

Radiothérapie et les cancers de l'endomètre : actualités



ONCOBOURGOGNE 28/03/2023

DR THIBOUW



Avant la biologie moléculaire

Adjuvant radiotherapy in stage I-II endometrial cancer							
Trial	Enrollment	No. of patients	Surgery	Eligibility	Randomization	Loco-regional recurrence	Survival
GOG-99 ⁴	1987-1995	392	TH-BSO+LND	Stages IB/C; stage II (occult)	EBRT vs NAT	2 years: 3% vs 12% (p=0.007)	4 years: 86% vs 92% (p=0.0557)
PORTEC-1 ⁵	1990-1997	714	TH-BSO	Stages IB G2-3; stages IC G1-2	EBRT vs NAT	5 years: 4% vs 14% (p<0.001)	5 years: 85% vs 81% (p=0.31)
Swedish ⁷	1997-2008	527	TH-BSO	Stage I intermediate risk	VBT vs VBT+EBRT	5 years: 5% vs 1.5% (p=0.013)	5 years: 90% vs 89% (p=0.55)
ASTEC/EN.5 ⁶	1996-2008	905	TH-BSO±LND	Stages IA/B G3; IC; stage II; serous/CC	EBRT vs NAT	5 years: 6% vs 3% (p=0.02)	5 years: 84% vs 84% (p=0.98)
PORTEC-2 ⁸	2002-2006	427	TH-BSO	Age >60 and stage IB G3 or stages IC G1-2; stage IIA	EBRT vs VBT	5 years: 5% vs 2% (p=0.17)	5 years: 85% vs 80% (p=0.57)

- Stade FIGO
- Type histologique
- Grade
- Embols

Avant la biologie moléculaire

1) Stade I, EC

Faible risque (FIGO IA G1-2, sans embols) : Surveillance

Risque intermédiaire (FIGO IB G1-2, pas d'embols) : curiethérapie seule

Risque intermédiaire haut (FIGO IA ou IB G1-2 embols +, FIGO IA G3) : curiethérapie +/- RTH

Haut risque (FIGO IB G3) : RTH + curie +/- chimiothérapie séquentielle

2) Stade II, EC

G1-2 embol - : curie

G3 ou embols : RTH + curie

3) Stades III, EC : RTH + chimiothérapie séquentielle +/- curie

4) Tumeurs non endométrioïdes : Chimiothérapie + RTH +/- curie (sauf IA sans embols: curie seule)

PORTEC-3

De Boer, Lancet Oncol 2019

Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial

Stephanie M de Boer, Melanie E Powell, Linda Mileskin, Dionyssios Katsaros, Paul Bessette, Christine Haie-Meder, Petronella B Ottevanger, Jonathan A Ledermann, Pearly Khaw, Alessandro Colombo, Anthony Fyles, Marie-Helene Baron, Ina M Jürgenliemk-Schulz, Henry C Kitchener, Hans W Nijman, Godfrey Wilson, Susan Brooks, Silvestro Carinelli, Diane Provencher, Chantal Hanzen, Ludy C H W Lutgens, Vincent T H B M Smit, Naveena Singh, Viet Do, Romerai D'Amico, Remi A Nout, Amanda Feeney, Karen W Verhoeven-Adema, Hein Putter, Carien L Creutzberg, on behalf of the PORTEC study group*

De Boer, Lancet Oncol 2018



Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial

Stephanie M de Boer, Melanie E Powell, Linda Mileskin, Dionyssios Katsaros, Paul Bessette, Christine Haie-Meder, Petronella B Ottevanger, Jonathan A Ledermann, Pearly Khaw, Romerai D'Amico, Anthony Fyles, Marie-Helene Baron, Ina M Jürgenliemk-Schulz, Henry C Kitchener, Hans W Nijman, Godfrey Wilson, Susan Brooks, Sergio Gribaudo, Diane Provencher, Chantal Hanzen, Roy F Kruitwagen, Vincent T H B M Smit, Naveena Singh, Viet Do, Andrea Lissoni, Remi A Nout, Amanda Feeney, Karen W Verhoeven-Adema, Hein Putter, Carien L Creutzberg, on behalf of the PORTEC Study Group*

- Population :
 - Carcinomes endométrioïdes : Stades I GIII avec atteinte myomètre et/ou embols / stades II-III
 - Carcinomes séreux ou à cellules claires stades I à III
- Nov 2006-Dec 2013, 660 pts opérées

RTH 48,6Gy/27 fr (n=330)

versus

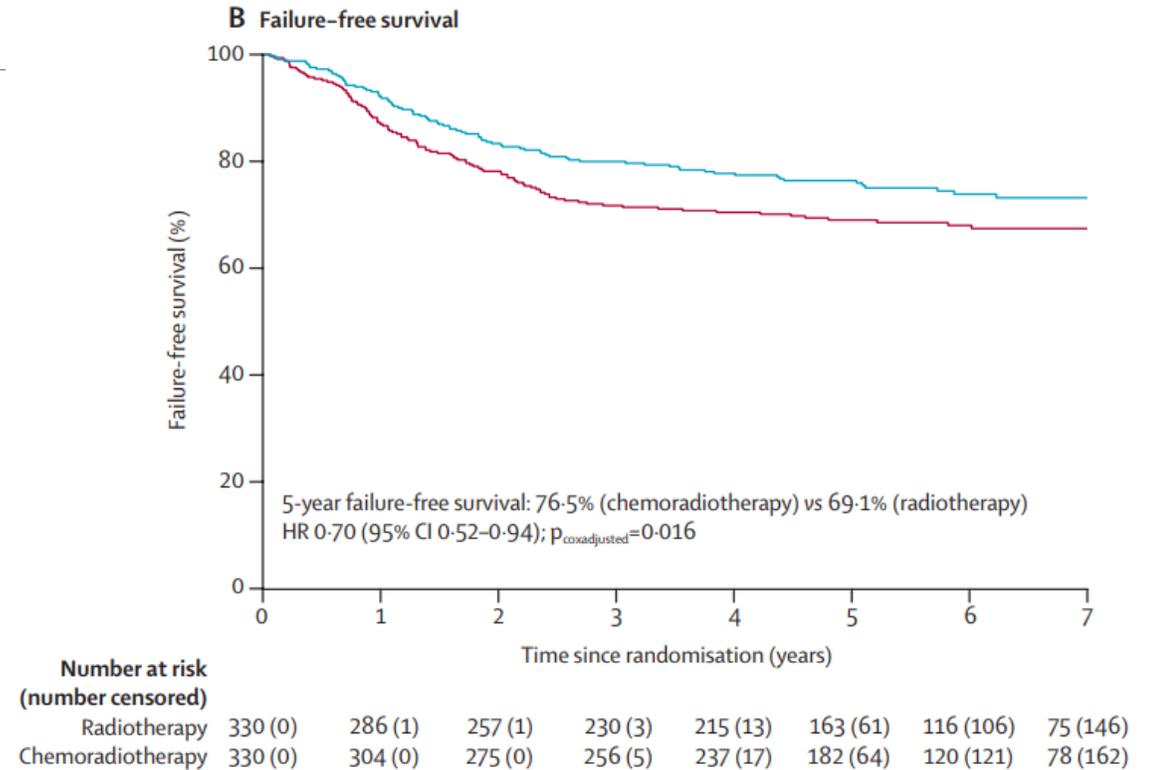
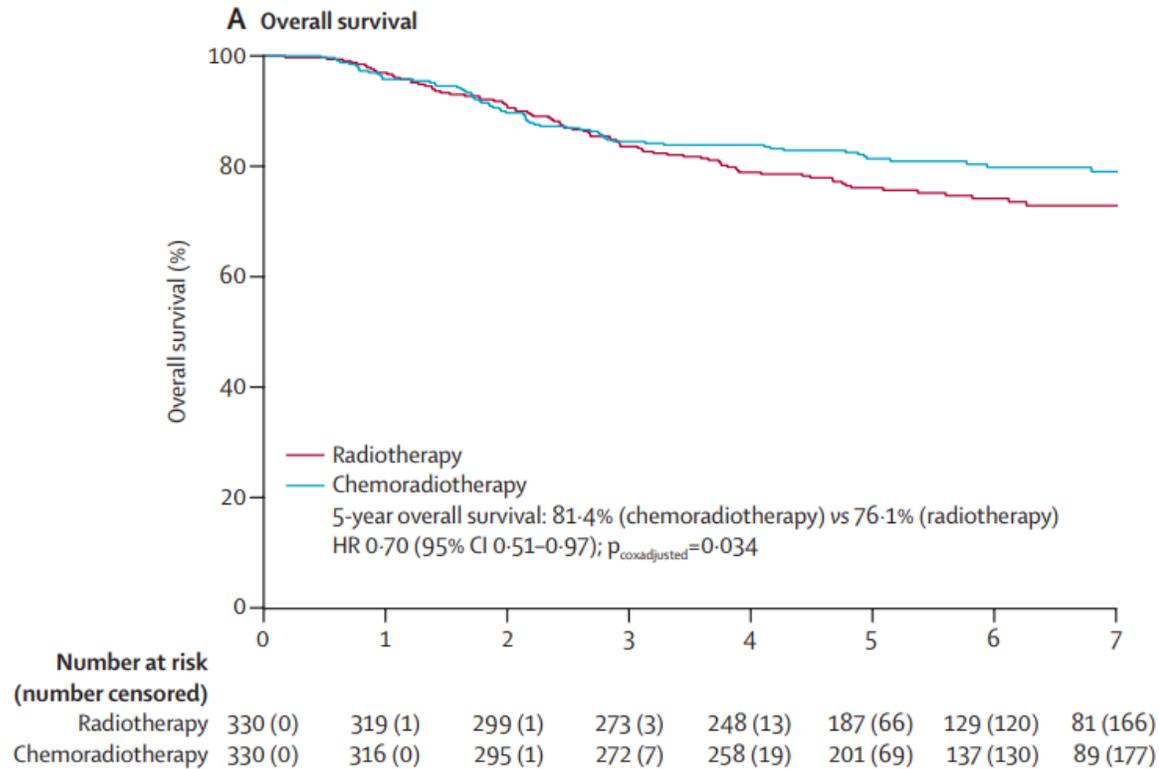
RTH 48,6Gy/27fr +CDDP (50mg/m² S1-S4) puis CT adjuvante (4 Carboplatine AUC5 + Paclitaxel 175mg/m²) (n=330)

- *Objectif principaux* : survies globale et sans récidence
- *Objectifs secondaires* : récurrences vaginales, pelviennes et métastatiques / Toxicités / Qualité de vie

PORTEC-3 : modes de récurrence

Recurrence outcomes by treatment group				
	Number of events	5-year probability (95% CI)	Hazard ratio (95% CI)	Log-rank p value*
Vaginal recurrence (first recurrence)				
Chemoradiotherapy	1	0.3% (0.0-2.1)	0.99 (0.06-15.90)	0.99
Radiotherapy alone	1	0.3% (0.0-2.1)
Pelvic recurrence (first recurrence)				
Chemoradiotherapy	3	0.9% (0.3-2.8)	0.75 (0.17-3.33)	0.71
Radiotherapy alone	4	0.9% (0.3-2.8)
Distant metastases (first recurrence)				
Chemoradiotherapy	78	21.4% (17.3-26.3)	0.74 (0.55-0.99)	0.047
Radiotherapy alone	98	29.1% (24.4-34.3)
Vaginal recurrence (total)				
Chemoradiotherapy	8	2.1% (1.0-4.4)	0.99 (0.37-2.65)	0.99
Radiotherapy alone	8	2.1% (1.0-4.4)
Pelvic recurrence (total)				
Chemoradiotherapy	20	5.5% (3.5-8.6)	0.63 (0.36-1.11)	0.11
Radiotherapy alone	31	8.5% (5.9-12.1)
Distant metastases (total)				
Chemoradiotherapy	80	22.1% (17.9-27.0)	0.75 (0.56-1.01)	0.057
Radiotherapy alone	99	29.4% (24.7-34.6)

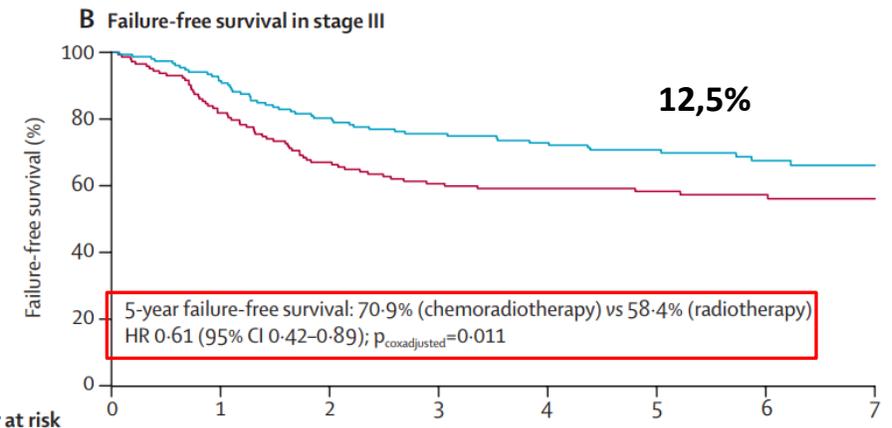
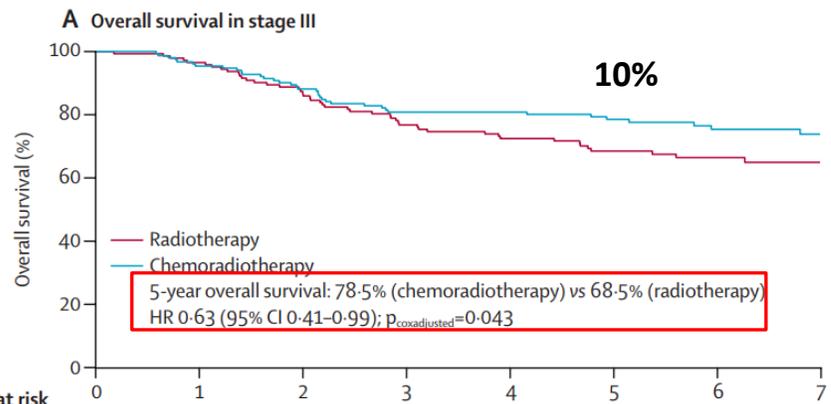
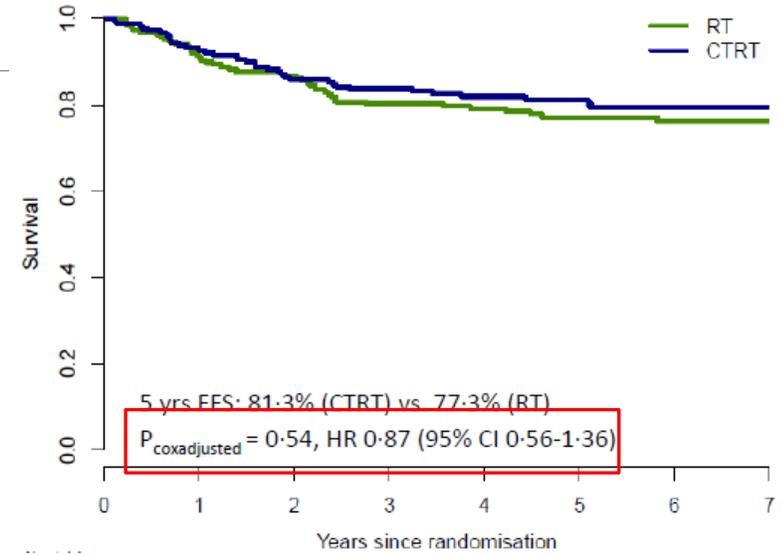
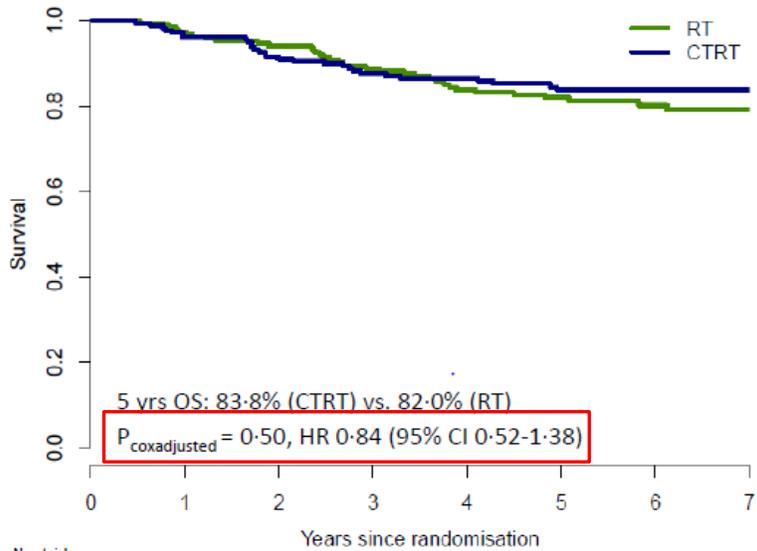
PORTEC-3 : CJP



Amélioration des 2 CJP à 5 ans (FU 72 mois)

- **OS** : 5% (HR 0,70 ; IC95% [0,51-0,97])
- **FFS** : 7% (HR 0,70 : IC95% [0,52-0,94])

PORTEC-3 : stades



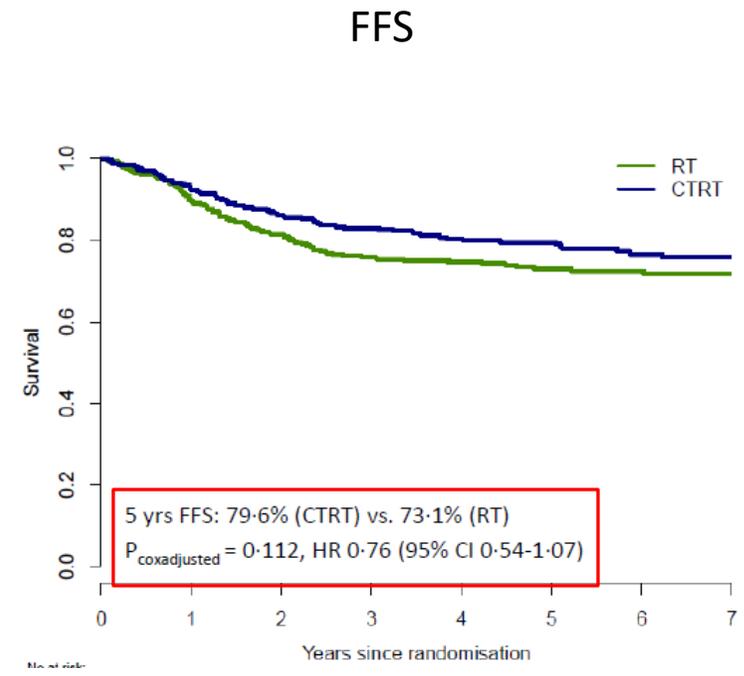
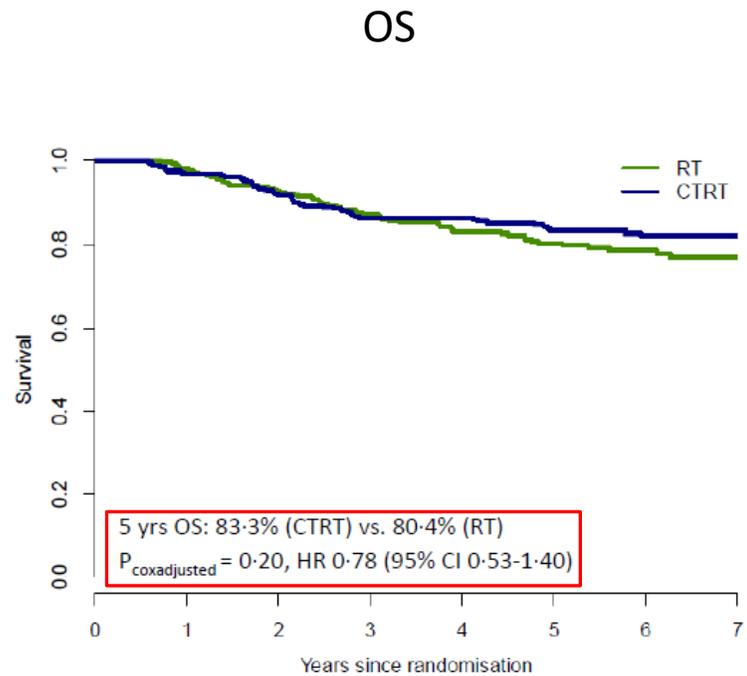
Number at risk (number censored)

	0	1	2	3	4	5	6	7
Radiotherapy	143 (0)	137 (1)	123 (1)	109 (1)	99 (5)	78 (21)	55 (42)	28 (68)
Chemoradiotherapy	152 (0)	145 (0)	133 (1)	119 (4)	117 (6)	93 (27)	65 (52)	43 (73)

Number at risk (number censored)

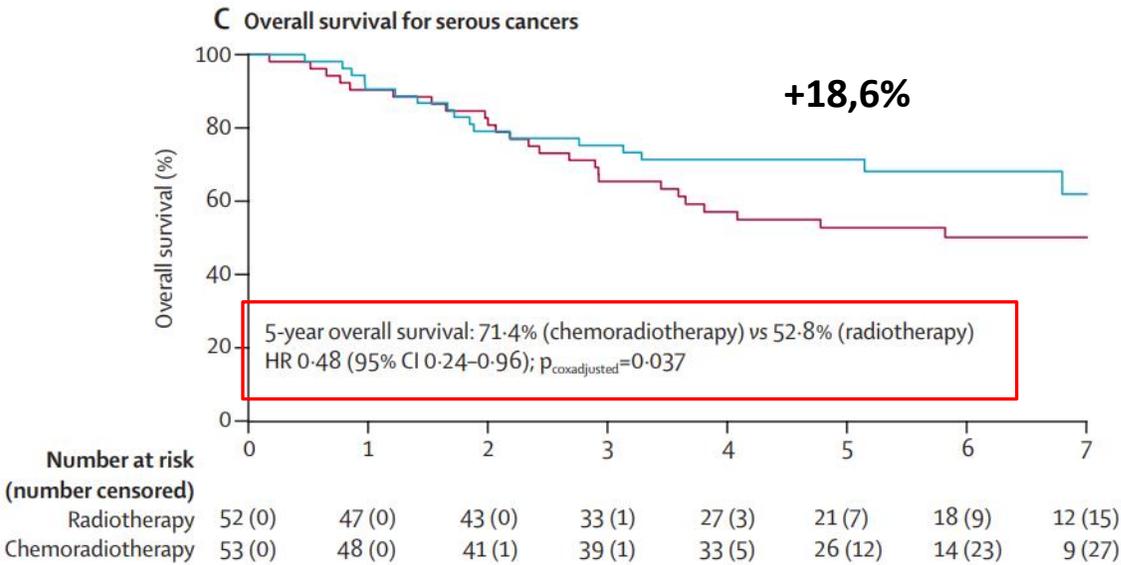
	0	1	2	3	4	5	6	7
Radiotherapy	143 (0)	116 (1)	95 (1)	85 (2)	78 (7)	63 (21)	48 (35)	26 (56)
Chemoradiotherapy	152 (0)	139 (0)	122 (0)	111 (4)	105 (6)	81 (27)	55 (50)	35 (69)

PORTEC-3 : types histologiques

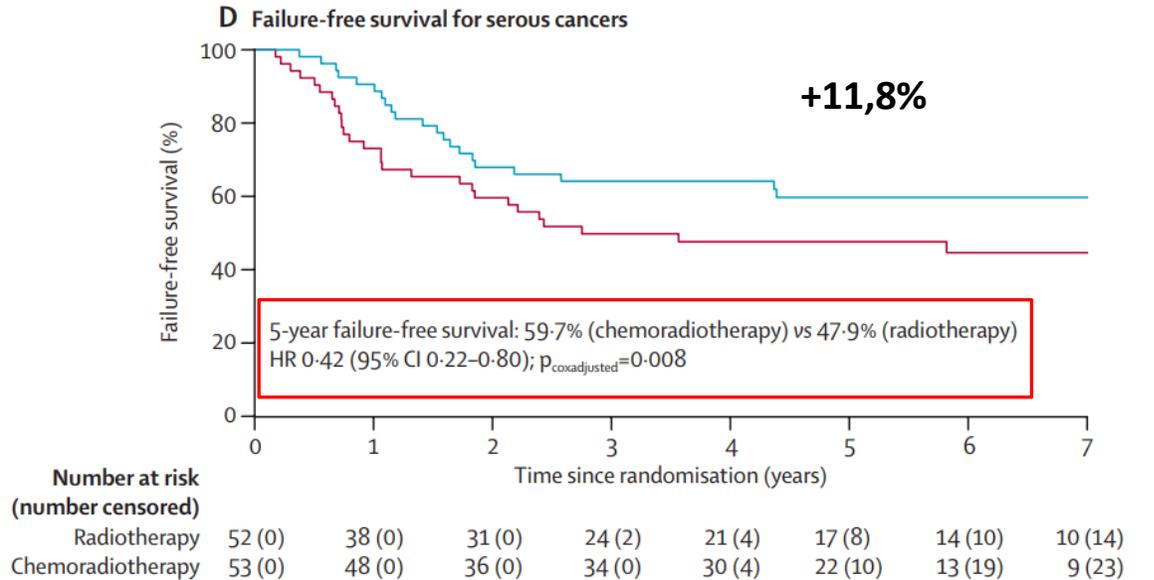


**Carcinomes endométrioides,
Carcinomes à cellules claires**

PORTEC-3 : types histologiques



Survie globale



Survie sans récurrence

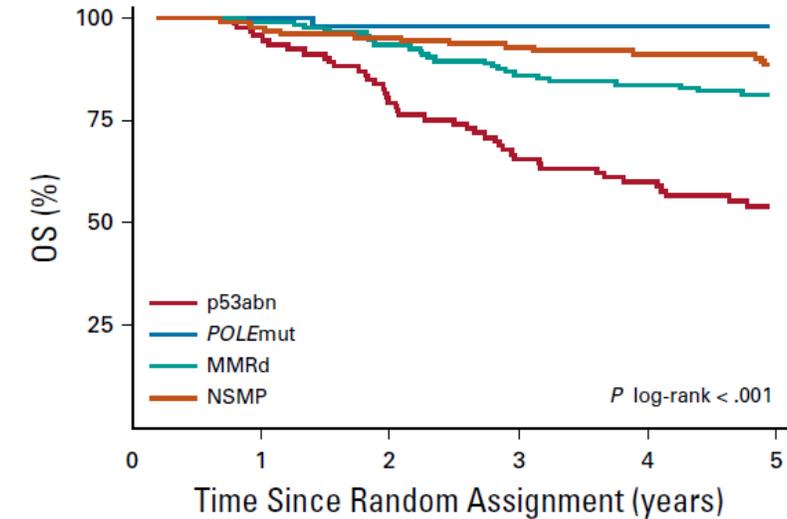
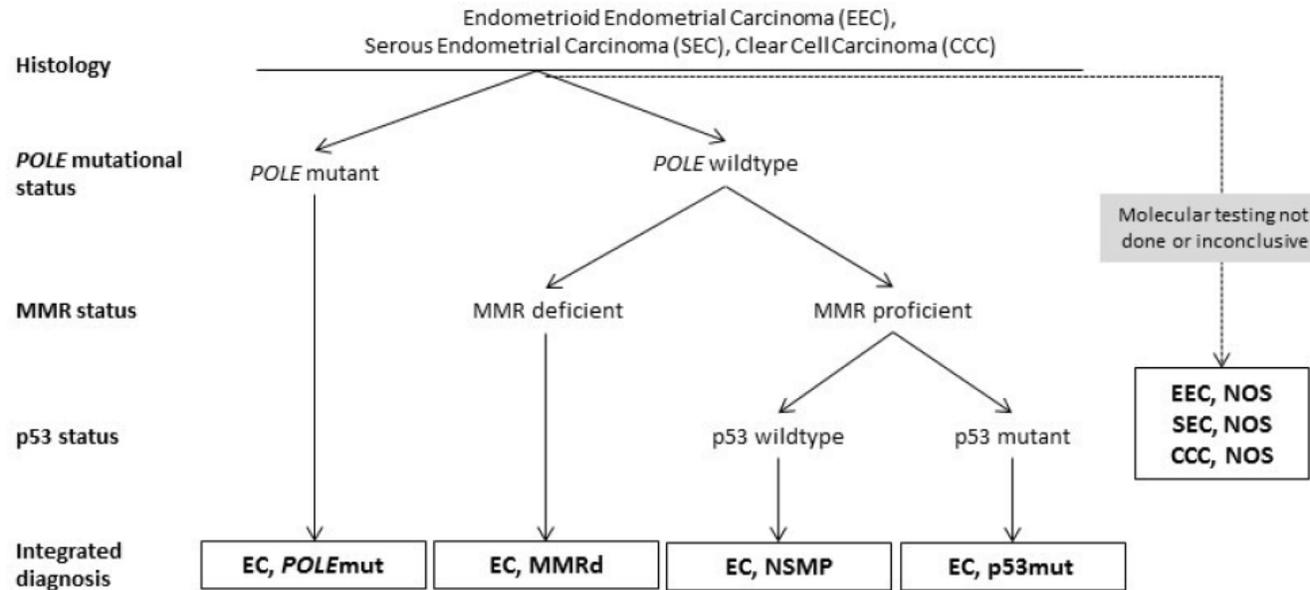
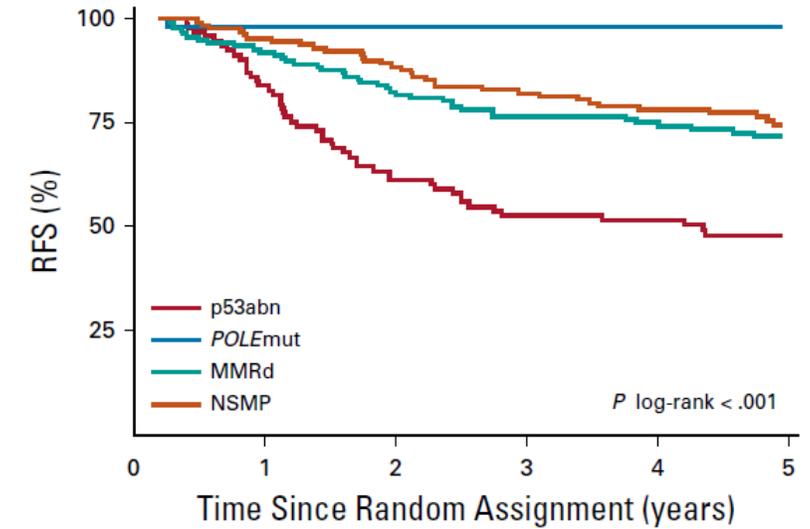
Carcinomes séreux

Classification moléculaire

Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy

Alicia León-Castillo, MD¹; Stephanie M. de Boer, MD²; Melanie E. Powell, MD³; Linda R. Mileskin, MBBS⁴; Helen J. Mackay, MD⁵; Alexandra Leary, MD, PhD⁶; Hans W. Nijman, MD, PhD^{6,7}; Naveena Singh, MD, MBBS⁸; Pamela M. Pollock, PhD⁹; Paul Bessette, MD¹⁰; Anthony Fyles, MD¹¹; Christine Haie-Meder, MD¹²; Vincent T. H. B. M. Smit, MD, PhD¹; Richard J. Edmondson, MD¹³; Hein Putter, MD¹⁴; Henry C. Kitchener, MD¹³; Emma J. Crosbie, MD, PhD¹³; Marco de Bruyn, PhD²; Remi A. Nout, MD²; Nanda Horeweg, MD, PhD²; Carlen L. Creutzberg, MD, PhD²; and Tjalling Bosse, MD, PhD¹ on behalf of the TransPORTEC consortium

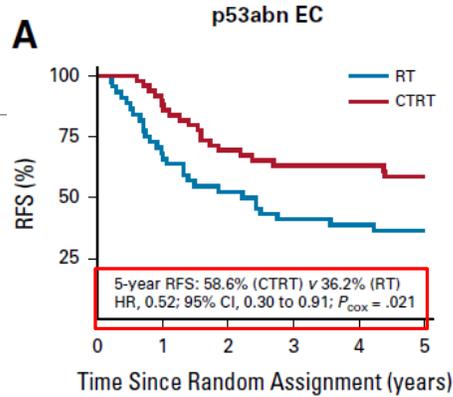
	Fréquence
P53 abn	10%
MMRd	25%
POLE mut	6%



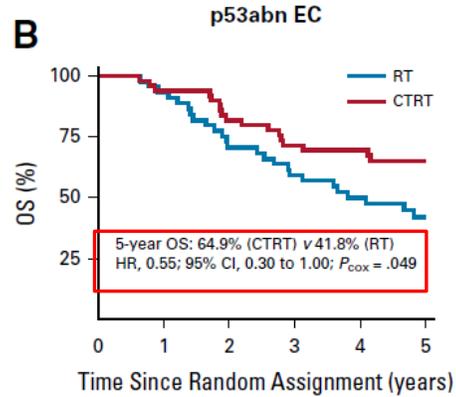
Van den Heerik AS, IJGC 2021
Leon-Castillo A, JCO 2020

PORTEC-3 : classification moléculaire

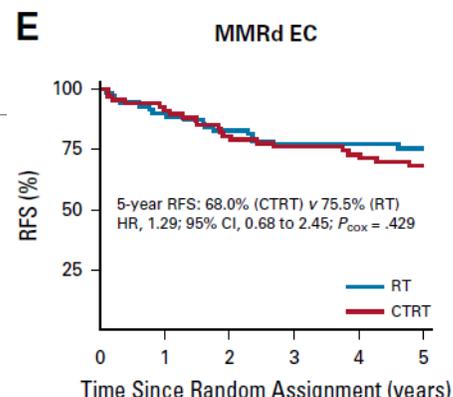
→ 71% carc séreux p53abn
 → 51 % p53abn non séreux : pas de différence évolutive avec carc séreux p53abn



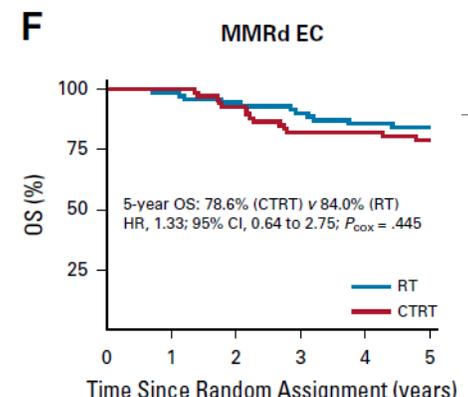
No. at risk:	0	1	2	3	4	5
RT	44	29	23	18	16	10
CTRT	49	43	34	31	28	22



No. at risk:	0	1	2	3	4	5
RT	44	41	31	26	21	13
CTRT	49	46	40	35	31	24



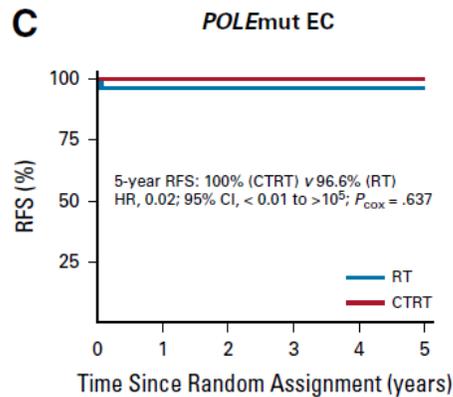
No. at risk:	0	1	2	3	4	5
RT	70	63	58	53	49	39
CTRT	67	61	54	49	47	35



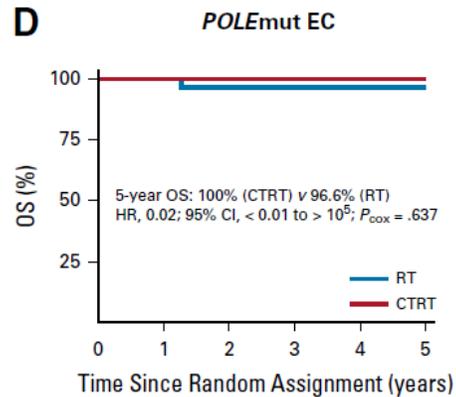
No. at risk:	0	1	2	3	4	5
RT	70	69	66	62	55	43
CTRT	67	67	62	53	53	42

→ RTH seule

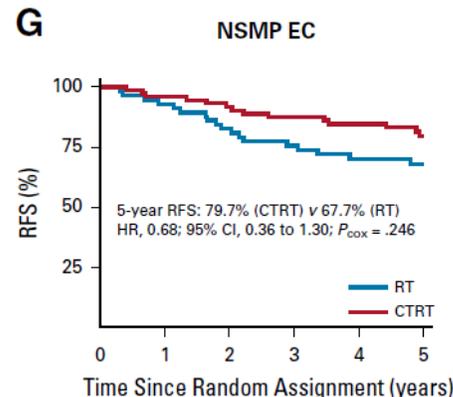
→ haute charge mutationnelle : réponse LcT amplifiée



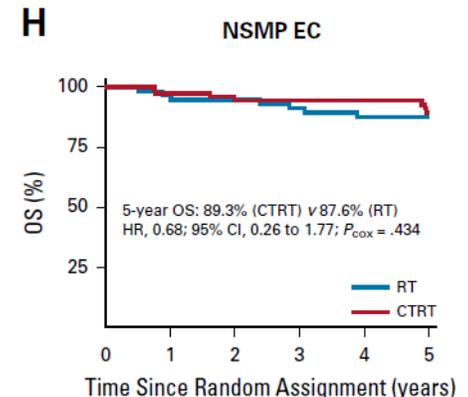
No. at risk:	0	1	2	3	4	5
RT	29	28	28	28	27	23
CTRT	22	22	22	21	21	14



No. at risk:	0	1	2	3	4	5
RT	29	29	28	28	27	23
CTRT	22	22	22	21	21	14



No. at risk:	0	1	2	3	4	5
RT	57	53	47	43	38	28
CTRT	72	69	66	62	56	41



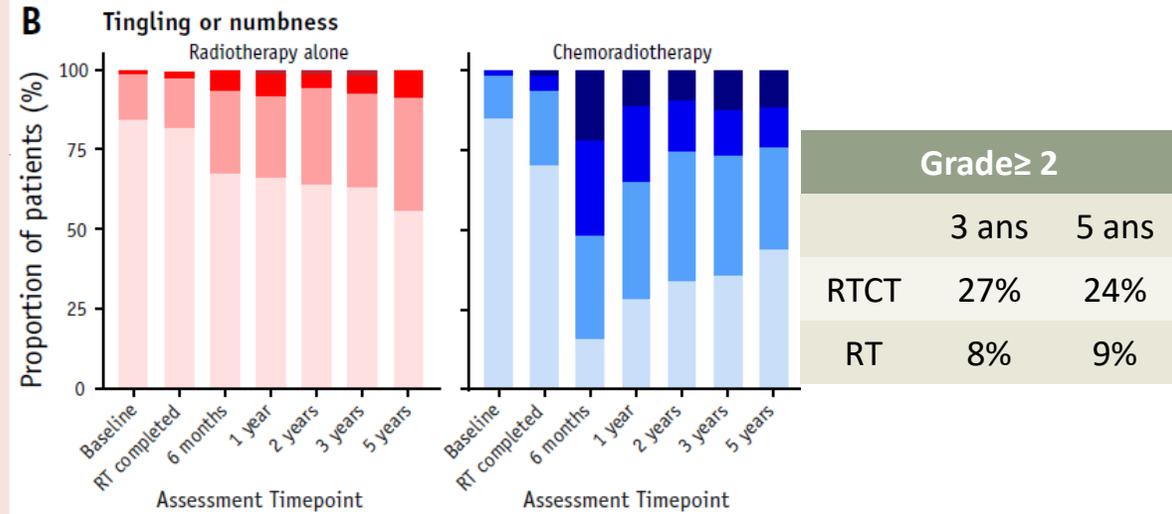
No. at risk:	0	1	2	3	4	5
RT	57	55	54	52	48	38
CTRT	72	70	68	66	62	47

PORTEC-3 : toxicités et QDV

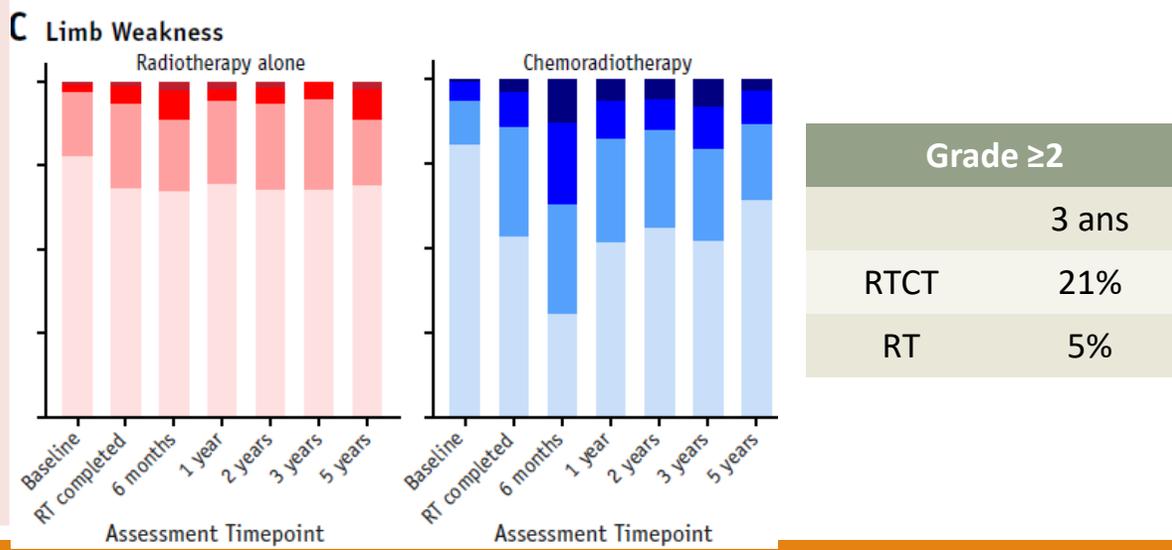
De Boer SM, Lancet Oncol. 2019 ;20
Post C, IJROBP 2021; 109

	Grade 2			Grade 3*		
	Chemoradiotherapy group (n=201)	Radiotherapy alone group (n=187)	p value†	Chemoradiotherapy group (n=201)	Radiotherapy alone group (n=187)	p value‡
Any	59 (29%)	33 (18%)	0.002	16 (8%)	10 (5%)	0.24
Allergic reaction or hypersensitivity	0	0	0.48	0	1 (1%)	0.48
Auditory or hearing	4 (2%)	1 (1%)	0.29	2 (1%)	1 (1%)	1.00
Hypertension	16 (8%)	16 (9%)	0.87	4 (2%)	4 (2%)	1.00
Lymphatics (oedema)	5 (2%)	0	0.06	0	0	1.00
Gastrointestinal (any)	16 (8%)	9 (5%)	0.19	2 (1%)	1 (1%)	1.00
Constipation	3 (1%)	1 (1%)	1.00	0	1 (1%)	1.00
Diarrhoea	7 (3%)	7 (4%)	1.00	0	0	1.00
Ileus or obstruction	2 (1%)	1 (1%)	0.37	2 (1%)	0	0.50
Haematological (any)	5 (2%)	5 (3%)	1.00	0	0	1.00
Lymphocytes	3 (1%)	4 (2%)	0.74	0	0	1.00
Infection (without neutropenia)	2 (1%)	0	0.12	2 (1%)	0	0.50
Neuropathy (any)	13 (6%)	0	<0.0001	1 (<1%)	0	1.01
Motor neuropathy	1 (<1%)	0	0.50	1 (<1%)	0	1.02
Sensory neuropathy	12 (6%)	0	<0.0001	1 (<1%)	0	1.03
Neurology (other)	1 (<1%)	0	0.25	2 (1%)	0	0.50
Pain (any)	13 (6%)	5 (3%)	0.15	3 (1%)	3 (2%)	1.00
Joint pain	7 (3%)	2 (1%)	0.14	2 (1%)	1 (1%)	1.00
Muscle pain	1 (<1%)	1 (1%)	0.61	0	1 (1%)	0.48
Back/pelvic/limbs	0	2 (1%)	0.11	0	1 (1%)	0.48
Abdomen/cramps	2 (1%)	0	0.12	2 (1%)	0	0.50
Other	2 (1%)	1 (1%)	1.00	1 (<1%)	1 (1%)	1.00
Musculoskeletal (other)	0	1 (1%)	1.00	1 (<1%)	0	1.00
Genitourinary
Incontinence	8 (4%)	9 (5%)	1.00	0	0	1.00
Urinary frequency	8 (4%)	2 (1%)	0.14	0	1 (1%)	0.48
Constitutional
Fatigue	0	3 (2%)	0.11	0	0	1.00
Other	0	0	1.00	1 (<1%)	0	1.00
Other toxicity	4 (2%)	4 (2%)	1.00	3 (1%)	2 (1%)	1.00

B



C



Classification moléculaire et groupes à risque

Risk group	Molecular classification unknown	Molecular classification known*†
Low	<ul style="list-style-type: none"> ▶ Stage IA endometrioid + low-grade‡ + LVSI negative or focal 	<ul style="list-style-type: none"> ▶ Stage I-II POLEmut endometrial carcinoma, no residual disease ▶ Stage IA MMRd/NSMP endometrioid carcinoma + low-grade‡ + LVSI negative or focal
Intermediate	<ul style="list-style-type: none"> ▶ 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, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion 	<ul style="list-style-type: none"> ▶ 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	<ul style="list-style-type: none"> ▶ Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ▶ Stage IB endometrioid high-grade‡ regardless of LVSI status ▶ Stage II 	<ul style="list-style-type: none"> ▶ 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	<ul style="list-style-type: none"> ▶ 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 	<ul style="list-style-type: none"> ▶ 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	<ul style="list-style-type: none"> ▶ Stage III-IVA with residual disease ▶ Stage IVB 	<ul style="list-style-type: none"> ▶ Stage III-IVA with residual disease of any molecular type ▶ Stage IVB of any molecular type

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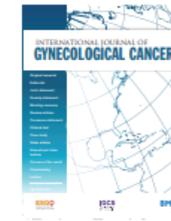


Clinical practice guidelines

Radiotherapy for endometrial cancer

Radiothérapie des cancers de l'endomètre

C. Chargari^{a,*}, K. Peignaux^b, A. Escande^c, S. Renard^d, C. Lafond^e, A. Petit^f,
J.-M. Hannoun-Lévi^g, C. Durdux^h, C. Haie-Méderⁱ



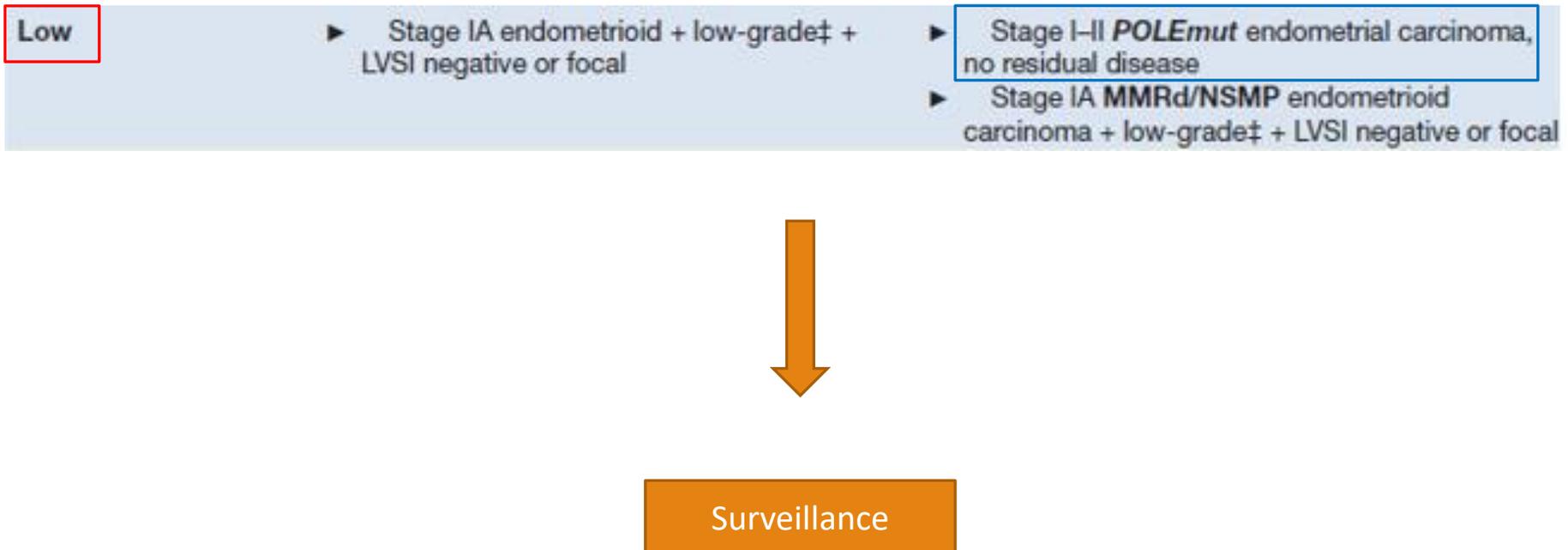
ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Nicole Concin^{1b},^{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 Creutzberg³⁰

Concin N, IJGC 2020

Chargari C, Peignaux, Cancer Radioth 2022

Groupes à risque et traitements adjuvants



Classification moléculaire et groupes à risque

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, undifferentiated 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

Standard : curiethérapie
Options : surveillance si <60 ans ou si absence d'invasion myométriale

Classification moléculaire et groupes à risque

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

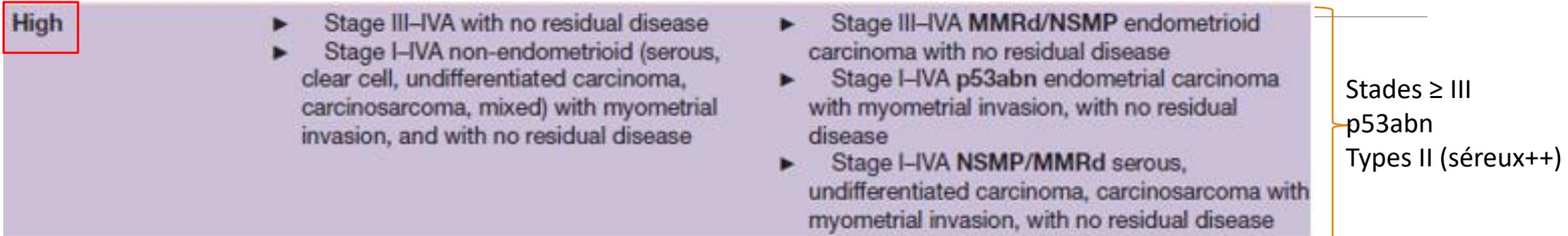


- pN0 :
 - Standard : curiethérapie
 - Option : RTH si embols ≥ 5 ou stade II
CT si GIII et/ou embols ≥ 5
- cN0 :
 - Standard : RTH
 - Option : CT si GIII et/ou embols ≥ 5
(Curiethérapie exclusive si CE stade II GI)

PORTEC-4

Concin N, IJGC 2020
Chargari C, Cancer Radioth 2022

Classification moléculaire et groupes à risque

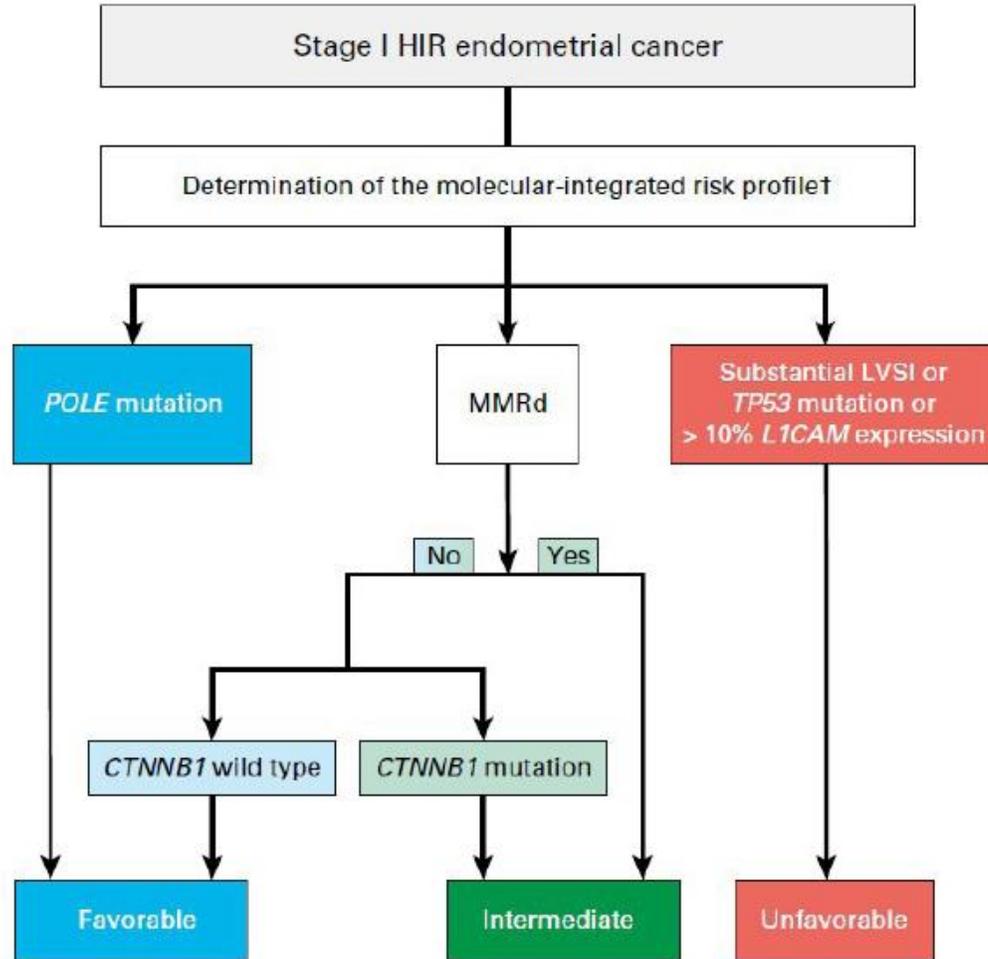


Radiochimiothérapie concomitante + chimiothérapie adjuvante (PORTEC-3)
Ou RTH et CT séquentielle

Concin N, IJGC 2020
Chargari C, Cancer Radioth 2022

PORTEC-4

PORTEC-4a: international randomized trial of molecular profile-based adjuvant treatment for women with high-intermediate risk endometrial cancer

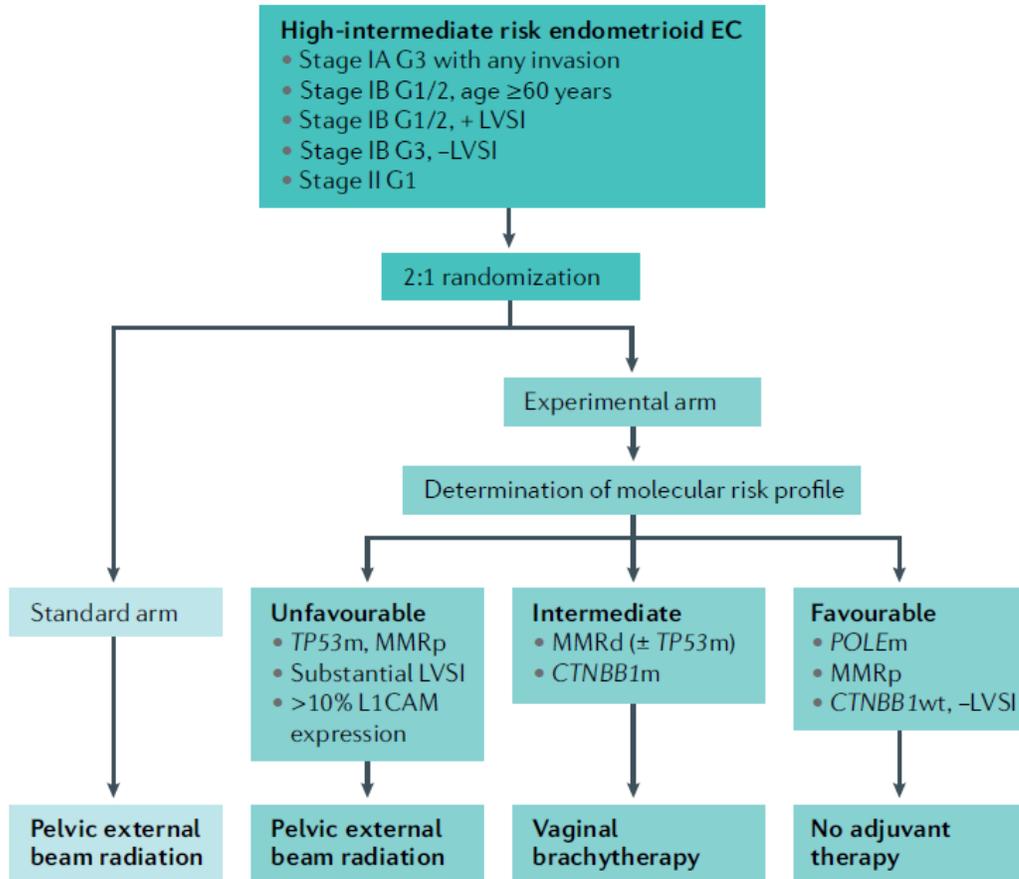


Intégration de nouveaux sous-groupes moléculaires pour définir un modèle de risque :

- sur-expression L1-CAM : FDR indépendant de rechute LR et méta
- Mutation exon 3 CTNNB1

PORTEC-4

PORTEC-4a: international randomized trial of molecular profile-based adjuvant treatment for women with high-intermediate risk endometrial cancer



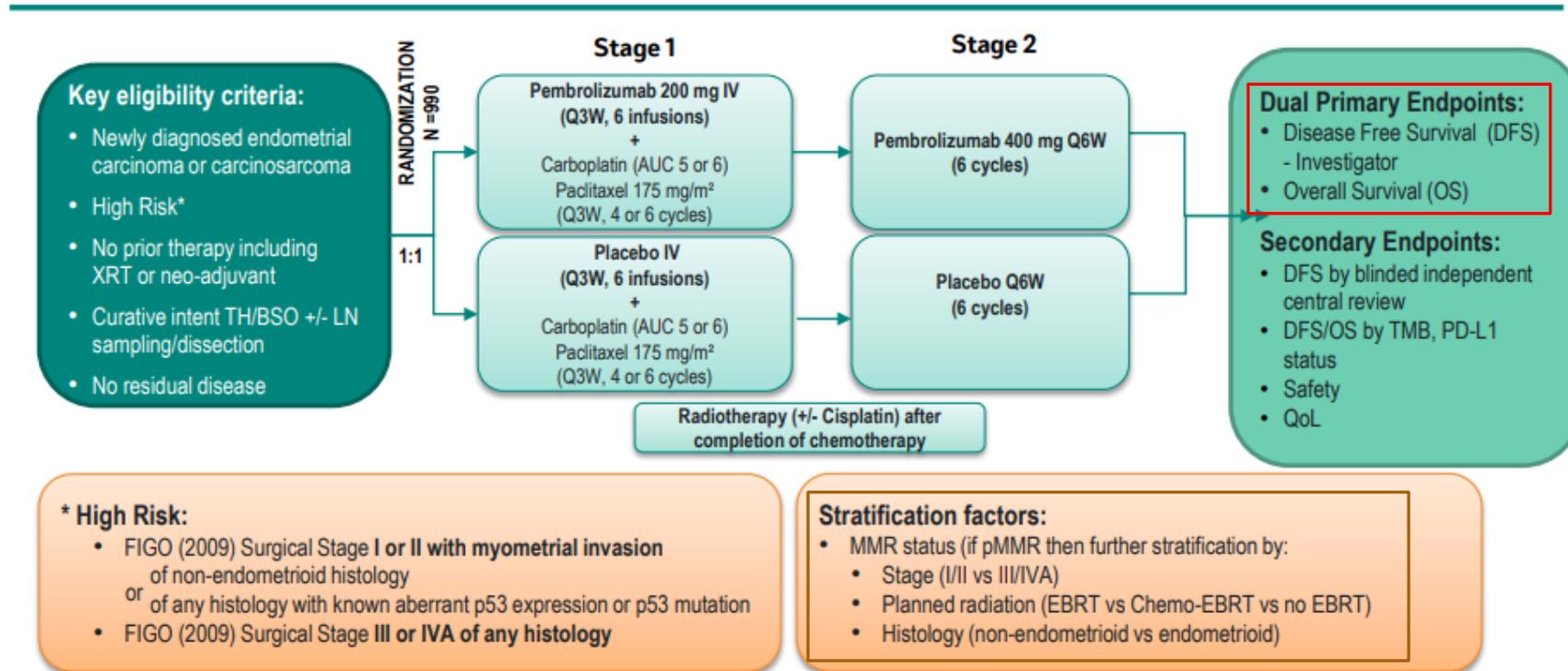
Application des nouveaux sous-groupes moléculaires aux profils intermédiaires hauts définis par les PORTEC 1 et 2



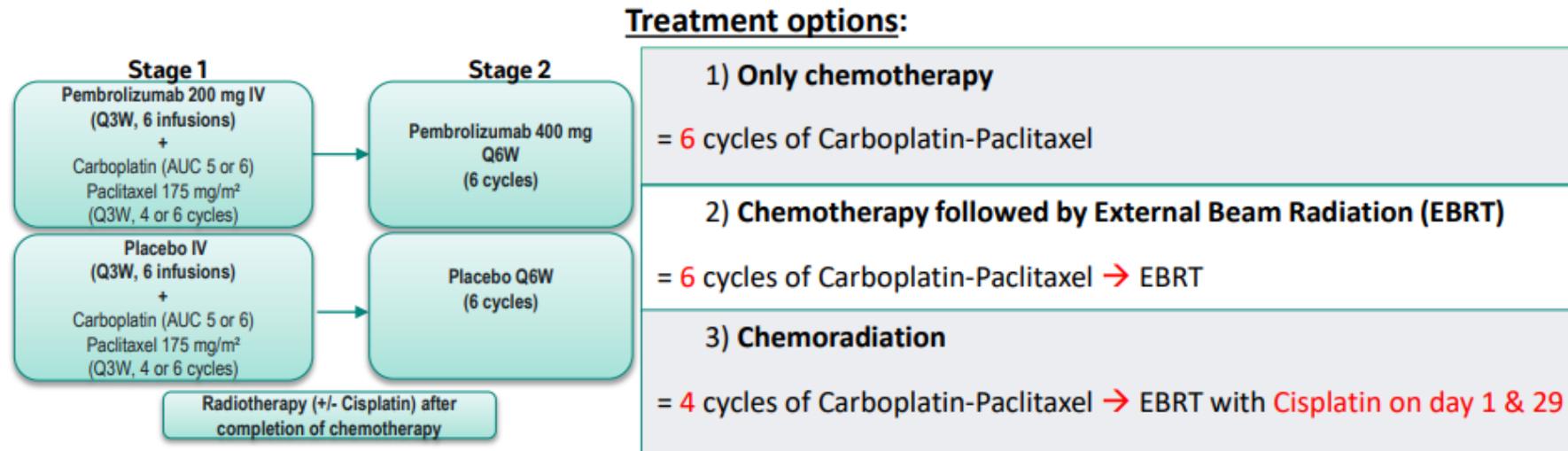
Méthode : phase III rando 2:1, multicentrique, 500 ptes
CJP : récurrence locale
Objectifs : éviter le sur-traitement (et le sous-ttt chez qq ptes)
sans compromettre le contrôle vaginal et la survie sans récurrence

MK3475-B21 ENGOT en-11 GOG-3053 : A Phase 3, Randomized, Double-Blind Study of Pembrolizumab versus Placebo in Combination With Adjuvant Chemotherapy With or Without Radiotherapy for the Treatment of Newly Diagnosed High-Risk Endometrial Cancer After Surgery With Curative Intent

Study Diagram



MK3475-B21 ENGOT en-11 GOG-3053 : A Phase 3, Randomized, Double-Blind Study of Pembrolizumab versus Placebo in Combination With Adjuvant Chemotherapy With or Without Radiotherapy for the Treatment of Newly Diagnosed High-Risk Endometrial Cancer After Surgery With Curative Intent



- ✓ Brachytherapy is optional in all treatment options
- ✓ **ALWAYS** first chemotherapy
- ✓ Radiotherapy can only be given after completion of chemotherapy

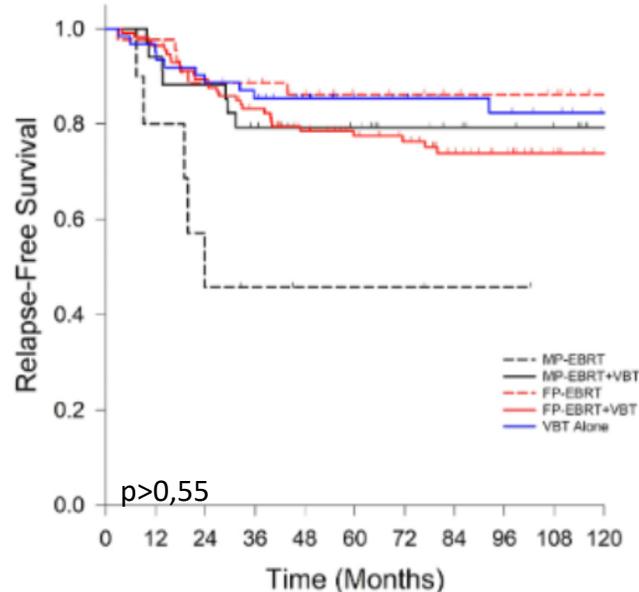
De-escalade de la RTH stades II?

Adjuvant Radiotherapy in Stage II Endometrial Cancer: Selective De-intensification of Adjuvant Treatment

K. Paulson*, N. Logie*, G. Han*, D. Tilley†, G. Menon*, A. Menon*, G. Nelson†, T. Phan†, B. Murray*, S. Ghosh*, R. Pearcey*, F. Huang*, E. Wiebe*



- Cohorte rétrospective, 264 patientes, jan 2010-dec 2014
- Stades II opérés => Full pelvis-RT ou Mini-pelvis-RT +/- curie
- Mini pelvis : ≤ 12 cm, max 2 cm au dessus bord inf art sacro iliaque, vagin, paramètres résiduels



Pas de différence entre FP et MP-RT + curie (récidive LR 24,6% vs 20,6%)

Diminution toxicités digestives et urinaires

Pas de prise en compte du profil moléculaire

=>Alternative pour stades II cN0 sans embols ni profil moléculaire défavorable?

En bref

- Hypofractionnement :

RT-PACE: A Pilot Study of Adjuvant Hypo-Fractionated Radiotherapy for Non-Metastatic Cervical and Endometrial Cancer (université de l'Utah, Dr Rachel Kingsford)

Essai pilote d'hypofractionnement sur 3 semaines dans maladies localisées opérées.

Endpoint tox GI

- Associations RTH-drogues :

p53abn : déficit recombinaison homologue → rajout d'inhibiteurs de PARPs à la RT-CT?

De Jonge MM, Clin Cancer, 2019

p53abn + HER2/neu : 20-25% carc séreux → trastuzumab (+- pertuzumab) + CT

Phase II



DISPOSITIF SPÉCIFIQUE
RÉGIONAL DU CANCER
BOURGOGNE-FRANCHE-COMTÉ