Faut-il opérer un cancer du col utérin après radiochimiothérapie initiale?

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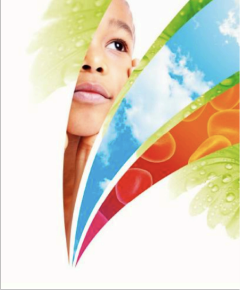
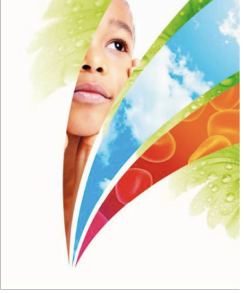


Le contexte actuel

- Taux de réponse élevé à l'association RCC dans les cancers du col utérin (>80%)
- Amélioration de la technologie d'irradiation
- Amélioration des techniques de curiethérapie (PDR 3D)
- Evaluation de qualité de la réponse (IRM 45gy)

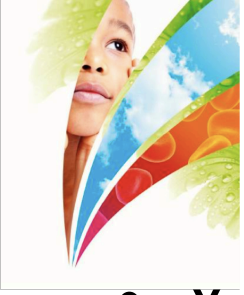
Question: Y a t'il encore une place pour une chirurgie de clôture?



Y a t'il encore une place pour une chirurgie de clôture?

Modulation en fonction de:

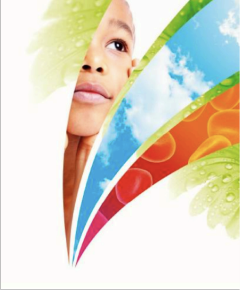
- Réponse à la RCC (< ou >50% du volume)
  - Importance de l'IRM à 45gy
- Respect du délai de curiethérapie (10-15j max)
  - Importance d'une coordination avec les centres de radiothérapie dans un réseau de soins
- En cas d'échec balistique de la curiethérapie
  - Implantation echoguidée
- Quelle chirurgie: Col, ggl pelviens?



Vision oncologique transversale

- Y a t'il encore une place pour une chirurgie de clôture après association radio-chimiothérapique?
  - Dans le cancer du canal anal
  - Dans le cancer de l'œsophage
  - Dans les cancers des VADS

- Pourquoi le cancer du col serait si différent…
- Facteurs pronostiques du K Col localement avancé



Facteurs pronostiques des K localement avancés du col utérin

Retrospective study from January 1998 to December 2010

Two-centric (ICR Toulouse, COL Lille)

IB2 to IVa FIGO Stage cervical cancer

All aortic lymph node negative (surgically staged)

All were considered ‘good responders’

All had RTCT + brachytherapy

Données partielles
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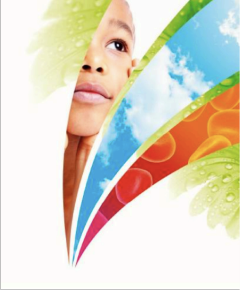

Material and Methods – Study Design

A three step analysis

1. Identify factors with prognostic value on Recurrence Free Survival
2. Determine a new cut-off of the variable 'Reduction tumor rate' to improve the RFS
3. Identify factors with prognostic value on 'Time to local relapse'

Données partielles
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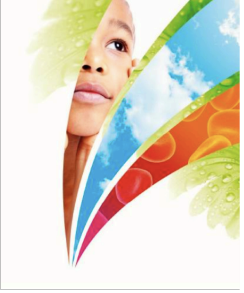

390 pts

Localy advanced cervical cancer

minus 179 patients:
+unknown response (84 pts)
+not protocol adapted (50 pts)
+peritoneal carcinosis (10 pts)
+bad responders treated as good (35 pts

Surgical aortic lymph node harvesting

81 pts

LN NEG

LN POS

IRM 45 Gy

Non operated/operated

Response ≤50 %

Response ≥50 %

17 pts

Surgery

Brachytherapy

8 pts

Données partielles
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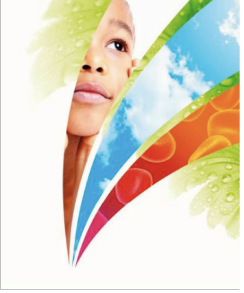
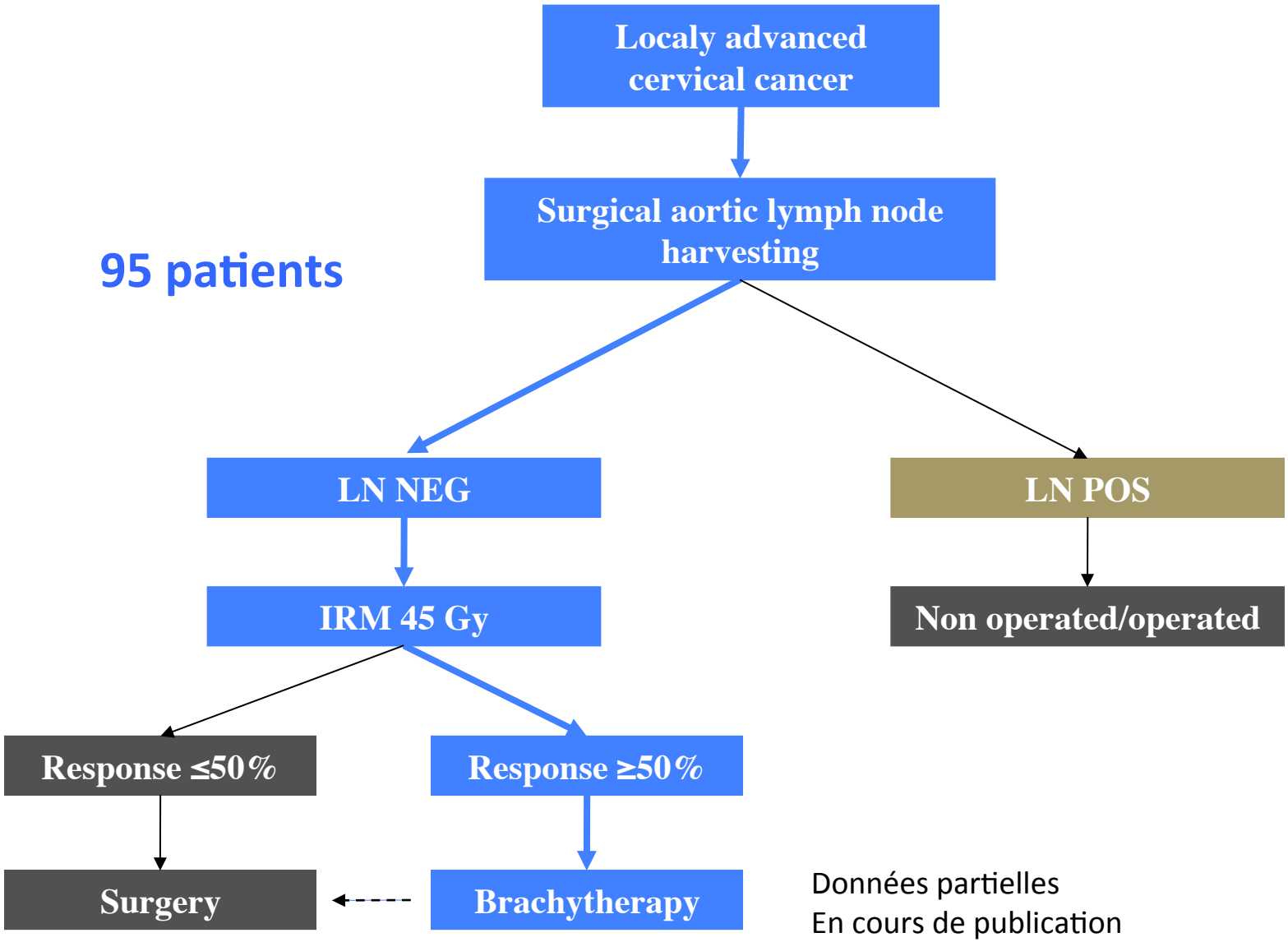


95 patients



Données partielles
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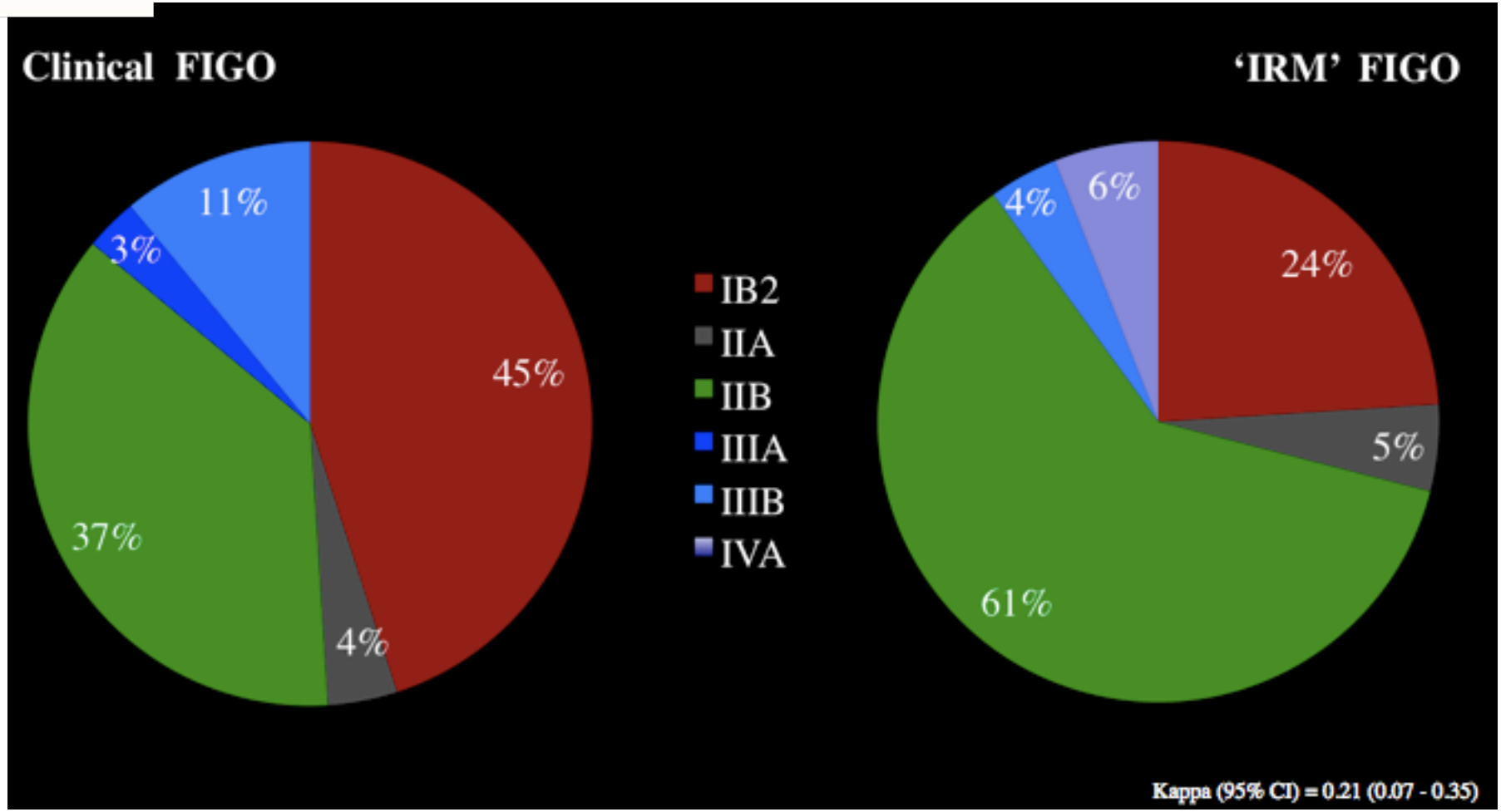
Results – Study population

95 patients – Tumor characteristics



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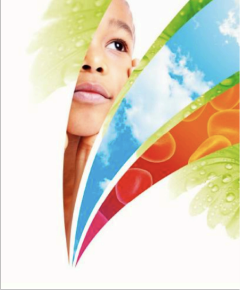
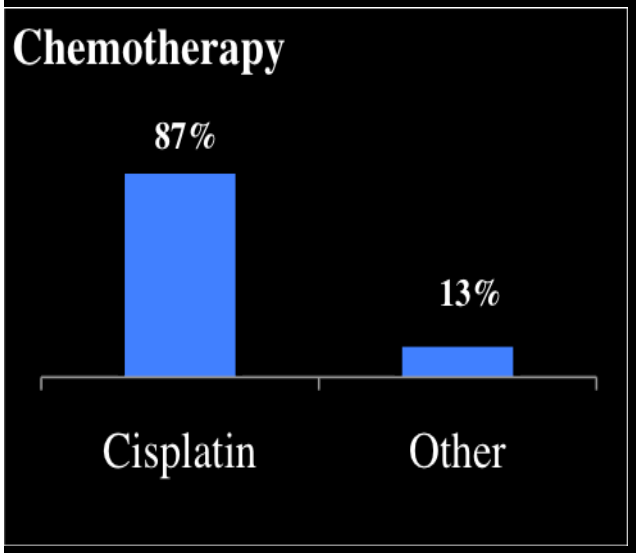
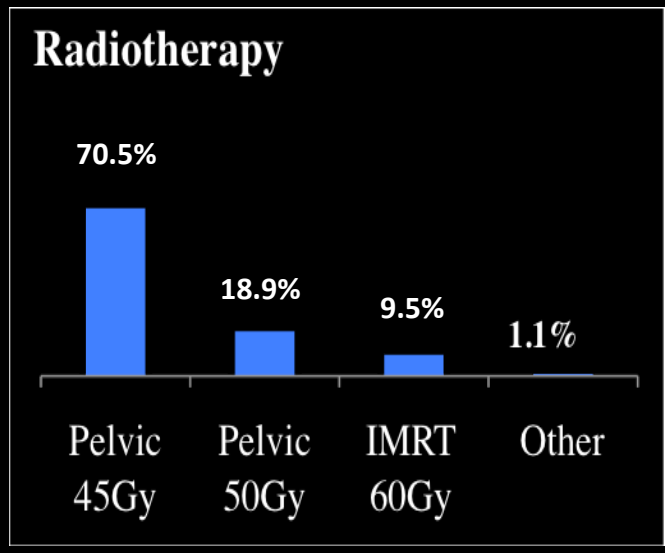


Results – Study population

95 patients – Treatment

All had concomittant chemoradiotherapy





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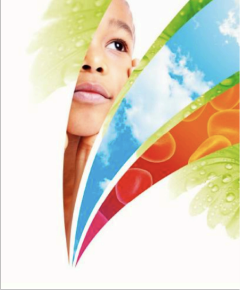

Results – Study population

95 patients – Tumor characteristics

All had more or equal to 50% reduction of the largest tumor diameter

Tumor size (cm) – IRM * evaluation

Before RTCT

Median: 5
Range: 2 – 15.7

After 45Gy pelvic

Median: 1.4
Range: 0 - 4

Median tumor reduction rate: 72.4%

Données partielles
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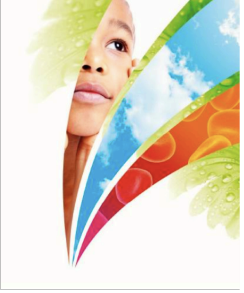
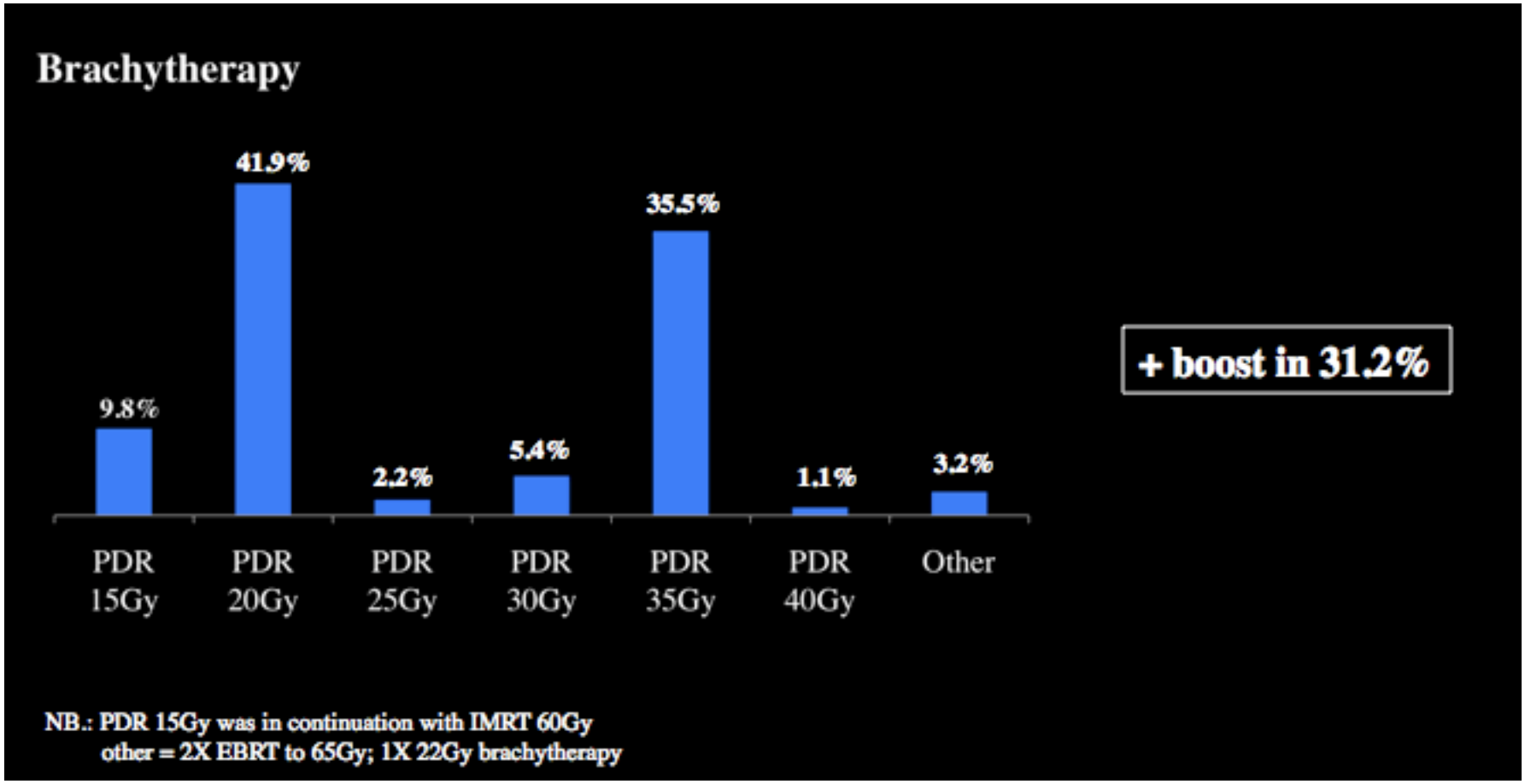


Results – Study population

95 patients – Treatment



Données partielles
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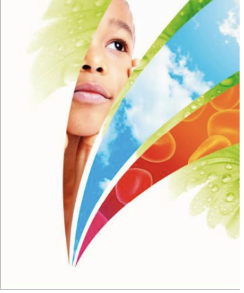

Results – Recurrence Free Survival

17/95 were dead of which 14 from cervical cancer

28/95 had recurrence

- **16/28 had local recurrence**
- **4/28 had nodal recurrence**
- **11/28 had metastasis**

Données partielles
En cours de publication
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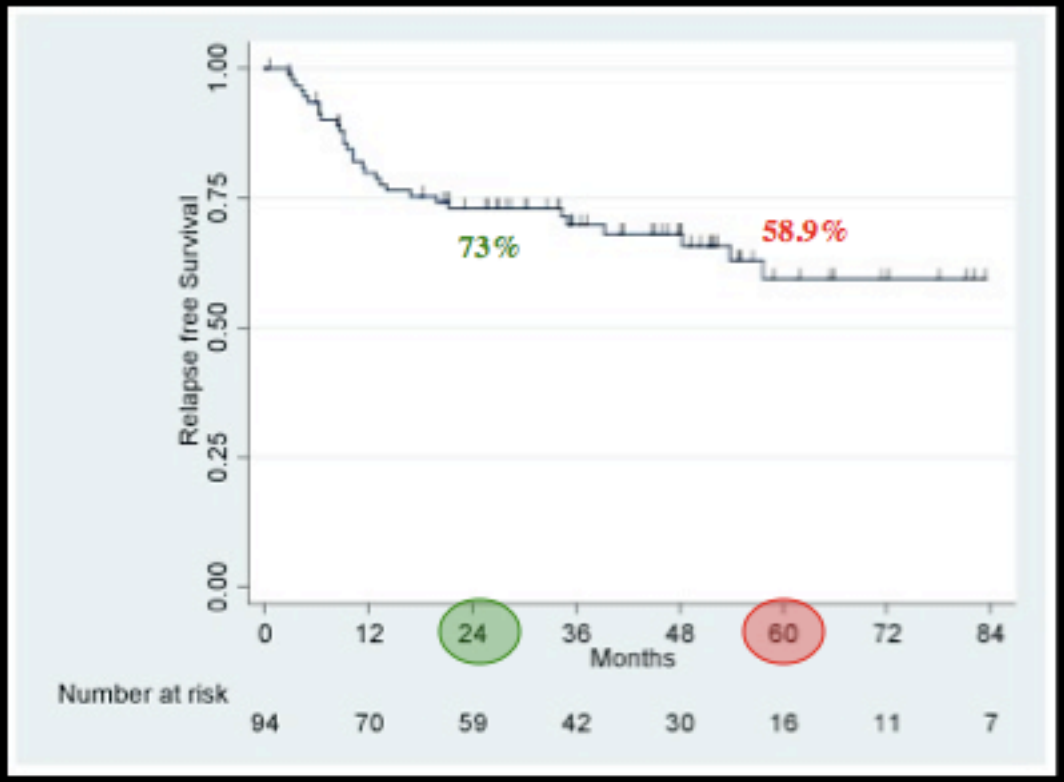
Results – Recurrence Free Survival

Median follow-up of 47.8 months
(CI 95% = 37.6-53.8)



Recurrence Free Survival curve

Données partielles
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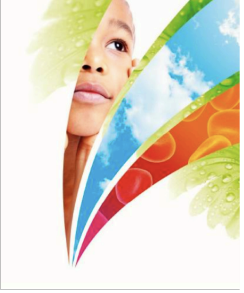

Results – Prognostic variables RFS

Univariate analysis (*)

		RFS	
Variable	**Categories**	**HR (95%CI)**	**P-value**
Tumor size (before treatment)	Continuous	1.14 (1.00-1.29))	0.04
Pelvic staging	Yes vs. No	3.59 (1.35-9.52)	0.006
Reduction tumor rate	Continuous	0.97 (0.95-1.00)	0.04
Response	>50% vs. =50%	0.32 (0.13-0.80)	0.01
Total treatment duration	Continuous	1.14 (0.99-1.31)	0.05

Données partielles
En cours de publication
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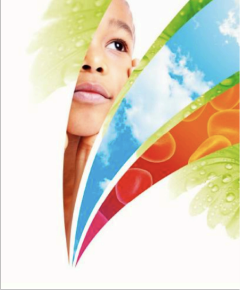

Results – Prognostic variables RFS

Multivariate analysis

Variable	HR (95%CI)	P-value
C-index = 0.69		
Pelvic staging (Yes vs. No)	3.83 (1.42-10.36)	**0.008**
Total treatment duration	1.21 (1.04-1.40)	**0.01**
Reduction tumor rate	0.98 (0.96-1.00)	**0.03**
Booststrapping using 200 replications		

Données partielles
En cours de publication
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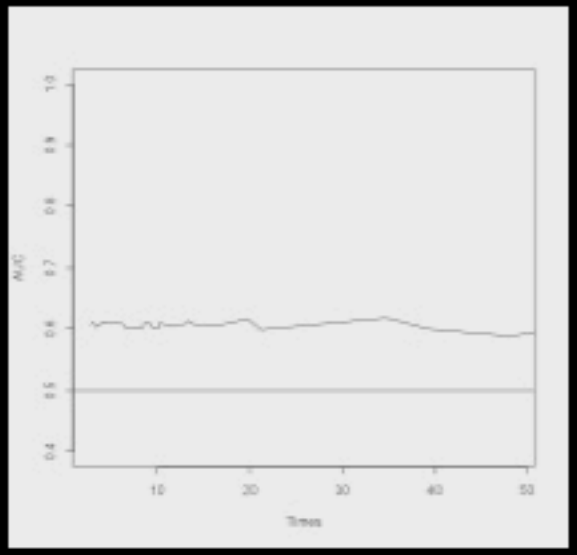
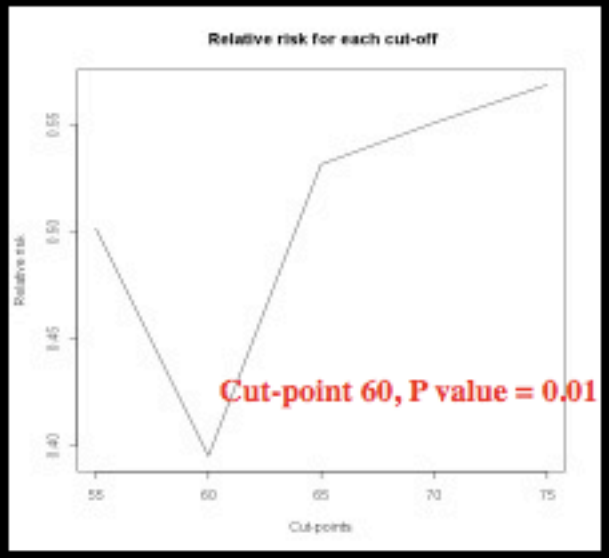
Results – Determining the ideal cut-off of the reduction tumor rate



Hagearty et al., Biometrics 2005



Mazumdar et al., Statist. Med. 2000; 19: 112-113

Validation using booststrapping (500 replications) confirms ideal cut-off of 60%

Données partielles
En cours de publication
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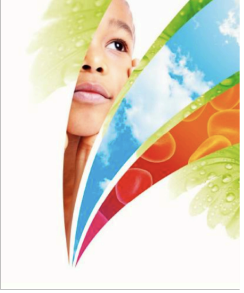

Results – Prognostic variables RFS including new cut-off

Multivariate analysis

Variable	HR (95%CI)	P-value
C-index = 0.70		
Tumor size (before treatment)	1.20 (1.04-1.37)	**0.01**
Total treatment duration	1.19 (1.04-1.37)	**0.01**
Response (>=60% vs. <60%) *	0.34 (0.16-0.73)	**0.006**
Booststrapping using 200 replications		

*** Replacing 'reduction tumor rate' by 'cut-off of 60%'**

Données partielles
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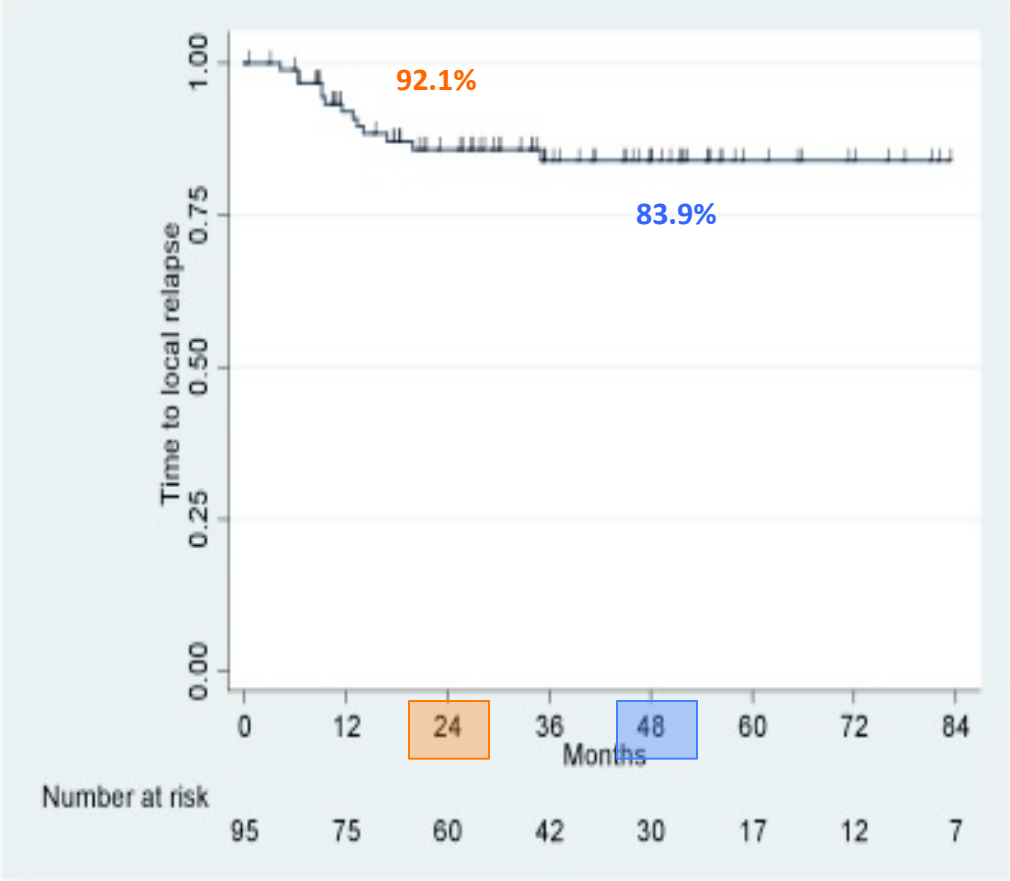
Results – Time To Local Relapse (TTLR)

13.7% had local relapse only (13/95)



Données partielles
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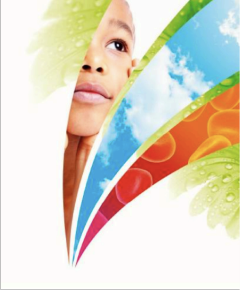
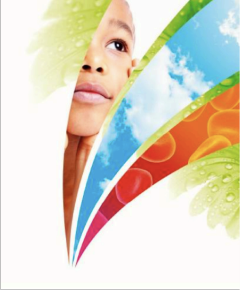


Results – Prognostic variables TTLR

Univariate analysis (*)

		TTLR	
Variable	**Categories**	**HR (95%CI)**	**P-value**
Clinical staging	**IIB-IIIB vs. IB2-IIA**	3.46 (0.95-12.58)	0.04
Reduction tumor rate	Continuous	0.96 (0.93-0.99)	0.03
Residual disease	Yes vs. No	6.09 (0.79-46.85)	0.05
Response	>50% vs. =50%	0.20 (0.06-0.65)	0.003

** BMI, age, co-morbidity, previous surgery, histology, LN image, chemotherapy, total dose of radiotherapy , total treatment duration, optimal cut-off : not significant*



Results – Prognostic variables TTLR

Multivariate analysis

Only the variable reduction tumor rate is significant

Données partielles
En cours de publication
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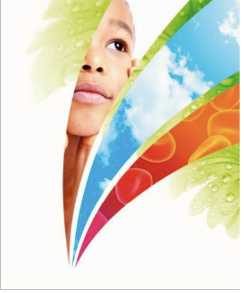
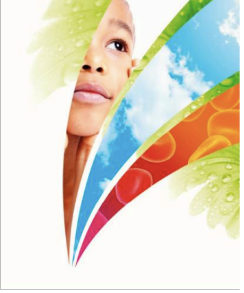


Importance

- Du respect du timing de traitement radio-chimiothérapique et de la curiethérapie
- Obtention d'une réponse de plus de 50-60%: Bon répondeur
- Réponse au traitement: facteur pronostic majeur
- Une chirurgie améliore t'elle ces résultats?
  - En cas de bonne réponse
  - En cas de radiorésistance



GOG #71, RTOG#84-12

- Bulky IB
- 256 pts
- Randomisation: RT+Curieth *vs* RT+Curieth +hysterectomie extrafaciale
- Donc: AVANT l'ère de la RCC

Keys HM et al. Gynecol Oncol 2003

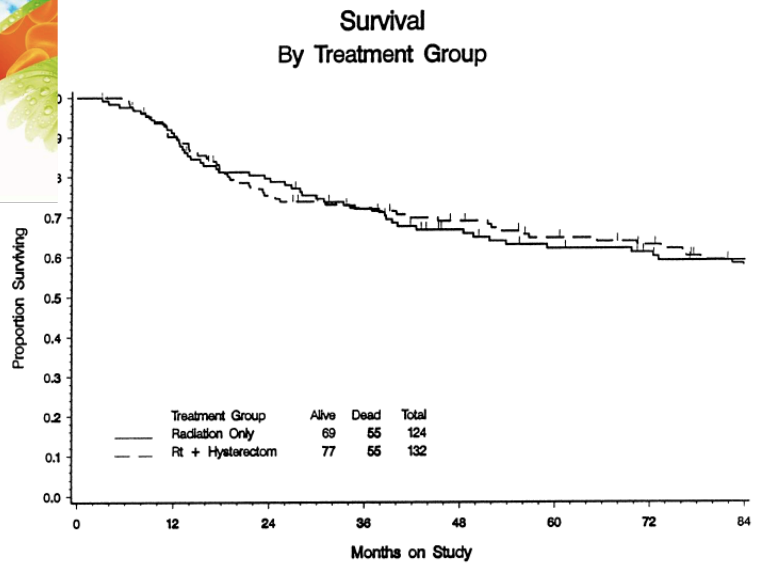


Fig. 2. Survival by treatment group.

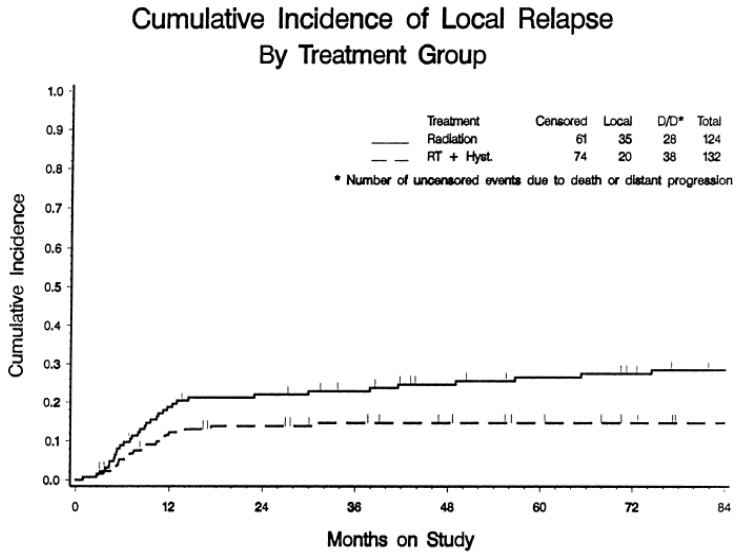


Fig. 3. Cumulative incidence of local relapse by treatment group.

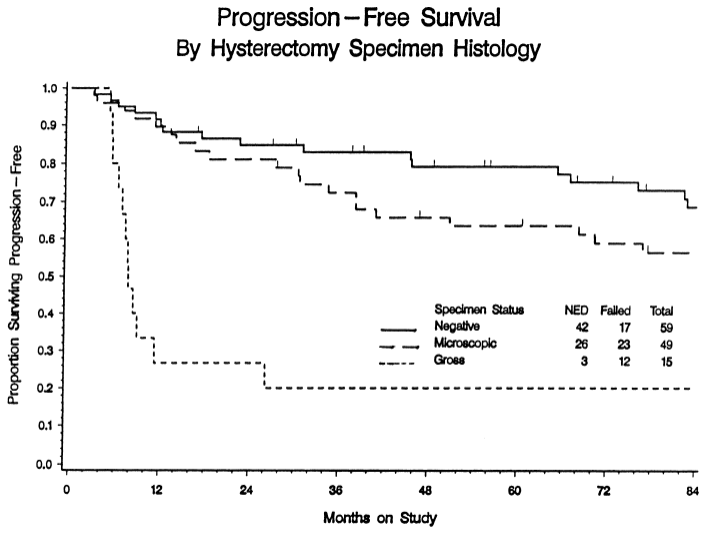
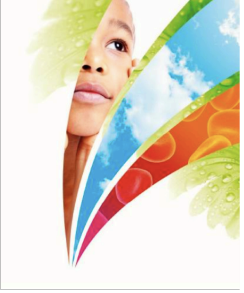


Fig. 4. Progression-free survival by hysterectomy specimen histology. NED, no evidence of disease.

Conclusion 1:
Un peu moins de récidive dans Gpe hysterectomie

Conclusion 2:
Plus la réponse histologique est importante, meilleur est le pronostic

Keys HM et al. Gynecol Oncol 2003



GYNECO #2

- FNCLCC
- FIGO IB2 et II, IRM et TEP négatif en extrapelv
- RCC 45-50gy + CDDP (40mg/m2 x5); Curieth UV (15gy) +/- boost lateropelv 15gy
- IRM evaluation S+6 (8)
- Randomisation en cas de réponse complète: Hysterectomie *vs* Surveillance
- Stat: End point PFS 3 ans; 160 pts par bras

Morice P, et al. The Oncologist 2012

GYNECO #2

- Fermeture en 2006 pour faute d'inclusion
- 61 pts inclus (31 *vs* 30)

Table 2. Site of first recurrence according to randomization arm

Location of the first recurrence	Arm A, hysterectomy (n = 31)	Arm B, no hysterectomy (n = 30)
Centropelvic alone (n = 3)	1	2
Centropelvic and nodal (n = 1)	1	–
Pelvic node and distant (n = 1)	1	–
Para-aortic nodes alone (n = 1)	1	–
Para-aortic nodes and distant (n = 3)	3	–
Distant without pelvic or nodal involvement (n = 2)	1	1
Total	8	3

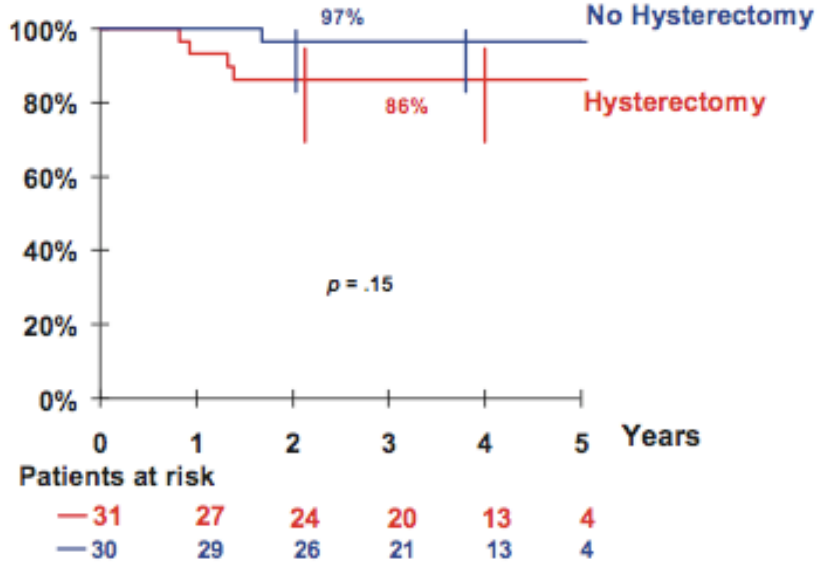
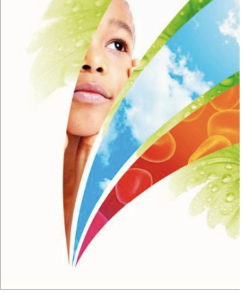


Figure 2. Kaplan–Meier estimates of the overall survival rate for patients in arm A (hysterectomy) and arm B (no hysterectomy).

L'hystérectomie de clôture systématique ne paraît pas justifiée

Morice P, et al. The Oncologist 2012



Mordibité de l'hystérectomie de clôture

Table 4. Postoperative complications of grade ≥2 according the Dindo et al. [15] classification

Characteristic	*n*	%
n of patients	37	25
n of deaths related to postoperative morbidity	2	1.3
Type of complication[a]		
Lymphedema	9	16
Lymphocyst	8	15
Abcess	5	9
Ureteral fistula	5	9
Bowel fistula	5	9
Peritonitis	3	5
Chylous ascites	3	5
Phlebitis	3	5
Bowel obstruction	2	4
Rupture of iliac vessels in large bowel[b]	2	4
Ureteral stenosis	2	4
Bladder retention	2	4
Wound dehiscence	2	4
Urinary incontinence	1	2
Unexplained epigastralgia	1	2
Bladder fistula	1	2
Vaginal vault dehiscence with abscess	1	2

[a]Several complications could be observed in the same patients.
[b]Both patients with rupture of iliac vessels in the large bowel were also included among the five patients with a bowel fistula.

Touboul C, et al. The Oncologist 2012

25% complications gde 3 et plus

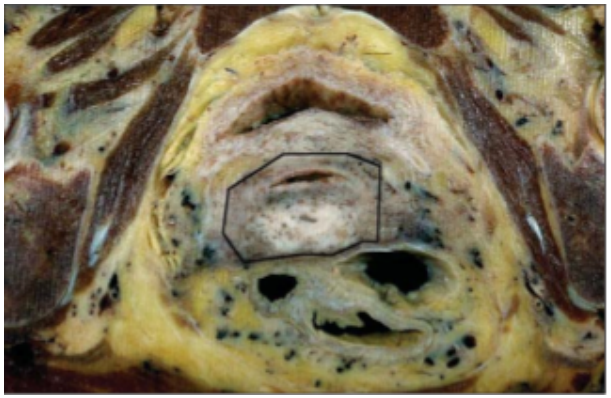
Table 3
Post treatment morbidity

Morbidity	*n*	Total
Grade 1		6
Diarrhea	3	
Neuralgia	1	
Wound infection	1	
Occlusion	1	
Grade 2		33
Ureteral stenosis	12	
Urinary fistulas	5	
Lymphocele	7	
Pelvic abscess	3	
Urinary infection	1	
Urinary incontinence	1	
Thromboembolism	2	
Hemorrhage	2	
Grade 3		12
Urinary or digestive fistulas	9	
Hemorrhage	1	
Occlusion	1	
Septic collapse	1	

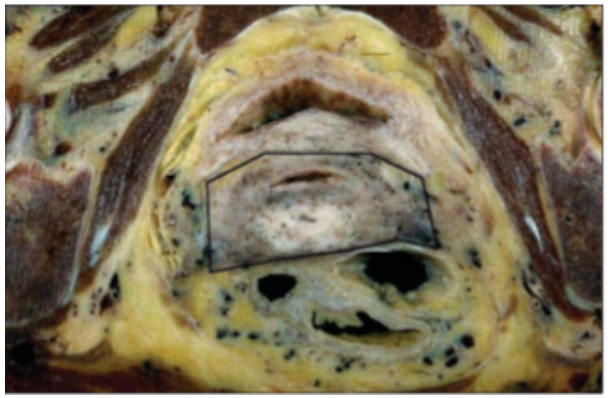
Classe JM, et al. Gynecol Oncol 2006

Particularité de l'hystérectomie après RCC et curieth

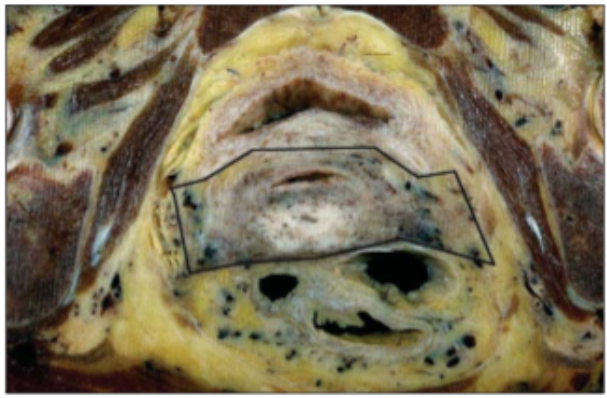
- Classiquement: Type A (Extrafaciale)



Type A



Type B1

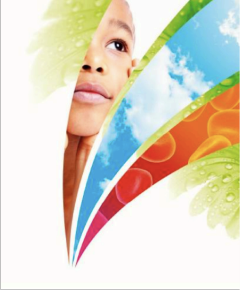


Type C2

- Mais difficile avec sclérose et rétraction
- Complications et séquelles fonctionnelles augmentent avec l'élargissement

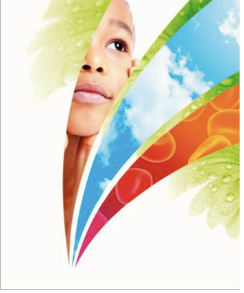
TVP: 7 *vs* 1%; Fistules: 4.8 *vs* 0.5%, Incontinence: 48 *vs* 2%

Querleu D, Morrow P. Lancet Oncol 2008
Magrina J, et al. Gynecol Oncol 2005



Place de l'hystérectomie chez les mauvais répondeurs

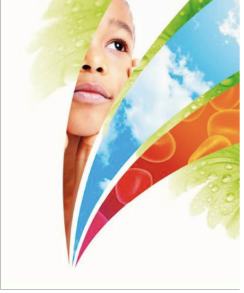
- Evaluation de la réponse
  - En per thérapeutique: IRM 45 gy
  - A distance de la curieth… 6 à 8 semaines
  - Savoir patienter…
  - Attention aux fausses images d'IRM (nécrose radique cervicale)(travail en cours)
  - Place du PET …
- Que faire en cas de pN+ aortique initial



Place de l'hystérectomie chez les mauvais répondeurs

- Quelle chirurgie réaliser?
  - Elargissement paramétrial svt nécessaire
  - Exentération pelvienne parfois
- Et les ganglions pelviens?
  - 16% pN+ résiduels
  - pN+ corrélé au volume résiduel

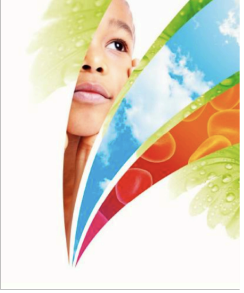
Houvenaeghel G et al. Gynecol Oncol 2006



Valeur thérapeutique de l'hystérectomie en cas de résidu

- Aucune étude de niv A de pertinence
- Qques articles (nombreux français) sur des expériences mono ou multicentriques
- Mauvais pronostique en cas de:
  - pN+ aortique
  - Marges positives
  - Résidu cervical > 1 à 2 cm

Morice P, et al. Gynecol Oncol 2007
Chéreau E, et al.Anticancer Res 2013



Conclusion

- La réponse à la RCC + curieth ne fait que refléter le pronostic
- En cas de réponse >50% chez une patiente ayant eu un traitement complet (curieth) et un bon timing: aucune place à une chirurgie
- En cas de mauvaise réponse
  - Evaluer pronostic de la patiente (pN+, taille résidu)
  - Discuter au cas par cas une eventuelle chirurgie qui devra être en marges saines
- Place du curage aortique: PHRC LILAC (D Querleu)