



A multidisciplinary approach to locoregionally advanced rectal cancer

Radiotherapy: Which type and for whom?

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Disclosures: last 5 years

- **Speaker:** Roche, Merck Serono, Sanofi Aventis, Pfizer
- **Advisory Boards:** Roche, Merck Serono, Sanofi Aventis, Astra Zeneca
- **Funding to attend meetings:** Roche, Merck Serono, Sanofi Aventis,
- **Research funding:** Roche, Merck Serono, Sanofi Aventis

Areas to cover

- Adjuvant radiotherapy evidence (NB mainly conventional surgery)

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- Allcomers or Selective approach using MRI (ie individualized)
- SCPRT (5x5Gy) versus Chemoradiation (CRT)
- Postoperative Chemoradiation

Which type?

Radiotherapy evolutionthe machines

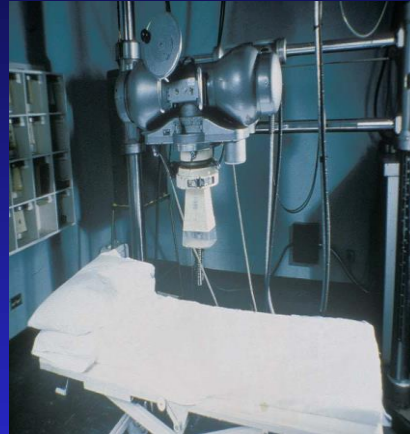


Radium moulds

Superficial 50-150kV

1920

xrays



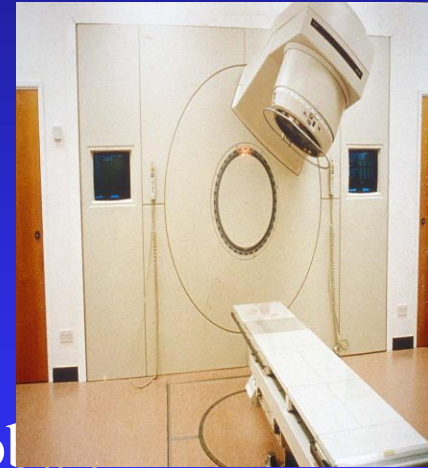
Orthovoltage 300kV

xrays



Megavoltage Cobalt 60

2MV gamma rays



Megavoltage

Linac

4-20MV x-rays

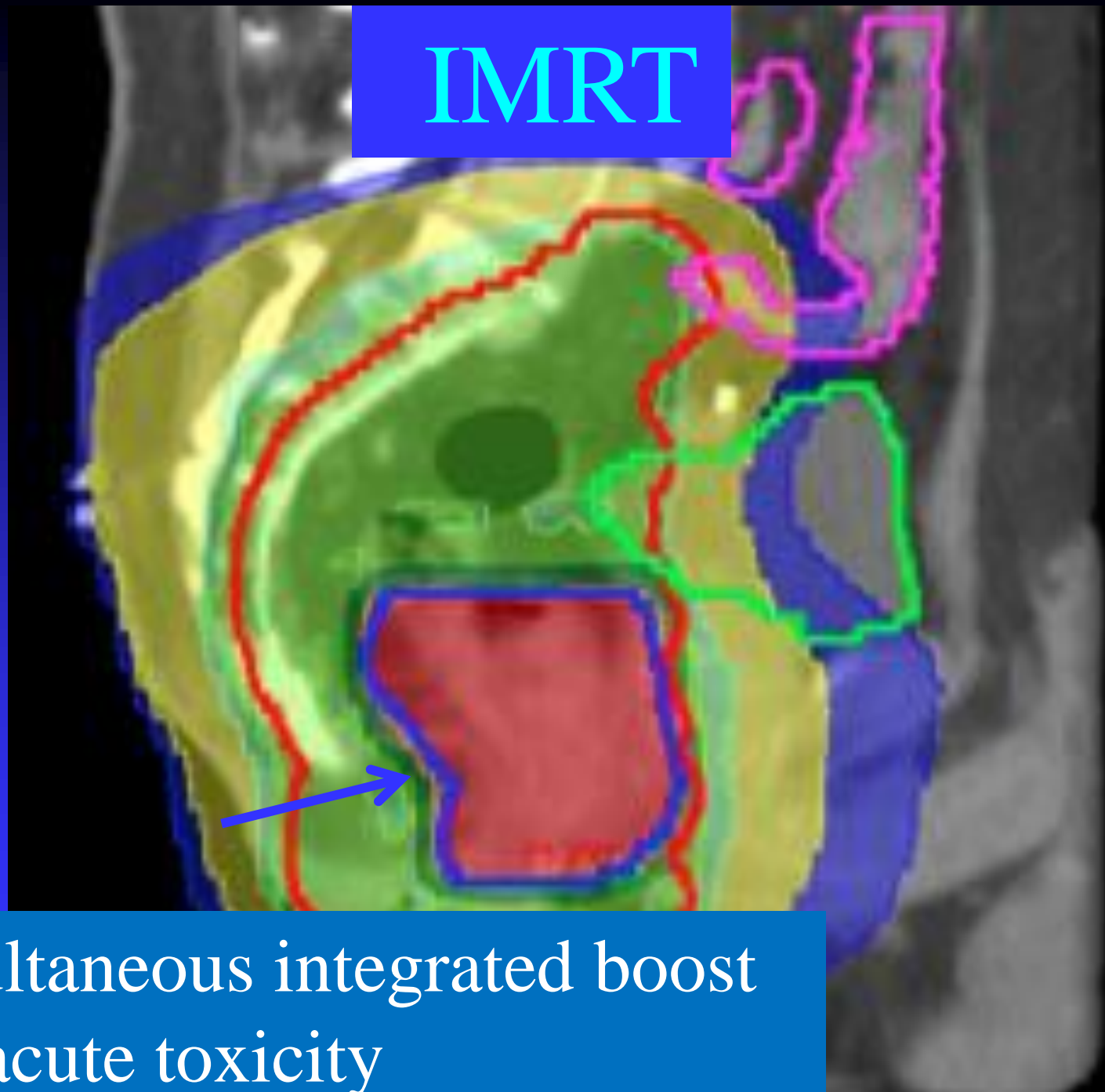
and 1990

Dosimetry has improved
So we can be more accurate

Many Options for External Beam

- Preoperative long course radiotherapy or long course CRT and surgery at 6-12 weeks
- Short course preoperative radiotherapy (5X5Gy) and immediate surgery
- Short course preoperative radiotherapy and delayed surgery at 6-12 weeks
- Postoperative CRT

IMRT



Simultaneous integrated boost
low acute toxicity

RTOG 0822

- Phase II
- 79 patients
- Deliverable
- Efficacy Results with IMRT comparable to standard RT

But NB Grade ≥ 3 late toxicity.

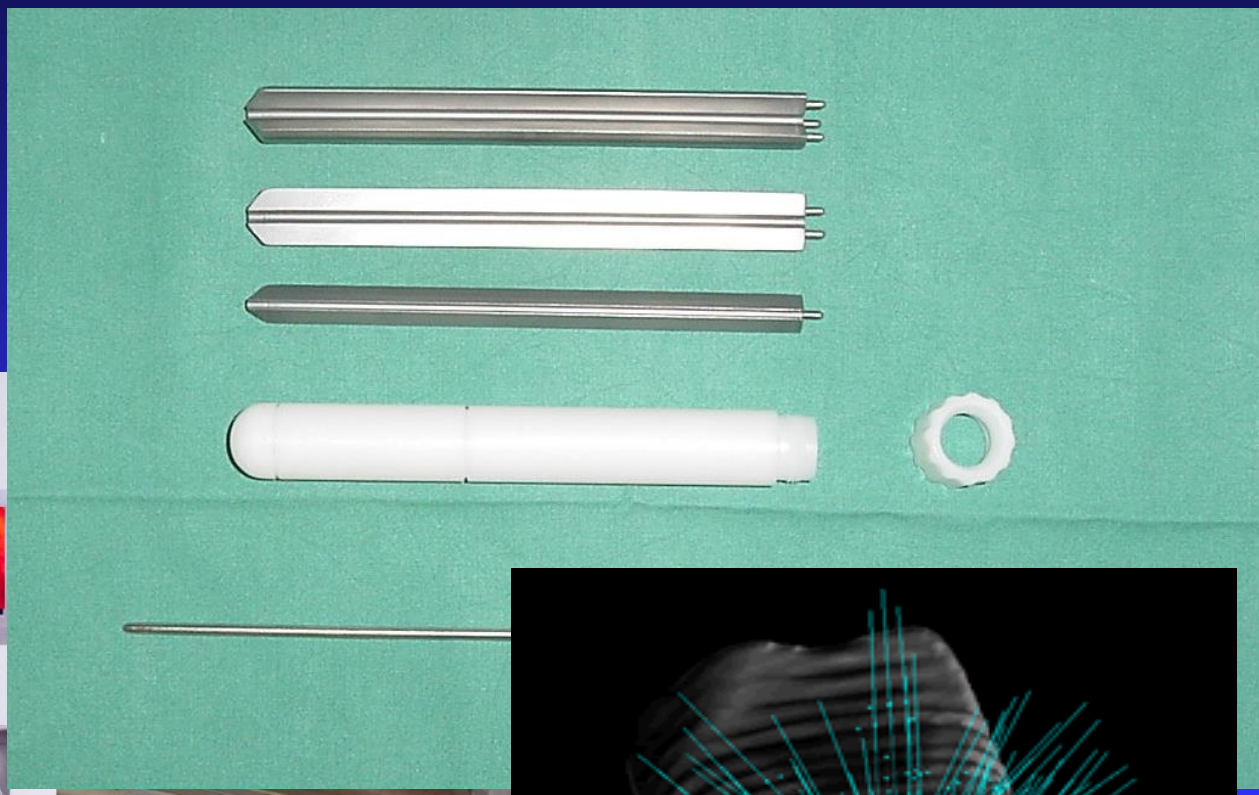
- Gastrointestinal 9%

- Urinary 4%,

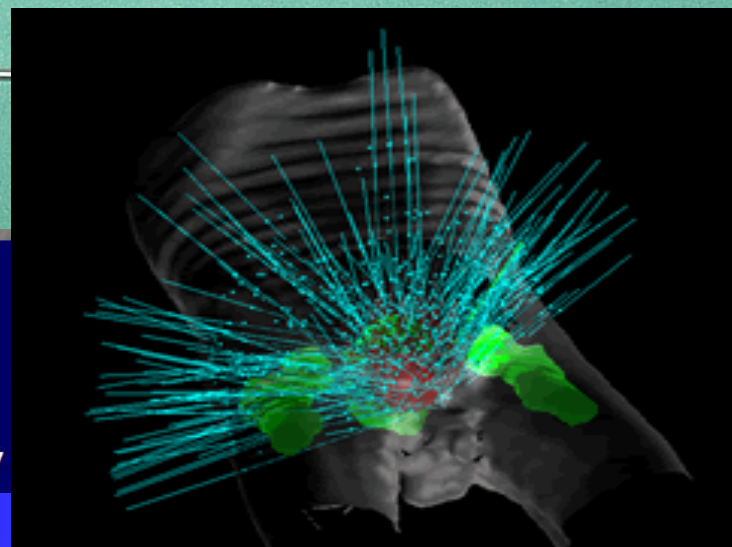
- Any 13%

- Engels B et al. Radiother Oncol 2014

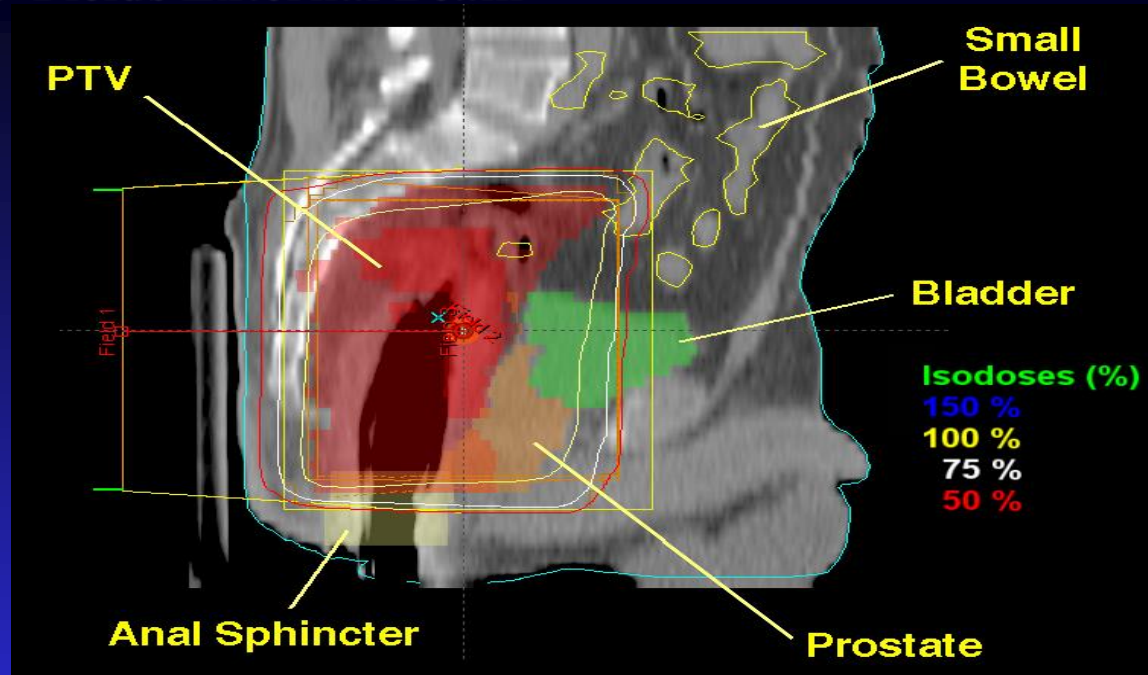
Additional Options for Contact or Brachytherapy or cyberknife as boost



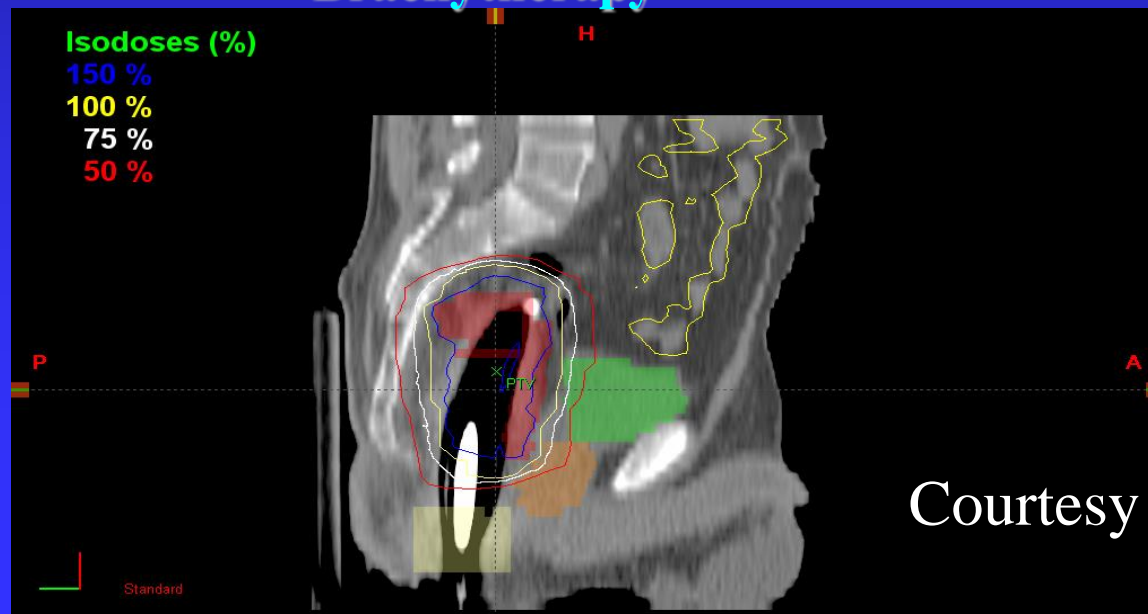
Papillon50™ :
intraluminal rectal
X-ray brachy 50 kv



3-Fields External Beam



Brachytherapy



Courtesy of Te Vuong

Cyberknife Theory

- High doses of radiation (15-45 Gy) given over a shorter period of time (1-5 days)
- can more effectively destroy cancer cells when compared to conventional radiation (50 Gy) given over a 5 week period.

What type for LARC

- External beam -3D – role for IMRT unproven

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- Evidence base /guidelines 45-50Gy preop as CRT (capecitabine or 5FU)

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- Evidence base /guidelines 45-50Gy preop as CRT (capecitabine or 5FU)
- or 5x5Gy SCPRT
- Brachytherapy alternative for resectable cancers

What type for LARC

- External beam -3D – role for IMRT unproven
- Evidence base /guidelines 45-50Gy preop as CRT (capecitabine or 5FU)
or 5x5Gy SCPRT
- Brachytherapy alternative for resectable cancers
- Boost not routine (unless unresectable or extends outside MRF or no surgery planned)

For whom?

“Chemoradiation is the standard treatment for locally advanced, clinically resectable (T3 and/or N+) rectal cancer.”

Bruce Minsky 2013

CR07

- “With a blanket approach to SCPRT and good surgery we can virtually eliminate local recurrence in rectal cancer”
- David Sebag-Montefiore 2009

There is always a tension

- Between evidence based medicine

And

- Individualized selection

Individualized Medicine in 2014

The ultimate goal of individualized medicine is to identify/define groups of patients

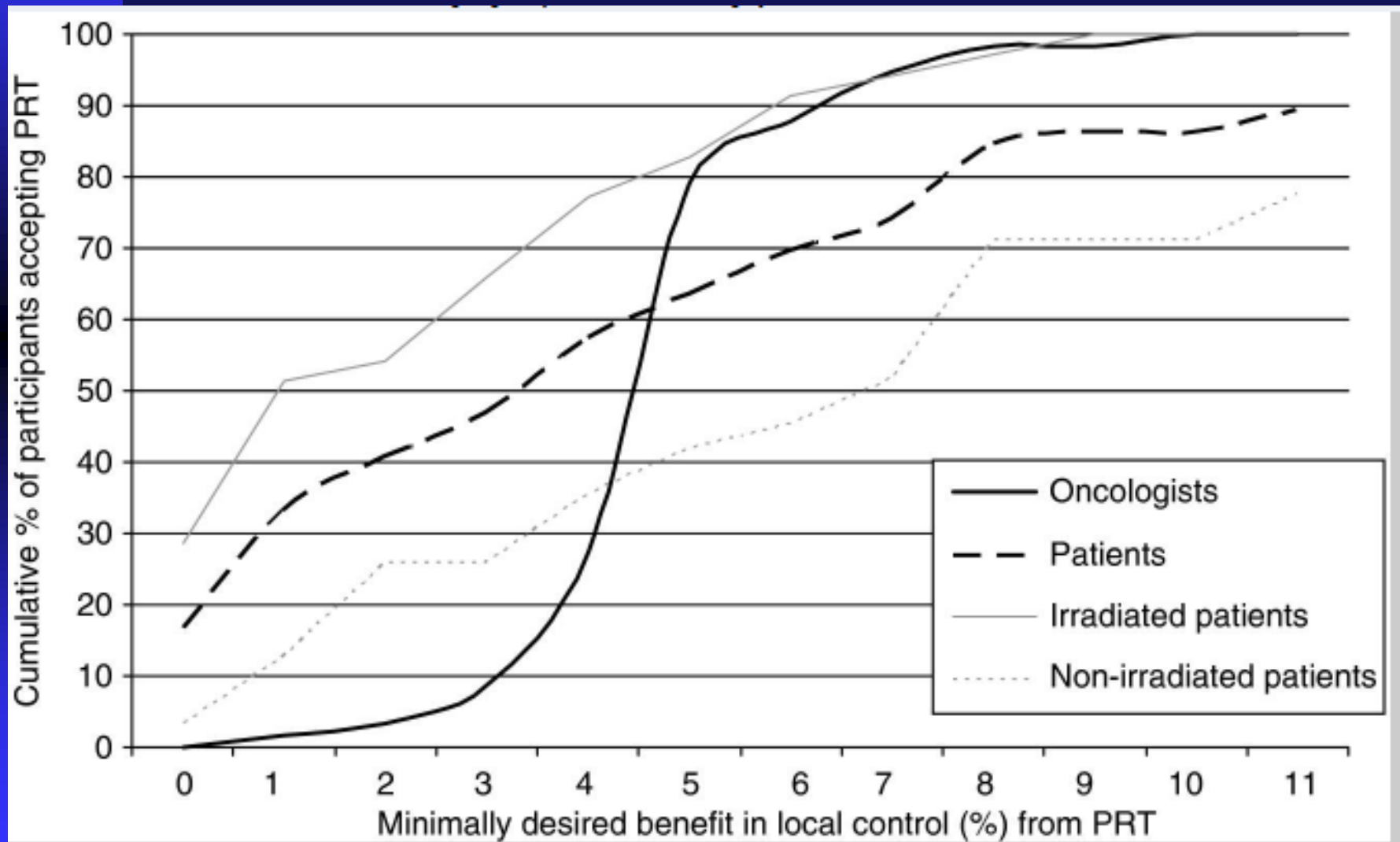
- most likely
- and least likely

to benefit from a particular intervention

Rectal Cancer and Radiotherapy: my mission statement

- I want the best chance of long-term survival
- Ideally avoiding permanent stoma
- Good function
- Minimal long term sequelae
- Good Quality of Life
- I want informed decision making for the patient

Patient and Oncologist preferences are different Pieterse et al., 2007

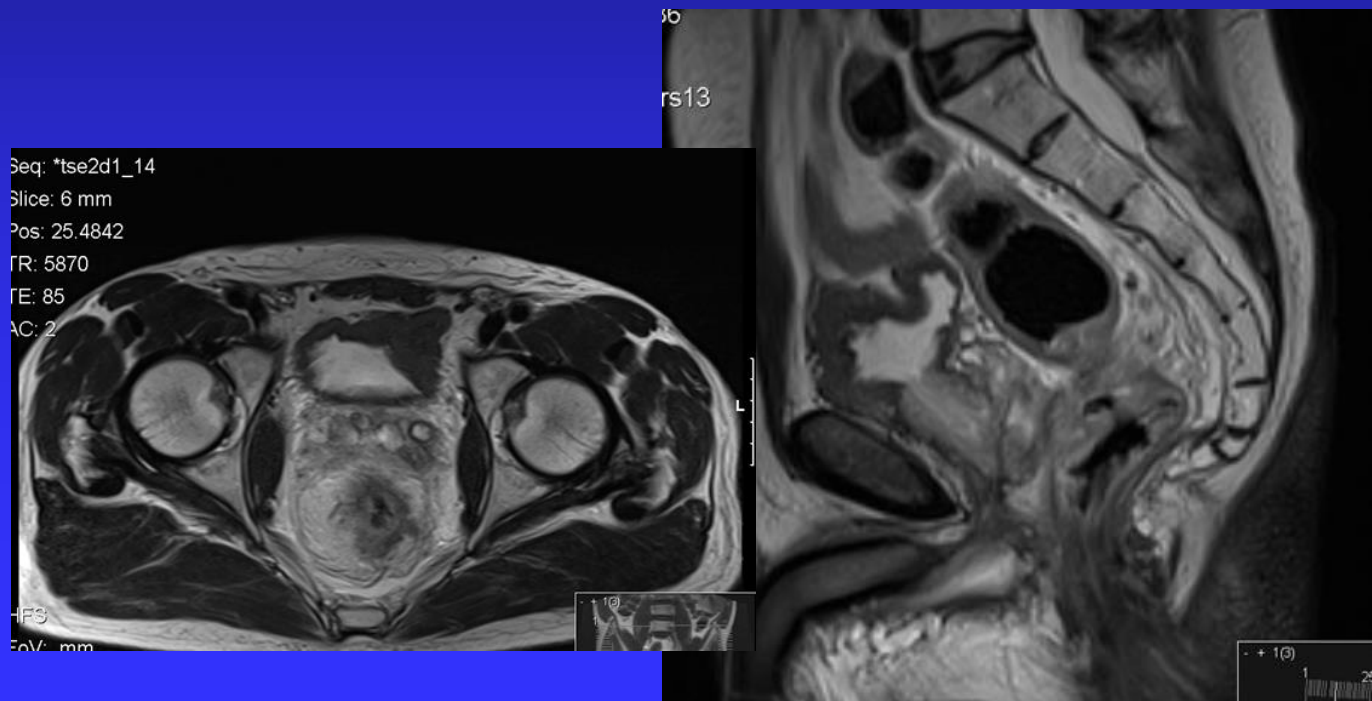


My Principles

- T4 CRT is a no brainer
- 75% of rectal cancer are T3
- All T3 are not created equal so do they all need RT?
- Preoperative SCPRT and CRT do not benefit all rectal cancer patients.
- No impact from CRT on DFS or OS
- Quality and Selection are the keys

Locally Advanced Rectal Cancer (LARC)

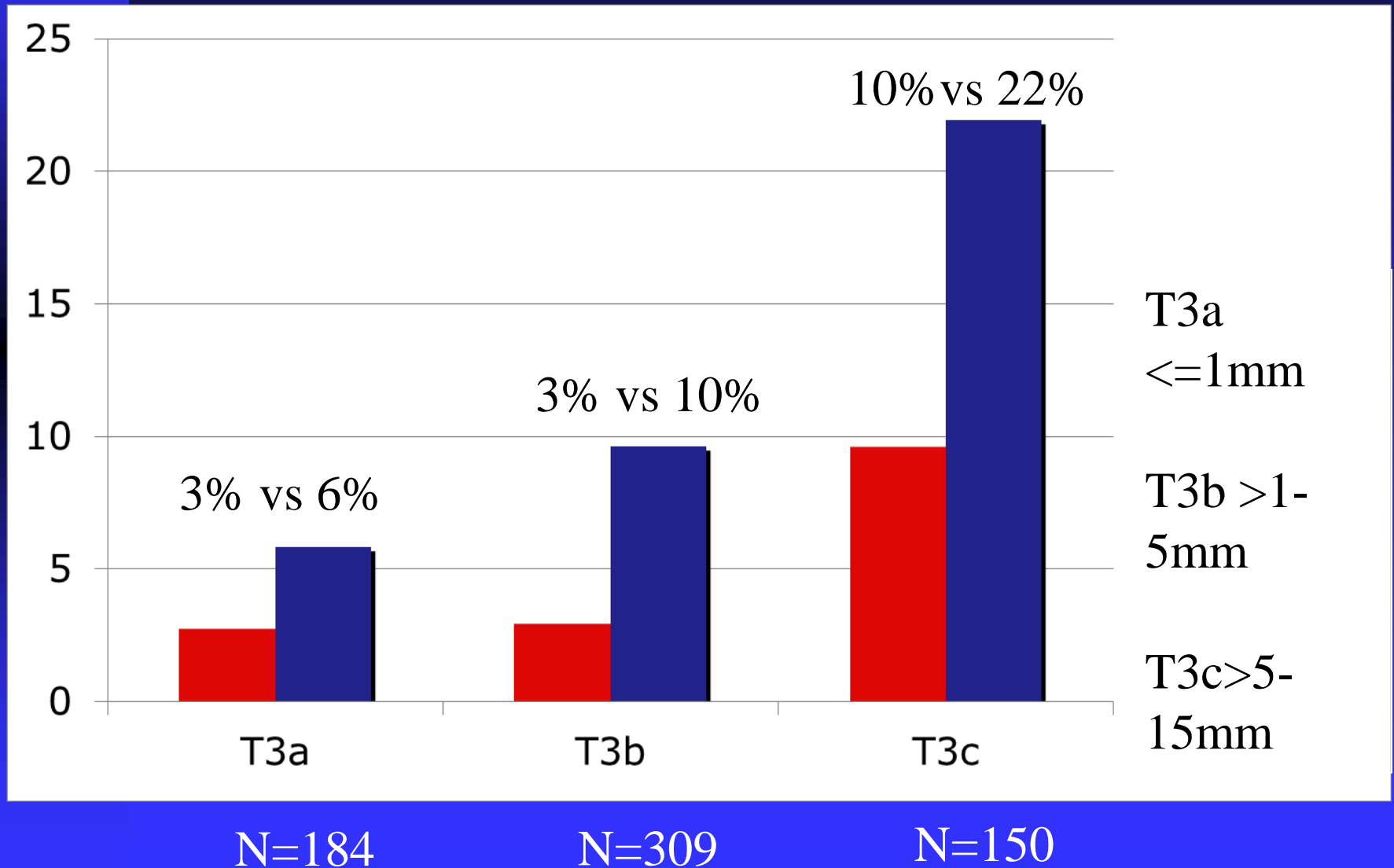
- Stage and rationale for CRT defined by MRI



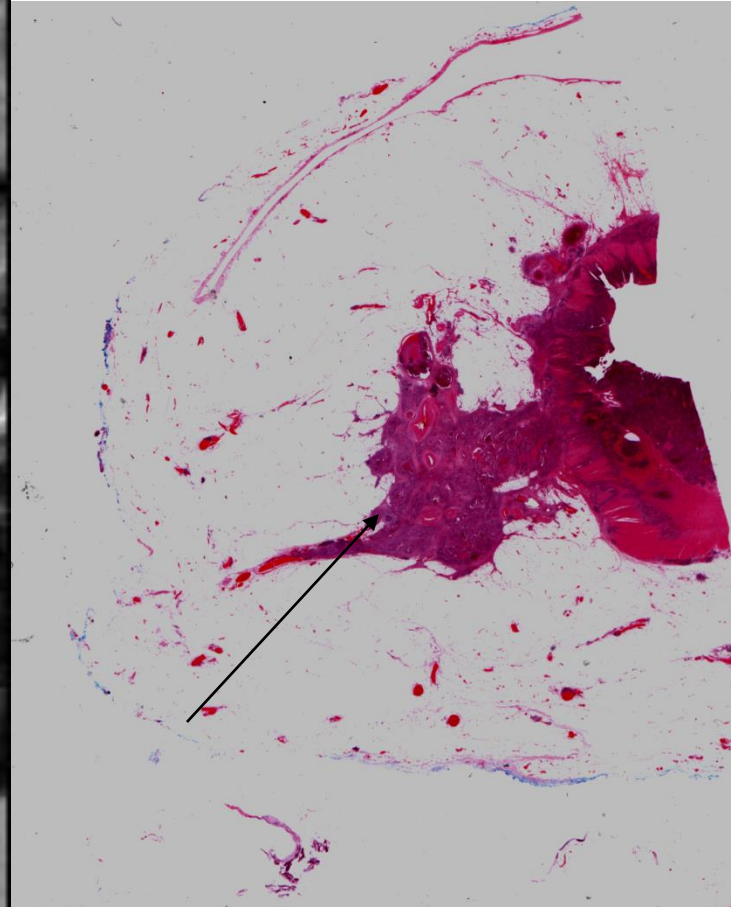
Margin at risk disease /T4 a 'no
brainer'



CR07 Local recurrence by T3 substage



Extramural venous invasion



With thanks to Gina Brown

The problems

- Not all using MRI (or good quality MRI)
- Not all using proforma for MRI
- Not all surgeons are doing high quality resections TME/APER
- Low rectal cancer T2/T4 different entity
- It is more difficult to predict levator involvement
- MRI technique /plane is more critical
- 15% LPLN for low tumours

Radiotherapy

- Is always going to be required to compensate for poor surgery

Rectal cancer is a heterogenous entity – outcomes may depend on

- Upper/middle/lower
- Anterior/ posterior
- Male/female
- Resectability/CRM
- T stage
- N stage
- EMVI/LVI/PNI
- Extranodal deposits

Relevant Endpoints in rectal cancer

- Local recurrence
- Disease-free survival
- Overall survival
- Sphincter sparing/organ sparing
- Late effects
- QOL
- Second malignancies

In decisions re SCPRT/CRT

So does the risk of local
recurrence trump everything
else?

Problems with SCPRT

- Faecal incontinence
- Urinary incontinence
- Sexual problems
- Insufficiency fracture
- Small bowel effects
- Second malignancies

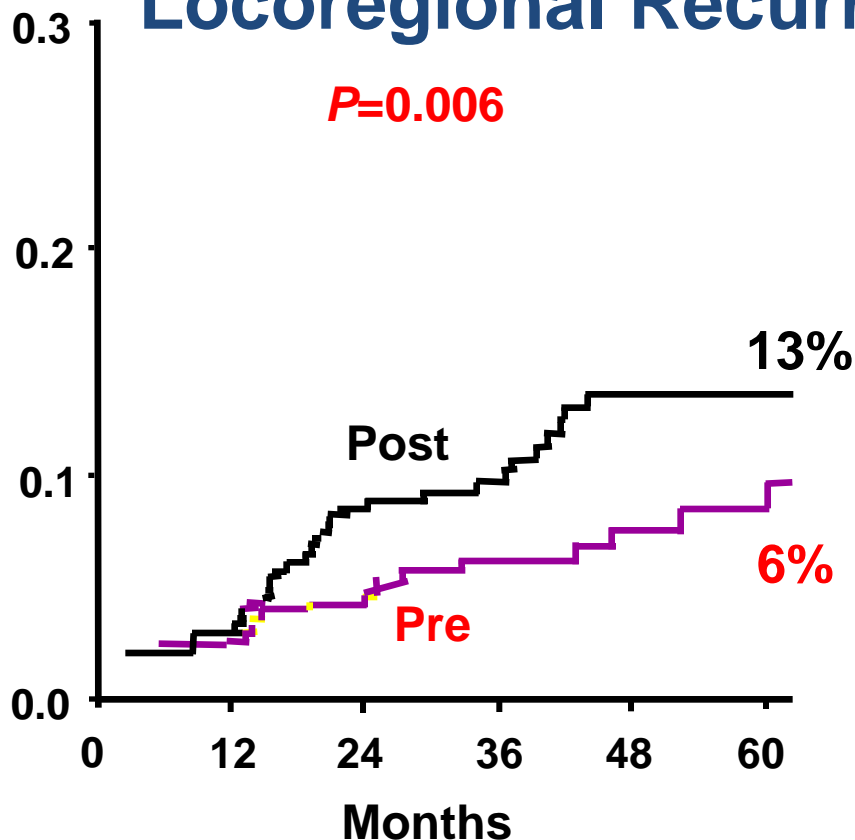
- Don't you have to explore these with the patient to find their priorities

ie informed decision making

- What is the evidence?

Pre- vs post-operative chemoradiation CAO/ARO/AIO-94

Locoregional Recurrences

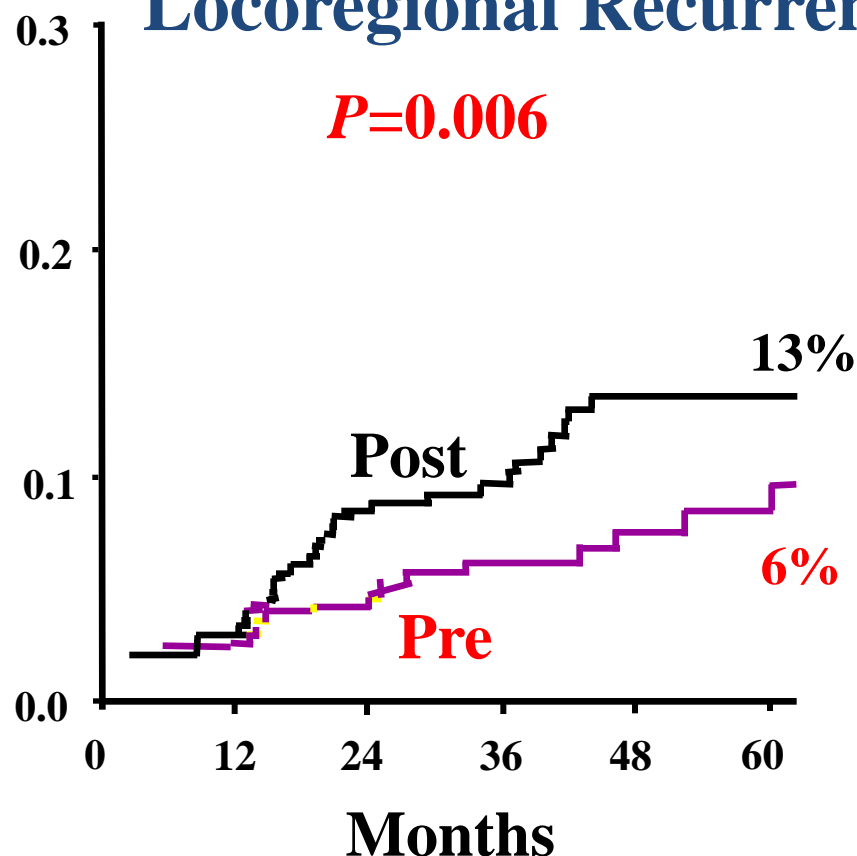


Acute G3/4 adverse events
27% vs 40% ($p=0.001$)

Long-term G3/4
adverse events
14% vs 24% ($p=0.01$)

Pre- vs post-operative chemoradiation CAO/ARO/AIO-94

Locoregional Recurrences



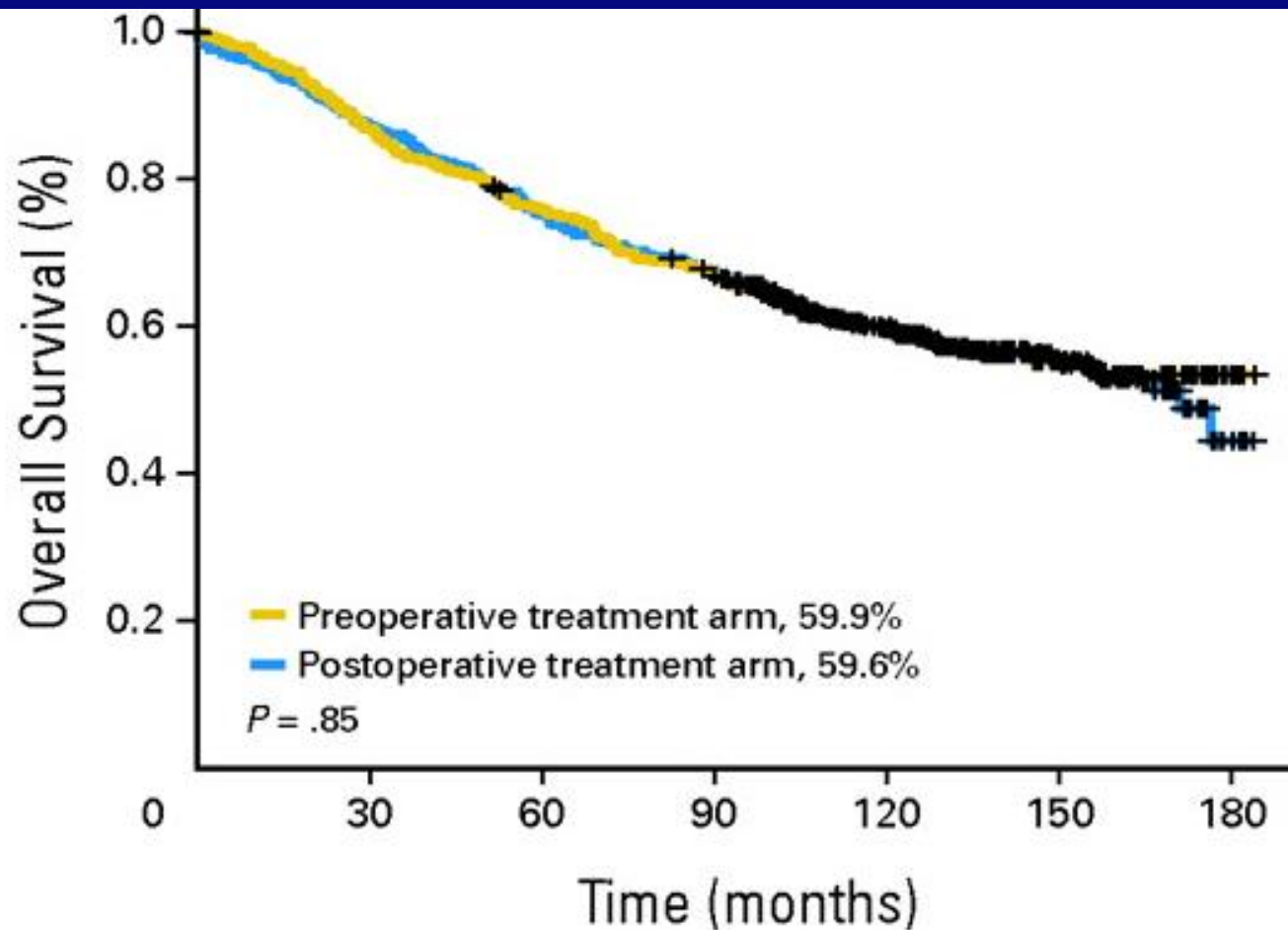
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Long-term G3/4
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**There is a standard
for chemoradiation**

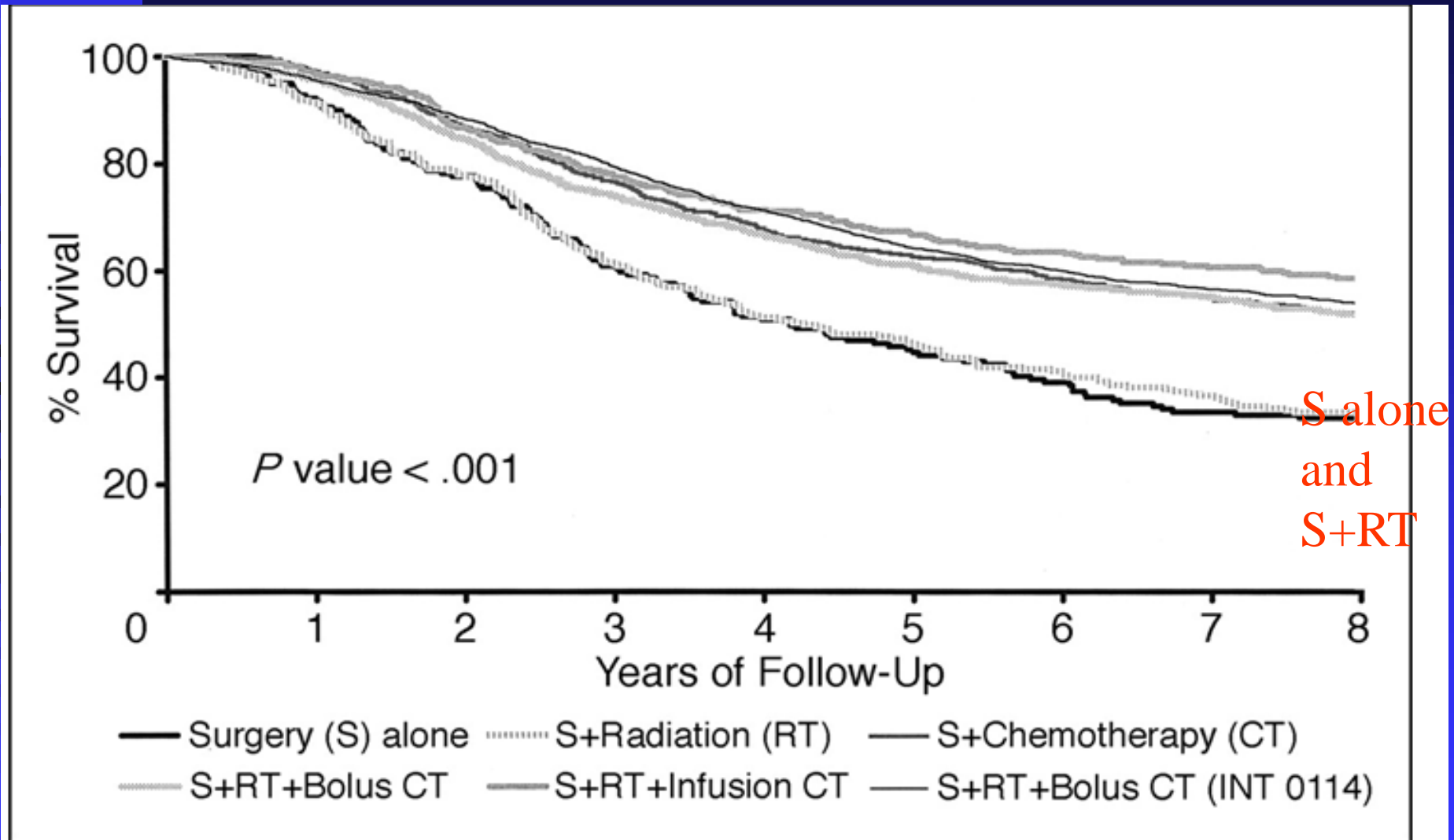
Pre- vs post-operative chemoradiation CAO/ARO/AIO-94



No. at risk							
Preop. CRT	404	351	305	268	174	67	6
Postop. CRT	395	342	295	262	172	70	6

- What if you decided to omit preoperative radiotherapy/chemoradiotherapy?

Impact on overall survival of 6 methods of treatment in rectal cancer pooled analysis



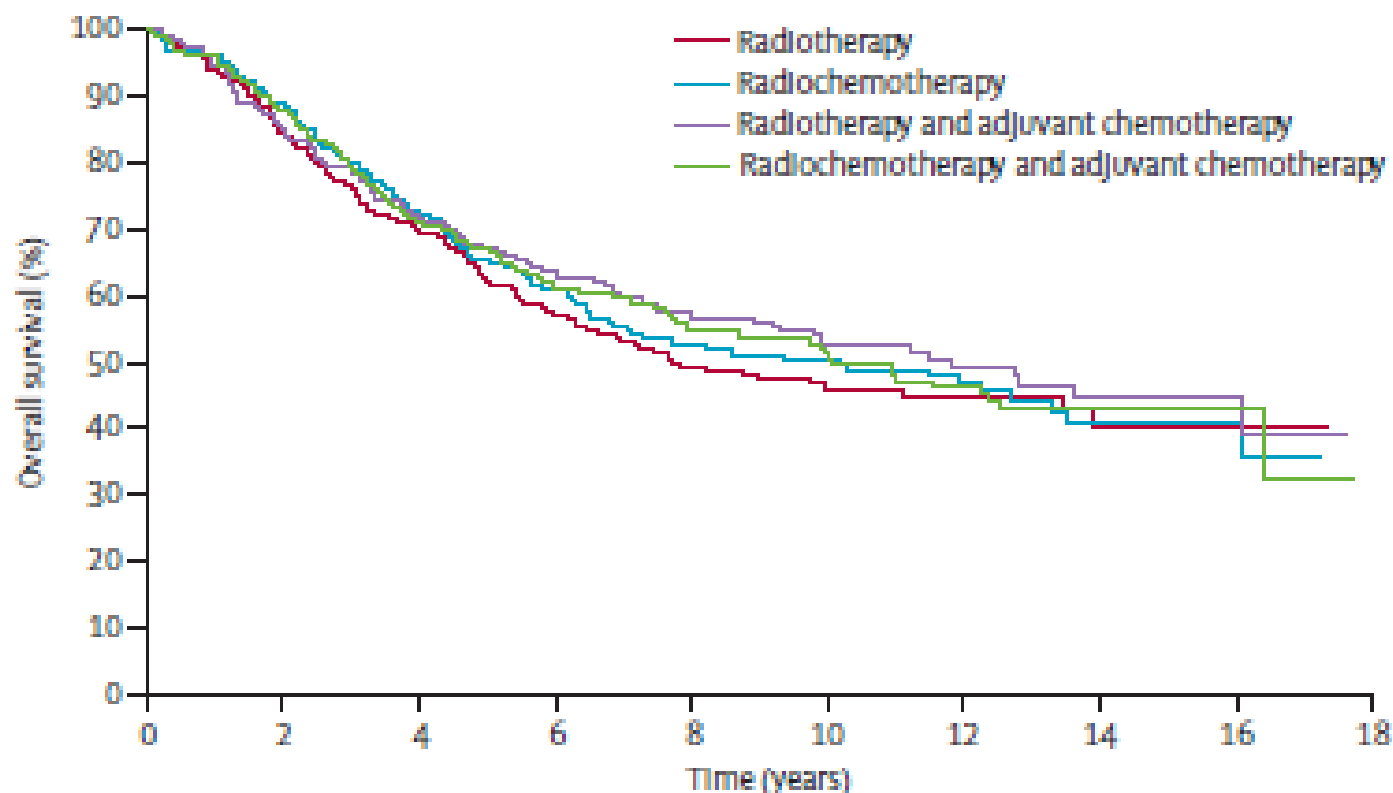
RT vs CTRT: local recurrence

	RT alone %	CTRT %
FFCD	16.5	8
EORTC 22921	17.1	8.7

Effect of neoadjuvant chemoradiation

		complete pathologic response cT3-T4		
		RT	RT + 5-FU	
Bosset JF et al	J Clin Oncol 2005 EORTC 22921	5.3%	13.7%	p<0.0001
Gerard JP et al.	J Clin Oncol 2006 FFCD 9203	3.6%	11.4%	p<0.05

EORTC 22921 – Overall Survival



Number at risk

Radiotherapy	252	208	165	129	98	62	32	15	5
Radiochemotherapy	253	223	173	135	96	66	41	19	9
Radiotherapy and adjuvant chemotherapy	253	212	171	140	102	69	42	18	8
Radiochemotherapy and adjuvant chemotherapy	253	221	174	143	108	77	44	18	4

- Preop CRT rather than RT alone

- Preop CRT rather than RT alone
- Postop CRT rather than RT alone

What about SCPRT?

- Huge evidence base that SCPRT reduces local recurrence

Polish trial Bujko et al Radiother Oncol 2004

T3/T4, resectable n=316
palpable on DRE, <75yrs .

Planned operation recorded

SCPRT (5x5Gy)

Immediate
surgery

Pre-op CRT
50.4 + 5FU/LV

6-8 week interval

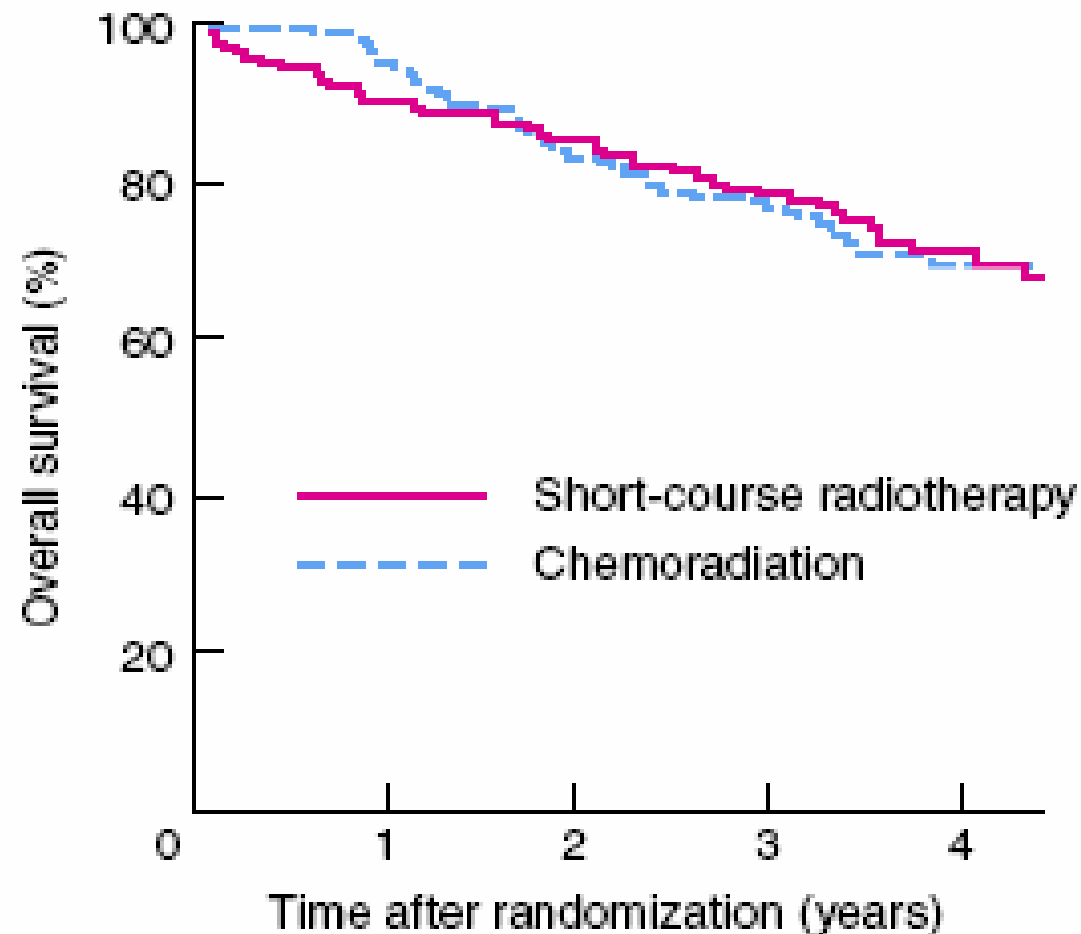
Surgery

Polish trial –outcomes

	SCPRT	CRT
Acute toxicity	3%	18%
Severe late toxicity	10%	7%
Sphincter sparing	61%	58%
Local recurrence	9%	14%
DFS	58%	56%

Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer

K. Bujko¹, M. P. Nowacki², A. Nasierowska-Guttmejer³, W. Michalski⁴, M. Bebenek⁵ and M. Kryj⁶
for the Polish Colorectal Study Group

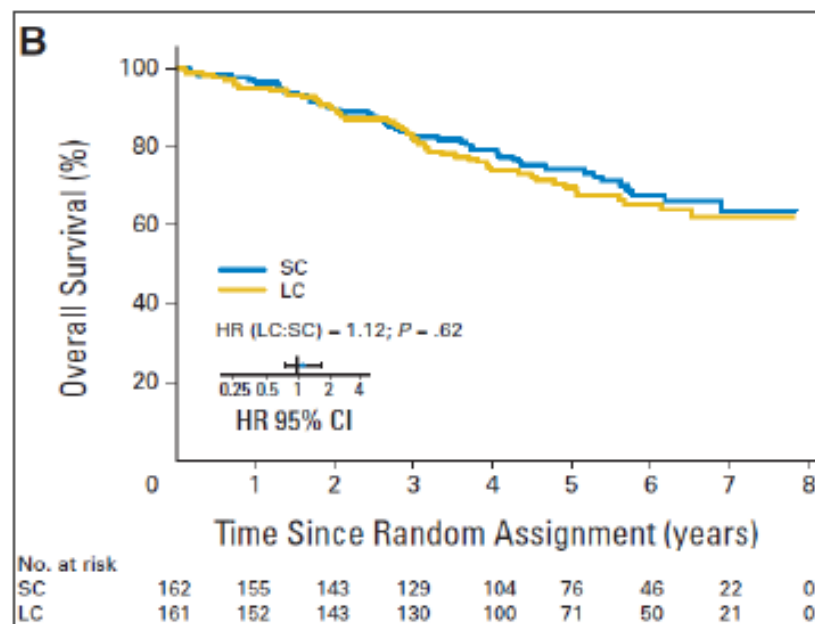
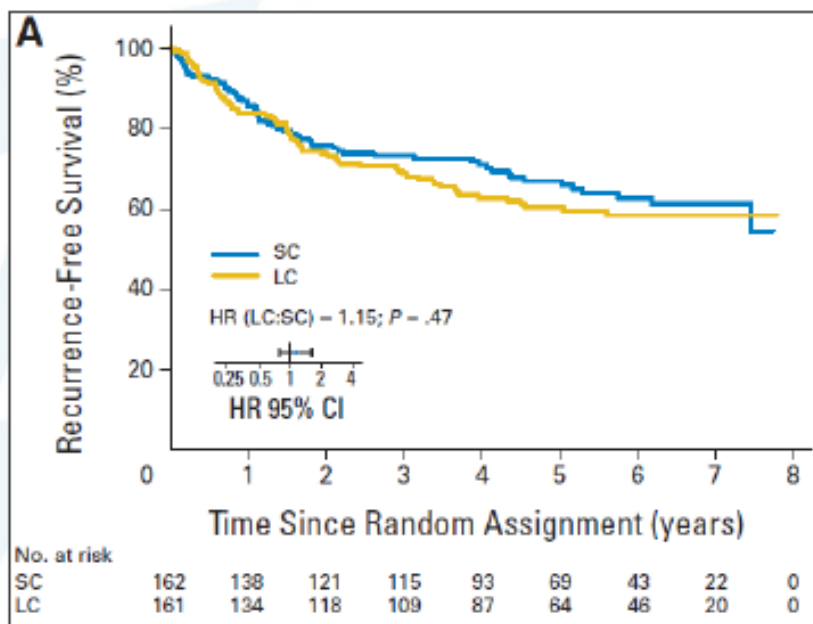


Long-term outcome the same

Randomized Trial of Short-Course Radiotherapy Versus Long-Course Chemoradiation Comparing Rates of Local Recurrence in Patients With T3 Rectal Cancer: Trans-Tasman Radiation Oncology Group Trial 01.04

Samuel Y. Ngan, Bryan Burmeister, Richard J. Fisher, Michael Solomon, David Goldstein, David Joseph, Stephen P. Ackland, David Schache, Bev McClure, Sue-Anne McLachlan, Joseph McKendrick, Trevor Leong, Cris Hartoatunu, John Zalberg, and John Mackay

No benefit in LR comparing 5x5 Gy to CRT

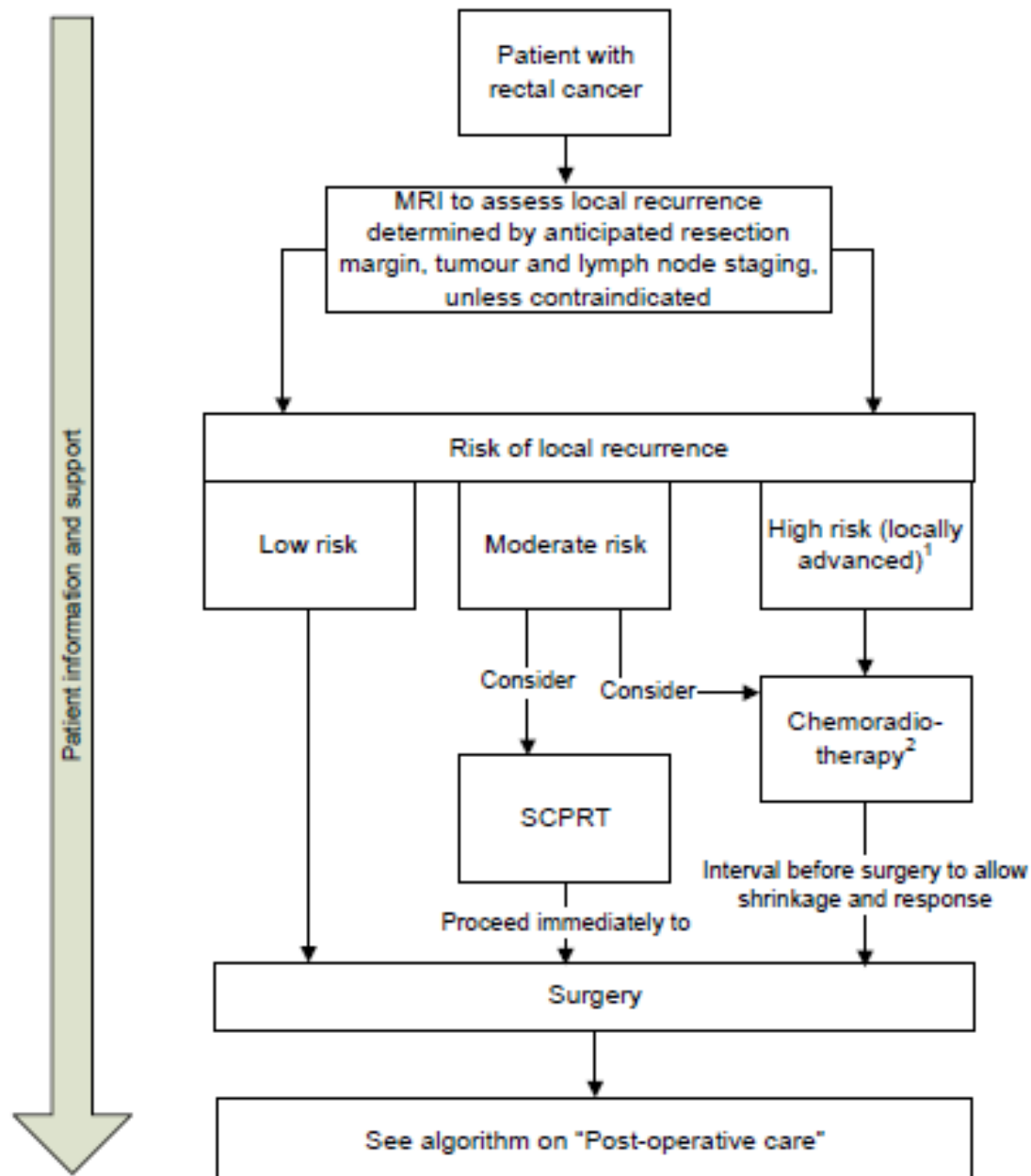


In locally advanced rectal cancer if
CRM/MRF not threatened

SCPRT = CRT??

NICE
2011

Management of local disease – patients with rectal cancer



NICE GUIDANCE from MRI

High-risk locally advanced

- a) a threatened resection margin,
- b) more than 5mm - 15mm (cT3c and cT3d) extension,
- c) more than 4 involved nodes (cN2), or
- d) the presence of macroscopic extramural vascular invasion;

CRT recommended

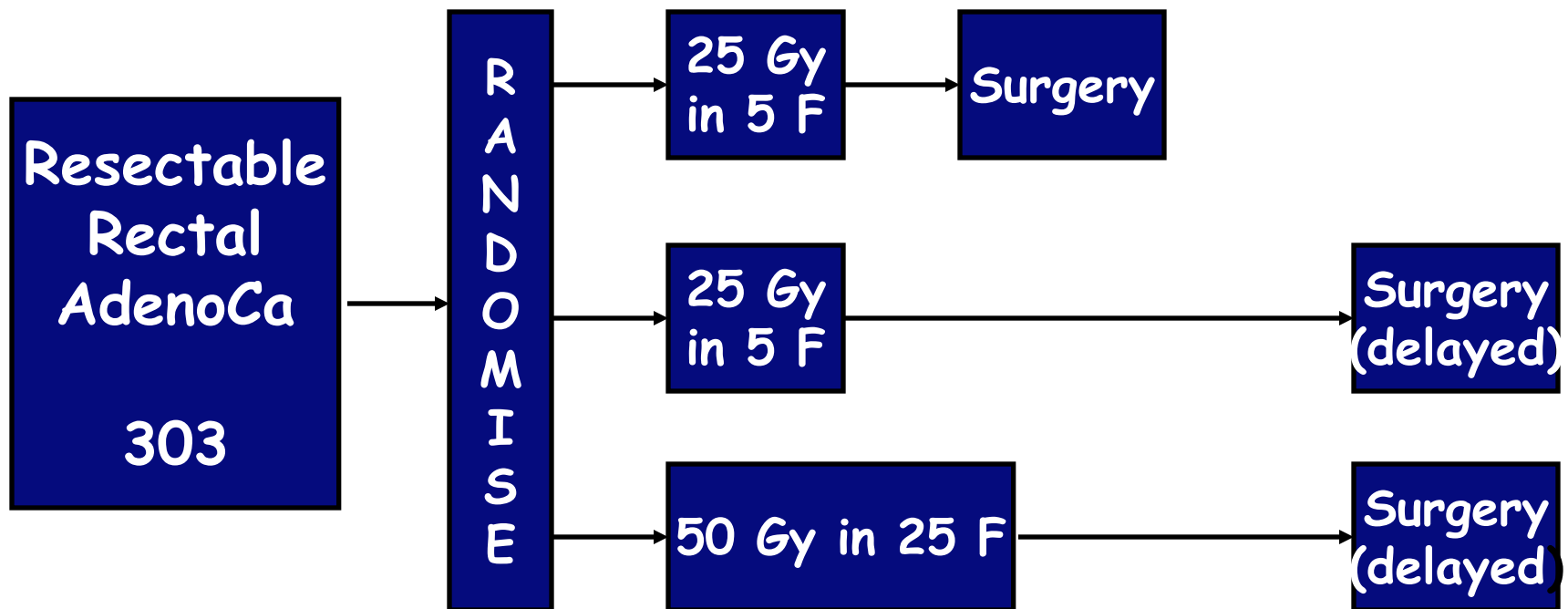
NICE GUIDANCE from MRI

Moderate-risk locally advanced

- a) up to 5mm (cT3a and cT3b) extension into the muscularis propria, or
- b) up to 4 involved nodes (cN1).

SCPRT or CRT

STOCKHOLM III

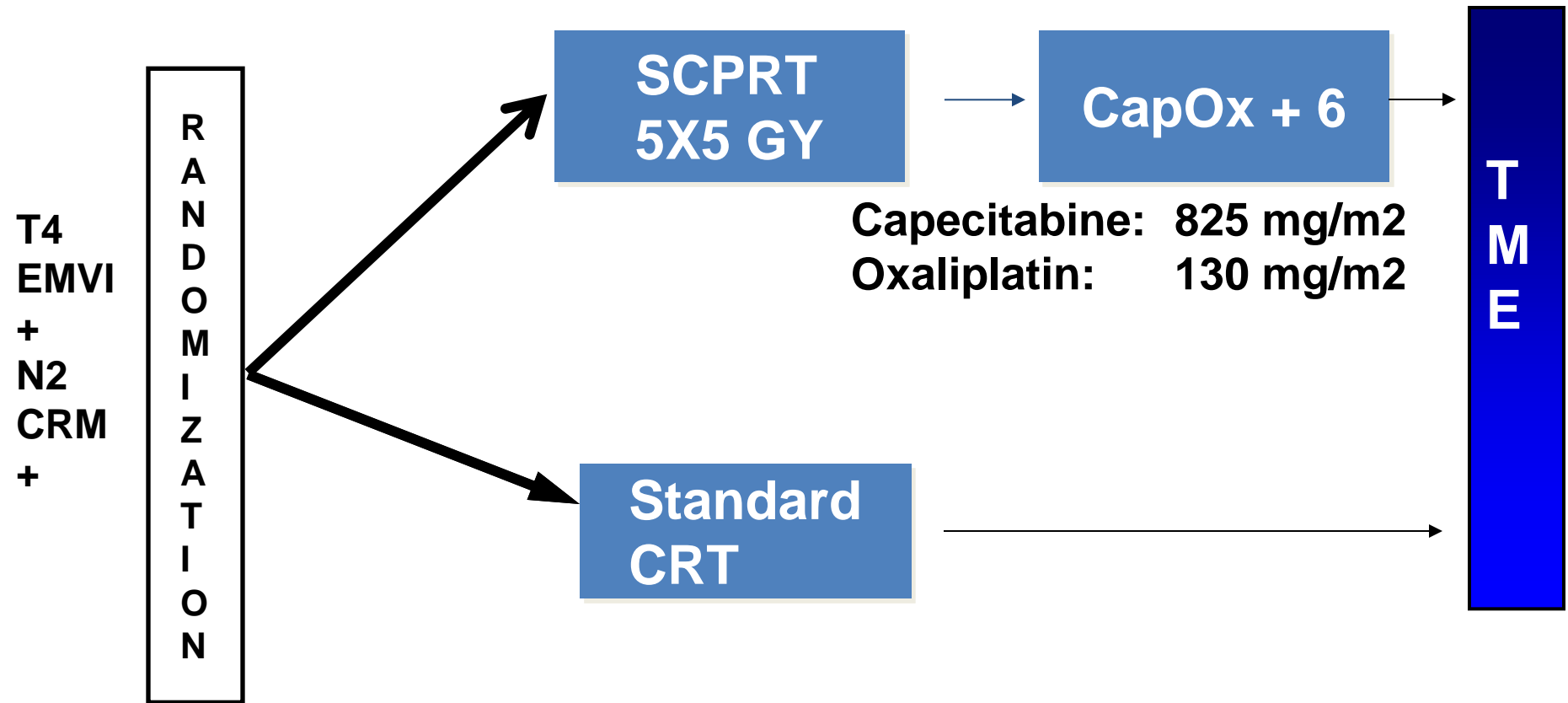


Primary endpoint: sphincter preservation rate

Pettersson et al BJS 2010

RAPIDO Trial

N = 885 patients



Primary endpoint 3 year DFS

How do we decide?

Alan Sokal 1996

- "Transgressing the Boundaries: Towards a Transformative Hermeneutics of Quantum Gravity",
- proposed that quantum gravity is a social and linguistic construct.

The value of radiotherapy

- Varies according to the historical context

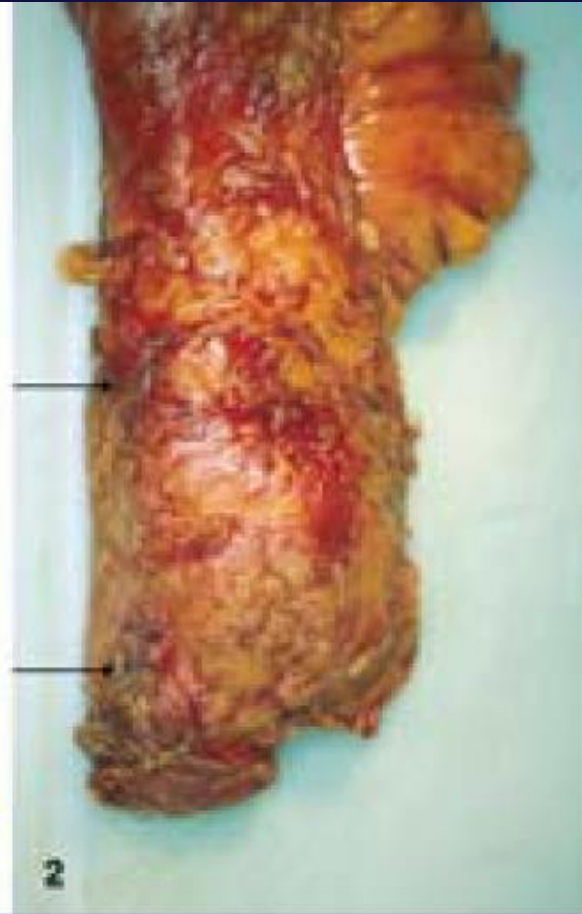
The value of radiotherapy

- Varies according to the historical context
- and the surgeons skill

Total Mesorectal Excision



Optimal TME



**Moderate,
irregularity
of mesorectal
surface**



Poor TME

CRM associations with plane of surgery

	Plane of surgery		
	Mesorectal	Intra-mesorectal	Muscularis propria
CRM +ve rate	9%	12%	19%
Stage I	29%	24%	27%
Stage II	27%	32%	30%
Stage III	44%	43%	41%

With thanks to Phil Quirke

TME Northern Europe: Good quality mesorectal plane: no RT

Study	Eligible	Good Quality Mesorectal	Local Recurrence	Actuarial
Swedish Rectal Cancer Trial 1997 (574)	T any N any	<10%	150/557 27%	>30%
CR07 overall (592) Quirke 2009	T any N any	51%	59/592 10%	11%
Dutch TME (180) Nagtegaal 2005	T any N any	56%	Not stated	8.7% at 2 years
CR07 (301) Quirke 2009	T any N any	100% (MRI not routinely used)	27/301 9%	7% at 3 years
Mercury* (122) Taylor 2011	T3a/b N any crm-	70%	4/122 3%	3.3% at 5 years
* NB MRI directed				

NNT in rectal cancer

- Local recurrence NNT for moderate risk 20-25
- NN Harm 10-12 for severe G3/G4 late toxicity
- NN Harm 20 for second malignancy

Randomised trials SCPRT

Trial	MRI mandated	EUS mandated	TME mandated	Good Quality TME	Median no of nodes resected
Swedish Rectal	No	No	No	?No	Not stated
Dutch TME	No	No	Yes	50%	7
Polish	No	No	Yes?	?	9
CR07	No	No	No	50%	11
TROG-0104	If US not possible	Yes	No	?	Not stated

Randomised trials Preop CRT

Trial	MRI mandated	EUS mandated	TME	Good Quality TME	Median no of nodes resected
German (Sauer 2004)	No	Yes	?	?	Collected but not stated
EORTC 22921	No	No	No	No	7 after CRT
FFCD 9203	No	No	No	No	Not stated
NSABP R03	No	?	No	No	Not stated
Polish	No	No	?	?No	8
TROG-0104	some	Yes	?	?	Not stated

- How can I use these trials data as my evidence base and relate the data to my practice in 2014

- When

No MRI/poor TME/ few nodes

Significant number elderly > 70

For individualized therapy we need

- Accurate Clinical staging (TNM) - precise risks for local recurrence and metastases.

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- The associated clinical characteristics which also define risks and different subpopulations (frailty/morbidity site etc...

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- The molecular pathways underpinning the disease

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- The molecular pathways underpinning the disease
- Patient preferences
- And....

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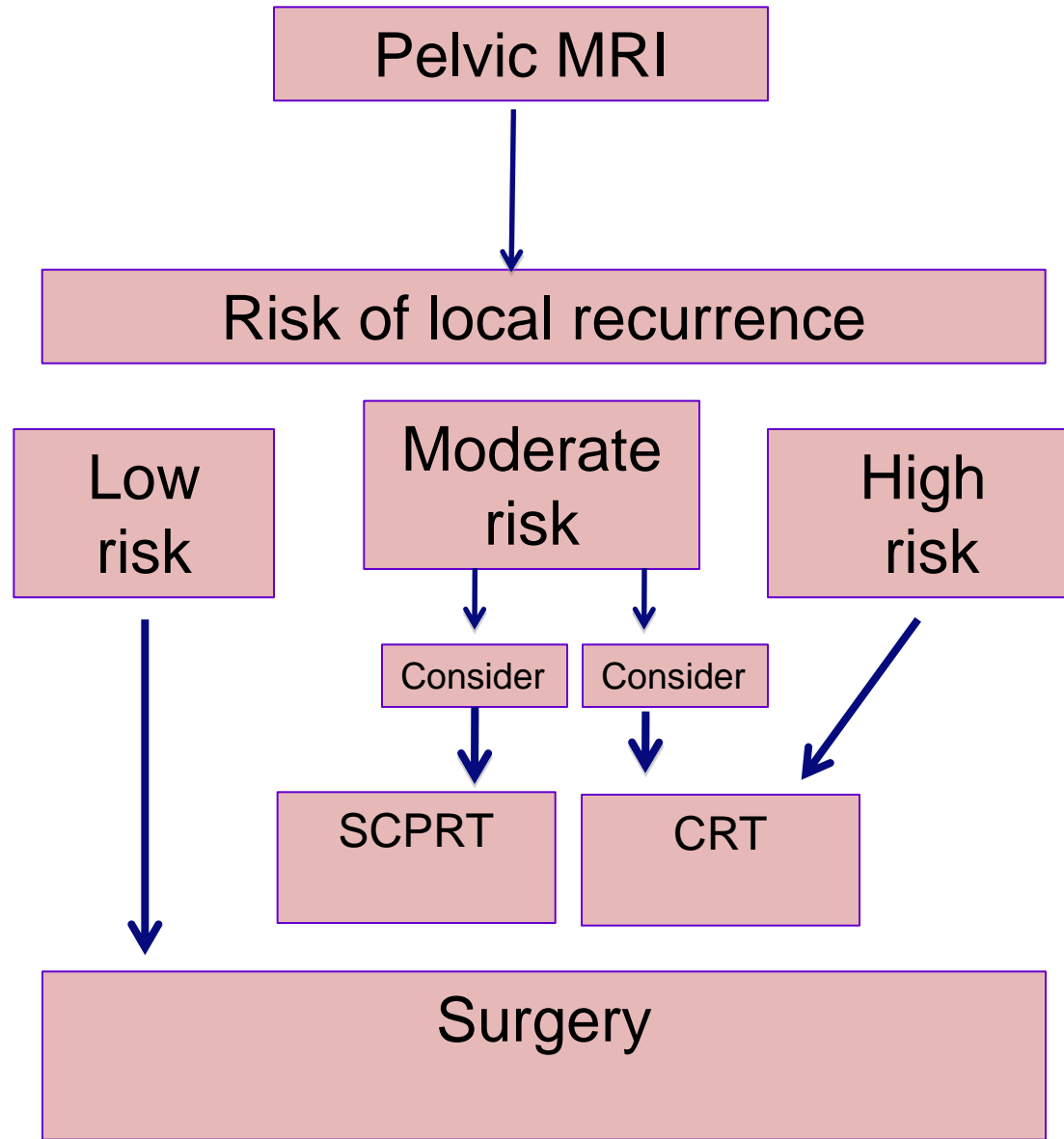
- The input from all members of the MDT
- And...

For individualized therapy we need

- The input from all members of the MDT
- And...
- The wishes and input of an informed patient for decision making

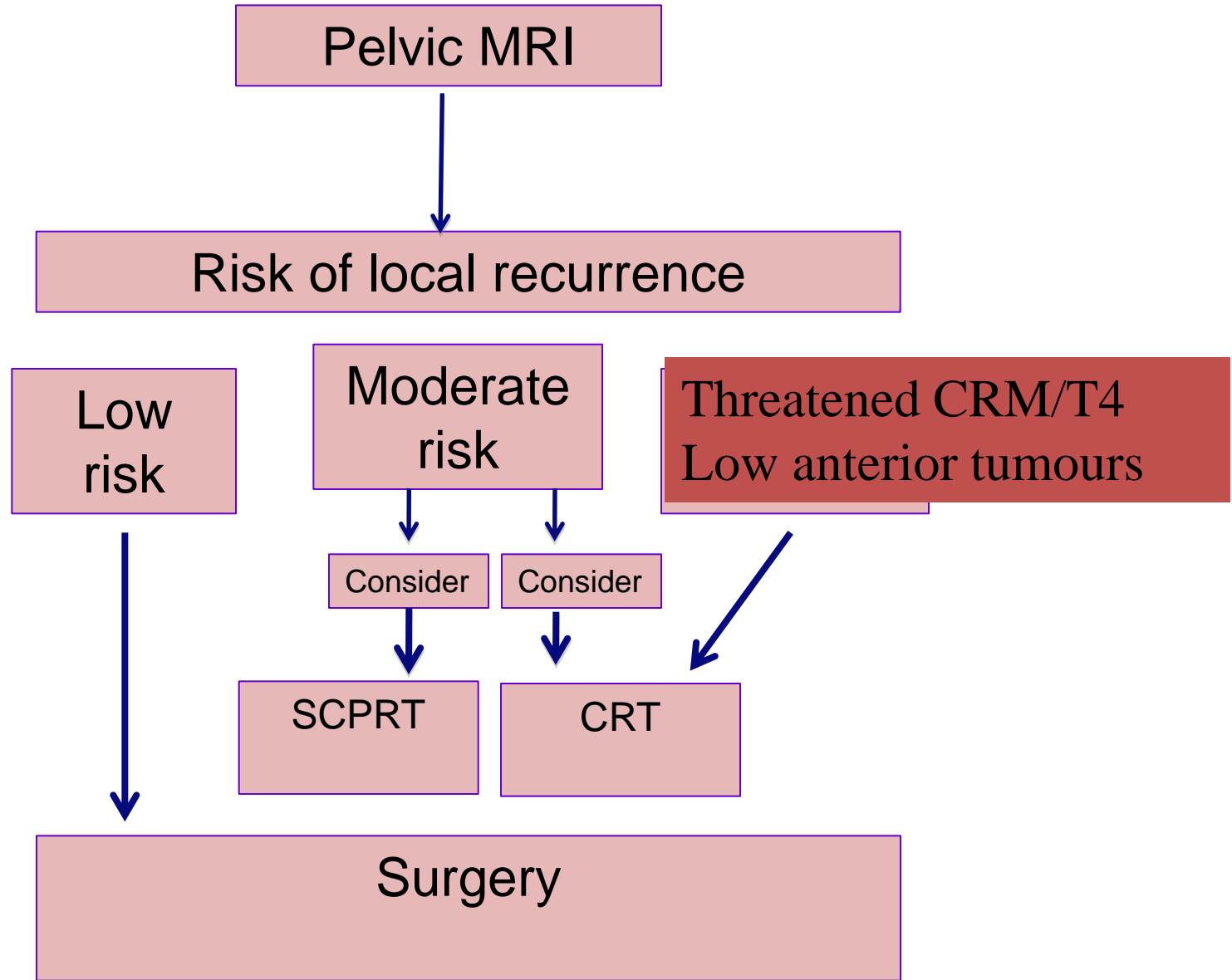
Pre-operative radiotherapy algorithm

NICE guidelines 2011



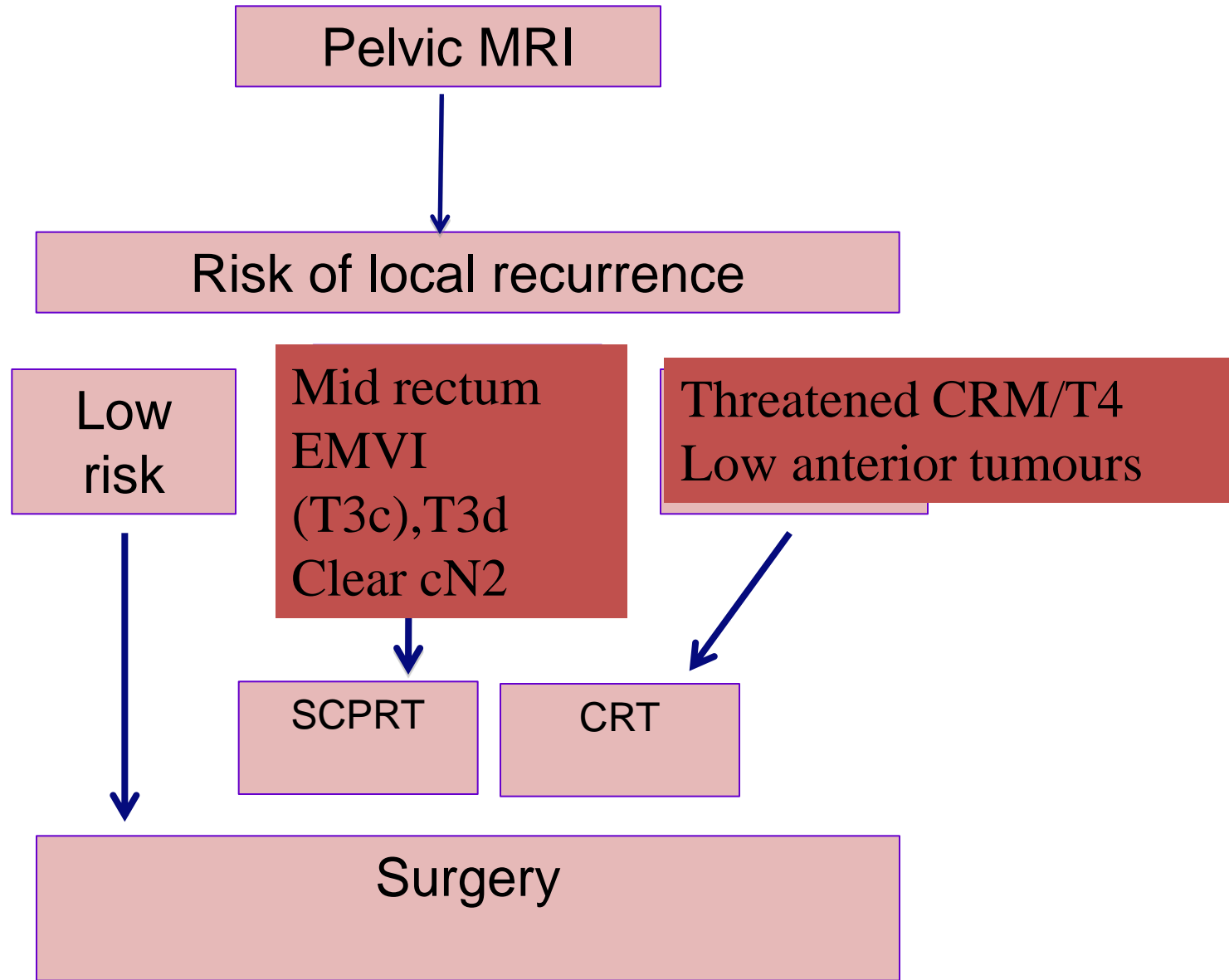
Pre-operative radiotherapy algorithm

My guidelines 2014



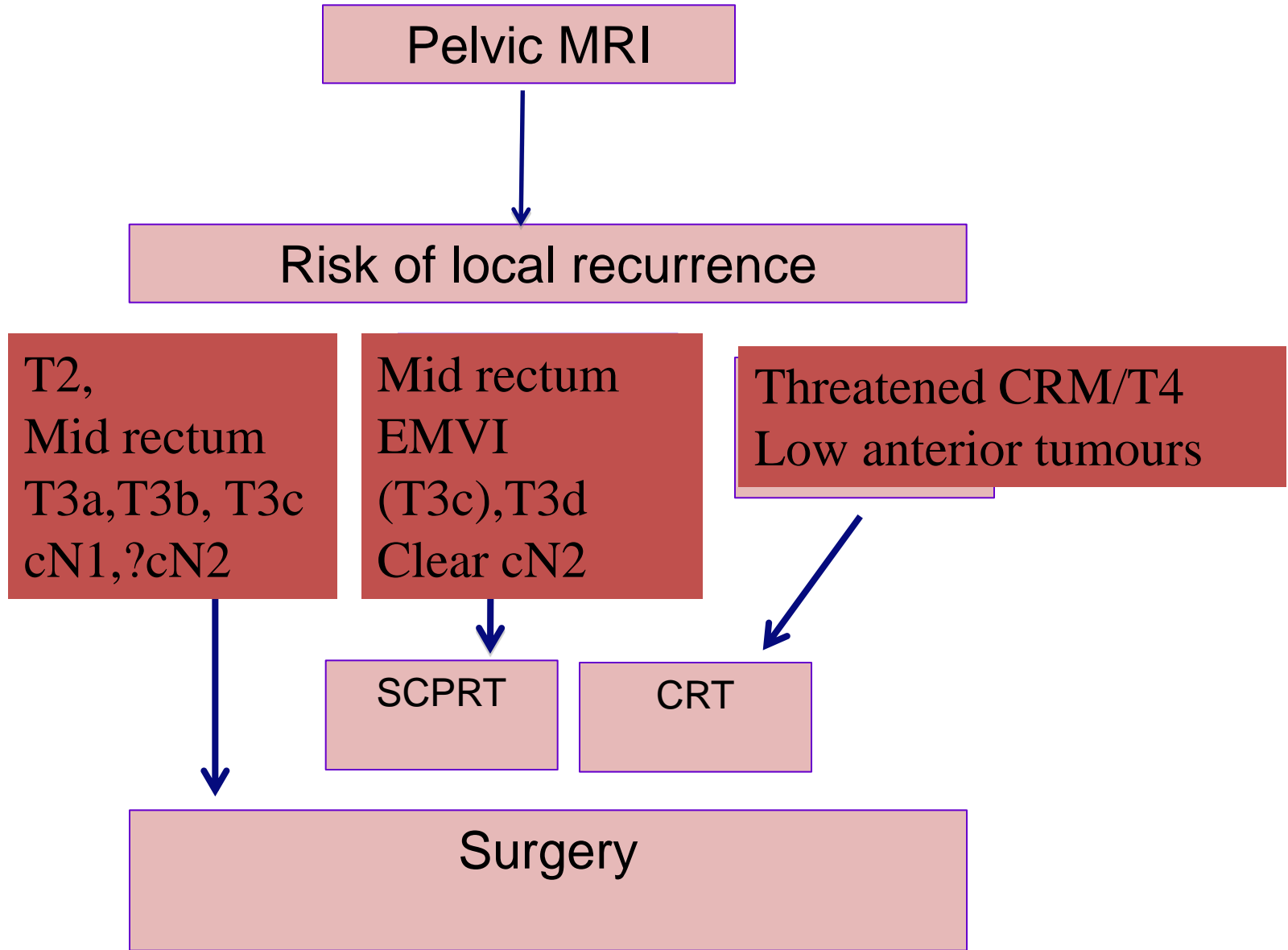
Pre-operative radiotherapy algorithm

My guidelines 2014



Pre-operative radiotherapy algorithm

My guidelines 2014



Postoperative CRT

- CRM +

If poor mesorectal quality

- Gross EMVI
- pN2
- Extracapsular spread
- Extranodal deposits

Conclusions: Radiation has a role in Unresectable cancer

For improving resectability

Conclusions: Radiation has a role in Resectable LARC

- Reducing recurrence in high risk but not low risk
- Both SCPRT and pre-op CRT are acceptable, but not necessary for all patients.
- Patients need to be informed and part of the decision making
- Each unit needs to audit results and feedback loop

The End

