



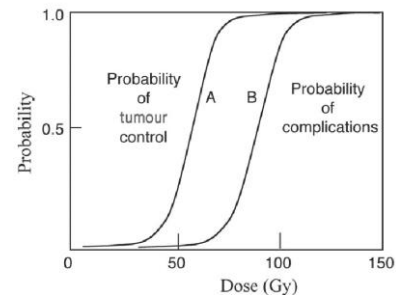
Comment réduire la toxicité génito-urinaire en curiethérapie ?

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Faculté de médecine H. Warembourg, Université de Lille

Le but de la présentation?

Amélioration du ratio thérapeutique bénéfiques/risques



Le ratio?

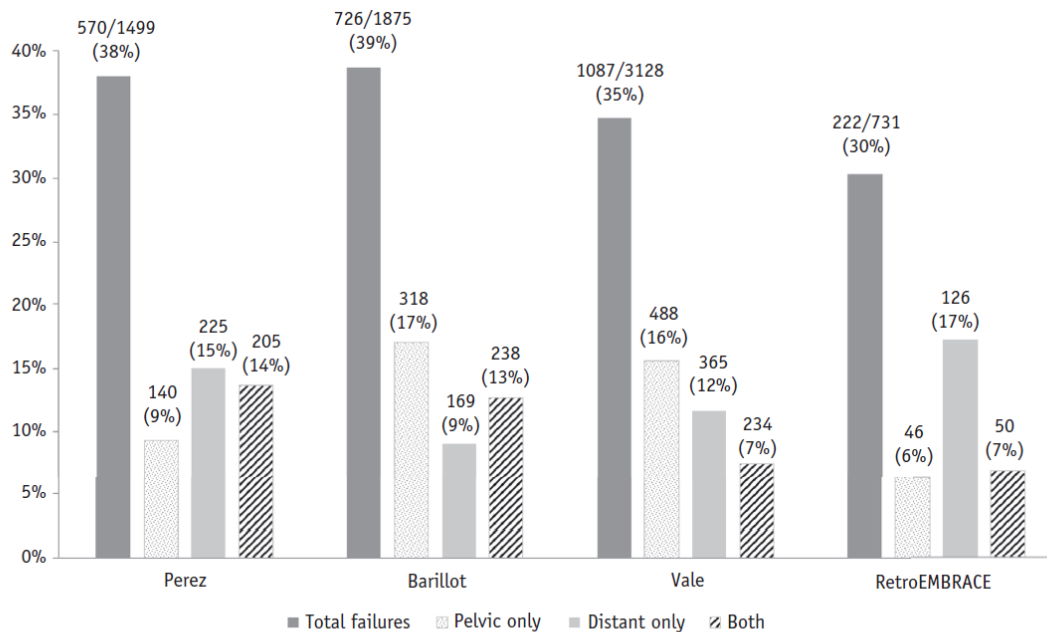
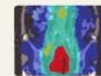
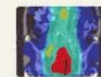


Fig. 4. Comparison of patterns of failures in RetroEMBRACE with selected cohorts from the literature (Perez and Barillot—radiation therapy alone; Vale—chemoradiation therapy + conventional brachytherapy). Percentages are expressed as a proportion of the total number in each cohort. Numbers above the bars refer to crude numbers.



Quel est le ratio actuel?

	Based on retroEMBRACE 3y/5y	Based on EMBRACE I 3y	Hypothesis EMBRACE II 3y
Local control			
Overall	91%/89%	91%	93%
≤30 cm ³ CTV _{HR}	96%	96%	96%
>30 cm ³ CTV _{HR}	87%	88%	91%
Stage IB, IIA	98%/98%	95%	98%
Stage IIB	93%/91%	90%	94%
Stage III	79%/75%	88%	89%
Stage IVA	76%/76%	87%	89%
Nodal control (incl. para-aortic)			
Overall	88%	84%	90%
N0 and Stage I + II	93%	91%	94%
N1 and Stage III + IVA	83%	79%	87%
Pelvic nodal control			
Overall	94%	89%	95%
Pelvic control (local + nodal)			
Overall	87%/84%		90%
Systemic control (excluding para-aortic failures)			
Overall	83%/79%	83%	86%
N0 and Stage I + II	90%	89%	91%
N1 and Stage III + IVA	74%	79%	79%
Cancer specific survival			
Overall	Consecutive ChT 81%/74%	NA	85%/78%
N0 and Stage I + II	90%/87%	NA	91%/88%
N1 and Stage III + IVA	69%/57%	NA	76%/64%
Overall survival			
Overall	Consecutive ChT 77%/67%	NA	81%/71%
N0 and Stage I + II	87%/82%	NA	88%/83%
N1 and Stage III + IVA	64%/49%	NA	71%/56%
Morbidity			
Bladder CTCAE ≥ G2		26%	21%
Bladder CTCAE ≥ G3		7%	6%
Rectum CTCAE ≥ G2		11%	9%
Rectum CTCAE ≥ G3		2%	2%
Bowel CTCAE ≥ G2		17%	12%
Bowel CTCAE ≥ G3		5%	4%
Vaginal CTCAE ≥ G2		27% (stenosis) 31% (all)	20% (stenosis) 24% (all)
Vaginal CTCAE ≥ G3		4% (all)	3% (all)



La bonne dose pour les OAR

Table 1 A Summary of the Evolution of the Recommended Target Objectives and OAR Dose Constraints From the GEC-ESTRO 2006 Publication to the Most Recent EMBRACE II Protocol in 2018.

		GEC-ESTRO ⁴	EMBRACE I ⁷¹	EMBRACE II ⁴⁹	
				Planning Aims	Limits for Prescribed Dose
Target Coverage Evaluation	HR-CTV D90 EQD _{2,10}	>90 Gy	75-96 Gy	>90 Gy <95 Gy	>85 Gy
OAR Parameters	Bladder D2cc EQD _{2,3}	<90 Gy	<90 Gy	<80 Gy	<90 Gy
	Rectum D2cc EQD _{2,3}	<70-75 Gy	<70-75 Gy	<65 Gy	<75 Gy
	Sigmoid D2cc EQD _{2,3}	<70-75 Gy	<75 Gy	<70 Gy	<75 Gy
	Vagina (recto-vaginal point) EQD _{2,3}			<65 Gy	<75 Gy
	Bowel D2cc EQD _{2,3}			<70 Gy	<75 Gy

Abbreviations: OAR, organs at risk.

The EQD2 is calculated using an $\alpha/\beta = 10$ for targets, an $\alpha/\beta = 3$ for OARs, and a repair half-time of 1.5 hour. The EQD2 values are a composite between external beam radiotherapy, assuming a dose of 45 Gy delivered over 25 fractions, and brachytherapy.

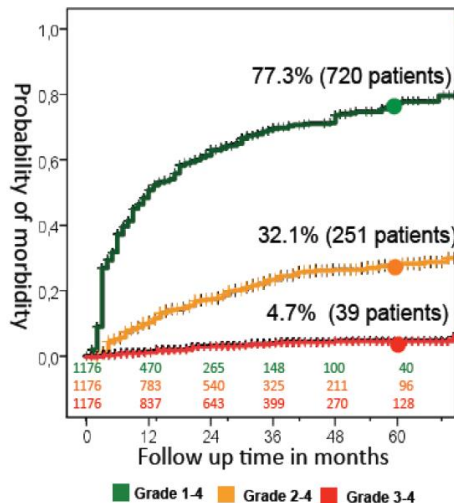


Quelles toxicités urinaires?

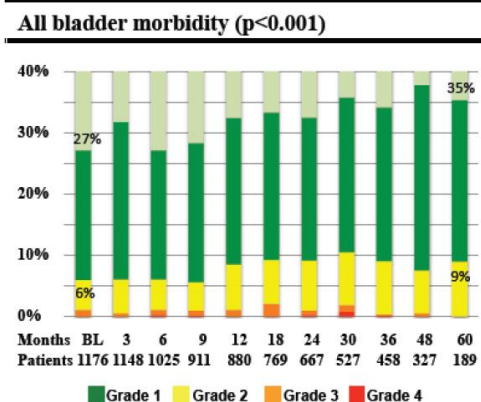
All bladder morbidity

All single CTCae endpoints grouped together

Kaplan-Meier estimates



Prevalence rates at follow up



Fokdal ESTRO 2017



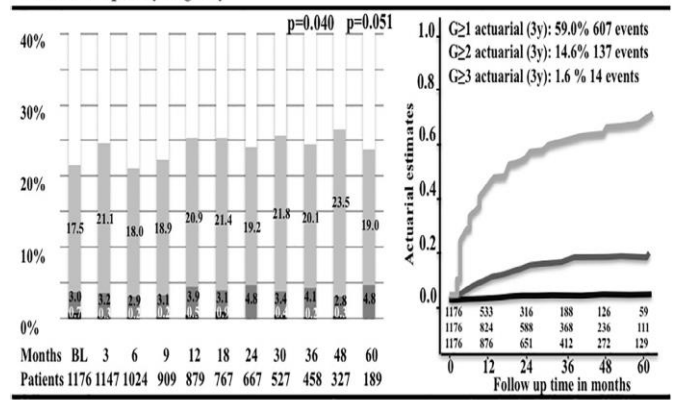
{ Image guided intensity modulated External beam radiotherapy and MRI based adaptive BRachytherapy in locally advanced Cervical cancer }



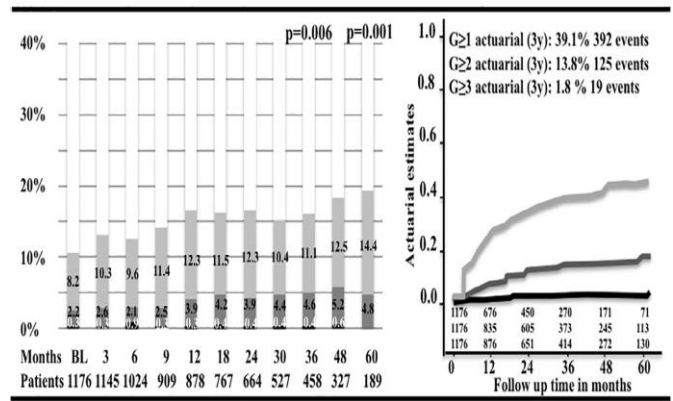
Toxicités par le médecin ?

1176 (884 pour EORTC) patientes
 EMBRACE I
 RT-CT 45Gy (+/- gg) + CDDP
 Curie selon centre
 Tox selon CTCAE et PROM selon EORTC
 FU 27 mois (1-83)

Bladder frequency/urgency



Bladder incontinence



CTCAE categories □ Grade 0 □ Grade 1 □ Grade 2 ■ Grade 3-4

Toxicités par le médecin ?

1176 (884 pour EORTC) patientes
EMBRACE I
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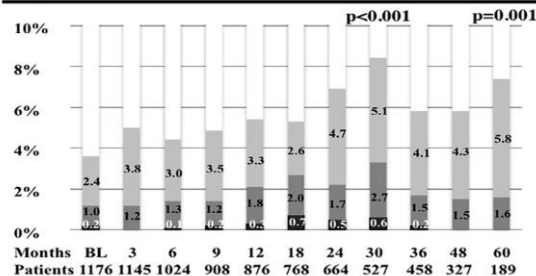


EMBRACE

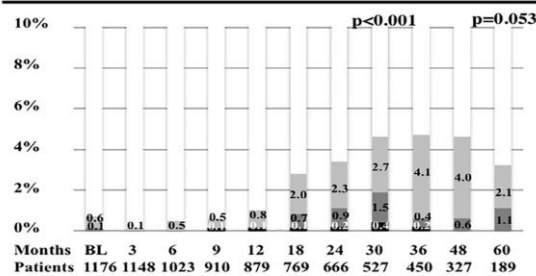
{ Image guided intensity modulated External beam radiotherapy and MRI based adaptive BRACytherapy in locally advanced Cervical cancer }



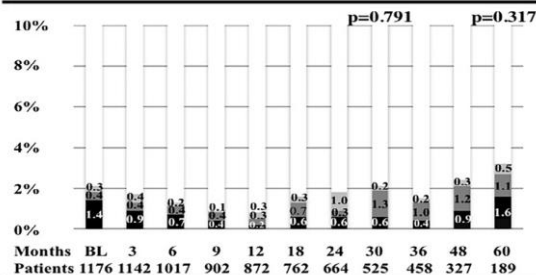
Cystitis



Bladder bleeding



Ureter stricture



CTCAE categories □ Grade 0 □ Grade 1 □ Grade 2 □ Grade 3-4



Toxicités par le patient ?

1176 (884 pour EORTC) patientes
EMBRACE I
RT-CT 45Gy (+/- gg) + CDDP
Curie selon centre
Tox selon CTCAE et PROM selon
EORTC
FU 27 mois (1-83)

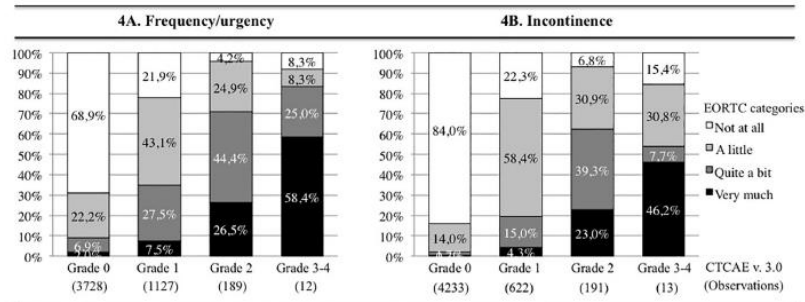
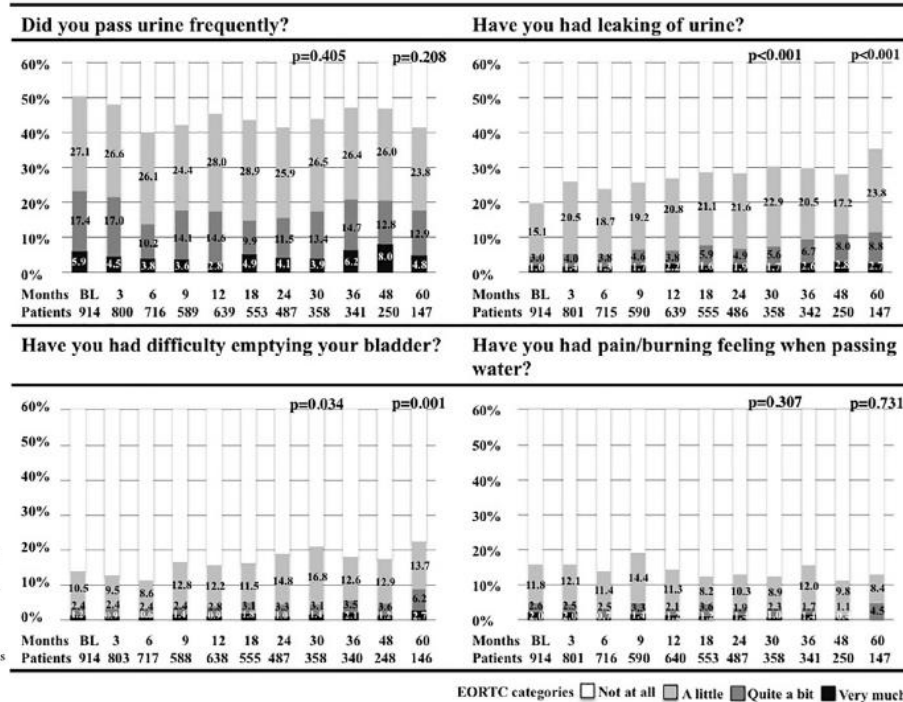


Fig. 4. Maximal incidence of CTCAE scoring and the corresponding patient reported outcomes for urinary frequency/urgency (1A) and incontinence (1B) for each visit (observations) during the course of follow up.



Toxicités au cours du temps ?

651 patientes

LAPERS

Late, persistent, substantial,
Treatment-Related Symptoms after
Radiation Therapy

EMBRACE I

RT-CT 45Gy (+/- gg) + CDDP

Curie selon centre

FU 42 mois (30-59)

Table 2: Overview of baseline prevalence, crude incidence, actuarial estimates, prevalence rates and LAPERS with or without baseline correction in four selected symptoms of the EORTC QLQ C30 and CX24. Events are defined as occurrence of the EORTC answer categories "quite a bit" or "very much" (substantial symptoms).

	Diarrhea		Difficulty controlling bowels		Urinary frequency		Leaking urine		
	number / total	%	number / total	%	number / total	%	number / total	%	
Baseline prevalence	34 / 651	5.2%	8 / 651	1.2%	141 / 650	21.7%	27 / 651	4.1%	
Crude incidence	205 / 651	31.5%	145 / 651	22.3%	292 / 650	44.9%	130 / 651	20.0%	
3/5-year Kaplan-Meier actuarial incidence	30.6% / 35.3%		21.3% / 26.3%		44.5% / 49.5%		19.4% / 22.8%		
Prevalence rates	3M	56 / 651	8.6%	41 / 651	6.3%	141 / 650	21.7%	36 / 651	5.5%
	12M	56 / 608	9.2%	33 / 601	5.5%	98 / 601	16.3%	36 / 601	6.0%
	24M	48 / 502	9.6%	32 / 504	6.3%	75 / 503	14.9%	31 / 503	6.2%
	36M	44 / 398	11.1%	29 / 397	7.3%	77 / 394	19.5%	32 / 394	8.1%
	48M	26 / 298	8.7%	20 / 297	6.7%	58 / 294	19.7%	24 / 294	8.2%
	60M	25 / 204	12.3%	25 / 206	12.1%	28 / 202	13.9%	17 / 200	8.5%
LAPERS events without baseline correction	48 / 651	7.4%	32 / 651	4.9%	93 / 650	14.3%	36 / 651	5.5%	
LAPERS events with baseline correction	44 / 651	6.8%	30 / 651	4.6%	72 / 650	11.1%	34 / 651	5.2%	



Quel OAR ?

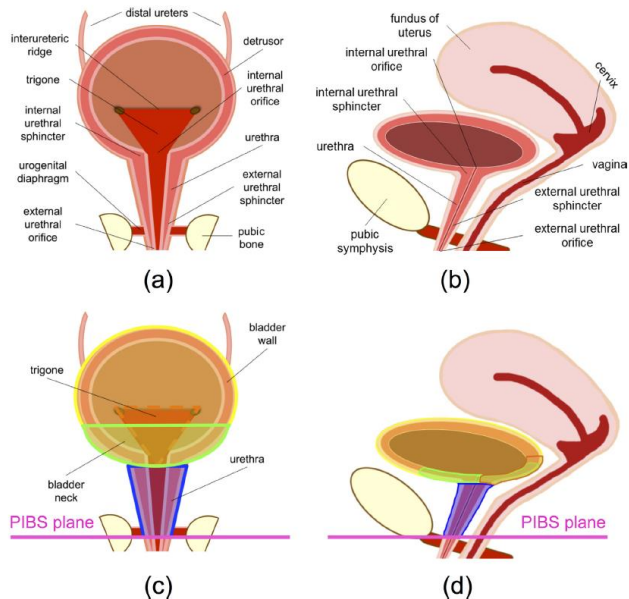


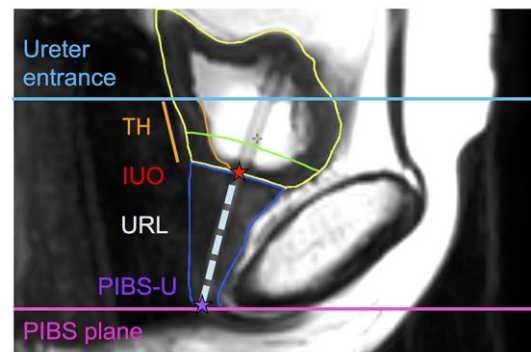
Fig. 1. a-b) Graphical illustrations of the lower urinary tract in coronal and sagittal section. c-d) Sub-structures considered in this study.

Table 2

Median (with interquartile range) volumes of bladder sub-structures and reference dimensions for each IGABT fraction, as well as relative and absolute differences in between 1st and 2nd IGABT fractions. Trigone volumes and dimensions for each fraction include patients in whom the ureters entrance was visible, while differences were calculated for patients in whom the ureters were visible in both fractions.

	1 st BT fraction median [IQR]	2 nd BT fraction median [IQR]	Relative difference median [IQR]	Absolute difference median [IQR]
Bladder (cm ³)	83.0 [64.0;106.0]	75.8 [61.7;96.9]	6.2 [-15.1;26.5]	22.8 [9.7;37.4]
Trigone (cm ³)	4.0 [3.1;5.2]	4.1 [3.5;4.8]	0.2 [-0.3;0.85]	0.7 [0.2;1.0]
Bladder neck (cm ³)	9.8 [6.5;13.7]	8.7 [5.9;13.5]	0.4 [-2.7;3.5]	3.4 [1.7;6.4]
ICRU BP to cranial trigone (cm)	0.9 [0.5;1.3]	1.0 [0.5;1.4]	0.1 [-0.2;0.4]	0.2 [0.1;0.5]
Trigone height (cm)	2.7 [2.4;2.9]	2.7 [2.4;2.9]	0 [-0.2;0.2]	0.2 [0.1;0.3]
Trigone width (cm)	4.4 [4.2;4.8]	4.5 [4.2;4.8]	-0.1 [-0.3;0.2]	0.2 [0.1;0.3]
Urethra reference length (cm)	3.1 [2.8;3.3]	3.1 [2.8;3.2]	0 [-0.2;0.1]	0.2 [0.1;0.3]

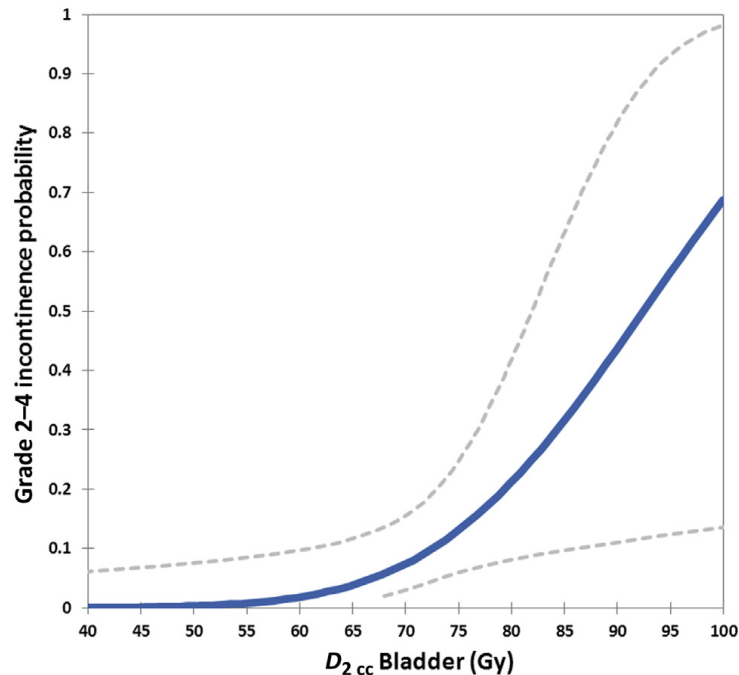
Abbreviations: IQR = InterQuartile Range (25th-75th percentile); ICRU BP = International Commission on Radiation Units and Measurement Bladder Point.



La bonne dose pour les OAR ?



69 patientes
Retro
RT + CT puis curie (CDDP)
PDR
FU 39 mois





La bonne dose pour les OAR mais quel type de tox ?

Table 3. Hazard ratios (HRs) with 95% confidence intervals and p-value for the factors tested in MVA for urinary frequency. Parallel MVAs were performed for bladder $D_{20\%}$, $D_{0.1cm3}$ and ICRU-BP dose if they had $p \leq 0.1$ in UVA. In this case, the HR for the other factors tested in UVA and the C-index are shown for the model with ICRU-BP dose, unless other dose parameters were more discriminative. The HRs (ORs) for the other dose parameters are also reported for comparison.

Variable	Physician assessed morbidity (CTCAE v.3)			Patient reported outcome (EORTC CX24)		
	G≥3 (n=16)	G≥2 (n=147)	LAPERS G≥1 (n=275)	"very much" (n=131)	"quite a bit" or worse (n=379)	LAPERS ≥"quite a bit" (n=153)
	HR (95% CI) p-value	HR (95% CI) p-value	HR (95% CI) p-value	HR (95% CI) p-value	HR (95% CI) p-value	HR (95% CI) p-value
Baseline (Yes vs. No)	4.316(1.615-11.78) 0.004	1.729(1.200-2.491) 0.003	2.313(1.651-3.242) <0.001	3.021(2.107-4.331) <0.001	2.497(1.993-3.128) <0.001	5.141(3.410-7.753) <0.001
Bladder $D_{20\%}$ (Gy)	-	-	-	1.016(0.995-1.037)	1.007(0.993-1.020)	-

Table 4. Hazard ratios (HRs) with 95% confidence intervals and p-value for the factors tested in MVA for urinary incontinence. Parallel MVAs were performed for bladder $D_{20\%}$, $D_{0.1cm3}$ and ICRU-BP dose if they had $p \leq 0.1$ in UVA. In this case, the HR for the other factors tested in UVA and the C-index are shown for the model with ICRU-BP dose, unless other dose parameters were more discriminative. The HRs (ORs) for the other dose parameters are also reported for comparison.

Variable	Physician assessed morbidity (CTCAE v.3)			Patient reported outcome (EORTC CX24)		
	G≥3 (n=16)	G≥2 (n=128)	LAPERS G≥1 (n=168)	"very much" (n=54)	"quite a bit" or worse (n=161)	LAPERS ≥"quite a bit" (n=47)
	HR (95% CI) p-value	HR (95% CI) p-value	OR (95% CI) p-value	HR (95% CI) p-value	HR (95% CI) p-value	OR (95% CI) p-value
Baseline (Yes vs. No)	3.311(1.133-9.677) 0.029	3.437(2.270-5.206) <0.001	3.628(2.308-5.705) <0.001	2.000(1.095-3.650) 0.024	2.203(1.565-3.100) <0.001	3.927(2.099-7.349) <0.001
Bladder $D_{20\%}$ (Gy)	-	1.012(0.989-1.035) 0.281	-	1.016(0.985-1.048) 0.309	-	-
Bladder $D_{0.1cm3}$ (Gy)	-	1.011(0.995-1.028) 0.169	-	1.022(0.998-1.047) 0.072	-	-



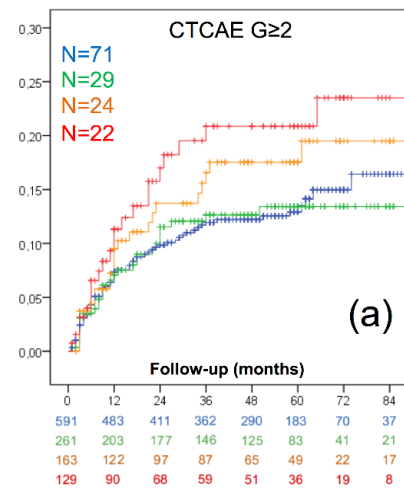
{ Image guided intensity modulated External beam radiochemotherapy and MRI based adaptive BRachytherapy in locally advanced Cervical cancer }



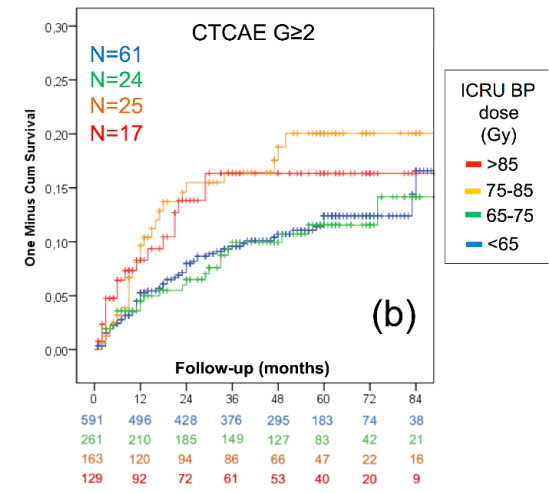
La bonne dose pour les OAR ?

1153 (884 pour EORTC) patientes
EMBRACE I
RT-CT 45Gy (+/- gg) + CDDP
Curie selon centre
Tox selon CTCAE et PROM selon
EORTC
FU 48 mois (3-120)

Urinary Frequency



Urinary Incontinence

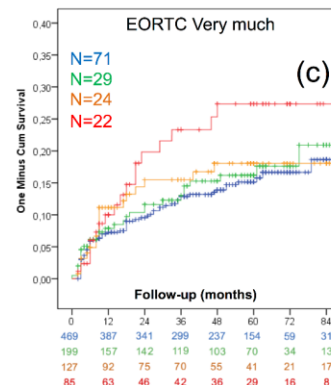




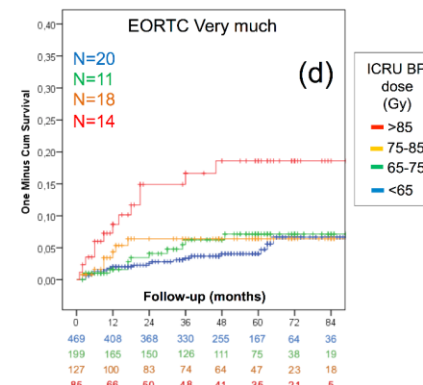
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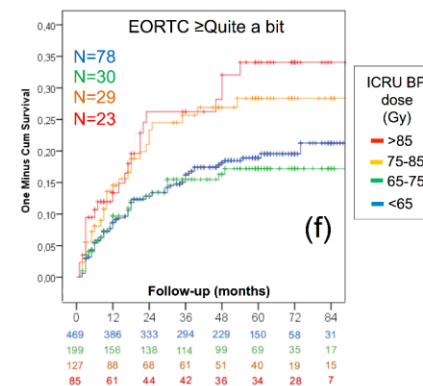
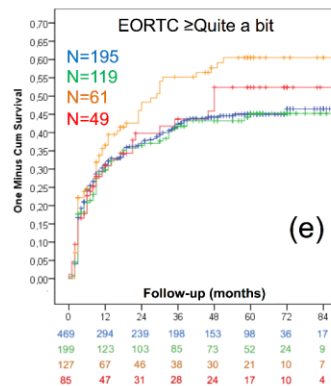
Urinary Frequency



Urinary Incontinence



ICRU BP dose (Gy)
■ >85
■ 75-85
■ 65-75
■ <65



ICRU BP dose (Gy)
■ >85
■ 75-85
■ 65-75
■ <65



La bonne dose pour les OAR ?

1153 (884 pour EORTC) patientes
EMBRACE I
RT-CT 45Gy (+/- gg) + CDDP
Curie selon centre
Tox selon CTCAE et PROM selon
EORTC
FU 48 mois (3-120)

Table 3. Hazard ratios (HRs) with 95% confidence intervals and p-value for the factors tested in MVA for urinary frequency. Parallel MVAs were performed for bladder $D_{20\%}$, $D_{0.1cm3}$ and ICRU-BP dose if they had $p \leq 0.1$ in UVA. In this case, the HR for the other factors tested in UVA and the C-index are shown for the model with ICRU-BP dose, unless other dose parameters were also more discriminative. The HRs (ORs) for the other dose parameters are also reported for comparison.

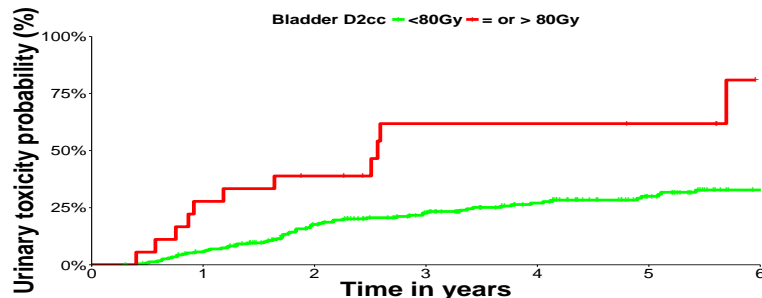
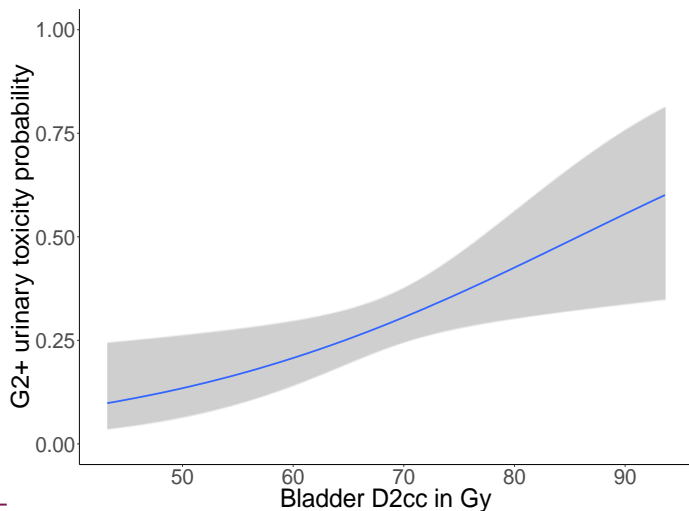
Variable	Physician assessed morbidity (CTCAE v.3)			Patient reported outcome (EORTC CX24)		
	G \geq 3 (n=16)	G \geq 2 (n=147)	LAPERS \geq 1 (n=275)	"very much" (n=131)	"quite a bit" or worse (n=379)	LAPERS \geq "quite a bit" (n=153)
	HR (95% CI) p-value	HR (95% CI) p-value	HR (95% CI) p-value	HR (95% CI) p-value	HR (95% CI) p-value	HR (95% CI) p-value
Baseline (Yes vs. No)	4.318(1.615-11.78) 0.004	1.729(1.200-2.491) 0.003	2.313(1.651-3.242) <0.001	3.021(2.107-4.331) <0.001	2.497(1.993-3.128) <0.001	5.141(3.410-7.753) <0.001
ICRU-BP dose (Gy)	-	1.013(0.999-1.026) 0.061	1.009(0.996-1.022) 0.183	1.009(0.993-1.027) 0.201	1.004(0.995-1.013) 0.396	1.013(0.997-1.030) 0.105

Table 4. Hazard ratios (HRs) with 95% confidence intervals and p-value for the factors tested in MVA for urinary incontinence. Parallel MVAs were performed for bladder $D_{20\%}$, $D_{0.1cm3}$ and ICRU-BP dose if they had $p \leq 0.1$ in UVA. In this case, the HR for the other factors tested in UVA and the C-index are shown for the model with ICRU-BP dose, unless other dose parameters were more discriminative. The HRs (ORs) for the other dose parameters are also reported for comparison.

Variable	Physician assessed morbidity (CTCAE v.3)			Patient reported outcome (EORTC CX24)		
	G \geq 3 (n=16)	G \geq 2 (n=128)	LAPERS \geq 1 (n=188)	"very much" (n=54)	"quite a bit" or worse (n=181)	LAPERS \geq "quite a bit" (n=47)
	HR (95% CI) p-value	HR (95% CI) p-value	OR (95% CI) p-value	HR (95% CI) p-value	HR (95% CI) p-value	OR (95% CI) p-value
Baseline (Yes vs. No)	3.311(1.133-9.677) 0.029	3.437(2.270-5.208) 0.001	3.628(2.308-5.705) <0.001	2.000(1.095-3.650) 0.024	2.203(1.565-3.100) <0.001	3.927(2.099-7.349) <0.001
ICRU-BP dose (Gy)	1.035(1.001-1.070) 0.045	1.020(1.006-1.035) 0.004	1.017(1.002-1.031) 0.023	1.027(1.008-1.048) 0.007	1.012(0.999-1.025) 0.064	1.022(0.999-1.047) 0.064

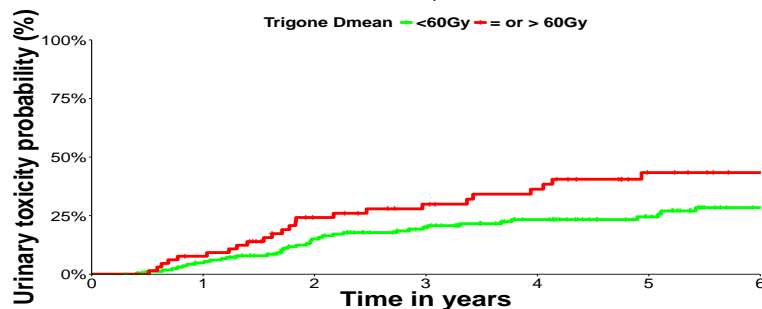
Quel OAR et Quelle dose ?

297 patientes
RT + CT puis curie (CDDP)
PDR
FU 4,9 ans



Number at risk

Bladder D2cc	0	1	2	3	4	5	6
<80Gy	233	215	170	141	112	81	57
>80Gy	18	13	10	5	5	4	0



Number at risk

Trigone Dmean	0	1	2	3	4	5	6
<60Gy	168	156	128	106	82	62	43
>60Gy	65	59	42	35	30	19	14





Comment faire ? Ovoïdes ou Ring ? IC/IS ?

902 patientes

EMBRACE I

Ring ou Ovoïde +/- IC

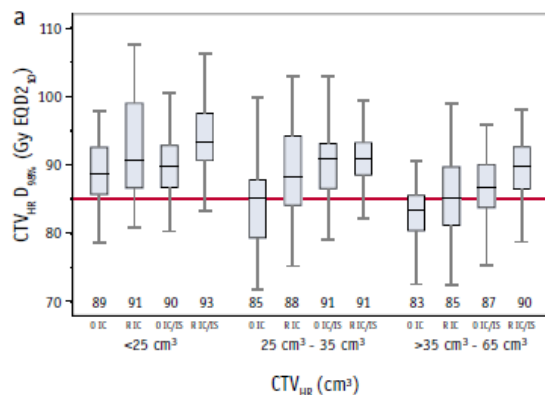
RT-CT 45Gy (+/- gg) + CDDP

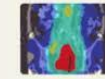
Curie selon centre

Table 1 Patient and treatment characteristics for each center group

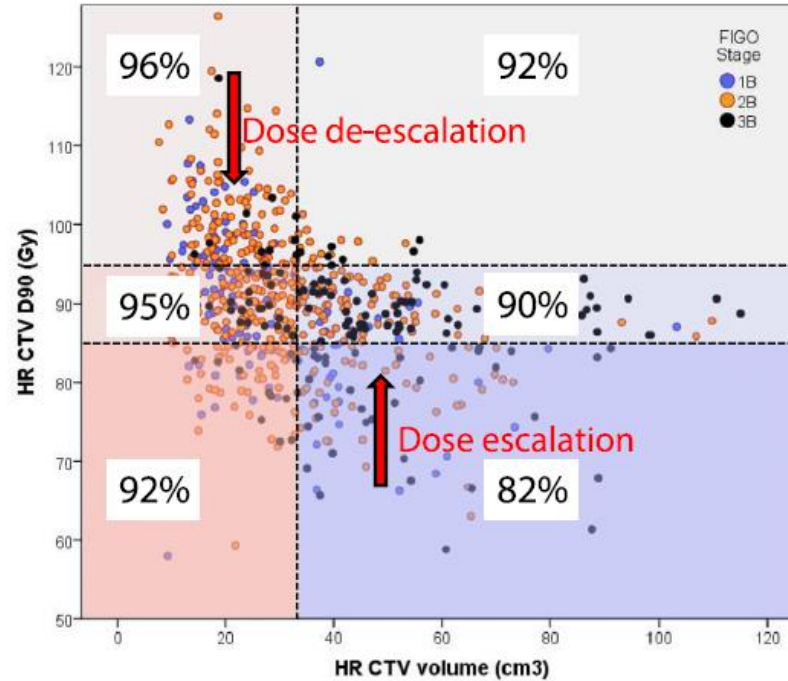
	Ovoids IC centers	Ring IC centers	Ovoids IC/IS centers	Ring IC/IS centers
No. of patients	119	114	180	489
No. of centers	4	5	4	6
Patient age, y	52 (14)	54 (17)	50 (14)	51 (13)
Local FIGO stage (I / II / III + IV), %	23/ 58/ 19	33/ 57/ 10	36/ 53/ 11	10/ 63/ 27
BT no. fractions (1 / 2 / 3 / 4 / 5), %	42/ 0/ 28 /30/ 0	24/ 0/ 21/ 44/ 11	16/ 22/ 14/ 48/ 0	1/ 41/ 0/ 51/ 7
HDR vs PDR (%)	58 / 42	77 / 23	62 / 38	58 / 42
IC vs IC/IS (%)	89 / 11	84 / 16	37 / 63	35 / 65
Average no. of needles in IC/IS	3.4 (1.2)	2.4 (1.2)	3.5 (1.8)	4.8 (2.5)
Tumor width diagnosis MR, cm	4.5 (1.5)	4.2 (1.4)	4.7 (1.4)	4.9 (1.4)
Tumor width at BT1 MR, cm	4.2 (1.1)	4.0 (0.9)	4.1 (1.0)	4.5 (0.9)
BT1 CTV _{HR} volume, cm ³	32.3 (16.1)	34.2 (19.3)	34.5 (17.9)	37.0 (20.4)
Point A dose in IC, Gy EQD2 ₁₀	75.9 (6.9)	76.0 (6.7)	73.9 (8.0)	71.3 (7.2)
CTV _{HR} D _{90%} , Gy EQD2 ₁₀	85.5 (7.3)	87.9 (9.3)	88.6 (5.9)	91.2 (5.1)
CTV _{HR} D _{98%} , Gy EQD2 ₁₀	76.4 (6.4)	78.6 (8.2)	79.6 (5.5)	82.2 (5.4)
V85Gy EQD2 ₁₀ , cm ³	89.0 (22.9)	71.1 (19.2)	78.3 (22.0)	73.5 (23.8)
V75Gy EQD2 ₁₀ , cm ³	124.6 (32.5)	99.4 (27.6)	107.8 (30.8)	102.3 (32.7)
V60Gy EQD2 ₁₀ , cm ³	304.2 (84.2)	249.8 (86.7)	246.2 (77.5)	247.9 (89.0)
Bladder ICRU-point, Gy EQD2 ₃	74.5 (17.4)	67.5 (15.1)	69.5 (14.9)	67.5 (12.7)
Bladder D _{2cm3} , Gy EQD2 ₃	82.9 (10.0)	75.2 (9.5)	79.4 (7.8)	75.1 (9.4)
ICRU rectovaginal point, Gy EQD2 ₃	68.7 (7.1)	63.1 (8.7)	69.6 (10.1)	64.8 (7.0)
Rectum D _{2cm3} , Gy EQD2 ₃	66.3 (7.2)	63.0 (6.9)	62.7 (7.4)	61.8 (6.3)
Sigmoid D _{2cm3} , Gy EQD2 ₃	65.4 (7.9)	64.6 (7.0)	63.4 (6.6)	64.4 (6.4)
Vagina 5 mm lateral point, Gy EQD2 ₃	87.3 (12.7)	106.9 (26.3)	87.0 (12.3)	109.4 (28.7)

Abbreviations: BT = brachytherapy; FIGO = International Federation of Gynecology and Obstetrics; HDR = high dose rate; IC = intracavitary; IS = interstitial; MR = magnetic resonance; PDR = pulsed dose rate.
Mean values and standard deviations (1 SD) are displayed.





Et sinon ? Diminution des doses ?





Quelles toxicités vaginales ?

588 patientes

EMBRACE I

RT-CT 45Gy (+/- gg) + CDDP

Curie selon centre

FU 15 mois (1-49)

Table 3 Crude incidences of treatment-related individual vaginal symptoms and overall vaginal morbidity in 588 patients with a median follow-up time of 15 months

Grade	Vaginal stenosis	Vaginal dryness	Vaginal mucositis	Vaginal bleeding	Vaginal fistula	Other vaginal symptoms	Overall vaginal morbidity
G0	241 (41%)	312 (53%)	415 (71%)	407 (69%)	582 (99%)	523 (89%)	155 (26%)
G1	256 (43%)	244 (42%)	146 (25%)	175 (30%)	2	47 (8%)	309 (53%)
G2	86 (15%)	32 (5%)	23 (4%)	5 (1%)	0	14 (2%)	111 (19%)
G3	5 (1%)	N.A.	3	1	4 (1%)	4 (1%)	12 (2%)
G4	N.A.	N.A.	1	0	0	0	1
G5	N.A.	N.A.	0	0	0	0	0

Abbreviation: N.A. = not applicable.

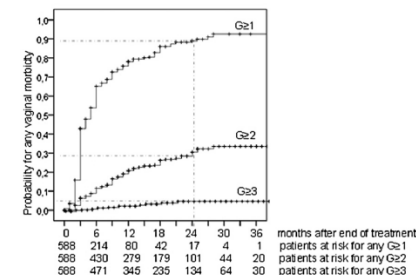
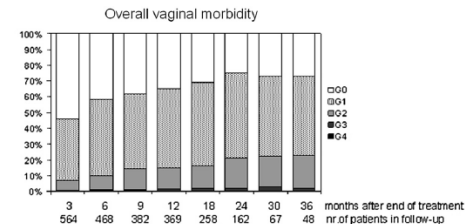
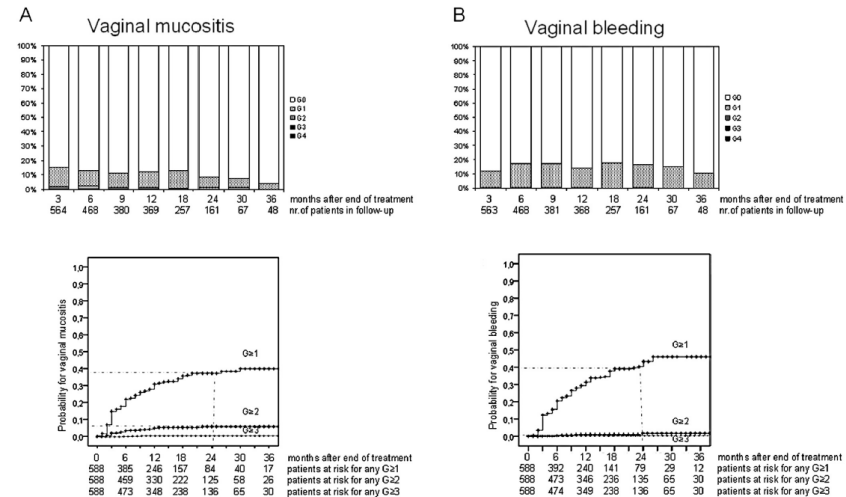
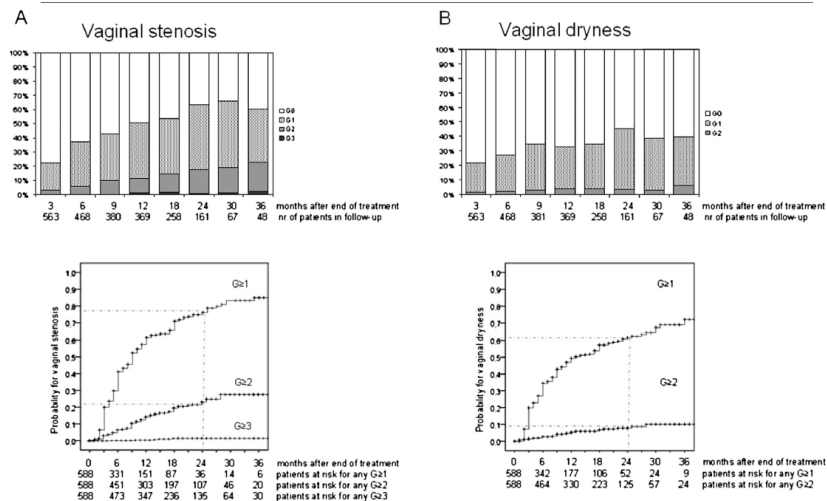


Fig. 1. Overall vaginal morbidity (all individual vaginal symptoms combined). Prevalence rates for all gradings at each follow-up visit are shown in bar charts. Actuarial incidences for grade ≥ 1 , grade ≥ 2 , and grade ≥ 3 are shown in Kaplan-Meier curves.



Quelles toxicités vaginales ?

Kirchheiner K et al., IJROBP, 2013





Quelles toxicités vaginales ?

630 patientes

EMBRACE I

RT-CT 45Gy (+/- gg) + CDDP

Curie selon centre

FU 24 mois (12-36)

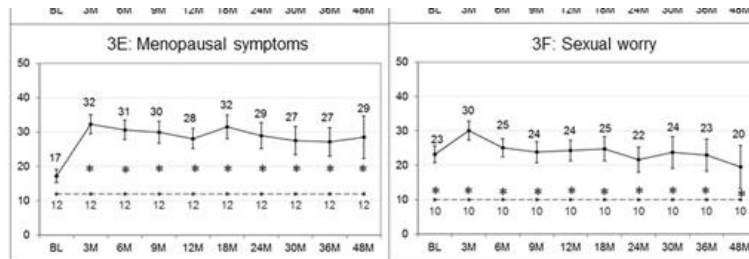


Figure 3 (A-F): EORTC QLQ-CX24 symptom scales over time, mean scores \pm 95% confidence intervals are shown between score 0 and 50. Higher scores represent higher symptom burden. The dotted line displays reference values of a female general population [Park et al. 2007]. Asterisk represent clinically relevant differences between the patients' cohort and the reference population (differences \geq 10)

Abbreviations: † BL baseline, †† M months of follow-up



Quelles toxicités vaginales ?

630 patientes
EMBRACE I
RT-CT 45Gy (+/- gg) + CDDP
Curie selon centre
FU 24 mois (12-36)

Table 3: EORTC QLQ-CX24¹ symptom scales. Mean \pm standard deviation shown. Higher scores in symptom scales denote higher symptom burden / higher functioning problems / worries. Higher scores in sexual activity and enjoyment represent higher activity and higher enjoyment.

	BL [†]	3M ^{††}	6M	9M	12M	18M	24M	30M	36M	48M
N of responders	726 -	615 -	561 -	446 -	456 -	360 -	285 -	201 -	179 -	94 -
(range)	740	629	569	458	471	374	297	211	188	104
	\pm 26,73	\pm 36,02	\pm 34,18	\pm 35,30	\pm 32,19	\pm 33,82	\pm 32,99	\pm 30,39	\pm 29,30	\pm 32,32
Sexual worry	23,23	30,08	25,13	23,84	24,34	24,81	21,64	23,71	23,02	19,50
	\pm 33,84	\pm 35,49	\pm 32,06	\pm 33,03	\pm 33,00	\pm 33,77	\pm 31,46	\pm 33,44	\pm 32,08	\pm 31,07
Sexual activity	9,78	16,13	20,01	19,27	21,24	21,00	21,03	19,39	20,29	19,28
	\pm 20,39	\pm 24,69	\pm 26,27	\pm 26,50	\pm 27,26	\pm 26,79	\pm 27,14	\pm 26,48	\pm 26,75	\pm 28,70
Subgroup of sexually active patients										
Number of responders	146 -	211 -	240 -	184 -	201 -	159 -	126 -	82 -	76 -	35 -
(range)	148	213	241	185	202	161	126	83	77	36
Sexual functioning	9,49	26,78	26,91	27,55	28,73	27,60	26,46	24,80	27,67	29,05



Quelles toxicités vaginales ?

630 patientes
EMBRACE I
RT-CT 45Gy (+/- gg) + CDDP
Curie selon centre
FU 24 mois (12-36)

Table 3: EORTC QLQ-CX24* symptom scales. Mean \pm standard deviation shown. Higher scores in symptom scales denote higher symptom burden / higher functioning problems / worries. Higher scores in sexual activity and enjoyment represent higher activity and higher enjoyment.

	BL [†]	3M ^{††}	6M	9M	12M	18M	24M	30M	36M	48M
N of responders (range)	726 - 740	615 - 629	561 - 569	446 - 458	456 - 471	360 - 374	285 - 297	201 - 211	179 - 188	94 - 104
	\pm 15,38	\pm 23,10	22,67	\pm 24,11	\pm 25,52	\pm 23,70	\pm 23,48	\pm 20,86	\pm 22,81	\pm 24,62
Sexual enjoyment	57,88	52,29	54,08	52,07	56,72	58,28	54,50	58,54	55,70	60,00
	\pm 32,61	\pm 32,83	\pm 30,93	\pm 32,18	\pm 30,38	\pm 29,28	\pm 30,87	\pm 27,99	\pm 29,51	\pm 31,10
Vaginal dryness	8,68	28,14	26,83	29,53	29,70	29,81	27,78	23,29	29,87	25,00
	\pm 18,39	\pm 30,26	\pm 30,72	\pm 29,63	\pm 32,20	\pm 29,49	\pm 28,83	\pm 24,82	\pm 29,91	\pm 24,40
Pain during intercourse	16,10	30,05	29,72	27,57	27,36	25,83	23,02	24,10	23,38	29,52
	\pm 25,69	\pm 29,04	\pm 28,70	\pm 29,12	\pm 27,84	\pm 26,69	\pm 25,11	\pm 23,46	\pm 26,53	\pm 28,89

|| Several patients did not complete the overall questionnaire, but only selected questions.

Abbreviations: * EORTC QLQ-CX24 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer Module 24, [†] BL Baseline, ^{††} M Months in follow-up



Quelles toxicités vaginales ?

208 patientes (104 contrôles et 104 traitées)
???

EORTC QLQ-CX24

Body image	73.1±25.2	79.6±18.8	0.036
Symptom experience	12.1±10.1	10.5±8.9	0.244
Lymphedema	20.2±28.0	12.2±21.8	0.022
Peripheral neuropathy	22.4±28.4	17.0±23.2	0.132
Menopausal symptoms	20.5±27.2	17.3±23.2	0.362
Sexual activity	32.1±24.5	30.1±26.6	0.583
Sexual enjoyment	40.1±24.3	37.8±25.9	0.537
Sexual/Vaginal functioning	80.6±20.6	85.4±16.8	0.077
Sexual worry	26.6±28.0	22.0±24.9	0.214

FSFI

Desire	3.0±1.0	2.9±1.1	0.617
Arousal	3.5±1.3	3.2±1.6	0.232
Lubrication	4.1±1.7	4.0±1.9	0.696
Orgasm	3.9±1.5	3.7±1.8	0.356
Satisfaction	4.0±0.7	3.9±1.2	0.363
Pain	4.5±1.7	4.1±2.0	0.214
Total	23.0±6.6	21.9±8.2	0.300



Impact dosimétrique ?

630 patientes

EMBRACE I

RT-CT 45Gy (+/- gg) + CDDP

Curie selon centre

FU 24 mois (12-36)

Table 2

Univariate and multivariable analyses of risk factors for vaginal stenosis $G \geq 2$ (Cox proportional hazards model); multivariable model stratified for center effects. *P*-values and Hazard Ratios with 95% confidence intervals (CI) shown.

N = 630	Univariate Cox regression, <i>p</i> -value	Univariate Cox Regression, Hazard Ratio [95% CI]	Multivariable Cox regression, <i>p</i> -value	Multivariable Cox Regression, Hazard Ratio [95% CI]
Comorbidities (binary)	0.704	1.057 [0.697-1.602]	-	-
Any tumor extension in the vagina at time of diagnosis (binary)	<0.001*	1.997 [1.372-2.906]	<0.001*	2.259 [1.519-3.360]
Overall center effect	<0.001*		Stratified for centers	
Centre 1	Reference	Reference		
Centre 2	0.070	0.548 [0.286-1.050]		
Centre 3	0.883	0.951 [0.489-1.849]		
Centre 4	0.423	0.730 [0.337-1.578]		
Centre 5	0.004*	0.051 [0.007-0.377]		
Centre 6	0.067	1.727 [0.962-3.102]		
Centre 7	0.292	0.687 [0.342-1.381]		
Centre 8	0.098	1.663 [0.910-3.040]		
EBRT dose (binary cutoff: 45 Gy in 25 fractions)	0.001*	1.893 [1.305-2.747]	0.056	1.770 [0.985-3.181]
Brachytherapy Dose Rate (binary HDR vs. PDR)	0.206	1.270 [0.877-1.841]		
Brachytherapy Technique (binary IC vs. IC/IS)	0.194	1.274 [0.884-1.835]	-	
Brachytherapy HR-CTV D90 (continuous)	0.012	0.990 [0.967-1.014]		
Recto-vaginal reference point dose in EQD2 (continuous)	0.003*	1.030 [1.010-1.051]	0.029*	1.025 [1.003-1.049]

Abbreviations: N = Number, CI = Confidence interval, EBRT = External Beam Radiotherapy, Gy = Gray, EQD2 = Equivalent Dose in 2 Gy Fractions, HDR = High Dose Rate, PDR = Pulse Dose Rate, IC = Intracavitary, IS = Interstitial, HR-CTV D90 = High-Risk Clinical Target Volume receiving 90% of the prescribed dose, ICRU = International Commission of Radiation Units and Measurements.

* Significant.



Impact dosimétrique ?

630 patientes
EMBRACE I
RT-CT 45Gy (+/- gg) + CDDP
Curie selon centre
FU 24 mois (12-36)

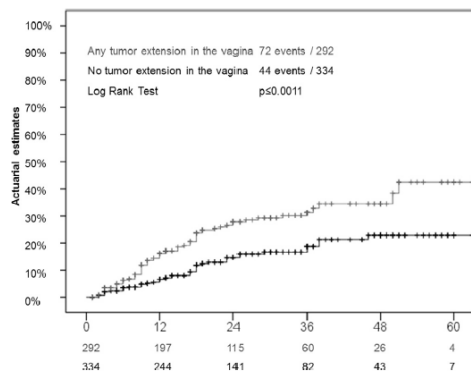


Fig. 2. Actuarial estimates for vaginal stenosis $G \geq 2$ in patients with or without tumor extension in the vagina at the time of diagnosis.

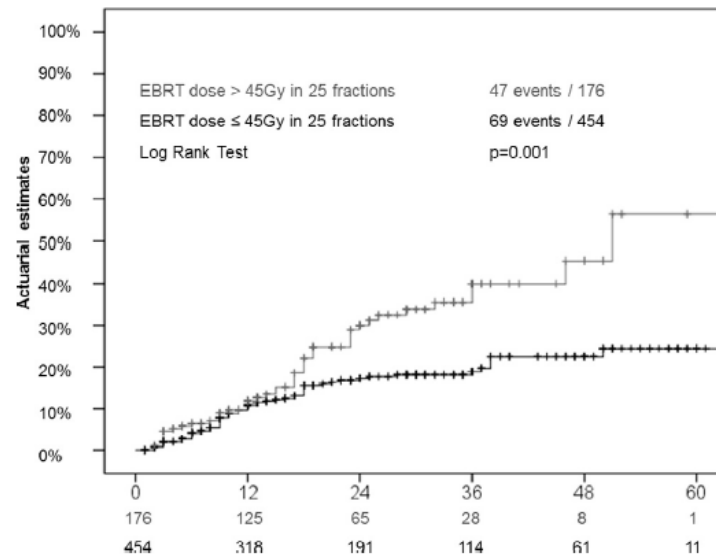


Fig. 3. Actuarial estimates for vaginal stenosis $G \geq 2$ in patients according to the EBRT dose.

Impact dosimétrique ?



630 patientes
EMBRACE I
RT-CT 45Gy (+/- gg) + CDDP
Curie selon centre
FU 24 mois (12-36)

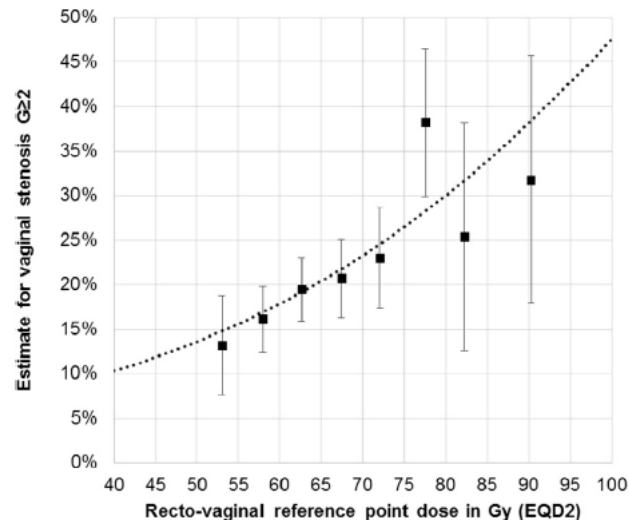
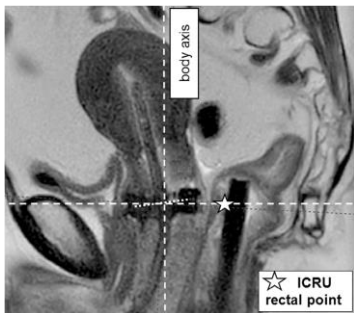


Fig. 4. Dose-effect relationship of the combined EBRT and brachytherapy dose to recto-vaginal reference point in EQD2 and vaginal stenosis $G \geq 2$ in $N=630$ patients.



Impact dosimétrique ?

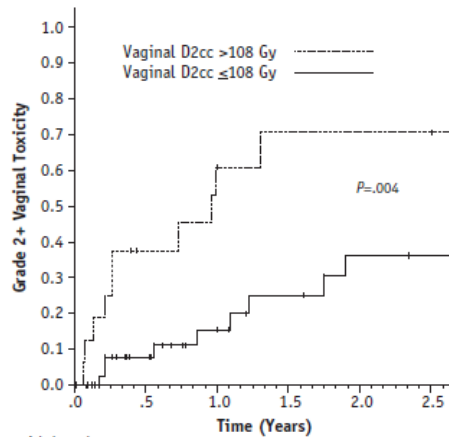
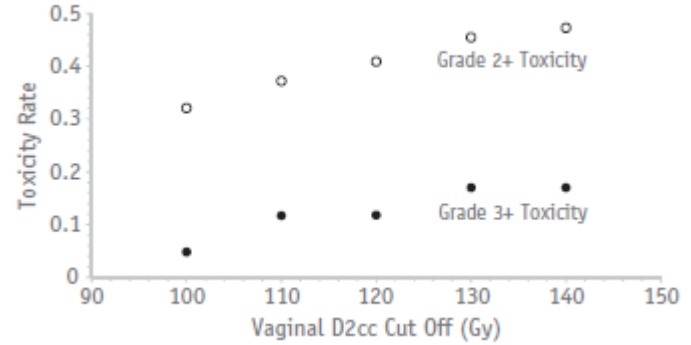
62 patientes

Retro

2009-2015

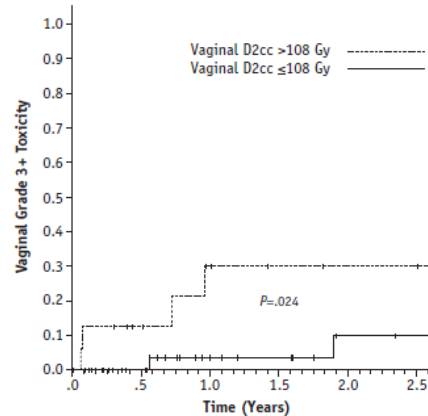
RT-CT 45Gy (+/- gg) +/- CDDP ?

Curie LDR ou HDR



number at risk (n=62)

≤ 108 Gy	46	30	19	15	11	10
> 108 Gy	16	8	5	3	3	3



number at risk (n=62)

≤ 108 Gy	46	32	20	18	13	12
> 108 Gy	16	11	7	5	4	4

Impact dosimétrique ?

169 patientes

Retro

2006-2013

RT-CT 45Gy (+/- gg) +/- CDDP ?

Curie PDR

Table 3
Dosimetric parameters associated to late vaginal toxicity Grade ≥ 2

Metrics	Median (IQR)	Univariate analysis	
		HR (CI 95%)	p-value
Mean dose	54.9 (53.3–57.0)	1.22 (1.13–1.31)	<0.001
D2cm ³	69.0 (65.8–74.1)	1.05 (1.03–1.07)	<0.001
D2 _{5%}	78.0 (74.0–87.8)	1.02 (1.01–1.03)	<0.001
D5 _{5%}	72.3 (68.8–80.4)	1.04 (1.03–1.06)	<0.001
D10 _{5%}	68.9 (64.9–74.9)	1.06 (1.04–1.07)	<0.001
D20 _{5%}	64.4 (61.5–69.2)	1.07 (1.05–1.10)	<0.001
D30 _{5%}	61.2 (58.9–64.9)	1.09 (1.06–1.13)	<0.001
D40 _{5%}	58.3 (56.1–61.1)	1.10 (1.05–1.15)	<0.001
D50 _{5%}	55.9 (52.9–58.2)	1.08 (1.02–1.15)	0.015
V60 _{Cy}	34.5 (25.6–42.8)	1.04 (1.02–1.06)	<0.001
V70 _{Cy}	8.1 (4.2–17.7)	1.05 (1.04–1.07)	<0.001
V80 _{Cy}	1.6 (0.6–5.2)	1.07 (1.05–1.10)	<0.001
V90 _{Cy}	0.35 (0.50–1.48)	1.10 (1.06–1.13)	<0.001
V100 _{Cy}	0.06 (0.01–0.4)	1.12 (1.08–1.17)	<0.001
V110 _{Cy}	0.01 (0.00–0.12)	1.15 (1.09–1.21)	<0.001
V120 _{Cy}	0.01 (0.00–0.03)	1.20 (1.11–1.29)	<0.001
V130 _{Cy}	0.00 (0.00–0.01)	1.31 (1.17–1.47)	<0.001
V140 _{Cy}	0.00 (0.00–0.01)	1.54 (1.29–1.85)	<0.001

Dx_{5%} values = minimum dose given to the hottest x% volume;
D2cm³ = minimum dose given to the hottest 2 cc volume; IQR = inter-quartile range; Vx_{Cy} values = the percentage volume that received a dose greater or equal to x Gy.

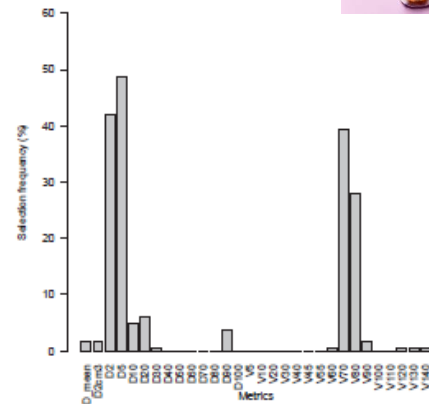


Fig. 3. Histogram of metrics selected over all bootstrap samples.

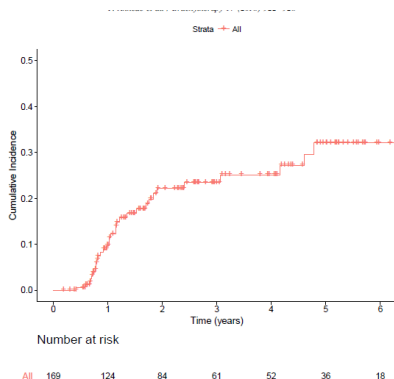


Fig. 1. Cumulative incidence of Grade ≥ 2 vaginal toxicity.

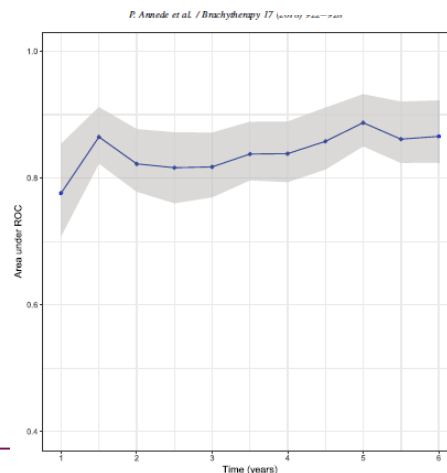


Fig. 2. Bootstrap time-dependent area under ROC curve (median with IQR).



Comment faire ? Ovoïdes ou Ring ? IC ?

902 patientes

EMBRACE I

Ring ou Ovoïde +/- IC

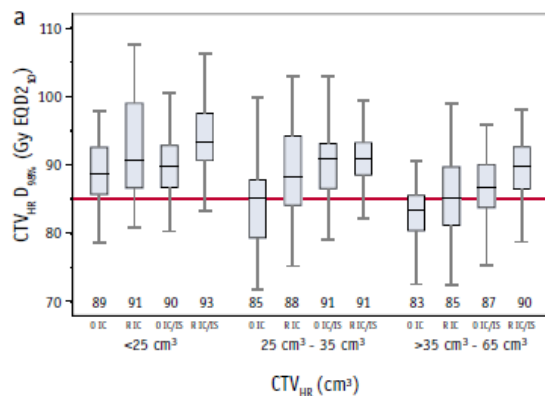
RT-CT 45Gy (+/- gg) + CDDP

Curie selon centre

Table 1 Patient and treatment characteristics for each center group

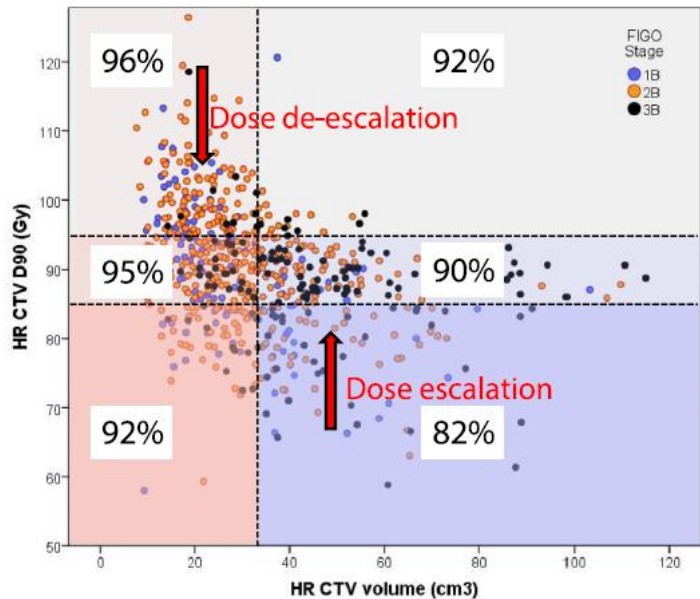
	Ovoids IC centers	Ring IC centers	Ovoids IC/IS centers	Ring IC/IS centers
No. of patients	119	114	180	489
No. of centers	4	5	4	6
Patient age, y	52 (14)	54 (17)	50 (14)	51 (13)
Local FIGO stage (I / II / III + IV), %	23/ 58/ 19	33/ 57/ 10	36/ 53/ 11	10/ 63/ 27
BT no. fractions (1 / 2 / 3 / 4 / 5), %	42/ 0/ 28 /30/ 0	24/ 0/ 21/ 44/ 11	16/ 22/ 14/ 48/ 0	1/ 41/ 0/ 51/ 7
HDR vs PDR (%)	58 / 42	77 / 23	62 / 38	58 / 42
IC vs IC/IS (%)	89 / 11	84 / 16	37 / 63	35 / 65
Average no. of needles in IC/IS	3.4 (1.2)	2.4 (1.2)	3.5 (1.8)	4.8 (2.5)
Tumor width diagnosis MR, cm	4.5 (1.5)	4.2 (1.4)	4.7 (1.4)	4.9 (1.4)
Tumor width at BT1 MR, cm	4.2 (1.1)	4.0 (0.9)	4.1 (1.0)	4.5 (0.9)
BT1 CTV _{HR} volume, cm ³	32.3 (16.1)	34.2 (19.3)	34.5 (17.9)	37.0 (20.4)
Point A dose in IC, Gy EQD2 ₁₀	75.9 (6.9)	76.0 (6.7)	73.9 (8.0)	71.3 (7.2)
CTV _{HR} D _{90%} , Gy EQD2 ₁₀	85.5 (7.3)	87.9 (9.3)	88.6 (5.9)	91.2 (5.1)
CTV _{HR} D _{98%} , Gy EQD2 ₁₀	76.4 (6.4)	78.6 (8.2)	79.6 (5.5)	82.2 (5.4)
V85Gy EQD2 ₁₀ , cm ³	89.0 (22.9)	71.1 (19.2)	78.3 (22.0)	73.5 (23.8)
V75Gy EQD2 ₁₀ , cm ³	124.6 (32.5)	99.4 (27.6)	107.8 (30.8)	102.3 (32.7)
V60Gy EQD2 ₁₀ , cm ³	304.2 (84.2)	249.8 (86.7)	246.2 (77.5)	247.9 (89.0)
Bladder ICRU-point, Gy EQD2 ₃	74.5 (17.4)	67.5 (15.1)	69.5 (14.9)	67.5 (12.7)
Bladder D _{2cm3} , Gy EQD2 ₃	82.9 (10.0)	75.2 (9.5)	79.4 (7.8)	75.1 (9.4)
ICRU rectovaginal point, Gy EQD2 ₃	68.7 (7.1)	63.1 (8.7)	69.6 (10.1)	64.8 (7.0)
Rectum D _{2cm3} , Gy EQD2 ₃	66.3 (7.2)	63.0 (6.9)	62.7 (7.4)	61.8 (6.3)
Sigmoid D _{2cm3} , Gy EQD2 ₃	65.4 (7.9)	64.6 (7.0)	63.4 (6.6)	64.4 (6.4)
Vagina 5 mm lateral point, Gy EQD2 ₃	87.3 (12.7)	106.9 (26.3)	87.0 (12.3)	109.4 (28.7)

Abbreviations: BT = brachytherapy; FIGO = International Federation of Gynecology and Obstetrics; HDR = high dose rate; IC = intracavitary; IS = interstitial; MR = magnetic resonance; PDR = pulsed dose rate.
Mean values and standard deviations (1 SD) are displayed.





Comment faire ? Diminution des doses ?



Aim

Priority

ICRU recto-vaginal point dose

<65 Gy EQD2 (EBRT + brachytherapy)

Primary

The ratio of vaginal TRAK and total TRAK

<30-40%

Secondary

Vaginal lateral dose points at 5 mm

<85 Gy EQD2 (EBRT + brachytherapy)

Secondary

Visual inspection of the 140% isodose

Intruding as little as possible into vaginal tissue, and preferentially located within the applicator

Secondary

PIBS - 2 cm

When vagina is not involved: $D_{PIBS-2cm} < 5$ Gy

Secondary



Comment faire ? Diminution des doses ?

50 patientes
Retro EMBRACE
50 patientes
Variation diminution de la dose dans
les ovoïdes et ring et augmentation
dans les aiguilles et tandem

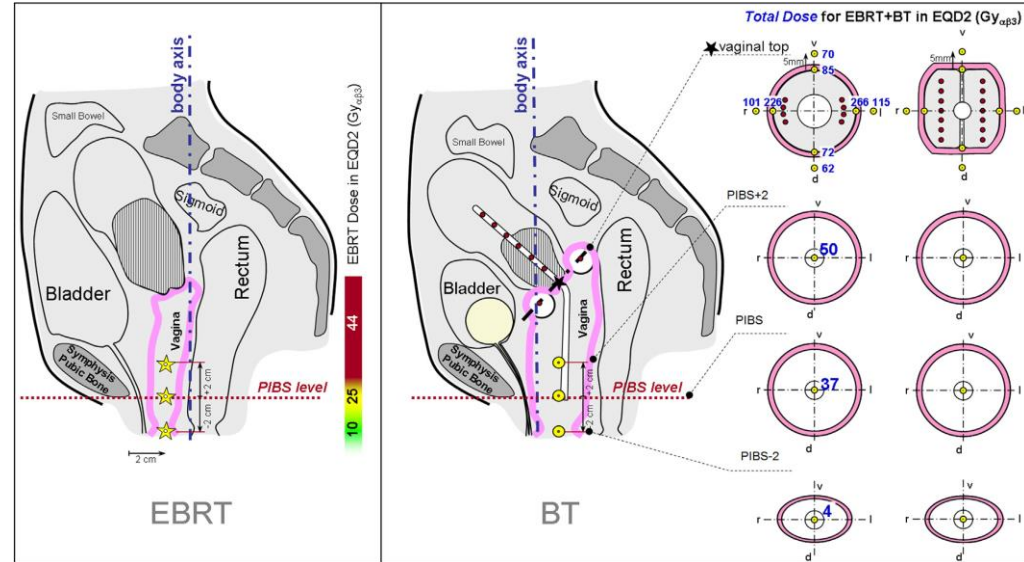
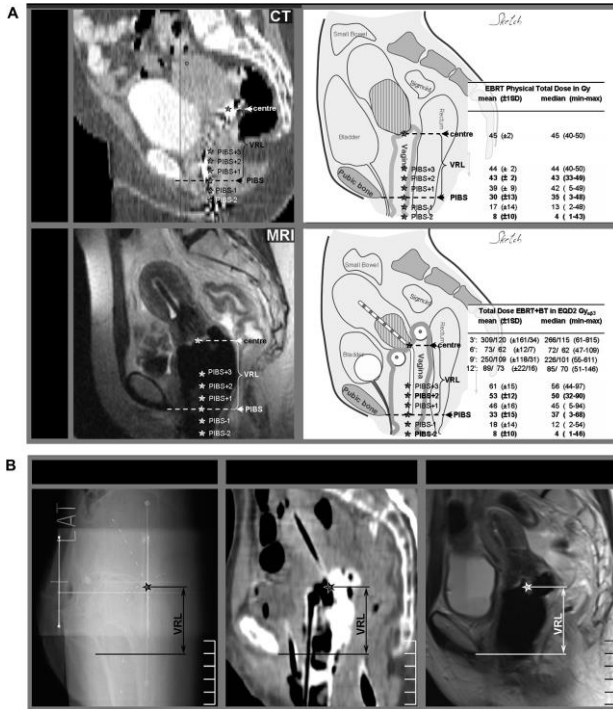
Table 1

Comparison of doses delivered by vaginal dose de escalation (VDD) and non-VDD plans for all the included patients from all centres. Doses are in total Gy EQD2, mean (SD).

All 50 pts	Non VDD plan	VDD plan	Difference	p value
GTV D98	100 (16)	103 (23)	4 (13)	0.08
HR-CTV D98	81 (7)	81 (6)	-0.3 (2)	0.23
HR-CTV D90	90 (7)	90 (7)	0.2 (2)	0.39
HR-CTV D50	126 (15)	130 (14)	4 (11)	0.02
IR-CTV D90	69 (5)	68 (4)	-1 (2)	<0.01
Bladder D _{2cm} ³	75 (9)	73 (10)	-2 (2)	<0.01
Rectum D _{2cm} ³	62 (7)	60 (7)	-3 (2)	<0.01
Sigmoid D _{2cm} ³	63 (7)	63 (7)	-0.2 (1)	0.25
Bowel D _{2cm} ³	64 (10)	64 (11)	0.07 (2)	0.85
ICRU recto-vaginal point	69 (11)	64 (11)	-4 (4)	<0.01
Vagina 0 mm (mean LT + RT)	266 (162)	137 (46)	-128 (140)	<0.01
Vagina 5 mm (mean LT + RT)	111 (57)	80 (18)	-32 (48)	<0.01
Vagina 5 mm ant	68 (8)	64 (6)	-4 (4)	<0.01
Vagina 5 mm post	83 (32)	77 (27)	-5 (9)	<0.01
PIBS point	48 (5)	47 (3)	-1 (2)	<0.01
PIBS + 2 point	59 (29)	55 (21)	-5 (10)	<0.01



Comment faire ? PIBS ?



Le but de la présentation?

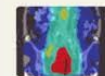
Table 1 Evidence for Dose-Effect and Volume-Effect Relationships for Endpoints Relevant for Brachytherapy

Target/OAR	Dose	Endpoint	Source of Clinical Data	# Patients	Level of Evidence*
CTV-T _{HR}	D90	Local control	retroEMBRACE ⁴³	488	High
			MUW ⁴⁴	141	
CTV-T _{HR}	D98 [†]	Local control	IGR ⁴⁵	225	High
			retroEMBRACE ⁴³	488	
CTV _{res}	D98 [†]	Local control	retroEMBRACE ⁴³	267	Intermediate
CTV-T _{HR}	D98 [†]	Local control	retroEMBRACE ⁴³	345	Intermediate
Bladder	D _{2cm3}	Bleeding, cystitis, fistula	EMBRACE	1340	High
Bladder	ICRU bladder point	Incontinence	EMBRACE	1340	High
Ureters	No reporting system	Ureter stenosis	IGR ⁴⁶	297	Under investigation
Rectum	D _{2cm3}	Bleeding, proctitis, fistula	EMBRACE ⁷	960	High
Rectum	ICRU rectovaginal point	Bleeding, proctitis, fistula	EMBRACE ⁷	960	High
Anus	?	Incontinence	EMBRACE	1340	Under investigation
Sigmoid	D _{2cm3}	Diarrhea, fistula, strictures, bleeding	EMBRACE	1340	No correlation / Under investigation
Bowel	D _{2cm3}	Diarrhea	EMBRACE	1340	High
Bowel	D _{2cm3}	Fistula, strictures, incontinence, bleeding	EMBRACE	1340	High
Vagina	ICRU rectovaginal point	Vaginal stenosis	EMBRACE ⁴⁷	630	High
Vagina	PIBS	Vaginal stenosis	EMBRACE	301	High
Vagina	Dose surface maps	Stenosis	UMCU ¹⁹	31	Under investigation
Normal tissue	V60Gy	Cystitis	EMBRACE	1340	High
Normal tissue	V60Gy	Pooled diarrhea + flatulence + bowel fistula & stenosis	EMBRACE	1340	High
Normal tissue	V60Gy	Fatigue	IGR ⁴⁶	260	High
Normal tissue	V60Gy	Fatigue	EMBRACE	1177	High

Abbreviations: IGR, Institute Gustave Roussy; MUW, Medical University of Vienna; UMCU, University Medical Center Utrecht.

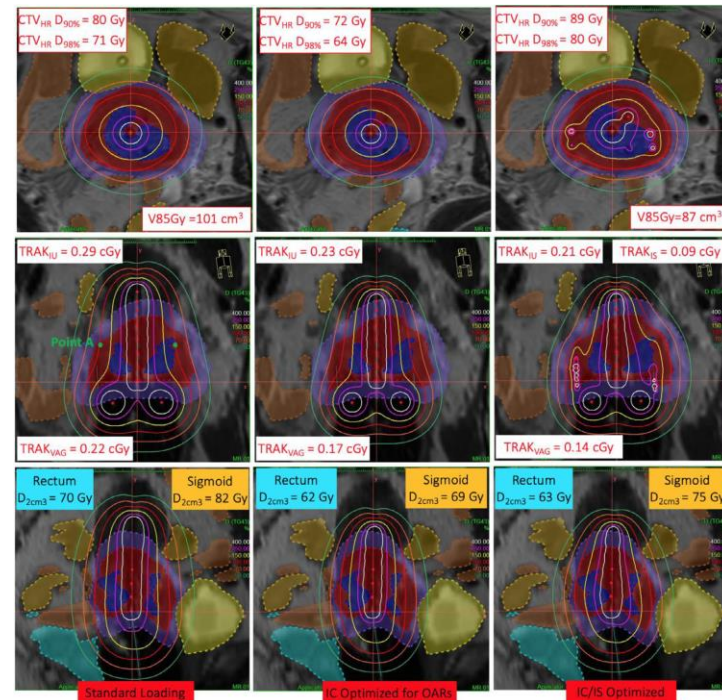
* Based on size of cohort and quality of reporting for morbidity endpoints (see further explanation in the text).

[†] In the retroEMBRACE study, D98 was not reported for GTV_{res}, CTV-T_{HR}, and CTV-T_{HR}. However, D98 can be interpolated from D90 and D100 with high accuracy⁴⁵ for which dose effect was established.

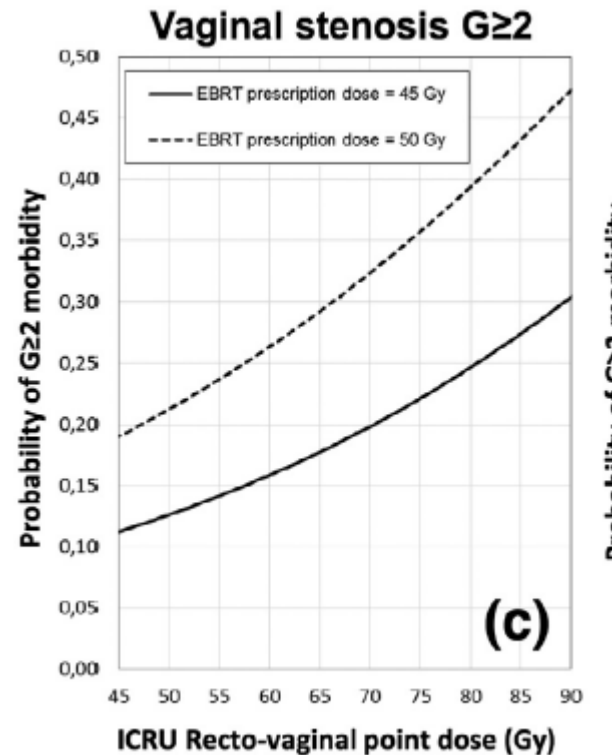
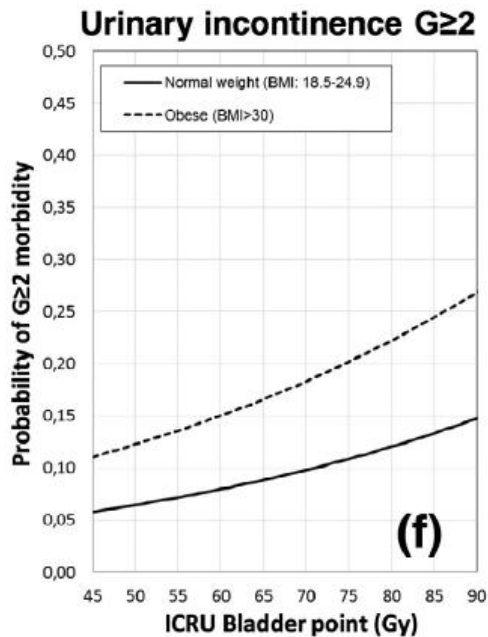
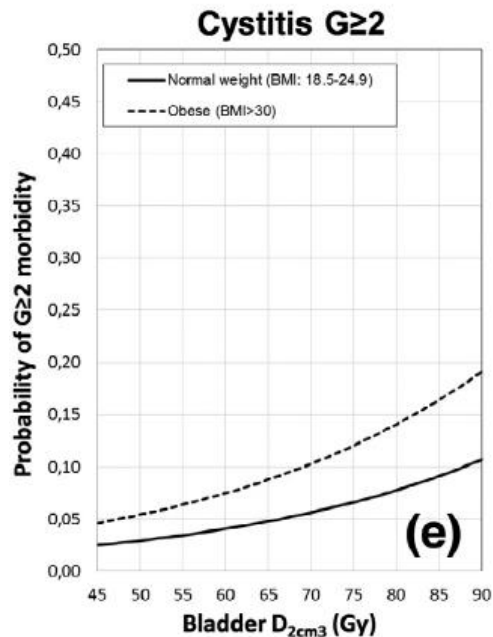


EMBRACE-II

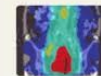
{ Image guided intensity modulated External beam radiotherapy and MRI based adaptive Brachytherapy in locally advanced Cervical cancer }



Le but de la présentation?



Le but de la présentation?



EMBRACE-II

{ Image guided intensity modulated External beam radiotherapy and MRI based adaptive BRACHYtherapy in locally advanced Cervical cancer }

← Increasing priority

Target Dose planning aims	D90 CTV-T _{HR} EQD2 ₁₀	D98 CTV-T _{HR} EQD2 ₁₀	D98 GTV _{res} EQD2 ₁₀	D98 CTV-T _{HR} EQD2 ₁₀	Point A EQD2 ₁₀	OTT [†]
Soft constraint*	> 90 Gy < 95 Gy [¶]	> 80 Gy	> 95 Gy	> 60 Gy	> 65 Gy	50 days
Hard constraint**	> 85 Gy	> 75 Gy	> 90 Gy	-	-	55 days

← Increasing priority

OAR Dose planning aims	Rectum D _{2cm3} EQD2 ₃	Bladder D _{2cm3} EQD2 ₃	ICRU Recto-vaginal point EQD2 ₃	ICRU bladder point EQD2 ₃	Bowel D _{2cm3} EQD2 ₃	Sigmoid D _{2cm3} EQD2 ₃
Soft constraint*	< 65 Gy	< 80 Gy	< 65 Gy	< 75Gy	< 65 Gy [§]	< 70 Gy [§]
Hard constraint**	< 75 Gy	< 85 Gy [¶]	< 75 Gy	< 85Gy	< 75 Gy [§]	< 75 Gy [§]

Et les incertitudes ?

	Target (HR CTV D90)	OARs (D _{2cm3})
Source strength	2%	2%
Dose and DVH calculation	3%	3%
Dwell position uncertainty (reconstruction and source positioning)	4%	4%
DVH addition across fractions (previously called “worst case assumption”)	NA	1%* -2%
Contouring (inter-observer)	9%	5-11%
Intra- and inter-fraction (intra-application) uncertainties** (5)	11%	20-25%
Total***	12%	21-26%

Et si on récapitule ?

Toxicités urinaires et vaginales importantes mais à mieux définir (Patientes ? Médecins ? Durée ? Importance ? Types ?)

Corrélation avec la dose même si encore beaucoup de question

Utilisation des aiguilles interstitielles pour les gros volumes indispensable

Et si on récapitule ?

Toxicités urinaires et vaginales
définir /

VIVEMENT EMBRACE II !

techniques pour les gros volumes

MERCI!

 Centre
Oscar Lambret
unicancer HAUTS-DE-FRANCE