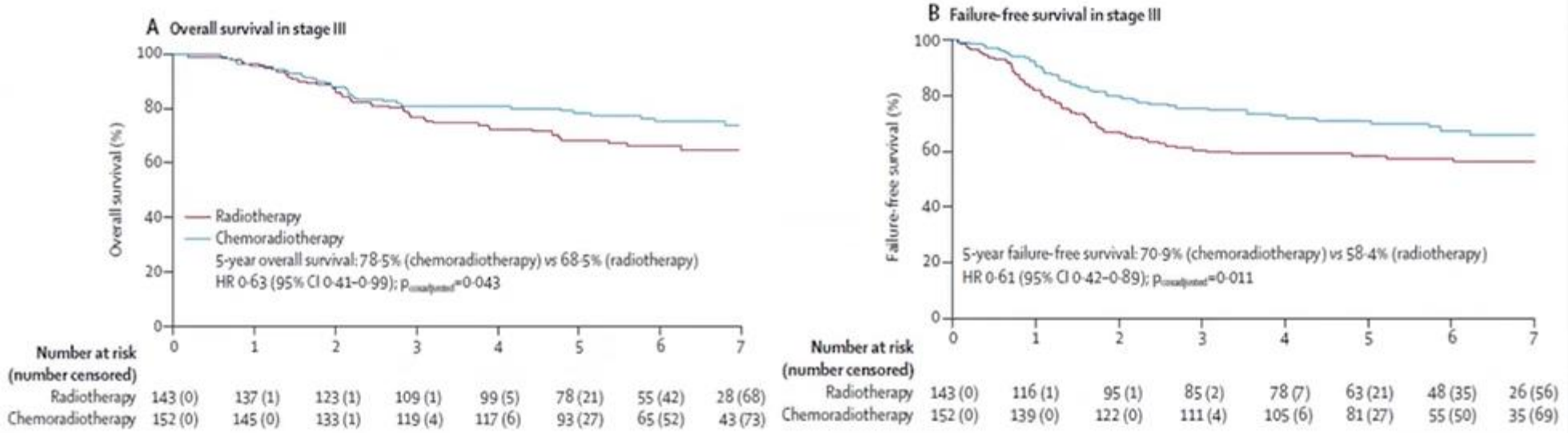


Bénéfice significatif en SG et SSR
HR = 0,7

A Leon-Castillo, J Clin Oncol, 2020

Etudes en sous groupes :

PORTEC 3: efficacité stades III



Bénéfice significatif en SG et SSR
HR = 0,6

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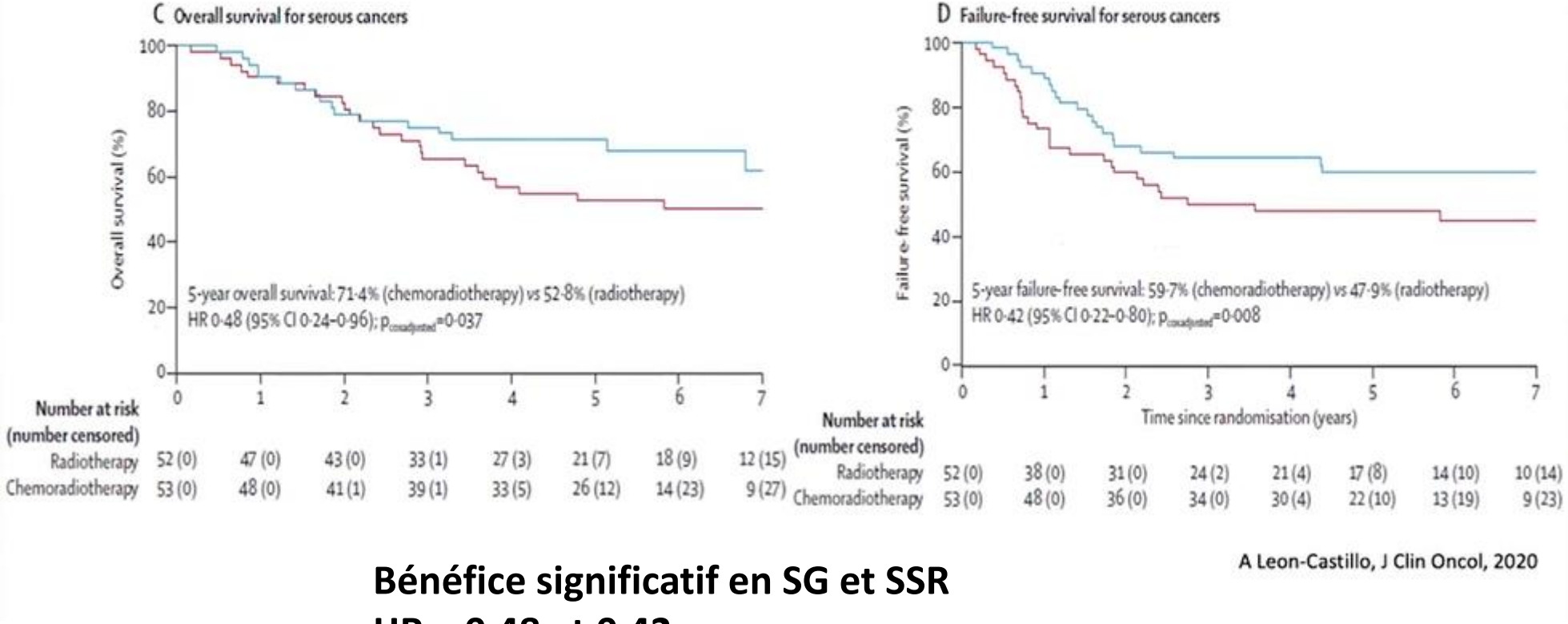
Etudes en sous groupes :

PORTEC 3: efficacité type séreux



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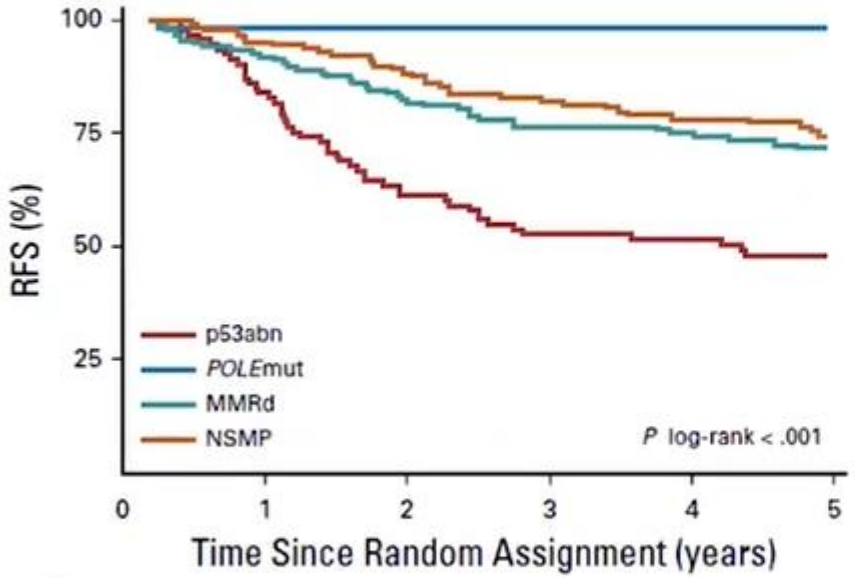
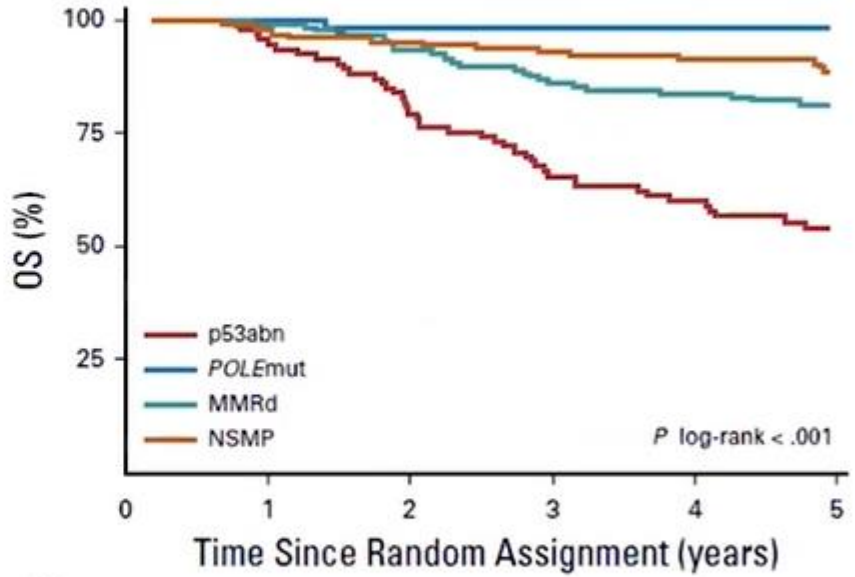
Bénéfice significatif en SG et SSR
HR = 0,48 et 0,42

PORTEC 3:

Valeur pronostique de la classification moléculaire



No. at risk:						
p53abn	93	72	57	49	44	32
*POLE*mut	51	50	50	49	48	37
MMRd	137	124	112	102	96	74
NSMP	129	122	113	105	94	69

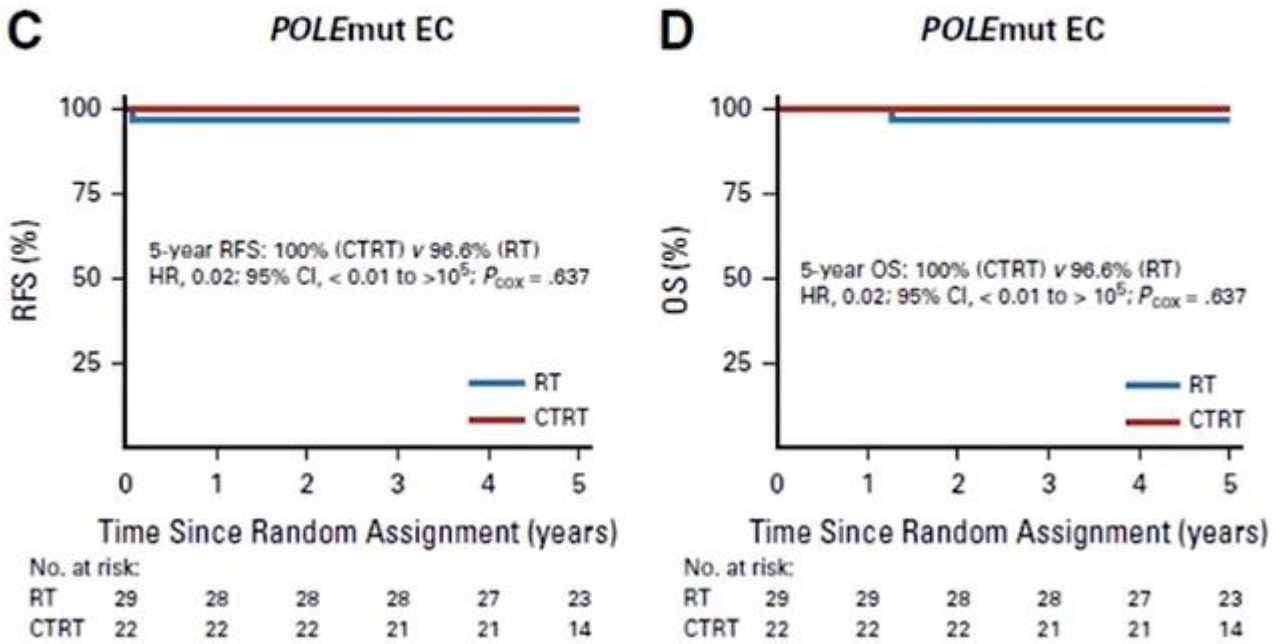


No. at risk:						
p53abn	93	87	71	61	52	37
*POLE*mut	51	51	50	49	48	37
MMRd	137	136	128	115	108	85
NSMP	129	125	122	118	110	85

A Leon-Castillo, J Clin Oncol, 2020

POLE: quel impact de la chimiothérapie adjuvante?

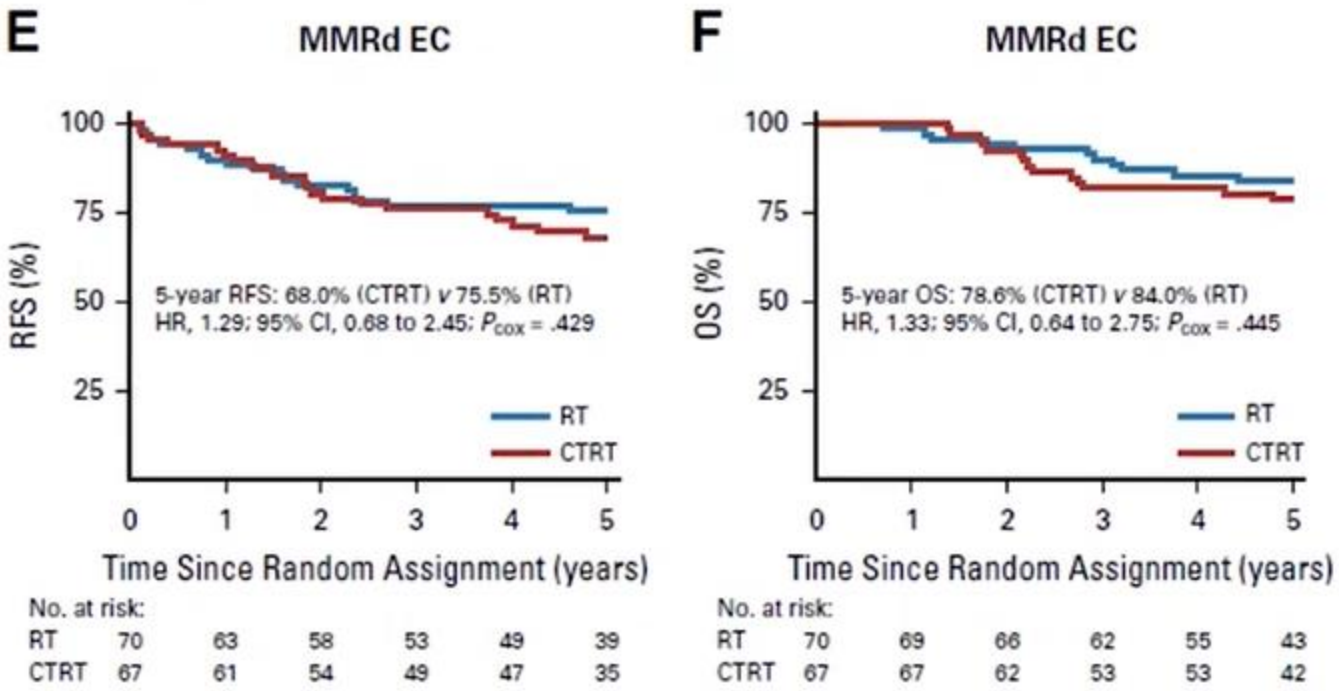
- ***POLE***: pas de bénéfice



A Leon-Castillo, J Clin Oncol, 2020

MSI: quel impact de la chimiothérapie adjuvante?

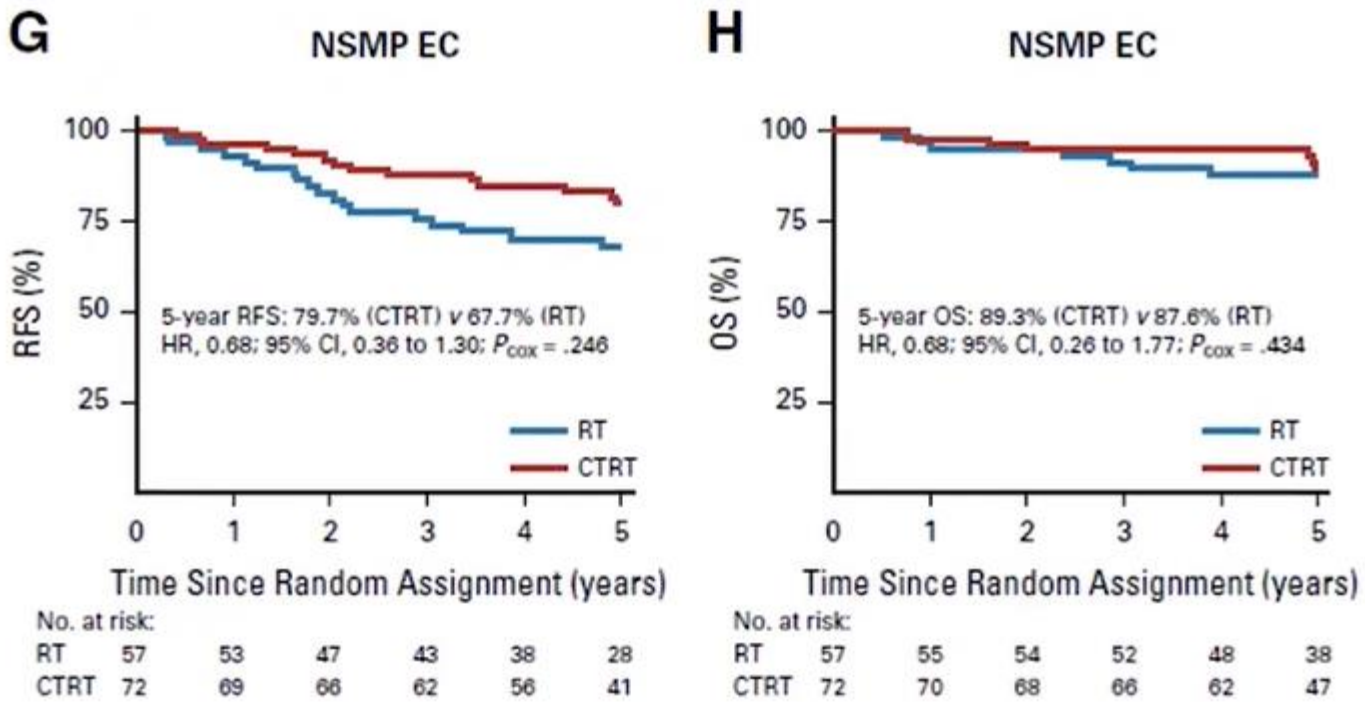
- **MSI**: pas de bénéfice



A Leon-Castillo, J Clin Oncol, 2020

NSMP: quel impact de la chimiothérapie adjuvante?

- **NSMP**: pas de bénéfice, mais tendance en RFS



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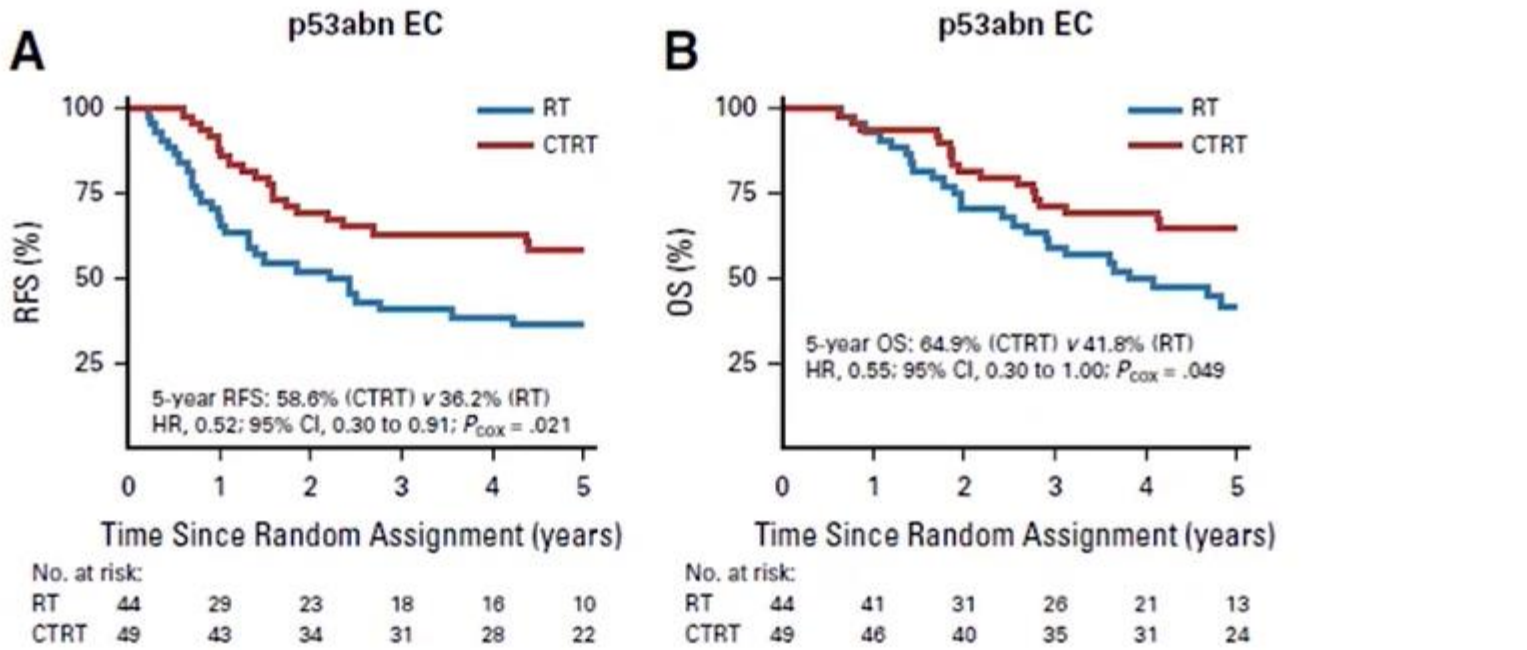
p53: quel impact de la chimiothérapie adjuvante?

- ***p53***: bénéfice en RFS et OS



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DONC :

- Impact pronostic notable de la classification moléculaire

(ce qui n'est pas le cas pour les critères anatomo-pathologiques classiques)

- D'où l'importance d'avoir le profil bio-moléculaire complet – le plus tôt possible – afin de pouvoir statuer sur la stratégie à adopter en situation adjuvante

- Stratégie bien précisée dans les recommandations ESGO 2021 et RPC Saint Paul 2023

Joint statement

ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Nicole Concin ,[1,2] Xavier Matias-Guiu,[3,4] Ignace Vergote,[5] David Cibula,[6] Mansoor Raza Mirza,[7] Simone Marnitz,[8] Jonathan Ledermann ,[9] Tjalling Bosse,[10] Cyrus Chargari,[11] Anna Fagotti,[12] Christina Fotopoulou ,[13] Antonio Gonzalez Martin,[14] Sigurd Lax,[15,16] Domenica Lorusso,[12] Christian Marth,[17] Philippe Morice,[18] Remi A Nout,[19] Dearbhaile O'Donnell,[20] Denis Querleu ,[12,21] Maria Rosaria Raspollini,[22] Jalid Sehouli,[23] Alina Sturdza,[24] Alexandra Taylor,[25] Anneke Westermann,[26] Pauline Wimberger,[27] Nicoletta Colombo,[28] François Planchamp,[29] Carien L Creutzberg[30]

Table 2 Definition of prognostic risk groups

Risk group	Molecular classification unknown	Molecular classification known*†
Low	► Stage IA endometrioid + low-grade‡ + LVSI negative or focal	► Stage I–II ***POLEmut*** endometrial carcinoma, no residual disease ► Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal
Intermediate	► Stage IB endometrioid + low-grade‡ + LVSI negative or focal ► Stage IA endometrioid + high-grade‡ + LVSI negative or focal ► Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	► Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal ► Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade‡ + LVSI negative or focal ► Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High–intermediate	► Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ► Stage IB endometrioid high-grade‡ regardless of LVSI status ► Stage II	► Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion ► Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status ► Stage II **MMRd/NSMP** endometrioid carcinoma
High	► Stage III–IVA with no residual disease ► Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	► Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ► Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease ► Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	► Stage III–IVA with residual disease ► Stage IVB	► Stage III–IVA with residual disease of any molecular type ► Stage IVB of any molecular type

DEFINITION OF PROGNOSTIC RISK GROUPS

WITH MOLECULAR CLASSIFICATION

	ENDOMETRIOID								NON-ENDOMETRIOID MMRd/NSMP
	POLEmut		MMRd/NSMP				p53abn		
	LOW GRADE	HIGH GRADE	LOW GRADE		HIGH GRADE		LOW GRADE	HIGH GRADE	
			LVSI -	LVSI +	LVSI -	LVSI +			
STAGE IA	LOW		LOW	H-I	INTERM	H-I	MYO-: INTERM		MYO-: INTERM
							MYO+: HIGH		MYO+: HIGH*
STAGE IB	LOW		INTERM	H-I	H-I		HIGH		HIGH*
STAGE II	LOW		H-I				HIGH		HIGH*
STAGE III-IVA	Insufficient data		HIGH				HIGH		HIGH*
STAGE III-IVA with residual disease	ADVANCED		ADVANCED				ADVANCED		ADVANCED
STAGE IVB	ADVANCED		ADVANCED				ADVANCED		ADVANCED

Pas d'indication à réaliser un traitement adjuvant

Daix MC, *et al. Int J Gynecol Cancer* 2021;**0**:1–2. doi:10.1136/ijgc-2021-003110

DEFINITION OF PROGNOSTIC RISK GROUPS

WITH MOLECULAR CLASSIFICATION

	ENDOMETRIOID								NON-ENDOMETRIOID MMRd/NSMP
	POLEmut		MMRd/NSMP				p53abn		
	LOW GRADE	HIGH GRADE	LOW GRADE		HIGH GRADE		LOW GRADE	HIGH GRADE	
			LVSI -	LVSI +	LVSI -	LVSI +			
STAGE IA	LOW		LOW	H-I	INTERM	H-I	MYO-: INTERM MYO+: HIGH		MYO-: INTERM MYO+: HIGH*
STAGE IB	LOW		INTERM	H-I	H-I		HIGH		HIGH*
STAGE II	LOW		H-I						
STAGE III-IVA	Insuffici								
STAGE III-IVA with residual disease	ADVA								
STAGE IVB	ADVANCED		ADVANCED				ADVANCED		ADVANCED

Une curiethérapie est recommandée
La surveillance est une option (<60 ans)

Chimiothérapie et RTE à discuter,
en particulier pour les carcinosarcomes

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DEFINITION OF PROGNOSTIC RISK GROUPS

WITH MOLECULAR CLASSIFICATION

	ENDOMETRIOID								NON-ENDOMETRIOID MMRd/NSMP
	POLEmut		MMRd/NSMP				p53abn		
	LOW GRADE	HIGH GRADE	LOW GRADE		HIGH GRADE		LOW GRADE	HIGH GRADE	
			LVSI -	LVSI +	LVSI -	LVSI +			
STAGE IA	LOW		LOW	H-I	INTERM	H-I	MYO-: INTERM		MYO-: INTERM
							MYO+: HIGH		MYO+: HIGH*
STAGE IB	LOW		INTERM	H-I	H-I		HIGH		HIGH*
STAGE II	LOW		H-I				HIGH		HIGH*
STAGE III-IVA									
STAGE III-IVA with residual disease									
STAGE IVB									

Curiethérapie recommandée
+/- Radiothérapie externe (pN0/Nx)
Chimiothérapie adjuvante à discuter en RCP si haut grade, emboles, stade II, MSS

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DEFINITION OF PROGNOSTIC RISK GROUPS

WITH MOLECULAR CLASSIFICATION

	ENDOMETRIOID								NON-ENDOMETRIOID MMRd/NSMP
	POLEmut		MMRd/NSMP				p53abn		
	LOW GRADE	HIGH GRADE	LOW GRADE		HIGH GRADE		LOW GRADE	HIGH GRADE	
			LVSI -	LVSI +	LVSI -	LVSI +			
STAGE IA	LOW		LOW	H-I	INTERM	H-I	MYO-: INTERM MYO+: HIGH		MYO-: INTERM MYO+: HIGH*
STAGE IB	LOW		INTERM	H-I	H-I		HIGH		HIGH*
STAGE II	LOW		H-I				HIGH		HIGH*
STAGE III-IVA	Insufficient data		HIGH				HIGH		HIGH*
STAGE III-IVA with residual disease	ADVANCED								
STAGE IVB	ADVANCED								

Indication formelle à une chimiothérapie adjuvante :
RT – CT concomitante (PORTEC3) ou séquentielle

Option : chimiothérapie seule

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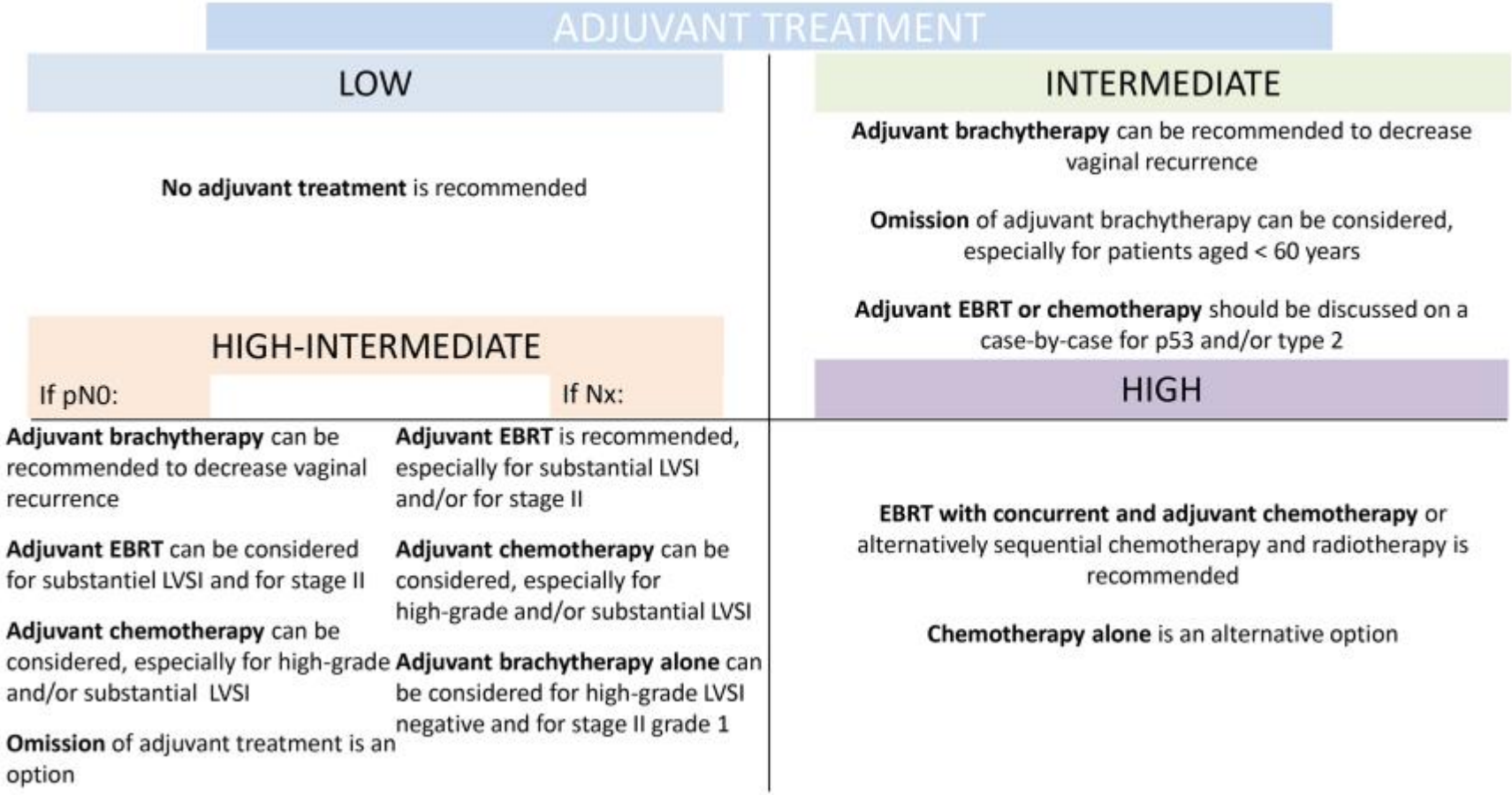

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Merci

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28 mars 2023