

Cancers de l'oesophage

Stratégies et Techniques de radiochimiothérapie

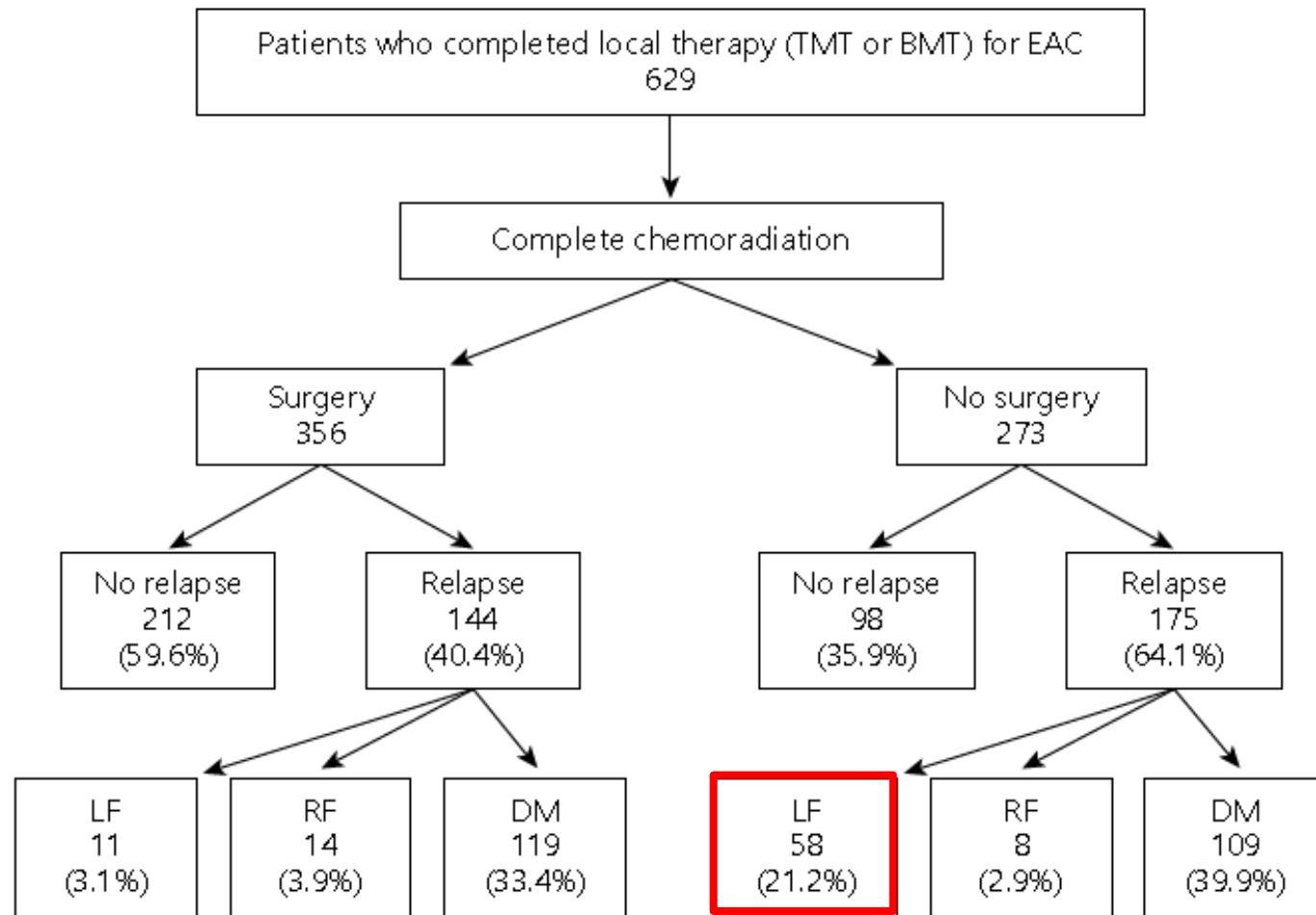
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18-06-2015*

Distribution des rechutes



Science- vs Conscience- vs Evidence-based Medicine

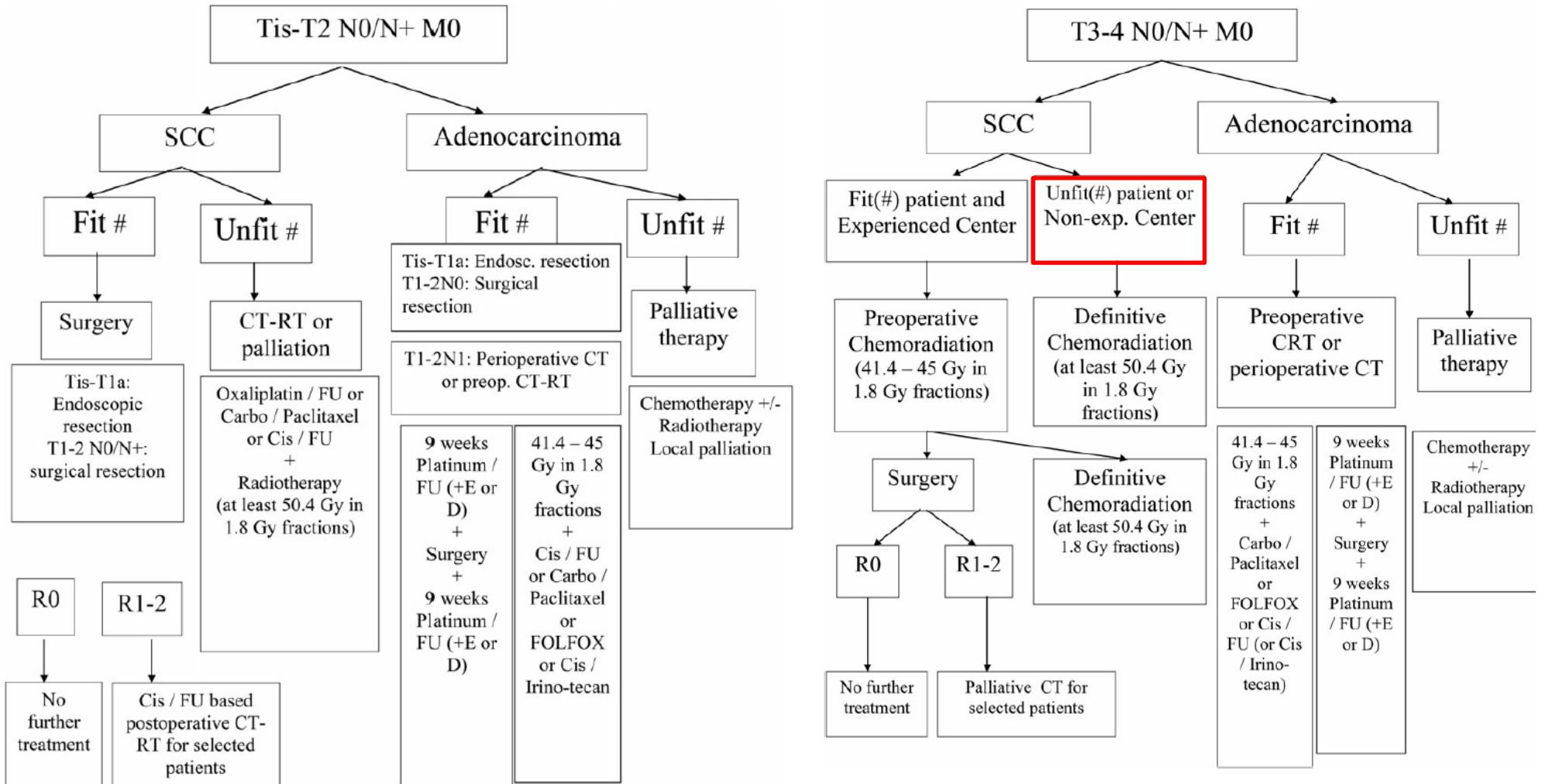
	CHIRURGIE	RTCT	RTCT-CHIR
Contrôle local	↗↗	↘↘	↗↗↗
Contrôle régional	↗	↗↗	↗↗
Contrôle à distance	-	↗	↗
Complications post thérapeutiques	↘↘	↘	↘↘↘
Mortalité globale	=	=	=
QDV	?	?	?

Chirurgie vs. RTCT

	Chirurgie	RTCT <u>(INT 0133 + RTOG 85-01)</u>
Survie médiane	18 mois	14 mois
Survie à 5 ans	25%	27%
Décès iatrogènes	6-10%	2%
Rechutes locales	31% (15% si RTCT préop) (+ 30% R1-R2)	45%

Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

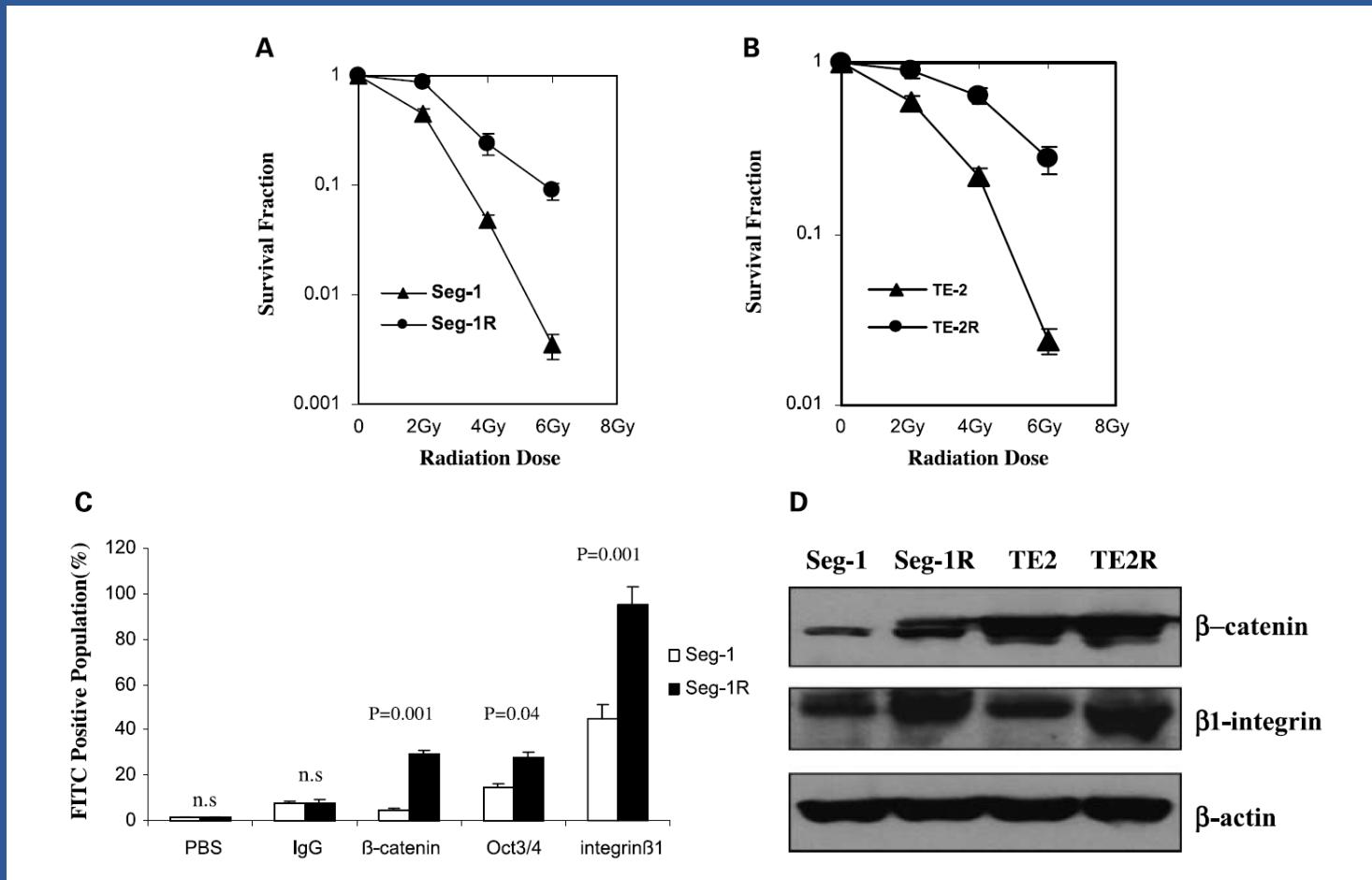
M. Stahl¹, C. Mariette², K. Haustermans^{3,4}, A. Cervantes⁵ & D. Arnold⁶, on behalf of the ESMO Guidelines Working Group*



T localisées (St I-II) : POUR la chirurgie

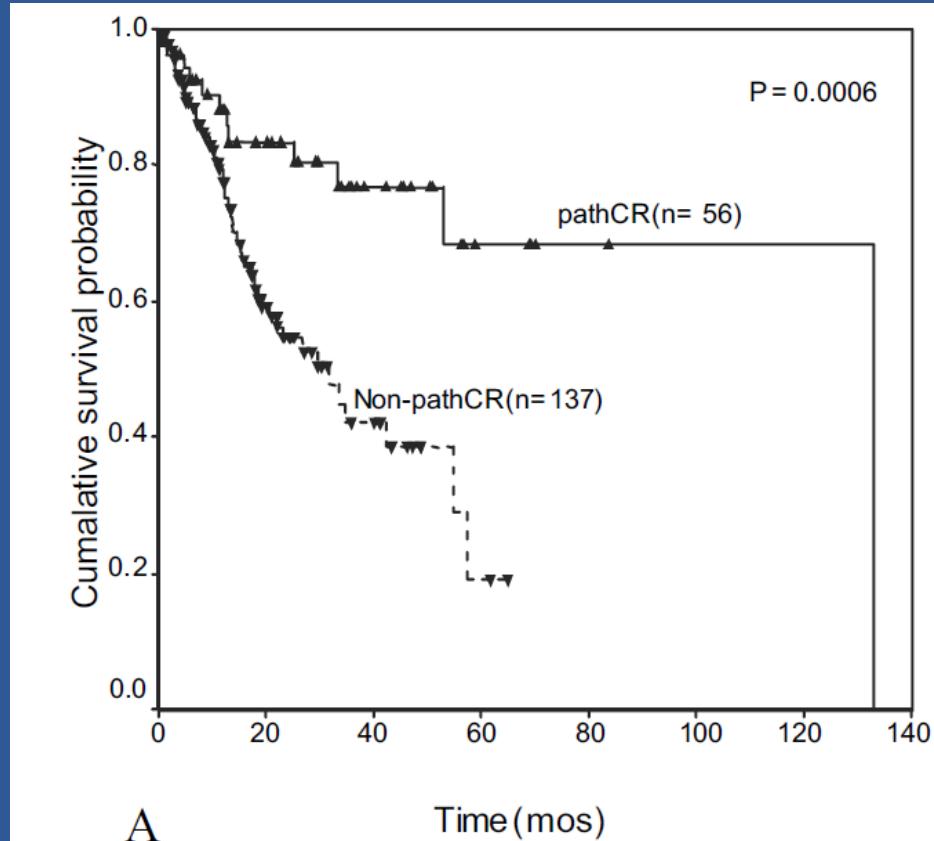
ESSAIS	HISTO	SURVIE	COMMENTAIRES
U Mich	SCC>	Non	15% (NS)
Walsh	ADK	Oui	6% survie si Chir
EORTC	SCC	Non (+DFS)	Schéma non conventionnel
TROG groupe	Mixte	Non	DT 35 Gy SCC> en sous (underpowered)
CALGB 9781	ADK>	Oui	56/500 pts.
FFCD 9901	SCC>	Non	Mortalité postop X3 si RTCT

Radiosensibilité des SCC vs. Adenok?

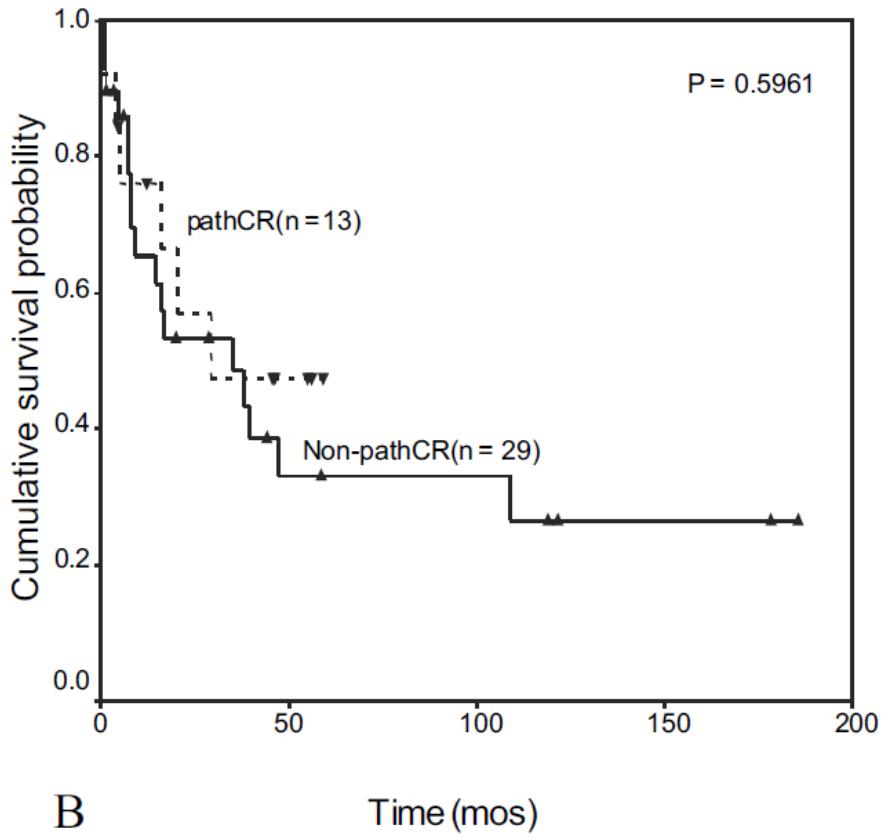


Zhang X et al., Clin Cancer Res 2008

Réponse RTCT ADK vs. SCC?



ADK



SCC

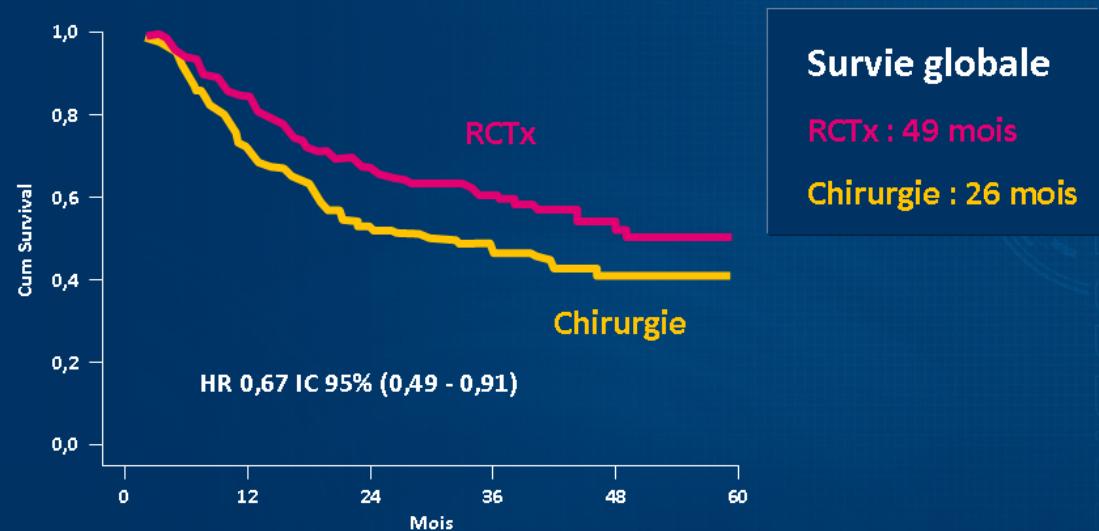
Rohatgi et al., Cancer 2006

XRT-CT préop en 2014 : localisés ou localement avancés?

CROSS trial

(Van Hagen P. et al., NEJM 2012)

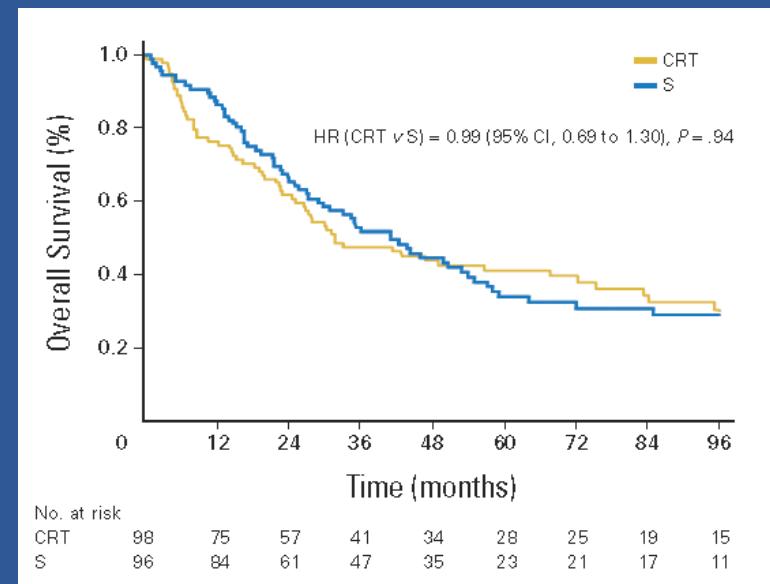
- N= 273 ADK/ 86 SCC
- Stade III >



FFCD 99-01

(Mariette C. et al., JCO 2013)

- N= 195 (> 65% SCC)
- Stades I-II



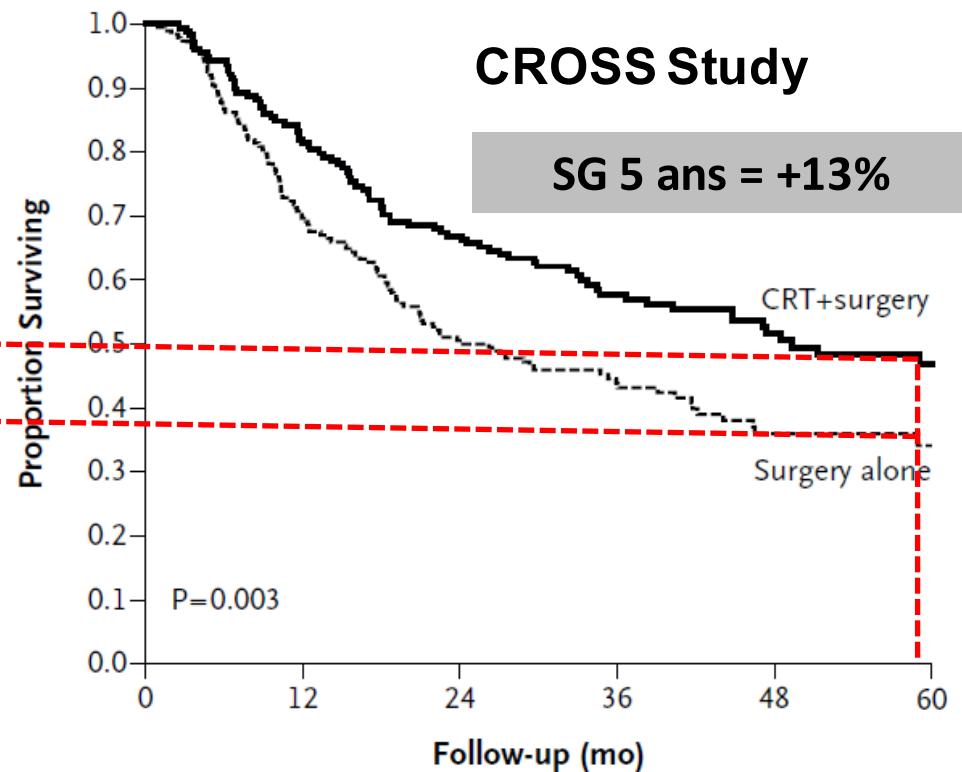
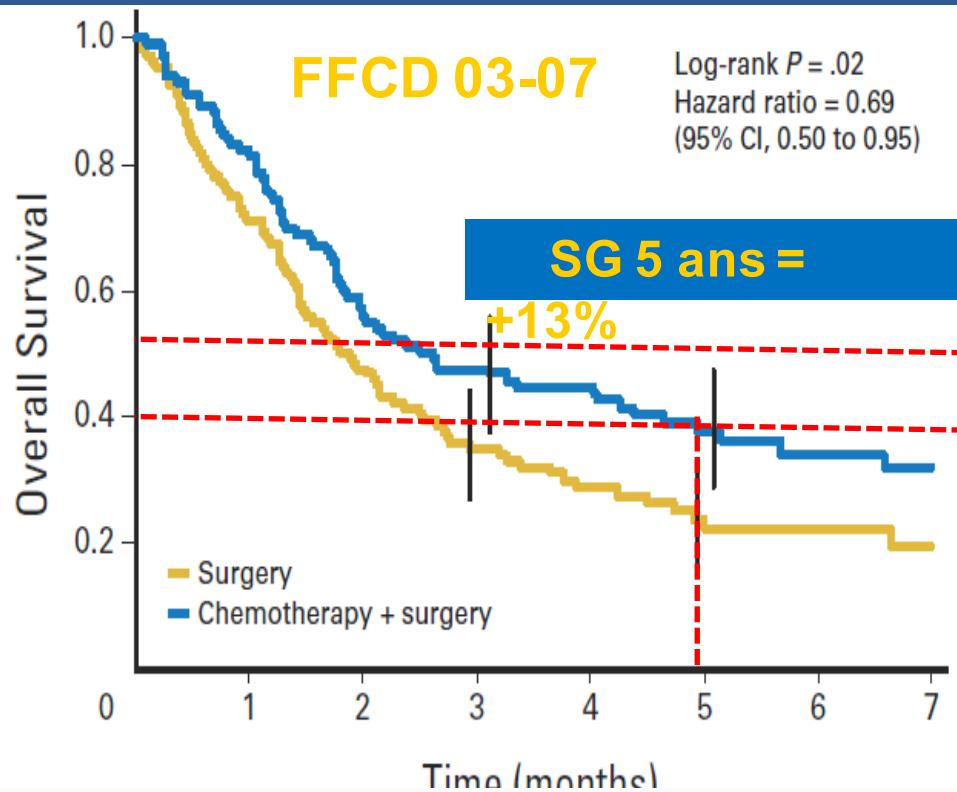
POET Phase III study

- 119/354 ADK uT3-4NxM0
- Hypothèse : SG 3 ans 25% 35%

	CT	Chir	XRT-CT Chir	Valeur du p
pCR	2%	15.6%		
ypN0	37.7%	64.4%		
SG 3 ans	27.7%	47.4%	0.07	
DC postop	3.8%	10.2%	0.26	

Stahl M et al., JCO 2009

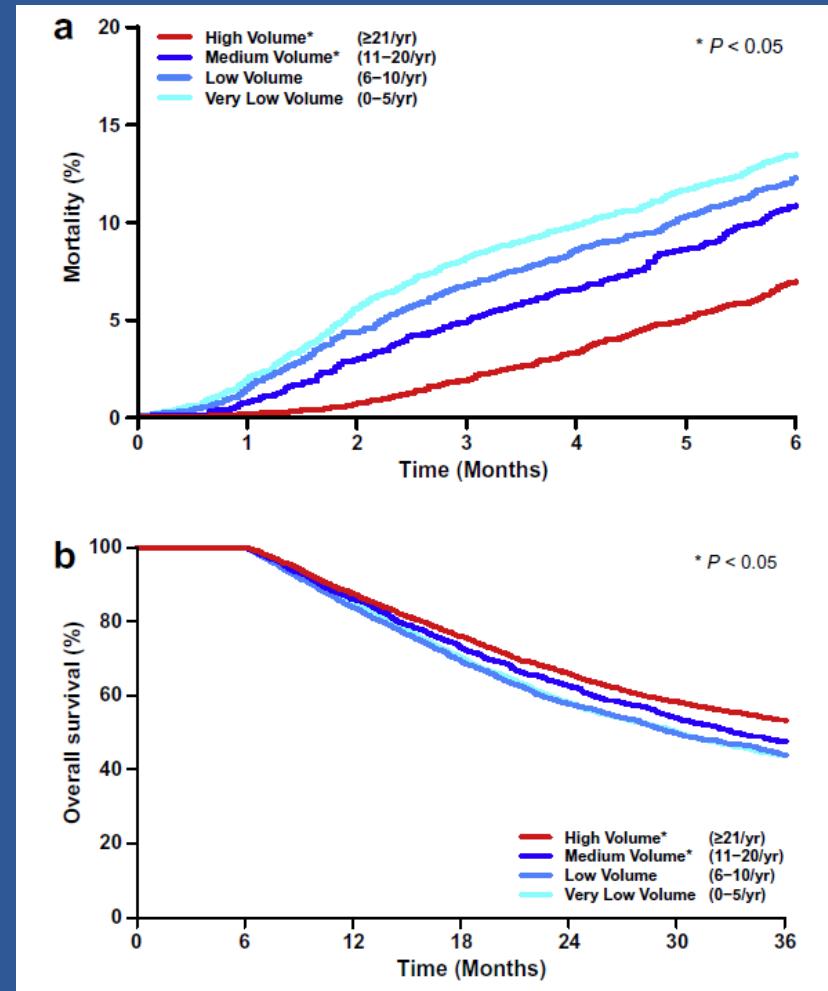
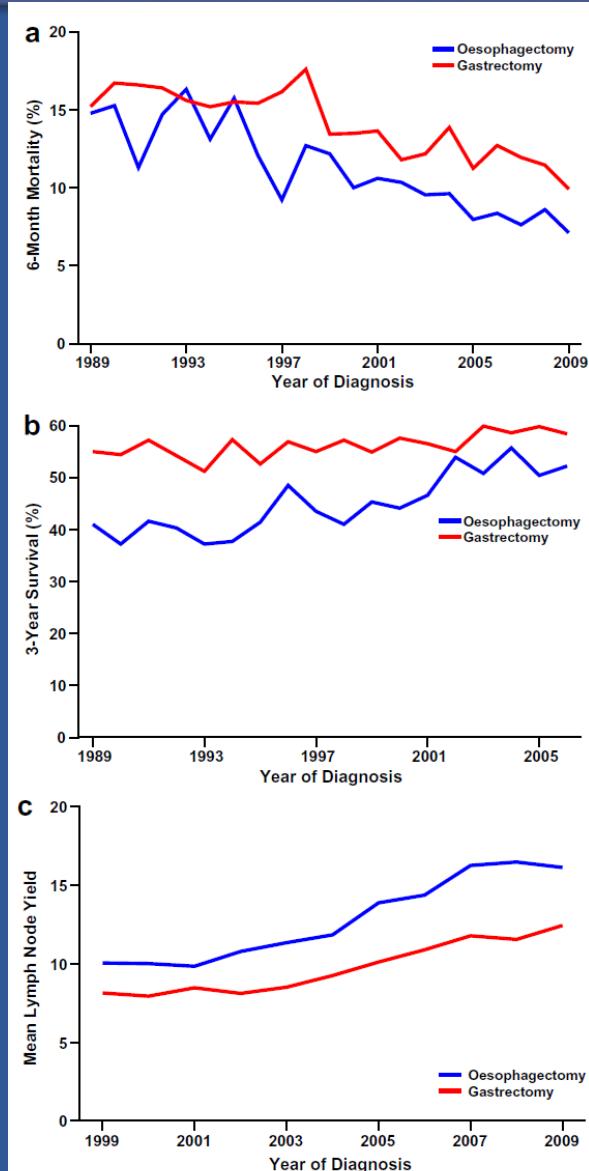
CT ou RTCT préop?



Cunningham D. et al., NEJM 2006
Ychou M. et al., JCO 2011

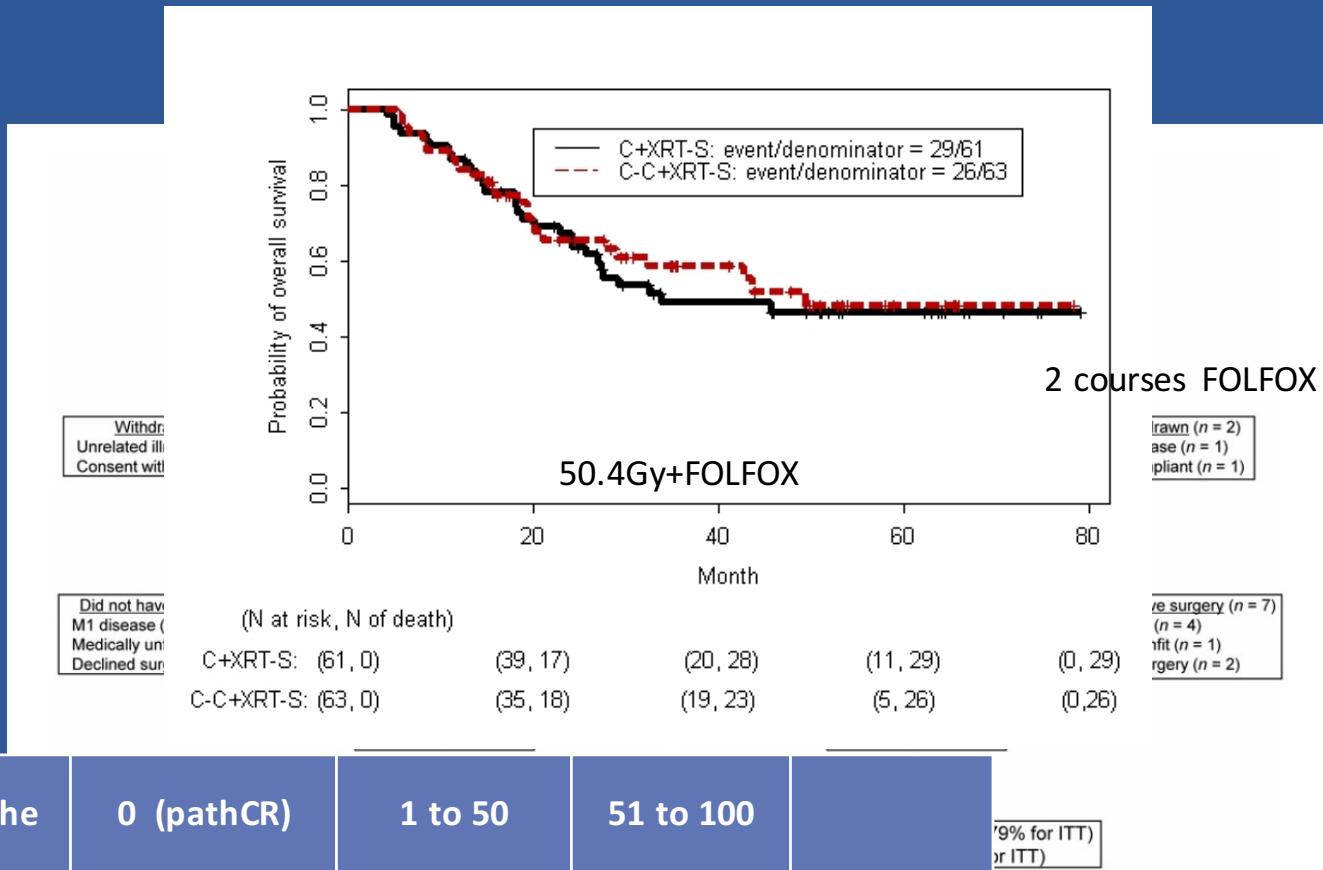
van Hagen P. et al., NEJM 2012

Chirurgien = F. pronostique+++



Dikken JL et al., EJC 2012

Trimodality vs « 3-step strategy »: phase IIR



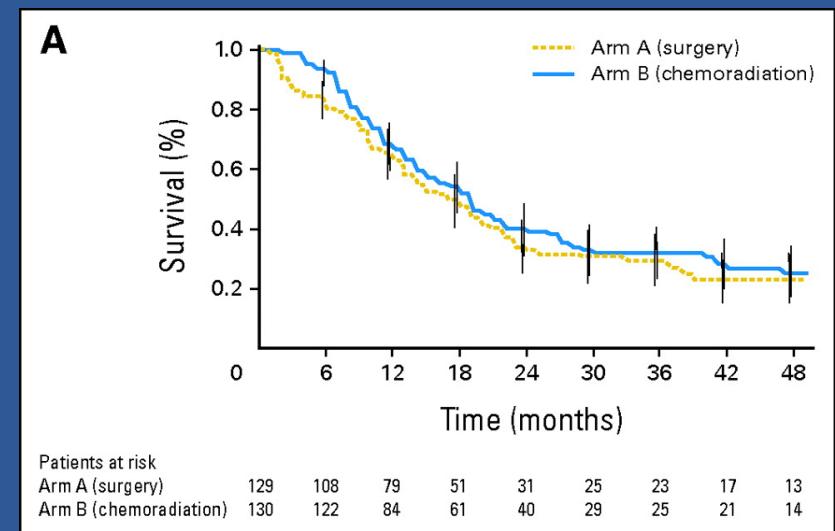
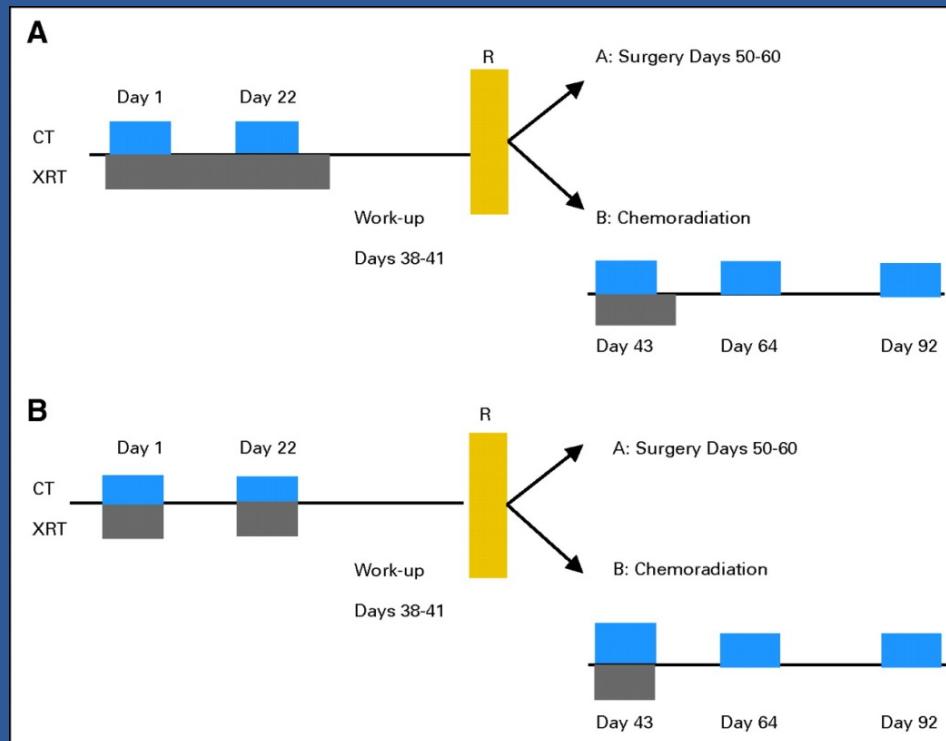
% Cancer Cells in the resected specimen	0 (pathCR)	1 to 50	51 to 100	$p = 0.126$
Arm A	7 (12.7%)	42 (76.4%)	6 (10.9%)	
Arm B	14 (25.9%)	32 (59.3%)	8 (14.8%)	

Ajani JA, Ann Oncol 2013

**RTCT exclusive ou
RTCT+Chirurgie si localement avancé?**

FFCD 9102 : XRTCT 66Gy

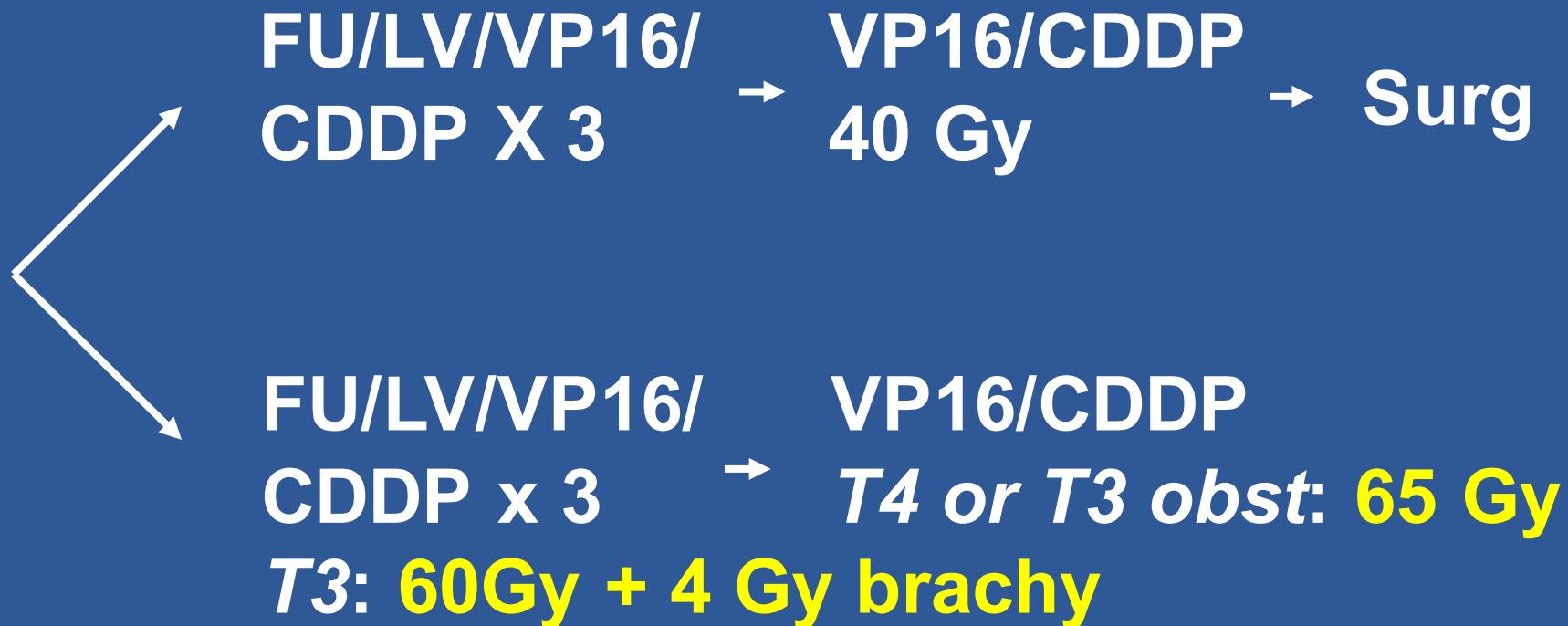
- 445 pts (cT3 N0-1 M1a) / SCC+:



- S médiane (18 vs. 19 m) et S. à 2 ans (34% vs. 40%)

German Oesophageal Cancer Study Group

172 pts SCC

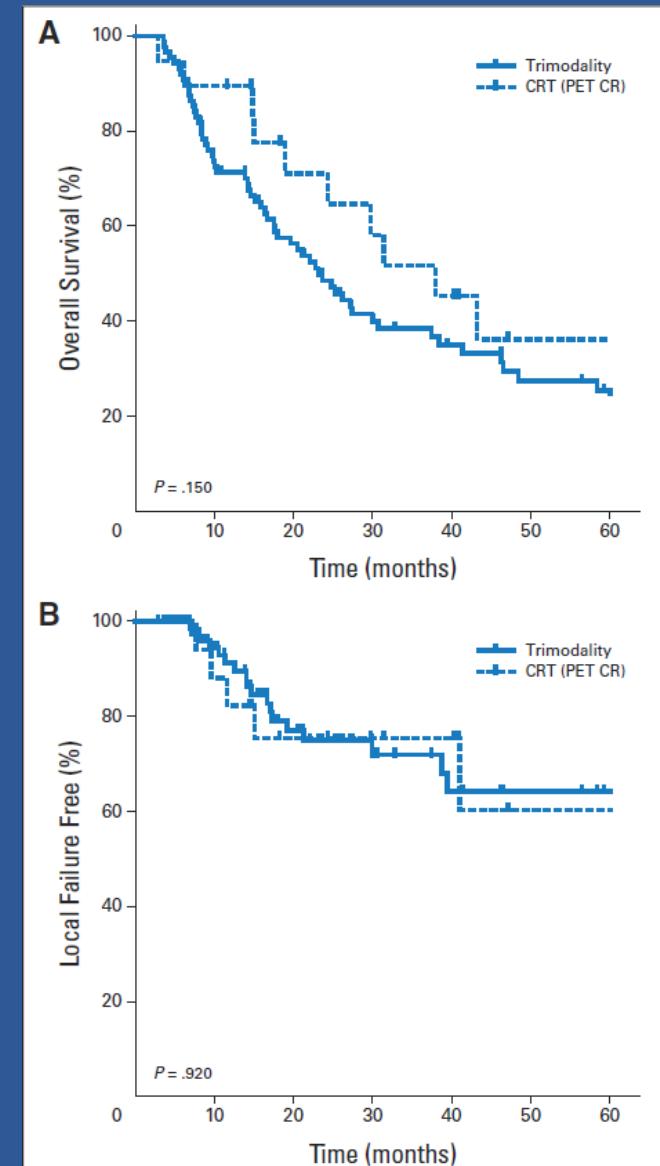


German Oesophageal Cancer Study Group

(%)Preop CT→CT-RT→OR	Defin. Preop CT→CT-RT
pCR	33%
Mortalité	13
RL à 2 ans	36
S méd	16 m
S à 3 ans	31%

EVALUATION DES REPONDEURS : PLACE DE LA TEP après XRT-CT

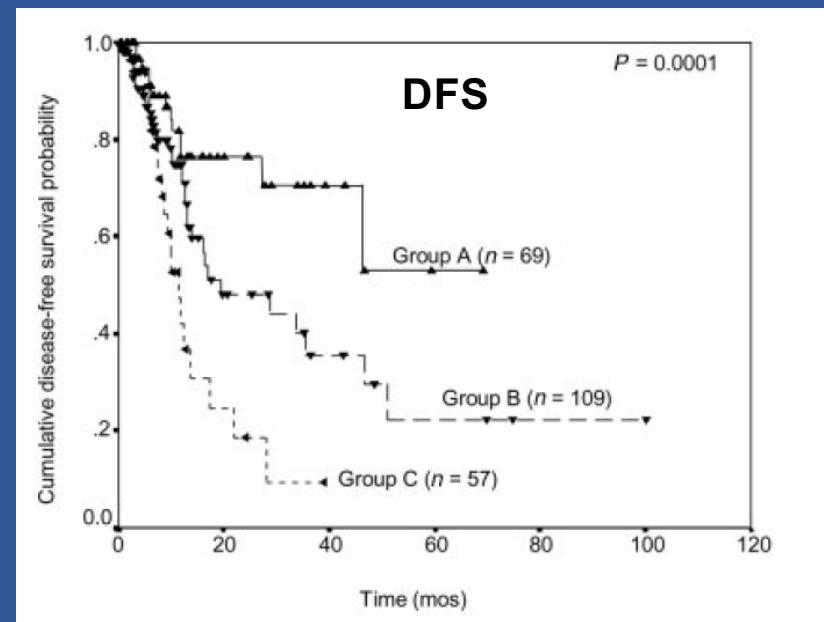
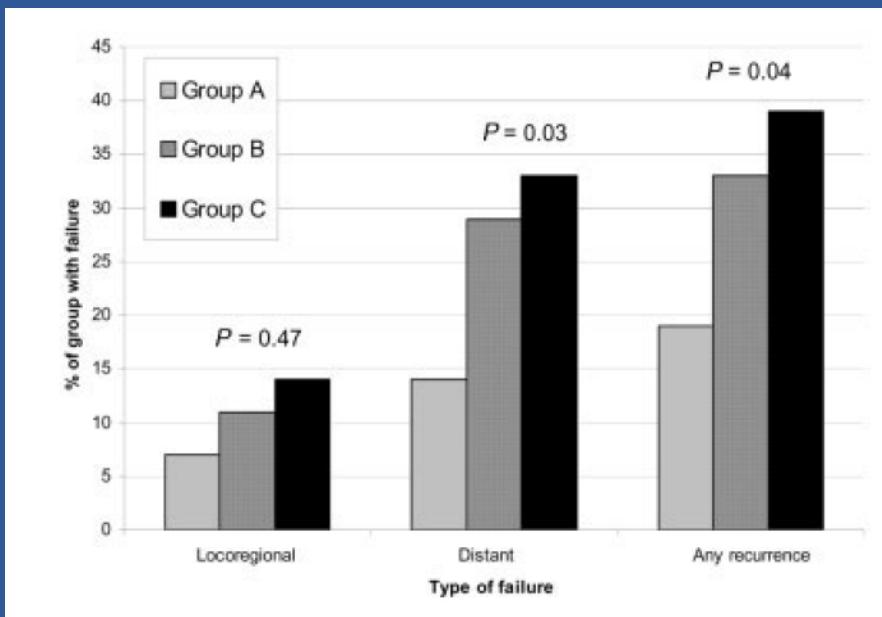
- N= 163 (41SCC)
- 105/163 post XRT-CT PET
- RC-PET = SUV ≤ 3
- XRT-CT exclusive :
- Survie à 2 ans 71% vs. 11% ($p < 0.01$)
- Pas de bénéfice si chirurgie (Résection du résidu)
- Pas de différence en fonction du type histo



Monjazeb A, JCO 2010

Impact pronostique du résidu tumoral après XRT-CT préop

- MDACC (n= 235 XRTCT préop)
- Groupe A = pas de résidu T (pCR)
- Groupe B = Résidu <50%
- Groupe C = Résidu >50%

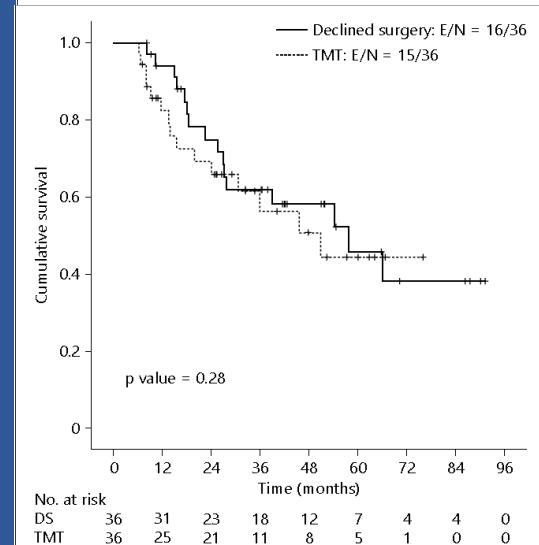
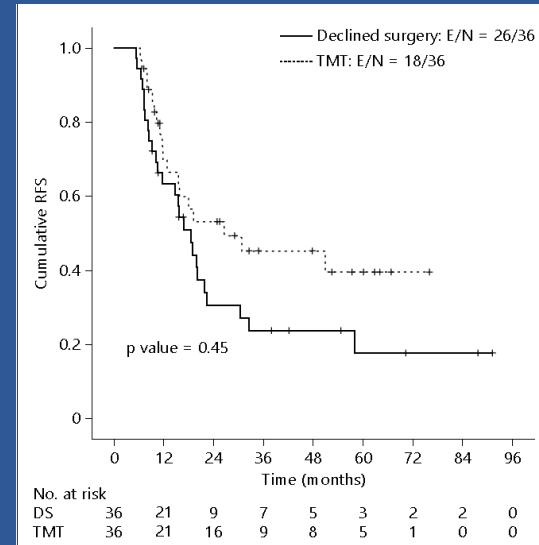


Rohatgi P. et al., Cancer 2005

Refus de la chirurgie après 50.4Gy

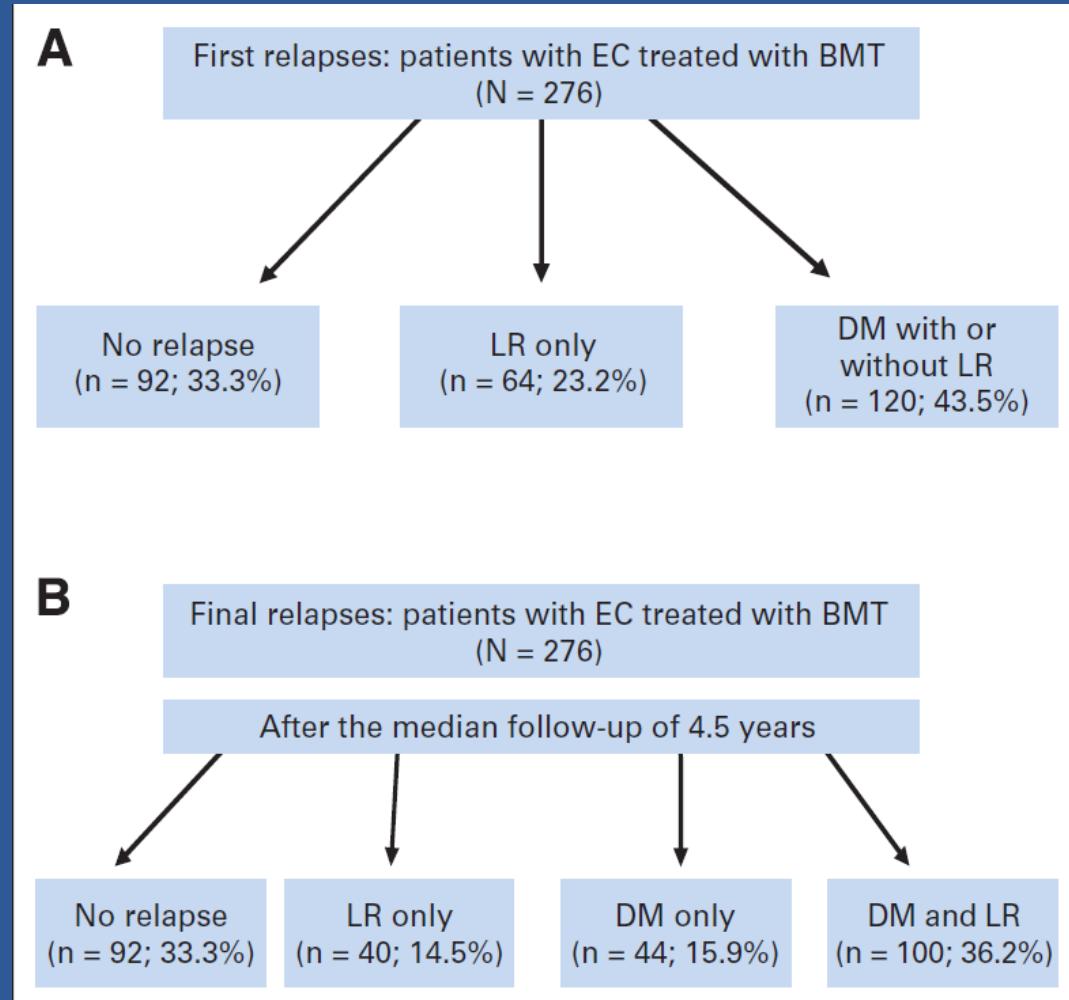
Contrôle local vs survie

- Propensity score matched population (n= 72, 16 co-variables+++)
- Patients refusant la chir : SCC, RC après RTCT
- TMT vs. RTCT (Refus de la chirurgie)
- 18 (50%) vs 26 rechutes (72.2%)
- 11 chir de rattrapage si refus de la chirurgie première



RTCT – Chirurgie de rattrapage

- Median dose 50.4Gy [45-66]
- 91% des rechutes < 2 ans
- 36% de RL isolées
- 8% de Chir de rattrapage



RTCT+Chir d'emblée vs. RTCT+ Chir de rattrapage

- 1987-2000 Série rétrospective
- Rattrapage <2% des oesophagectomies du MDACC

#		% Cervical Anastomosis	% Op Mortality	% 5-Yr Survival
Planifiée	99	37	6	25
Rattrapage	13	61	15	25

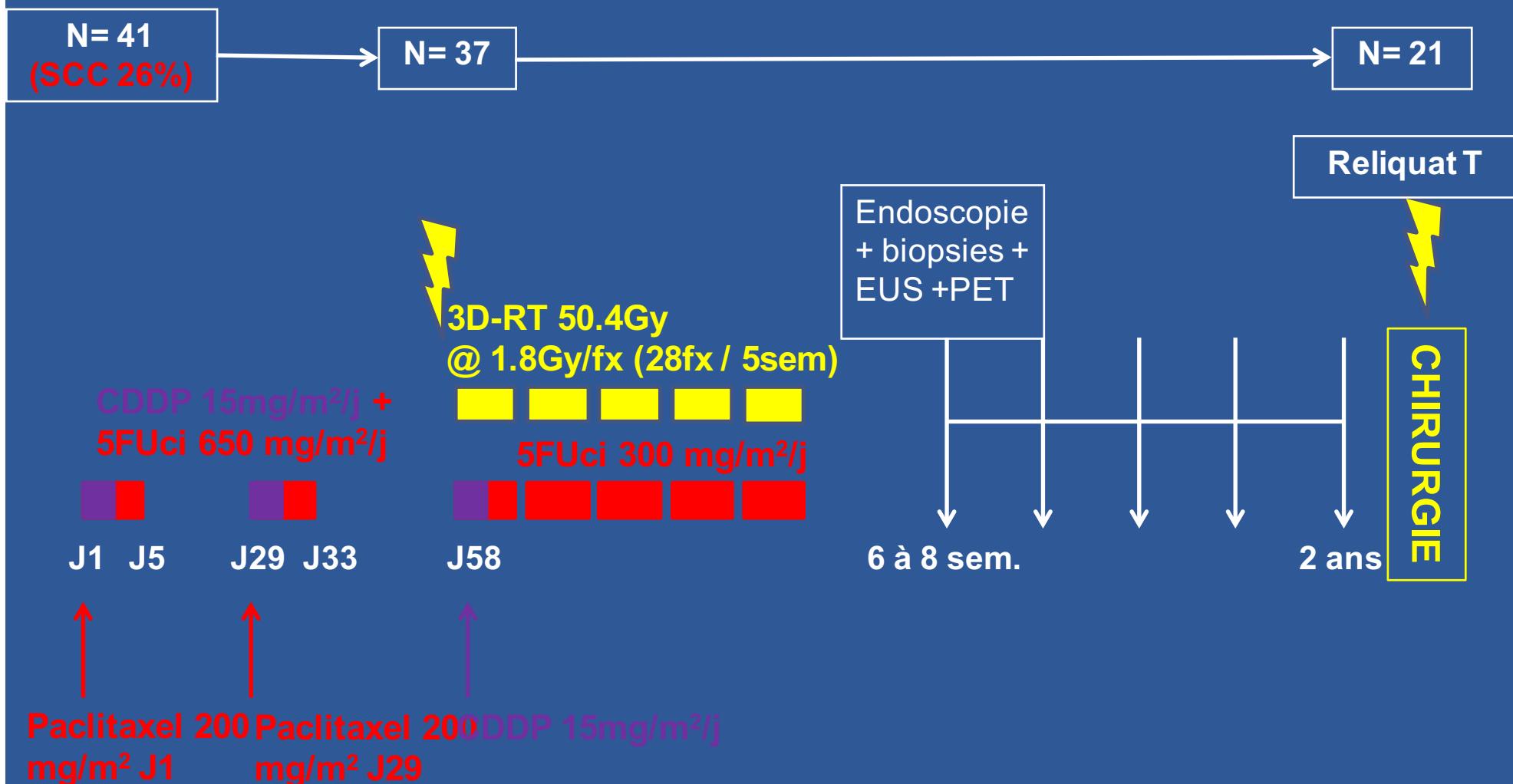
Swisher et al, MDACC, J ThoracCardiovasc Surg 2002

Recommandations ESMO 2013

In cases of response to neoadjuvant chemo(radio)therapy (40–50 Gy), further continuation of chemoradiation resulted in equivalent overall survival compared with surgery, albeit that the non-operative strategy was associated with higher local tumour recurrence [16, 17]. Therefore, chemoradiotherapy with planned surgery or definitive chemoradiotherapy with close surveillance, and salvage surgery for local tumour persistence or local tumour progression, may be considered as a definitive treatment of selected patients with locally advanced disease [22] [I, B]. Experienced multidisciplinary teamwork is warranted for this treatment approach and post-operative mortality will increase with the dose of radiotherapy applied.

Definitive chemoradiotherapy is recommended for cervically localised tumours [III, B].

Place de la chirurgie du residu : RTOG 0246



RTOG 85-01

		Week	1	5	8	11
5-FU	1000 mg/m ² x 4 d					
CDDP	75 mg/m ² d 1					
RT	50 Gy					
RT	64 Gy					

Herskovic A et al., NEJM 1992

RTOG 85-01

Table 1. Overall Survival by Treatment Group*

Time, y	No. (%) Alive Following Radiation Therapy Only (Randomized)	No. (%) Alive Following Combined Modality Therapy	
		Randomized	Nonrandomized
0	62 (100)	61 (100)	69 (100)
1	21 (34)	32 (52)	43 (62)
2	6 (10)	22 (36)	24 (35)
3	0 (0)	18 (30)	18 (26)
4	0 (0)	17 (30)	13 (19)
5	0 (0)	14 (26)	10 (14)
6	0 (0)	12 (22)	6 (10)†
7	0 (0)	12 (22)	2 (6)†
8	0 (0)	10 (22)	...
9	0 (0)	4 (20)†	...
10	0 (0)	3 (20)†	...
Total dead (median, mo)	62/62 (9.3)	48/61 (14.1)	65/69 (16.7)

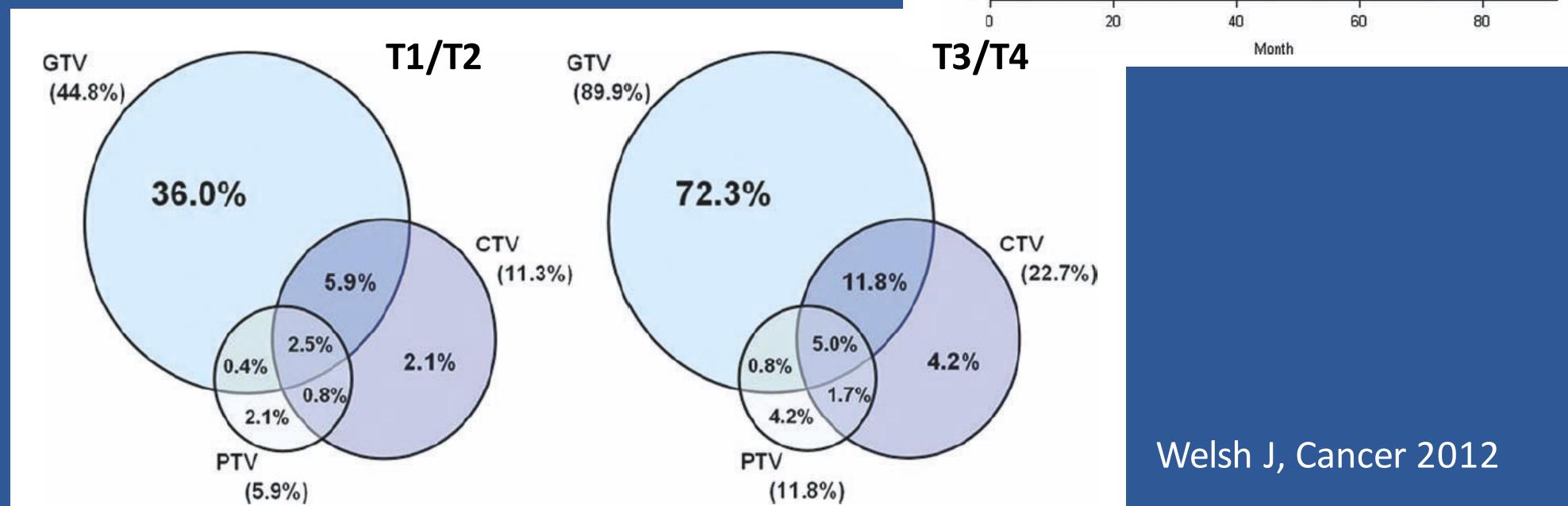
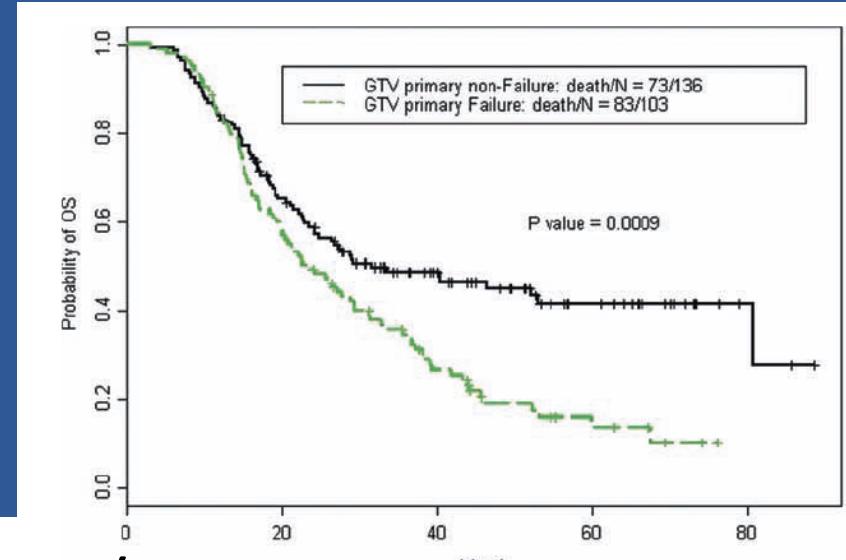
*Percentages are estimated. Data compiled by Kaplan-Meier method. Statistical test results of the log-rank test are: randomized comparison, $P < .001$; and combined modality therapy and radiation therapy (randomized vs nonrandomized), $P = .24$ (stratified by tumor stage). Ellipses indicate data not available because follow-up lasted less than 8 years.

†Percentages are unreliable due to the small number of people at risk.

Cooper J et al., JAMA 1999

Sites de rechutes après XRT-CT exclusive

- 239 exclusive XRT-CT
(76% Adeno)
- 50% LRF
- 48% Distant
- 31% NED



Rechutes LR : In-field?

- XRT ~~CT~~ sis.⁶ In addition, proton therapy to doses of 70–90 Gy (RBE) has been shown in several studies to produce high complete clinical response rates, as high as 78 %.^{21,22} Although RTOG 94-05 revealed no benefit for radiation dose escalation, it was performed in the pre-IMRT era.²³ We have previously demonstrated that with advanced IMRT treatment planning we could selectively increase the dose to the GTV by 28 % while also reducing the dose to both the heart and lung compared with traditional 3D techniques.²⁴ Similar benefits can also be achieved from the dosimetric advantage of intensity modulated protons therapy.²⁵
- In-field
- T per
- Bas

Site of first failure

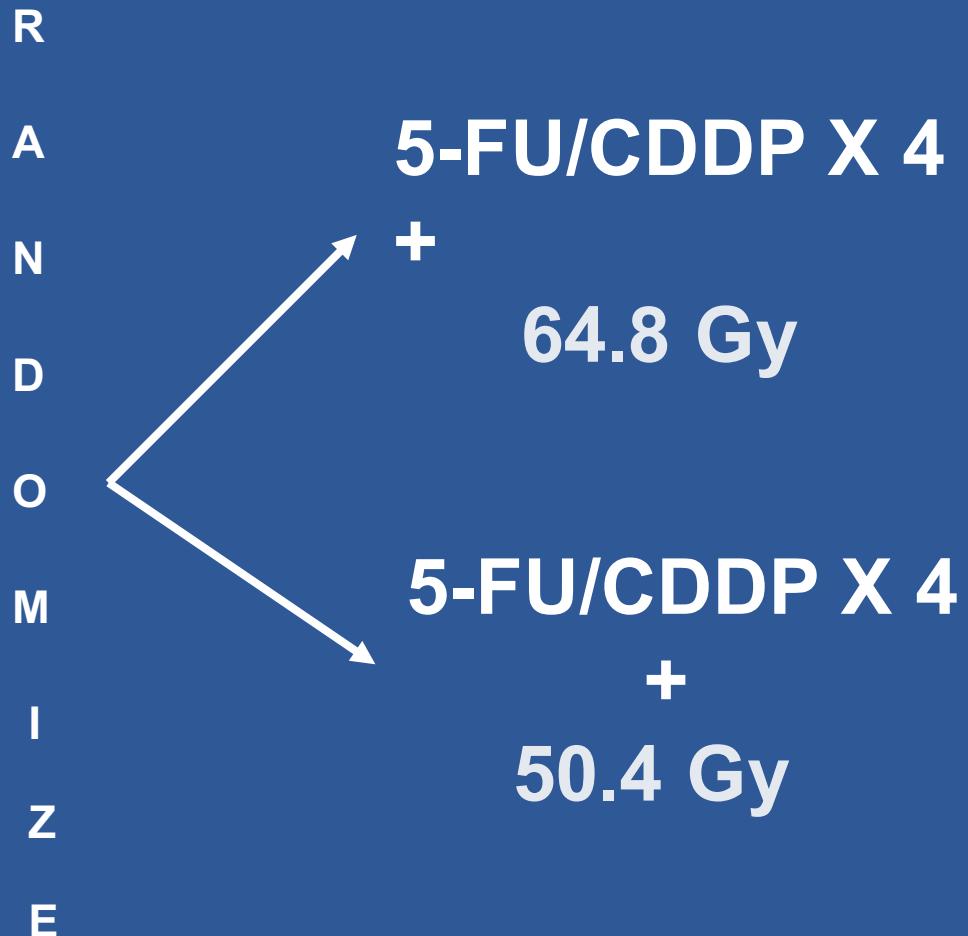
RTOG 9405 (INT 0123)

S
T
R
A
T
I
F
Y

Weight loss
> or < 10%

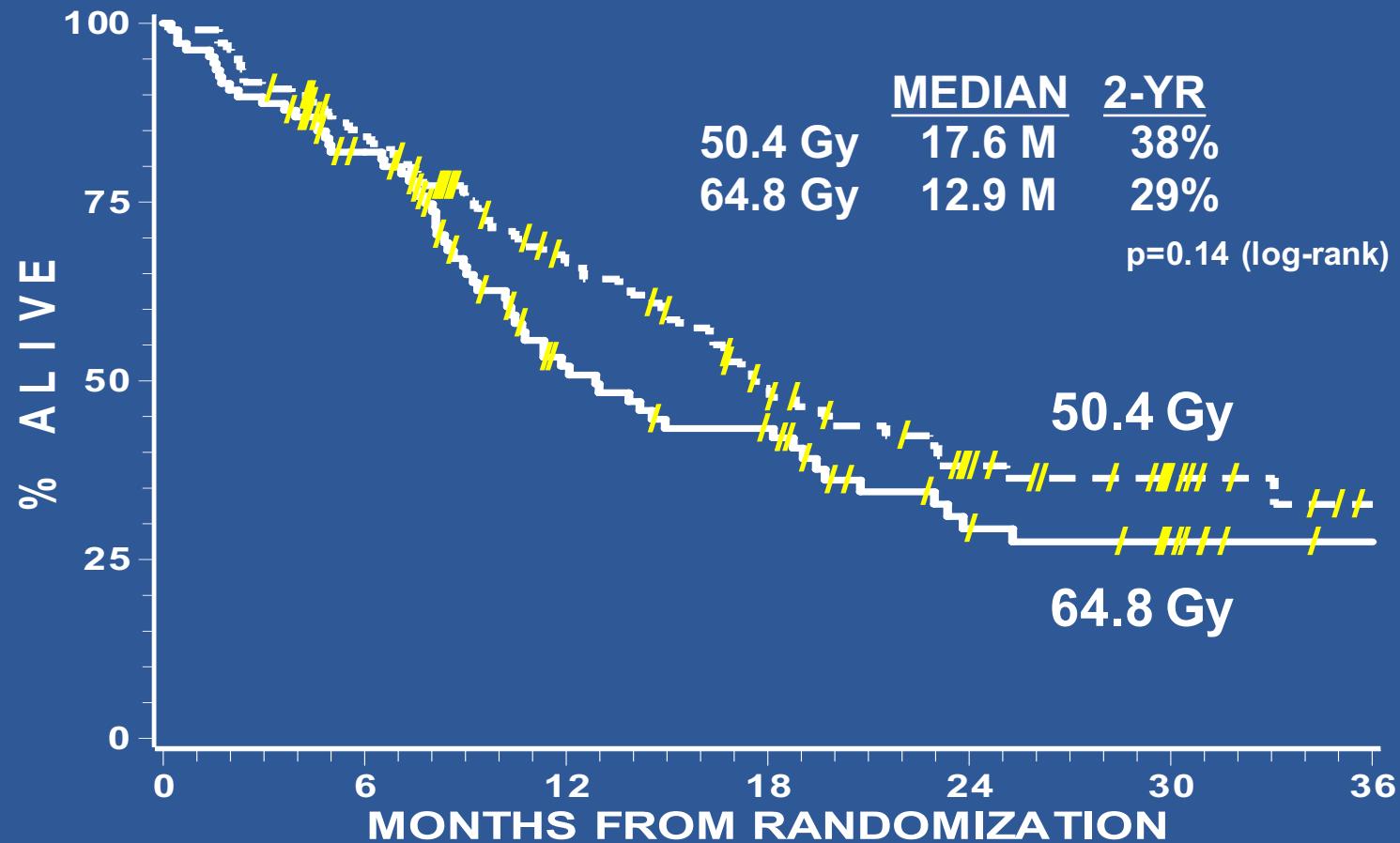
Tumor size
≤ or > 5 cm

Histology
Adeno
Squamous (87%)



Minsky B et al., JCO 2002

INT 0123



50.4 Gy 109

59

24

6

64.8 Gy 107

42

17

6

INT 0123 - First Failure (%)

	64.8 Gy	50.4 Gy
#	107	109
Total LR	61	60
LR persistence	44	42
LR failure	17	18
Distant failure	10	15

Int. 0123 - Décès toxiques

Dose reçue	Toxicité	Cause suspectée?
Bras 64.8 Gy		
5.4 Gy	Cardiaque	CT? > RT?
5.4 Gy	Cardiaque + GU	CT? > RT?
9.0 Gy	Hémato	CT
37.8 Gy	Respiratoire	RT?
43.2 Gy	Hémato + Infectieux + GU	CT
50.4 Gy	Infectieux	CT
50.4 Gy	GU	CT?
54.0 Gy	Infectieux	CT
61.2 Gy	Hémato	CT
64.8 Gy	Infectieux	CT
64.8 Gy	Fistule + GI	RT?
Bras 50.4 Gy		
50.4 Gy	Infectieux	CT
50.4 Gy	Infectieux	CT

FFCD 9102

Rechutes locales 46Gy-Chir/66Gy

Tous les patients	(161)
	27 (14)
Chirurgie	7 (13)
RC exclusive	10 (18)
Répondeurs	(88)
	14 (16)
Chirurgie	5 (12)
RC exclusive	9 (20)

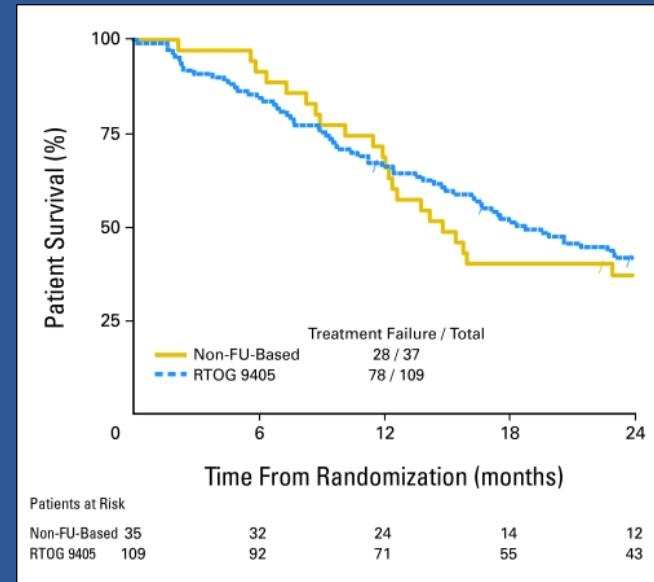
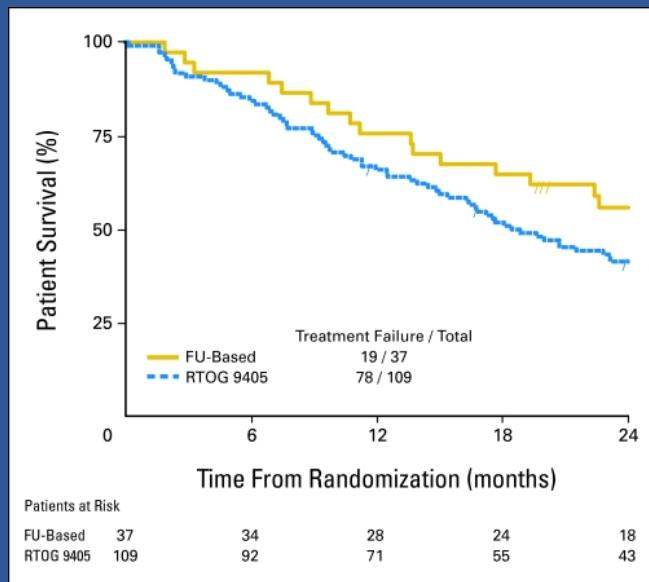
**Optimisation de la
radiopotentialisation?**

RTOG 0113 : Place des taxanes en XRT-CT exclusive

Induction 2 bras : CDDP-5FU-Taxol

XRT 50.4Gy +5-FU/Taxol

XRT 50.4Gy +CDDP/Taxol



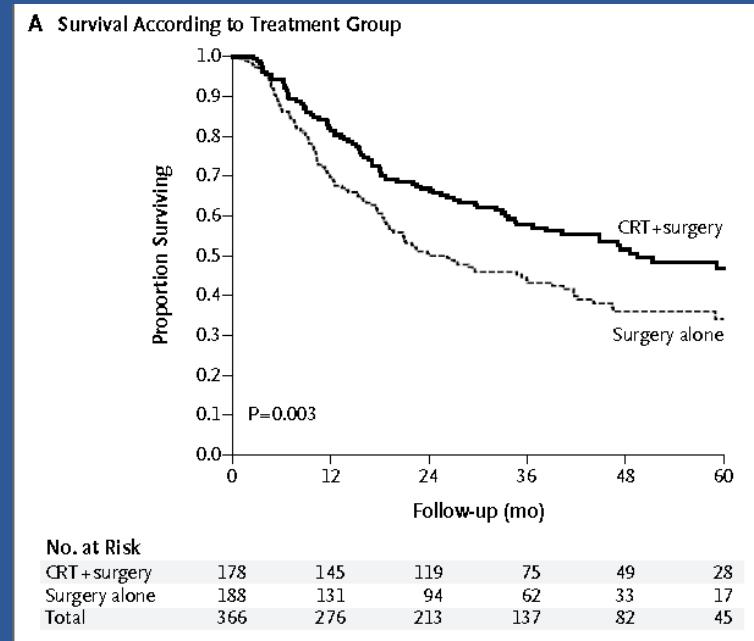
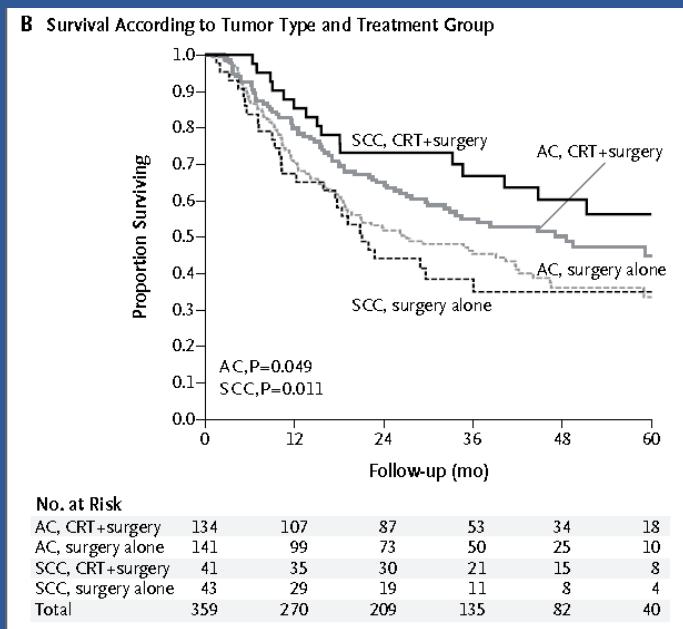
	G3	G4	G5
Acute	54%	27%	3%
Late	5%	3%	-

	G3	G4	G5
Acute	43%	40%	3%
Late	9%	3%	3%

Ajani JA et al., JCO 2008

CROSS Trial

- 273 ADK/ 86 SCC
- RTC-3D : 41.4Gy
- Carbo AUC 2
- Taxol 50 mg/m² hebdo

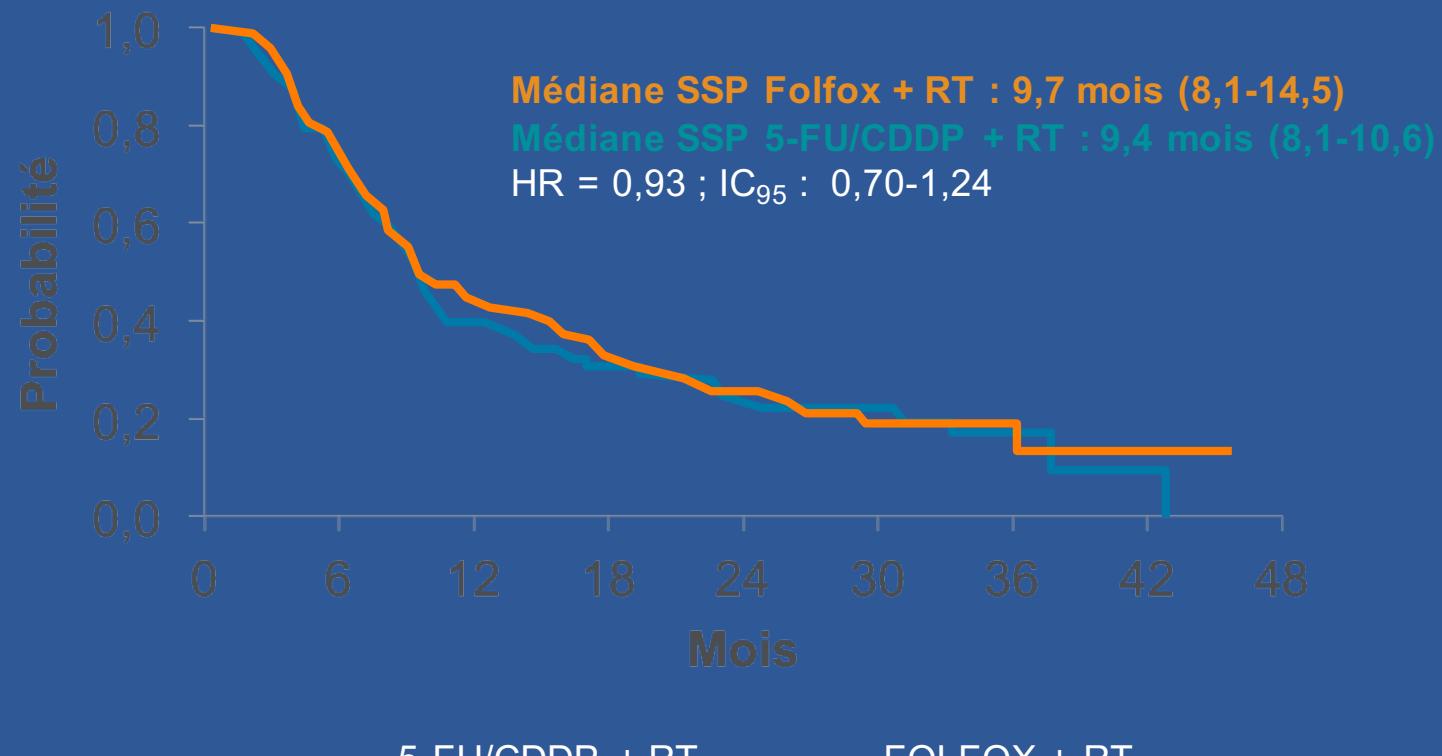


SG = 49 mois vs. 26 mois

Van Hagen P. et al., NEJM 2012

PRODIGE 5 / ACCORD 17

CDDP/5-FU vs. FOLFOX-4



Patients à risque

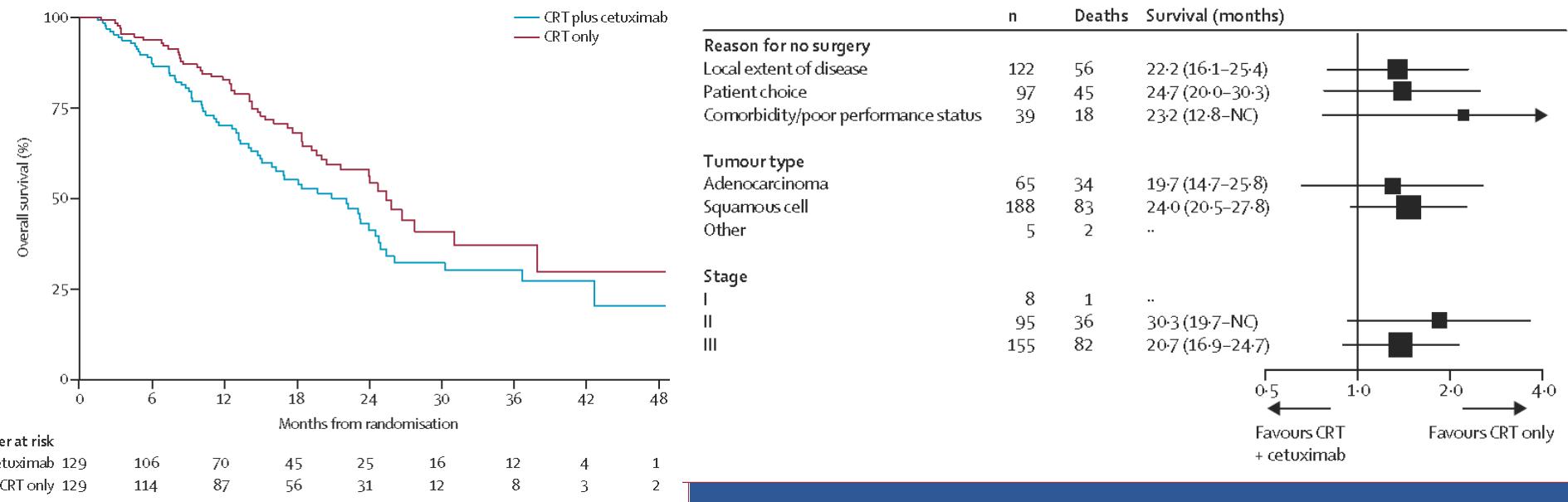
5-FU/CDDP + RP	133	89	44	29	18	11	5	1	0
FOLFOX + RT	134	90	50	29	17	8	4	3	2

ASCO® 2012 - D'après Conroy T et al., LBA4003 actualisé

PRODIGE 5-ACCORD 17 : toxicité

Toxicités (tous grades)	RTE + 5-FU-cisplatine	RTE + FOLFOX
Mucites (%)	32	26,7
Alopécie (%)	9,4	1,5
Insuffisance rénale (%)	11,7	3
Neuropathie périphérique (%)	0,8	18,3
Décès toxiques (%)	6,4	1,1

Scope 1



Med; OS 25.4 mos vs. 22.1 mos,
HR= 1.53 [1.03-2.27], p=0.035

Observance RT

RT50Gy : 70% vs 90%

No RT : 19% vs. 8%

Décès < 24 sem : 13% vs. 6%

Crosby T. et al., Lancet Oncol 2013

Quelles directions en radiochimiothérapie?

patient selection. The 2012 annual report of the UK National Oesophago-gastric Cancer Audit³⁸ has showed an improvement in outcomes for patients undergoing surgery, with 45% of patients surviving for 3 years. Both of these areas have scope for further development, namely the incorporation of CT-PET more directly into radiotherapy planning and assessment of caseload, with outcomes in specialist non-surgical services.

We believe, however, that by using newer radiotherapy techniques, such as intensity-modulated and image-guided radiotherapy, we can now safely deliver a higher dose of radiation to a highly conformal target volume.

Crosby T et al., Lancet Oncol

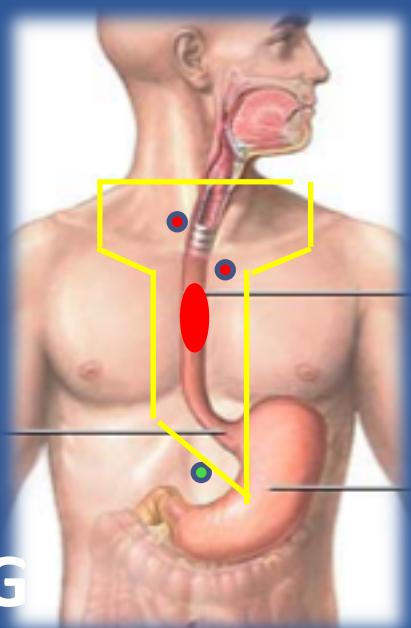
1.8 Gy are regarded as standard treatment of definitive radiotherapy in the United States. Increased radiation doses up to 60 Gy in fractions of 1.8–2.0 Gy are recommended in parts of Europe and Japan for definitive chemoradiotherapy. This is due to an obvious dose–response correlation of radiotherapy in oesophageal cancer and the positive experience with these radiation doses in prospective multi-centre trials [16, 17] (Figure 1).

colleagues' trial.¹ As Crosby and radiation doses of 60 Gy or higher are safe to deliver to patients with this disease, they cause significant morbidity. A successful combination of radiotherapy and a targeted therapy will advance against this disease and we

« ...la bonne dose dans le bon volume ?»

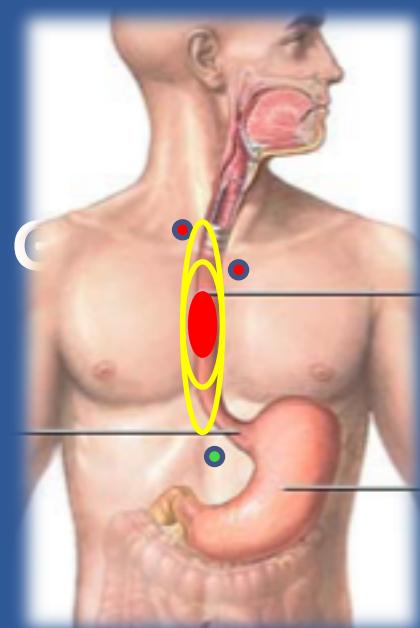
RTOG 85-01

- RT 2D
- ENI
- AP-PA
- 30 Gy
- Susclav – JOG
- Boost 2D
- T + 5cm : 20Gy



Int. 0123

- RT 2D
 - T + 5cm : 50.4 Gy
 - Pas d' ENI
 - Boost
 - T + 2cm : 14.4Gy
- (Impasse sur les N1!)



PAS D'ASSURANCE QUALITE DE LA RADIOTHERAPIE!!

Planification : Contourage GTV

- TEP : 47% discordance avec TEP/ CT (FN—
Vrieze O et al., Radiother Oncol 2004)
- 69% du GTV manqué sans TEP
Leong T et al. Radiother Oncol 2006
- 35% GTV>> et 21% GTV<<
Moureau Zaboutto L. et al. IJROBP 2005
- Hauteur GTV-T : CT 6.77cm vs PET 5.4cm vs EES 5.1 cm
Konski et al., IJROBP 2005



Données EC + CT + TEP + EES

Planification : Contourage CTV

- Pièces oesophagectomies (n= 34 SCC/32ADK)
- Extensions microscopiques

latérales (valeurs moyennes) =

- SCC : 10.5 ± 13.5 mm SUP et 10.6 ± 8.1 mm INF
- ADK : 10.3 ± 7.2 mm SUP et 18.3 ± 16.3 mm INF

Supéro-inférieures (valeurs moyennes) =

50mm = Couverture 100%

30mm = Couverture 94% (seulement sup si JOG)

Planification : Contourage ITV

- Mobilité de l'œsophage SAIN en respi libre
- Marges lat = 5 mm, 7 mm, 9 mm (sup, med, inf).
- Marges AP = 5 mm, 6 mm, 8 mm (sup, med, inf).
- Mobilité de l'œsophage DISTAL
- $95\% < 0.8\text{cm}$ radiaire
 $< 1.75\text{cm}$ inf

Dieleman EM et al., IJROBP 2007
Yaremko BP et al., IJROBP 2008

Planification : Contourage PTV

- MVCT quotidiens
- Définition de la marge pour l'incertitude d'installation
(set-up margin) =
moyenne + SD des valeurs absolues des déplacements

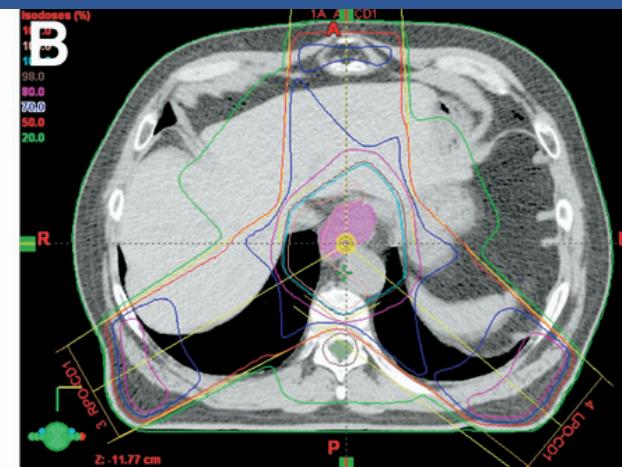
5 mm (AP), 11.1 mm (Lat), 12.7 mm (SI)

Dieleman EM et al., IJROBP 2007
Yaremko BP et al., IJROBP 2008

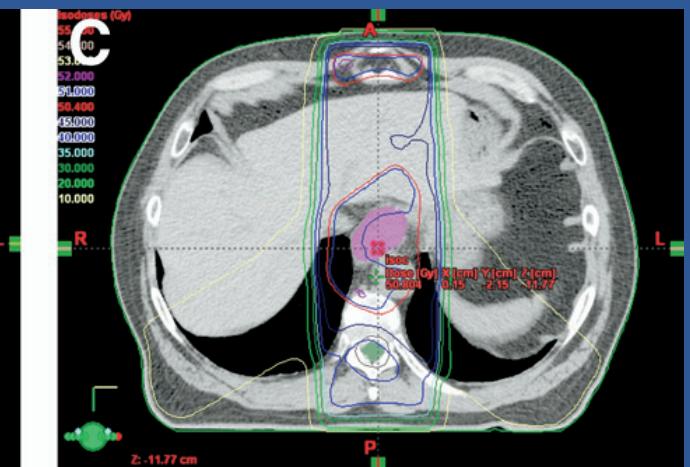
Dosimétrie : 3D



AP 30-40Gy



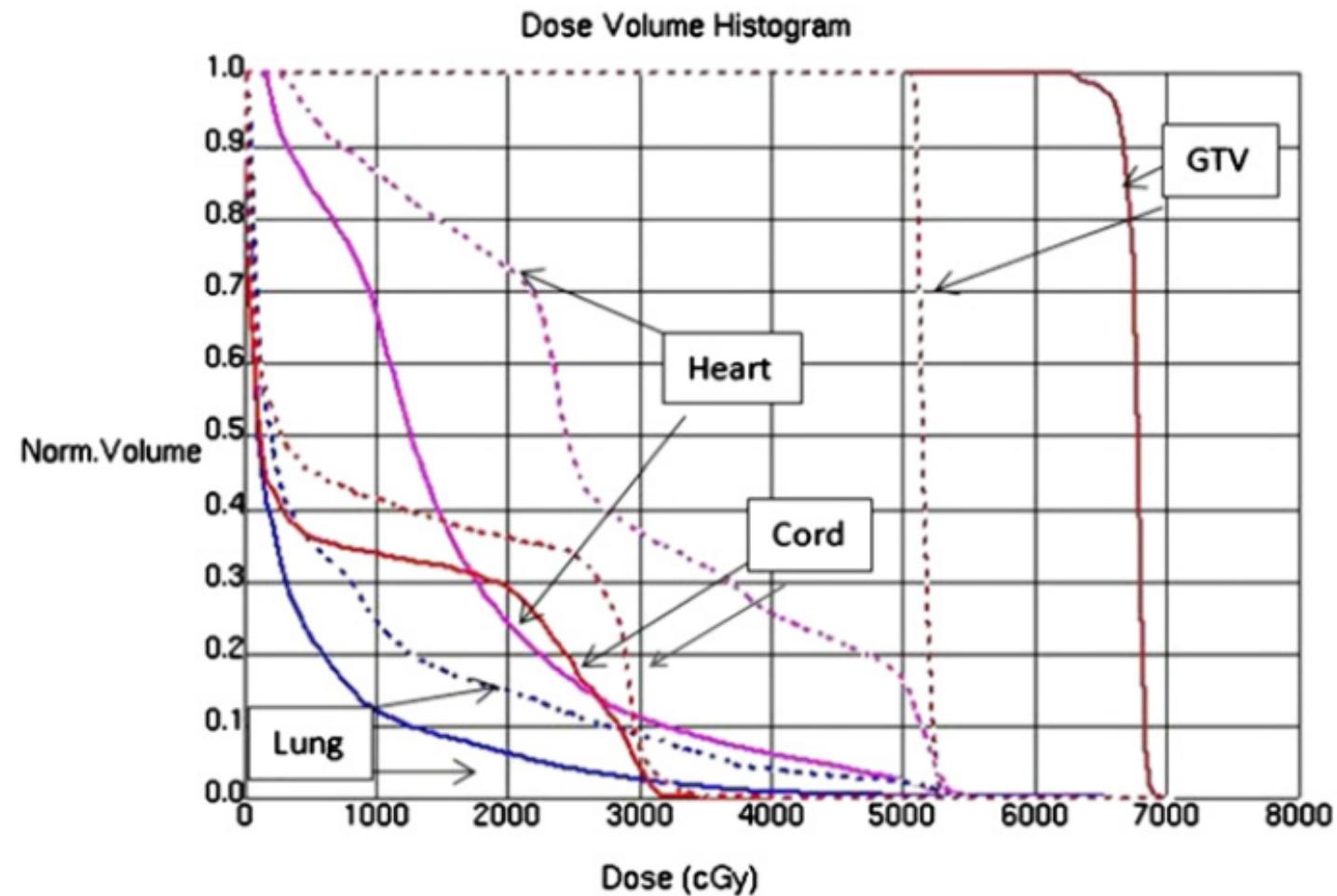
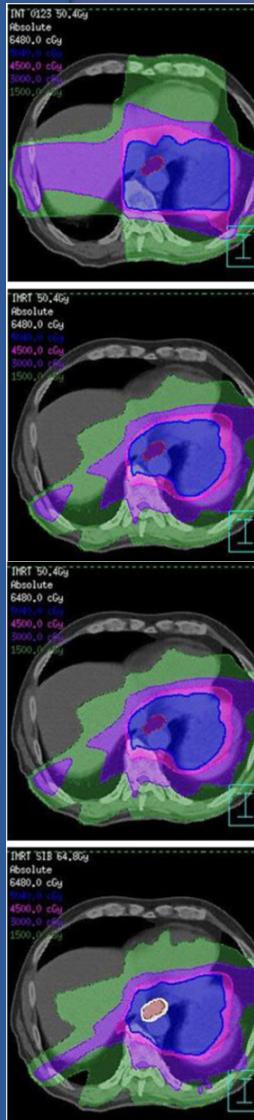
AP + 2 obliques post 10-
20Gy



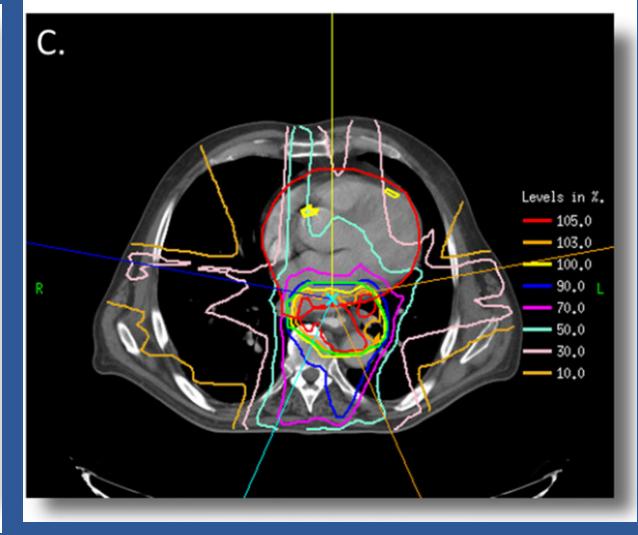
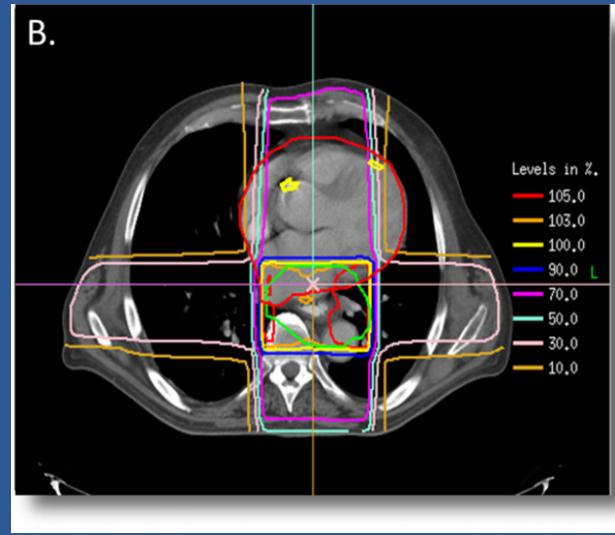
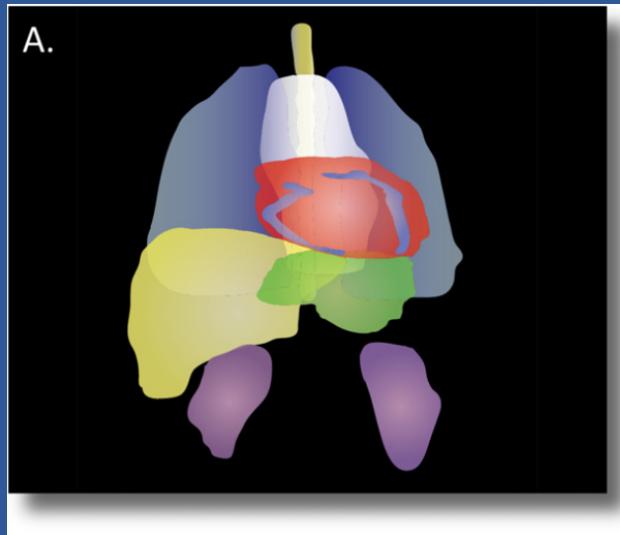
Cumulé
Cœur>>
Poumons > (NS)

Evolutions technologiques de la radiothérapie : Quels espoirs?

50.4Gy vs. 64.8Gy : 2D-RT vs. IMRT



3D-CRT vs. IMRT



Vol. cœur recevant 30 Gy : 61% vs. 25%
Protection artère coronaire D++

Dosimétrie : IMRT vs 3D

SIB = 50.4Gy ENI + 67.2Gy (Boost)

Réduction de V20 et V30 pulmonaire

Fu WH et al., World J Gastroenterol 2004

Oesophage Distal : 3DRT vs IMRT 4, 7 ou 9 chps

Réduction poumons V10 de 10% et de V20 de 5% et dose moyenne de 2.5Gy

Chandra A et al., Radiother Oncol 2005

Oesophage 1/3 moyen : 3D vs HT vs IMRTss

Augmentation de V10 en IMRT/HT

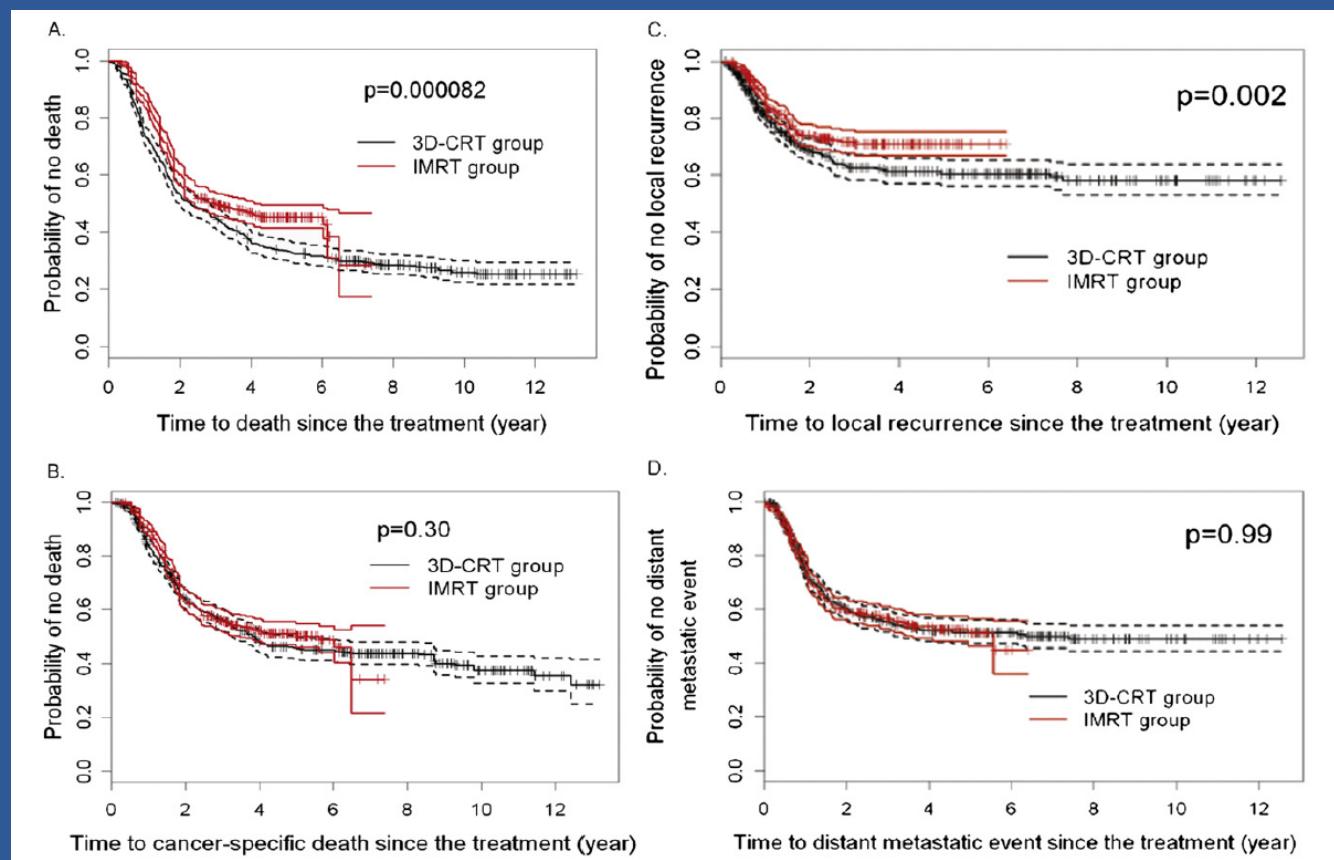
Diminution de V30 et V45 cœur

Chen YJ et al., Med Dosim 2007

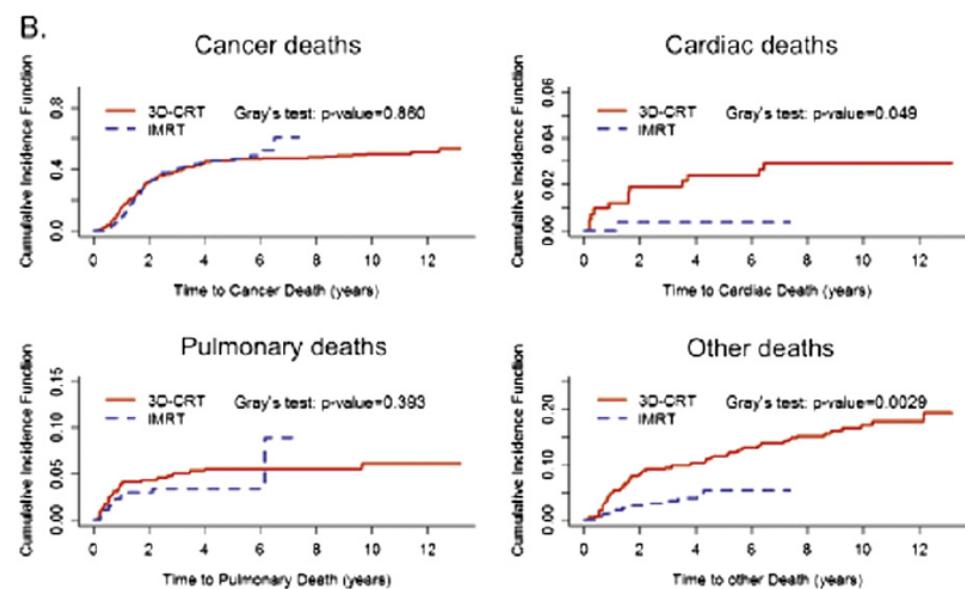
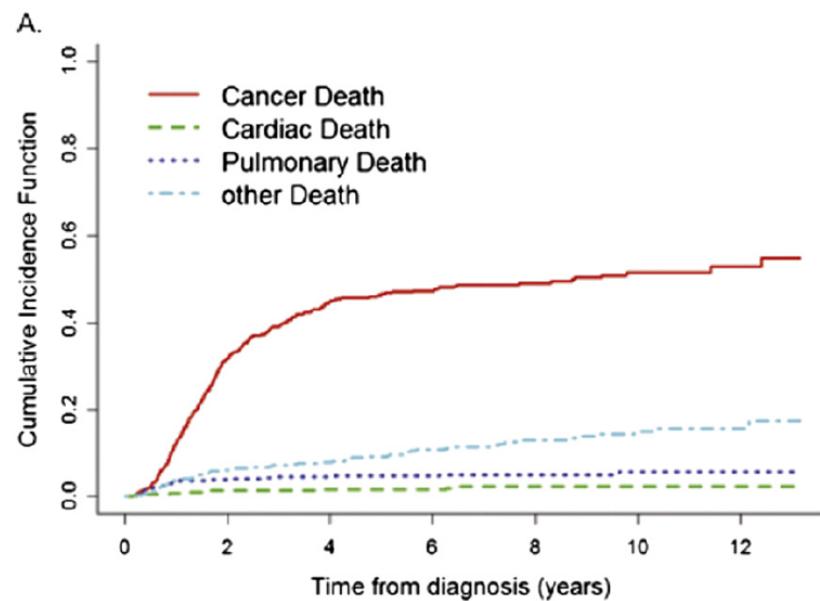
Moins hétérogène, meilleure conformationnelle+++

3D-CRT vs. IMRT

- N= 676
- 413 3D-CRT
- 263 IMRT
- RT dose
- Mean 50.4Gy
- Range [6.6-66.0]
- P= 0.84



IMRT : Evolution ou Révolution?



IMRT vs VMAT

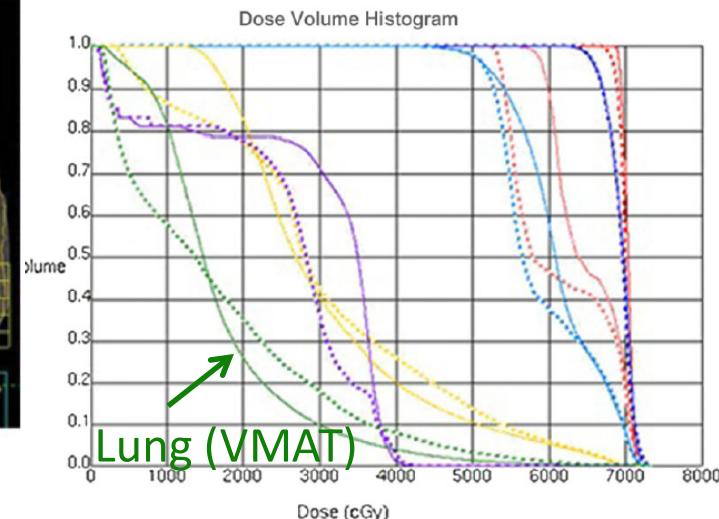
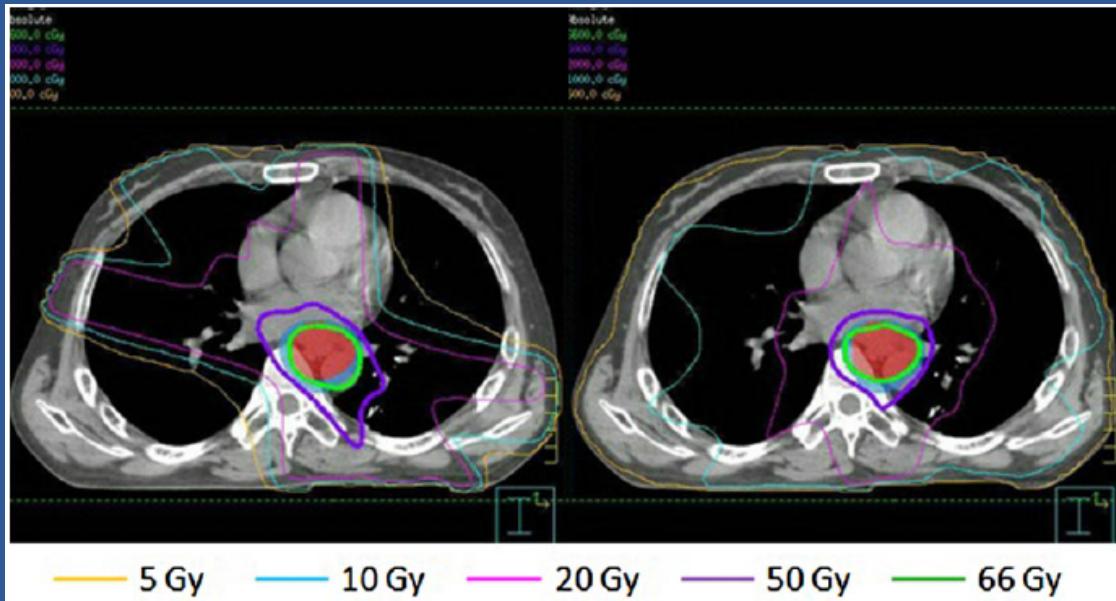
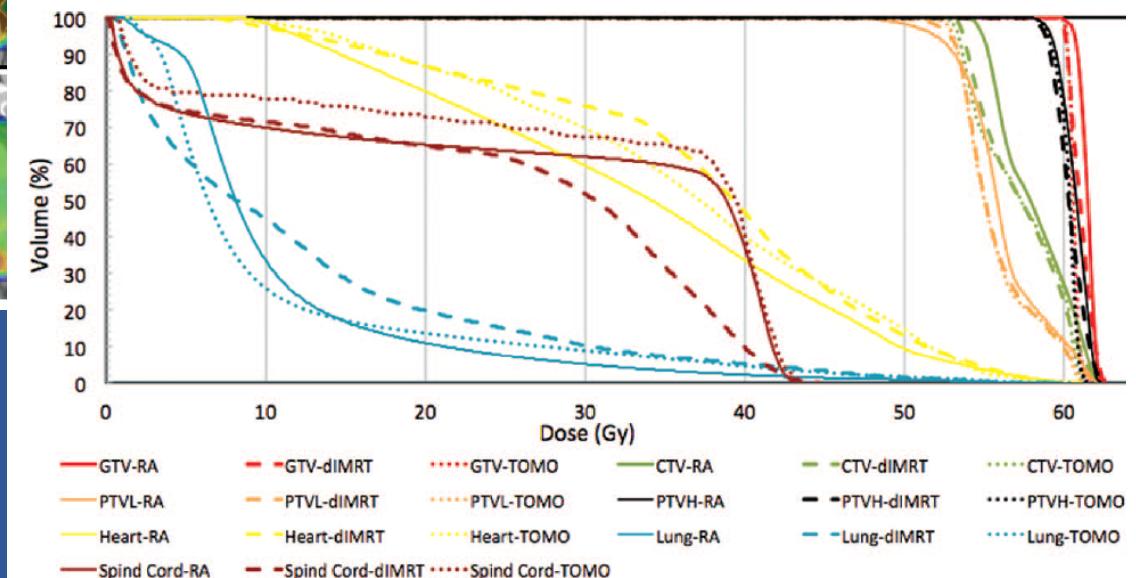
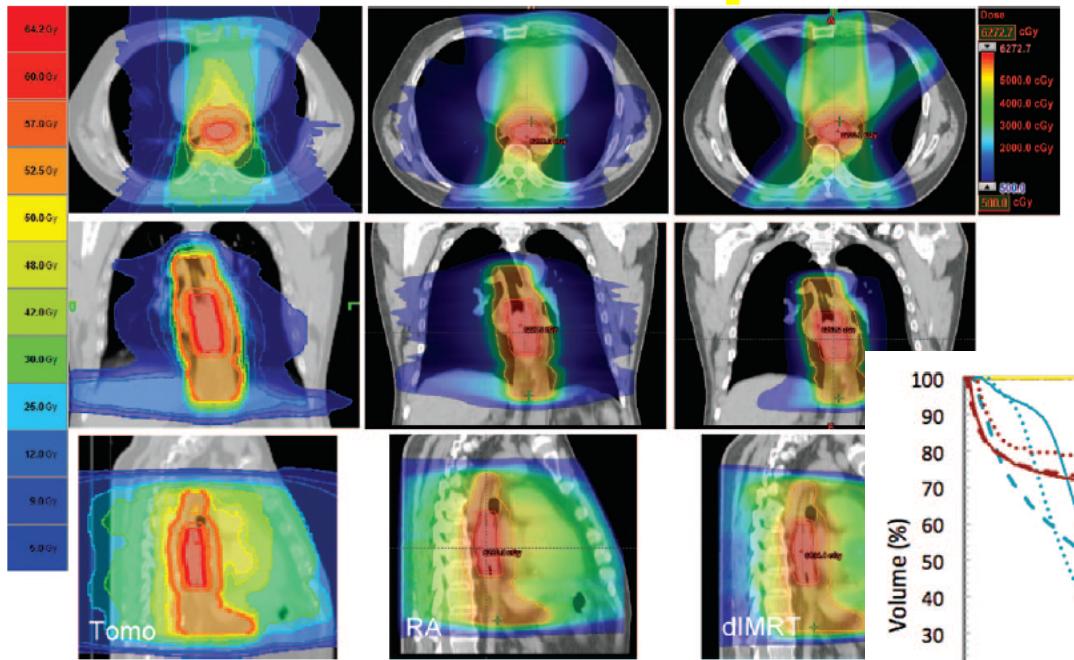


Fig. 2 Cumulative dose-volume histograms of clinical target volume 50 (CTV_{50}) (tomato), CTV_{66} (red), planning target volume 50 Gy (PTV_{50}) (light blue), PTV_{66} (blue), lung (green), heart (orange), and spinal cord (purple) for one patient obtained in fixed-field intensity-modulated radiotherapy (IMRT) (dashed lines) and volumetric modulated arc therapy (VMRT) (solid lines). (—) CTV_{66_VMAT} ; (—) CTV_{66_IMRT} ; (—) PTV_{66_VMAT} ; (—) PTV_{66_IMRT} ; (—) CTV_{50_VMAT} ; (—) CTV_{50_IMRT} ; (—) PTV_{50_VMAT} ; (—) PTV_{50_IMRT} ; (—) $heart_VMAT$; (—) $heart_IMRT$; (—) $lung_VMAT$; (—) $lung_IMRT$.

Tomothérapie/RapidArc/IMRT: lequel choisir?

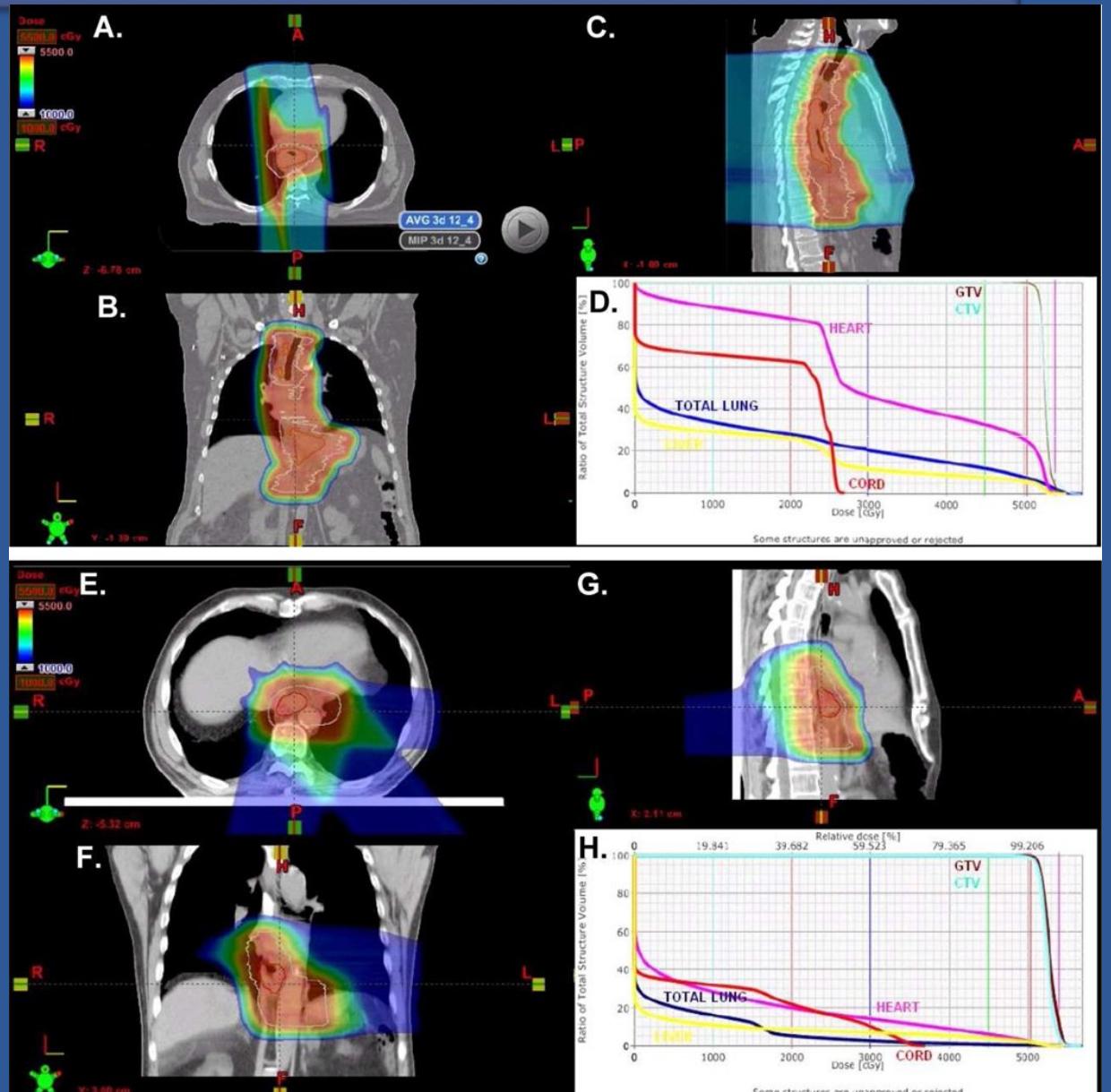


Volume de poumon recevant 5 Gy : 54,4Gy (Tomo) vs. 67,54Gy (RA) vs. 44,8Gy (IMRT), p< 0,001
V20 = tendance inverse
Cœur = pas de différences!

Wang YC et al, TCRT 2013

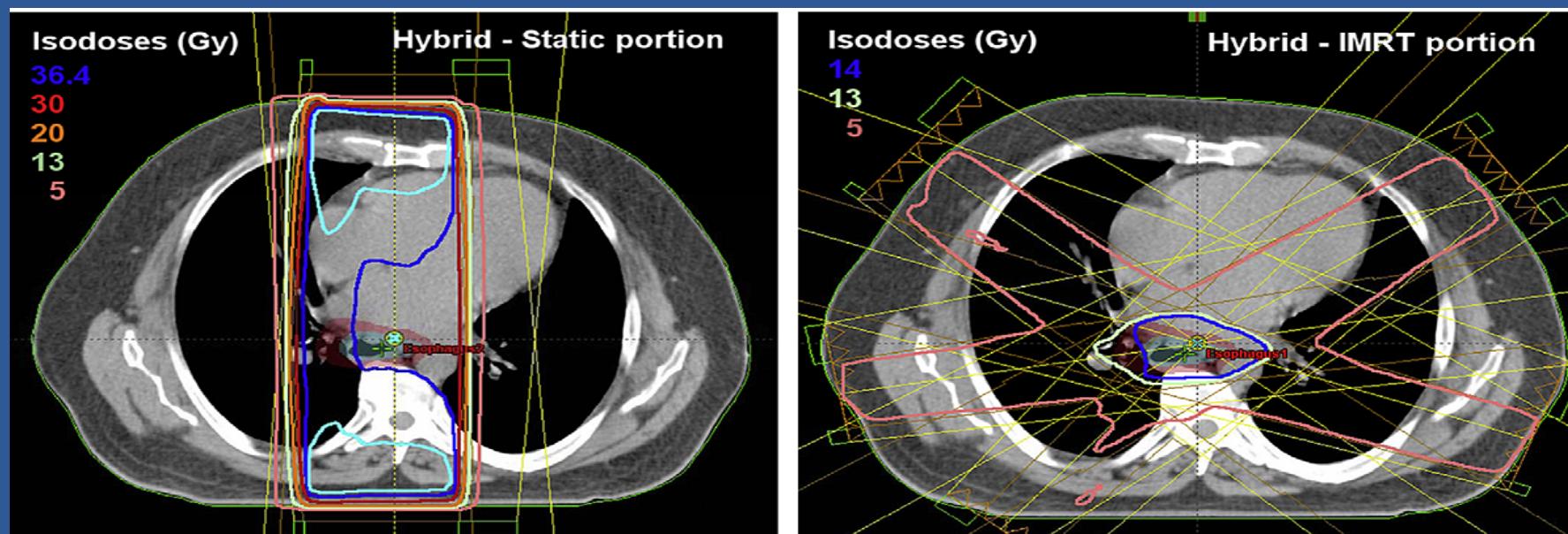
Radiochimiothérapie en IMPT (Protons)

- N=62 (29 preop)
- 2 or 3 fields
- 150-250 MeV
- 50.4 GyE
- FUmed 20 months
- pCR 28%
- Near pCR 50%
- Tox G3+
- Pneumo 1.6%
- Cut 3.2%
- Oeso 9.7%
- Dysphagie 9.7%



Hybrid-IMRT

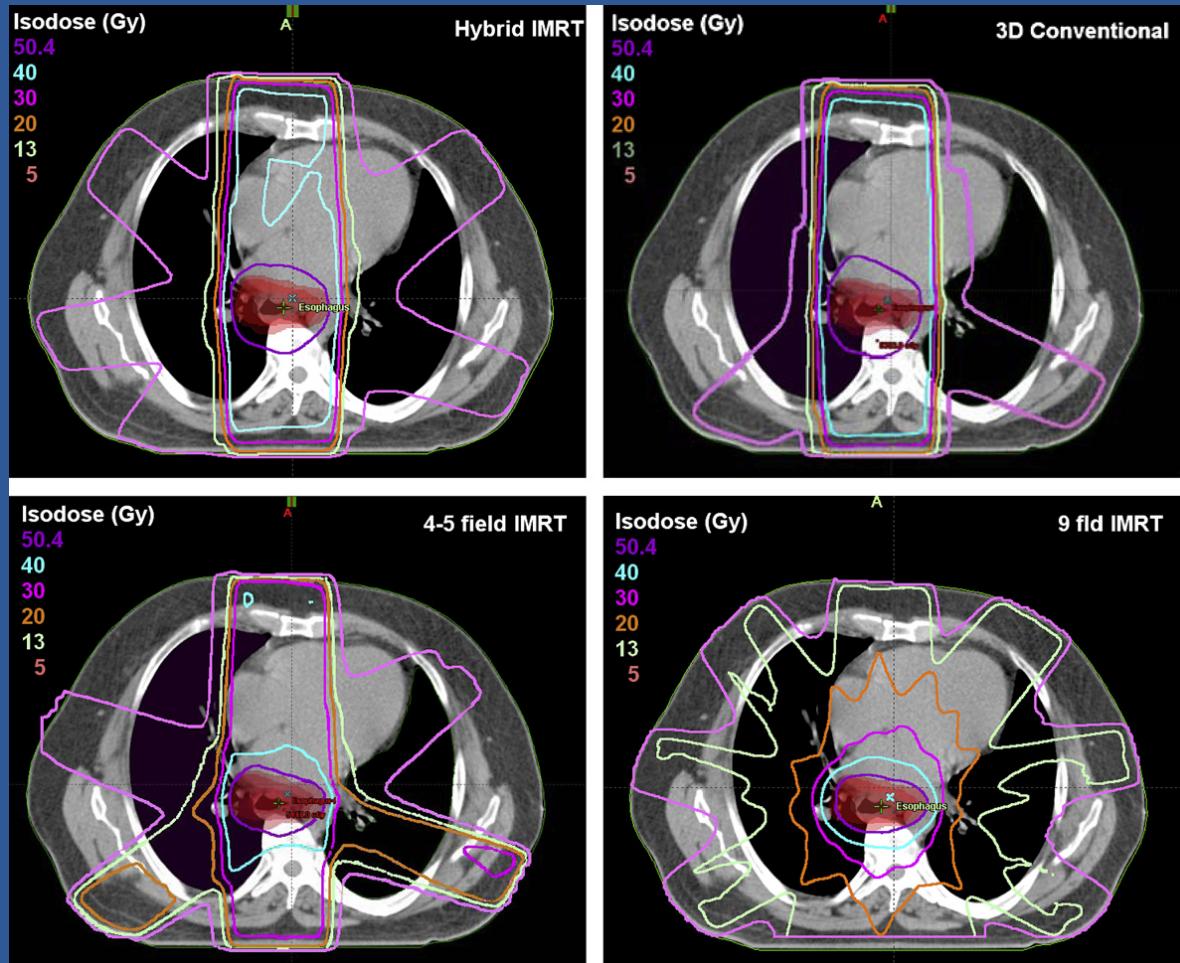
Hybrid = 2/3 dose champs statiques (technique 3D Conf) +
1/3 dose IMRT



Mayo CS et al., IJROBP 2008

Hybrid-IMRT

3DCRT vs IMRT 9 champs vs IMRT 5 champs vs Hybrid IMRT



Dose poumon
controlat
diminuée
 $V5 = -16\%$,
 $V13 = -20\%$
 $V20 = -7\%$

Mayo CS et al., IJROBP 2008

OAR

Guidelines US du National Comprehensive Cancer Network (NCCN)

- Foie V60%<30Gy
- 2/3 de 1 rein \leq 20Gy
- Moelle Dmax=45Gy
- Cœur 1/3<50Gy
- Poumons : ALARA

National Comprehensive Cancer Network guidelines, Clinical practice guidelines in oncology, Esophageal cancer, 2009.

<http://www.nccn.org>. Accessed 07 January 2009

OAR

COEUR

- Coronaropathies
- Pericardite 27.7% (à 5.3 mois)
- V30<46% vs >46% = 13% vs 73%
- FEV : 59% avant vs 54% après ($p<0.01$)

Carr ZA et al., IJROBP 2005

Wei X et al., IJROBP 2008

Tripp P et al., Dis esophagus 2005

POUMONS

- Poumons V20
<22% : 100% G0
22-31% : 8% G2
>32% : G3 apparaissent

>40% : 23% de G3-5
- V5, V10 (<40%+++), V13, V15 = facteurs prédictifs de pneumopathies

Graham MV et al., IJROBP 1999

Tsujino K et al., IJROBP 2003

Schallenkamp JM et al., IJROBP 2007

Lee HK et al., IJROBP 2003

CONCORDE (PRODIGE 26)

Centre

S

T

R

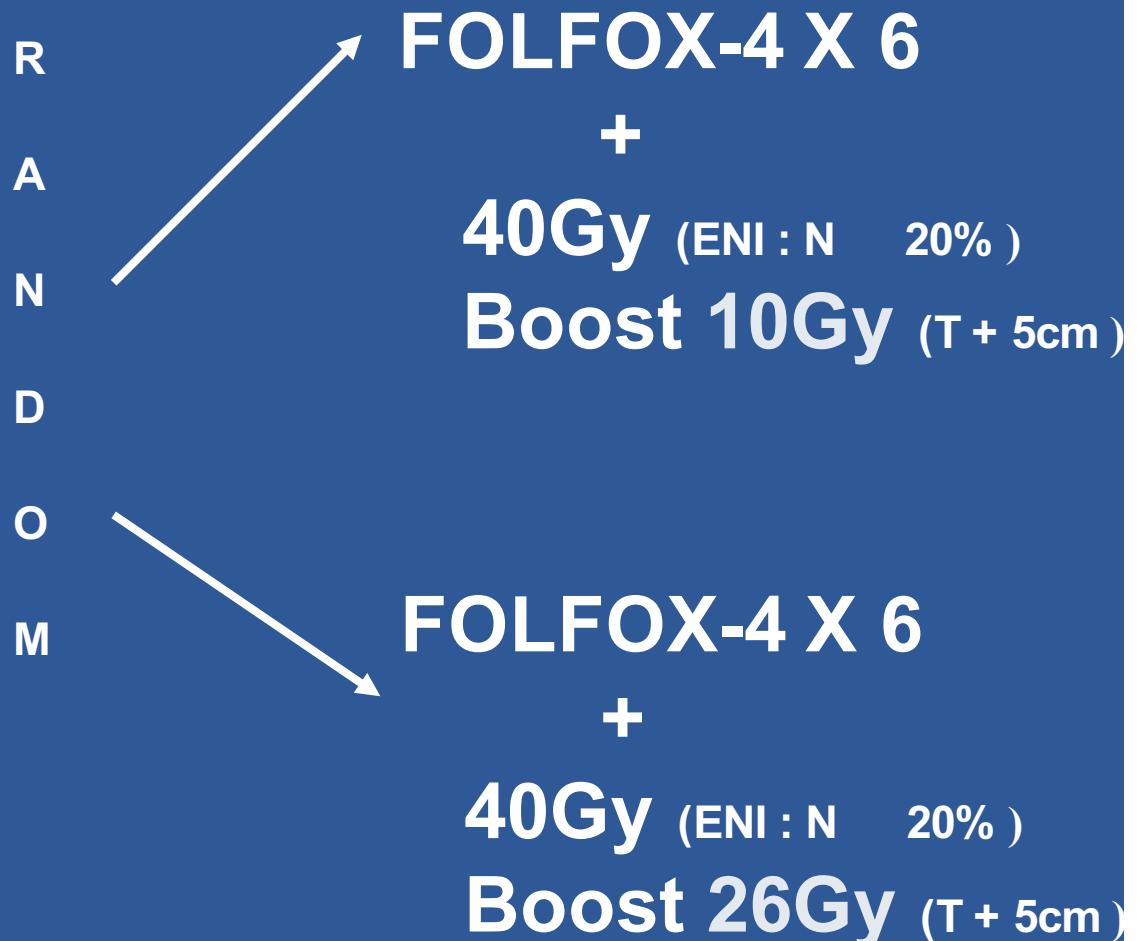
A

T

Perte de poids
 $> vs < 10\%$

Stade
I – II vs. III

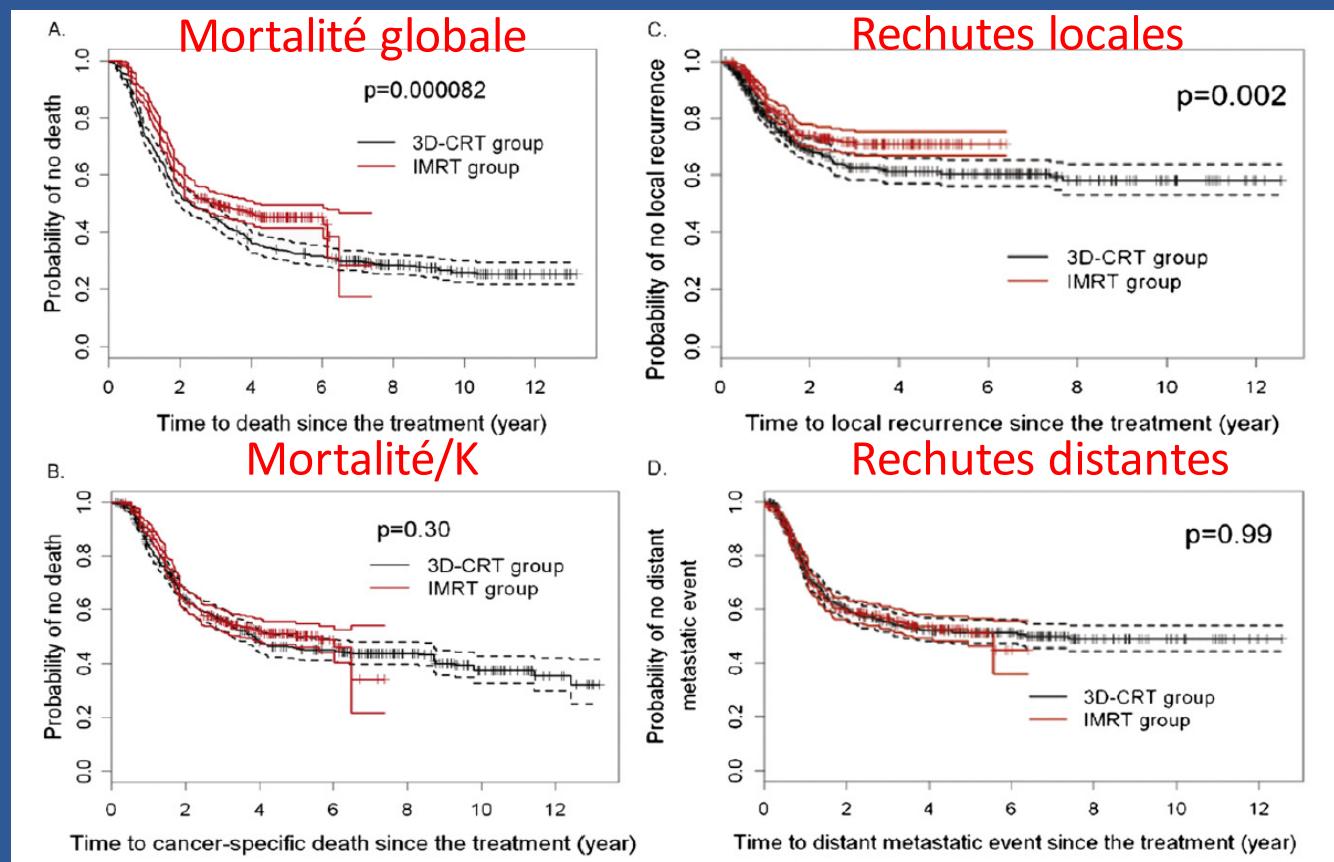
Histologie
Adeno vs.
Epidermoïde



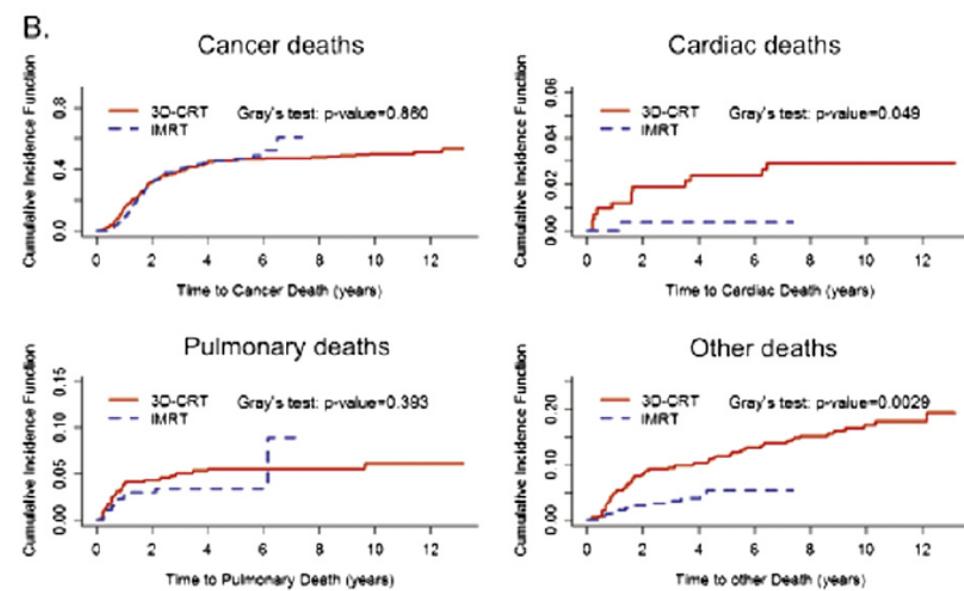
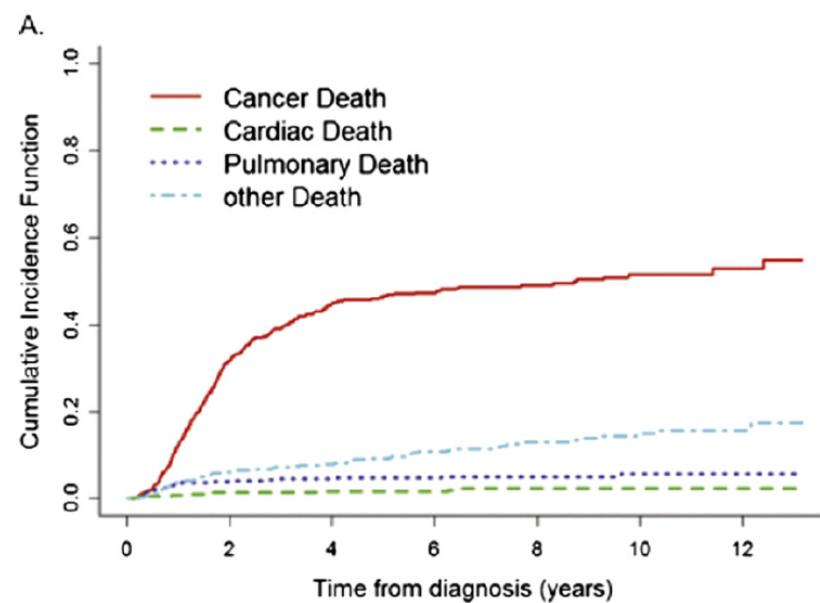
OBJECTIF PRINCIPAL : Survie sans rechute LR à 2 ans

3D-CRT vs. IMRT

- N= 676
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- 263 IMRT
- RT dose
- Mean 50.4Gy
- Range [6.6-66.0]
- P= 0.84



IMRT : Evolution ou Révolution?



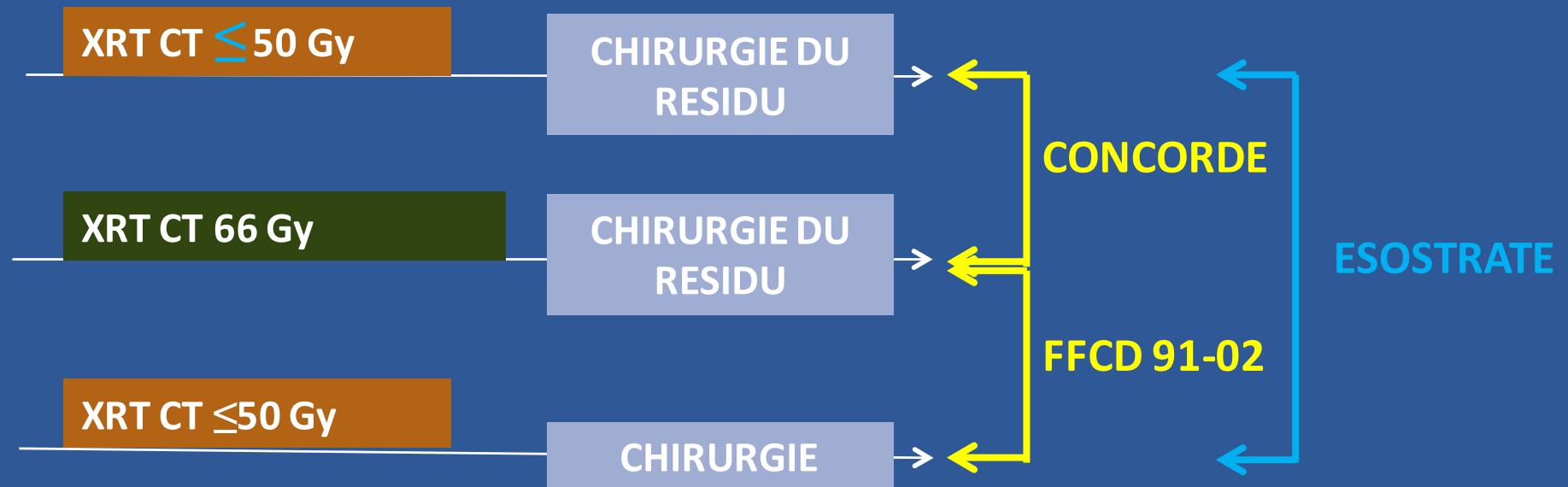
Place de la chirurgie apres une haute dose

	Chir (n= 35)	XRT-CT (66Gy) + Chir (n= 30)	P-value
Durée séjour en SI Mediane (min-max)	3 (0-148)	4,5 (0-85)	0.96
Durée hospitalisation Mediane (min-max)	18 (11-187)	16 (9-177)	0.61
Complications pulmonaires	21 (60%)	19 (63.3%)	0.80
Détresse respiratoire	18 (51.4%)	15 (50.0%)	1.0
Pneumonie	15 (42.9%)	14 (46.7%)	0.81
Chylothorax	0	1 (3.3%)	0,46
Mortalité opératoire	3 (8.6%)	5 (16.7%)	0.45

Hurmuzlu M; Radiother Oncol 2010

T3 et/ou N+

QUELLE(S) STRATEGIE(S)?



Conclusions

- RTCT = SG similaire, QDV et complications moindres, CL insuffisant à 50Gy, Résidu local = marqueur de la maladie métastatique?
- Chirurgie du résidu non recommandée en dehors de patients et chirurgiens sélectionnés
- Place de la chirurgie de ce résidu? Evaluation prospective+++
- RTCT-chir si ADK localisé ou localement avancé
- RTCT exclusive si SCC localement avancé ou ADK unfit
- Diminution de la morbidité avec IMRT préop? Evaluation prospective+++
- Chirurgie si SCC localisé ou localement avancé (chirurgien expert)
- Nouvelles technologies : CONCORDE peut il faire mieux que INT0123?
☞ Amélioration du contrôle local? De la DFS? Des décès non liés au cancer?