# Is there still room for improvement in surgery for locally advanced rectal cancer?

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### Disclosure slide

NO disclosures

# Is there still room for improvement in surgery for locally advanced rectal cancer?



# Improvement in surgery for locally advanced rectal cancer

#### **Options:**

- Extended resection
- Improving functional outcome
- Robotic surgery
- NIR fluorescence imaging
- Auditing
- Organ preservation

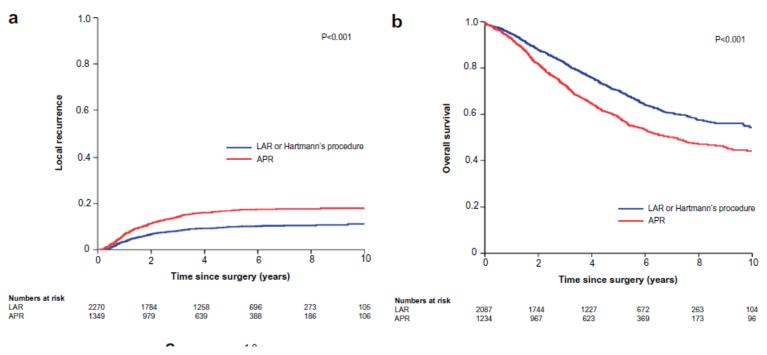
# 5 major goals in treatment of a patient with rectal cancer

- 1. Local control
- 2. Long-term survival
- 3. Preservation of anal sphincter
- 4. Preservation of pelvic nerves, for GI, bladder and sexual function
- 5. Maintenance or improvement in QoL

### High risk tumors

- Achieving a R0 resection
  - Required extent of the resection more challenging
  - 'En bloc' resection of the involved organs and structures
  - Very heterogeneous presentation
    - More different surgical solutions to achieve a radical en bloc resection
    - More differentiate or personalized approach required
    - Beyond TME Collaborative: high risk patients should be referred to a specialized center

#### **Unsatisfactory results APR**



The Swedish Rectal Cancer Trial (SRCT), TME trial, CAO/ARO/AIO-94 trial, EORTC 22921 trial and Polish Rectal Cancer Trial (PRCT) an APR procedure was associated with:

- increased risk of CRM involvement (OR 2.52, p < 0.001)
- increased LR rate (HR 1.53, p = 0.001)
- decreased CSS rate (HR 1.31, p = 0.002)

# Risk factors for adverse outcome after abdominoperineal resection

- Age
- T stage
- N stage
- CRM
- Distance of the tumor to the anal verge
- Tumor location

### **Unsatisfactory results APR**

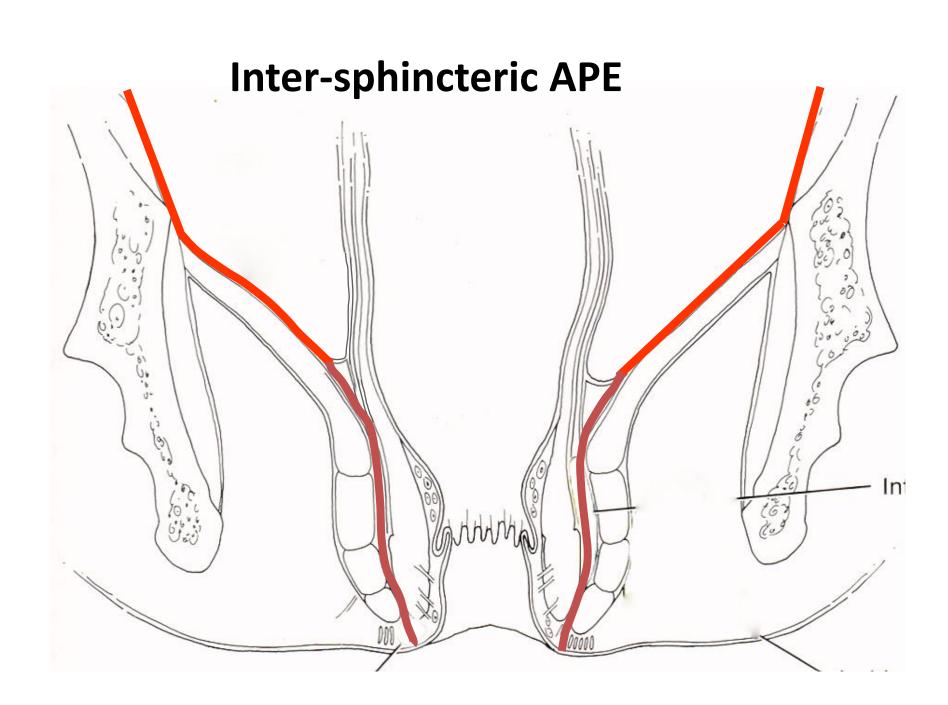
	CRM+	
LAR	10.7%	
		P=0.002
APR	30.4%	

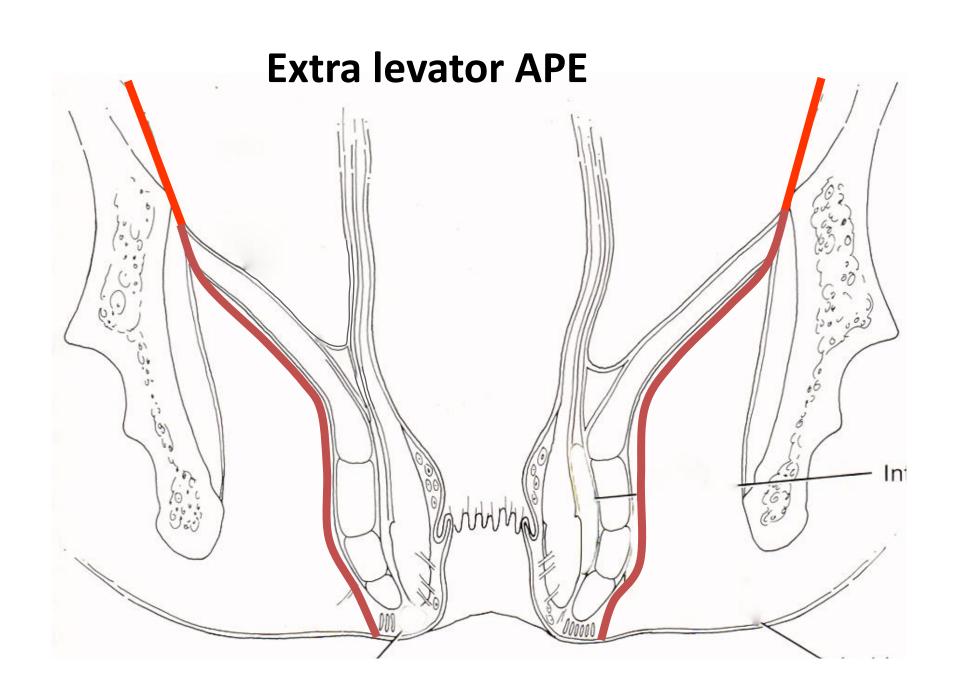


# Improvement in surgery for locally advanced rectal cancer

#### **Options:**

- Extended resection
- Improving functional outcome
- NIR fluorescence imaging
- Auditing
- Organ preservation
- Centralization to specialized centers

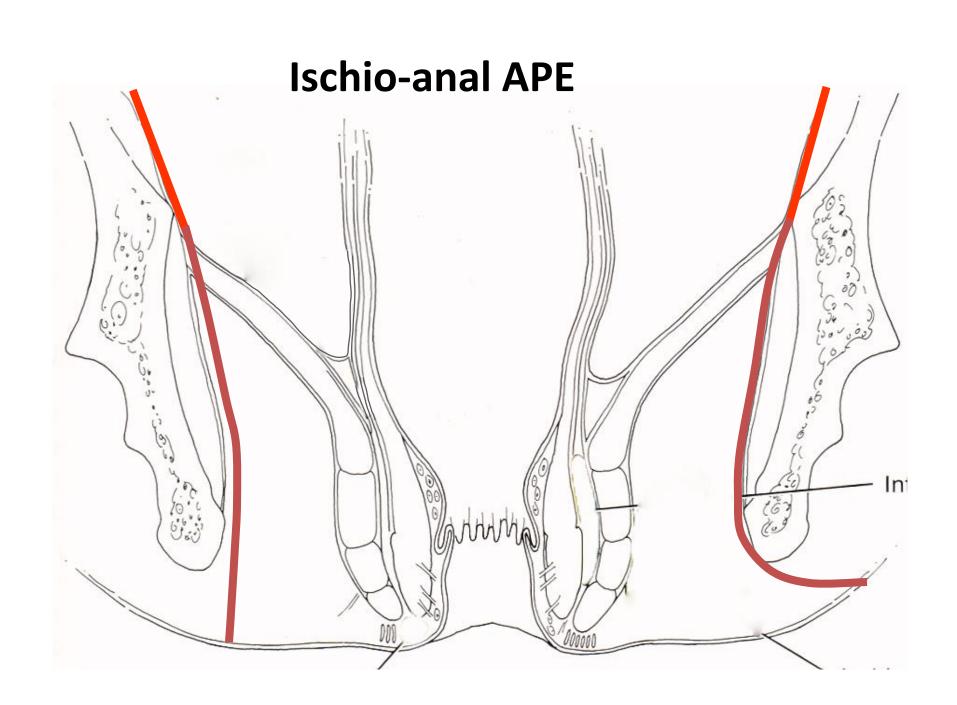




# Short-term results extralevator abdominoperineal excision from Swedish Colorectal Cancer Registry

Entire group: Extralevator APE did not result in fewer intraoperative perforations

- But fewer intraoperative perforations for:
  - Low tumours (≤4cm)
  - Early (T0-2) T-stages
- More postoperative wound complications for extralevator APE



#### Evidence of the Oncologic Superiority of Cylindrical Abdominoperineal Excision for Low Rectal Cancer

Nicholas P. West, Paul J. Finan, Claes Anderin, Johan Lindholm, Torbjorn Holm, and Philip Quirke

VOLUME 26 · NUMBER 21 · JULY 20 2008

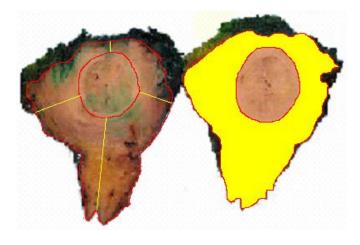
JOURNAL OF CLINICAL ONCOLOGY





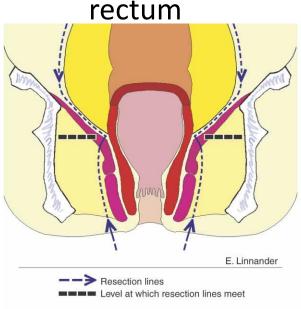




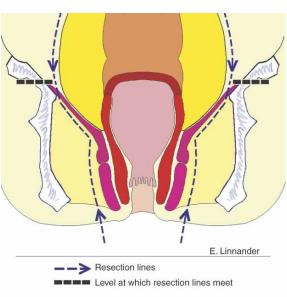


### Extended APR with gluteus maximus flap

- Mesorectum is not dissected off the levator muscles
- Perineal dissection is done in prone position
- En bloc resection levator muscles with the anus and lower









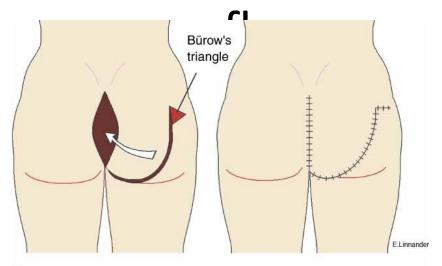
a Resection lines

**b** Specimen

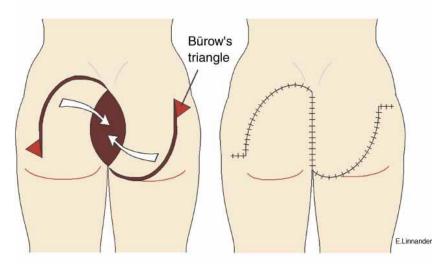
a Resection lines

**b** Side view of specimen

### Extended APR with gluteus maximus



a Unilateral flap

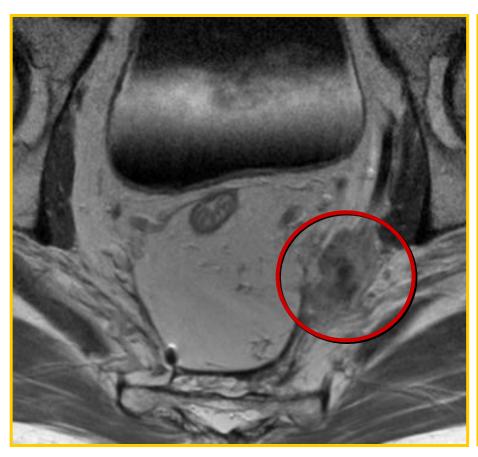


#### Extended APR with gluteus maximus flap

	All procedures		Curative procedures			
	Extralevator APE (n = 176)	Standard APE (n = 124)	P†	Extralevator APE (n = 142)	Standard APE (n = 72)	P†
Time to discharge (days)*	14 (11–19)	15 (12-22)	0.054‡	14 (11–19)	15 (12–22)	0.113‡
Wound complications						
Yes	57 (38.0)	11 (20)	0.019	50 (40.3)	10 (19)	0.009
Infection/breakdown/sinus	41 (72)	7 (64)		36 (72)	6 (60)	
Perineal hernia	5 (9)	1 (9)		4 (8)	1 (10)	
Other	11 (19)	3 (27.3)		10 (20)	3 (30)	
No	93 (62.0)	44 (80)		74 (59.7)	42 (81)	
Unknown	26	69		18	20	
Sexual/urinary problems						
Yes	13 (30)	12 (24)	0.640	11 (29)	12 (26)	0.810
Erectile dysfunction	6 (46)	4 (33)		5 (45)	4 (33)	
Urinary tract infection	0 (0)	3 (25)		0 (0)	3 (25)	
Urinary dysfunction	6 (46)	2 (17)		5 (45)	2 (17)	
Other	1 (8)	3 (25)		1 (9)	3 (25)	
No	30 (70)	37 (76)		27 (71)	34 (74)	
Unknown	133	75		104	26	

Values in parentheses are percentages unless indicated otherwise; \*values are median (interquartile range). APE, abdominoperineal excision. †Fisher's exact test unless indicated otherwise; ‡Mann–Whitney U test.

#### **Lateral nodes**

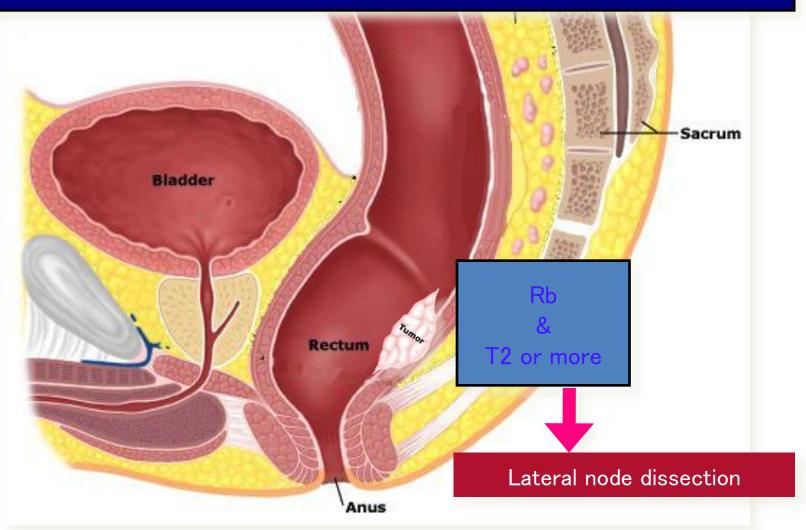




#### Standard of care in Japan

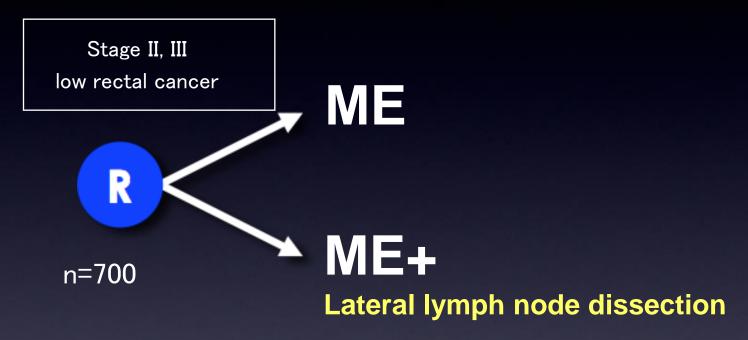
Tumor is located at or below the peritoneal reflection

Preoperative or intra-operative assessment for presence of LN metastases is not reliable.



### **JCOG0212**

Japan Clinical Oncology Group



**Primary endpoint: Disease-free survival** 

# Japanese trial – Lateral lymph node dissection

Stage II – III rectal cancer

TME alone versus TME + lateral lymph node dissection

- Lateral lymph node dissection:
  - Longer operation time (median 360 min vs. 254 min, p<0.0001))</li>
  - More blood loss (576 ml vs. 337 ml, p<0.0001)</li>
  - More grade 3-4 complications (22% vs. 16%, p=0.07)

### Comparison Dutch and Japanese results

		Lateral recurrence					
	n	LR	n	%	% in N+		
Japanese	324	6.9%	8	2.2	6.0		
RT+TME		5.8%	3	0.8	2.1		
TME alone	376	12.2%	11	2.7	7.9		



# Improvement in surgery for locally advanced rectal cancer

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- Organ preservation

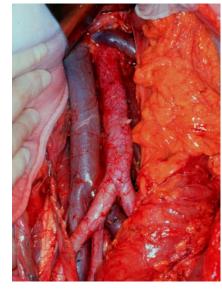
### History of rectal cancer surgery in Japan

1970 Extended surgery

1978 Komatubara initially reported NSS

1980

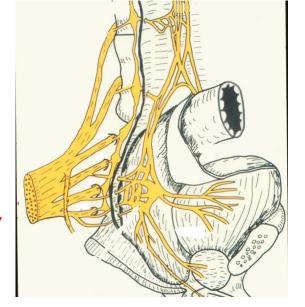




1984 Nerve Sparing Surgery

1990

2000



Based on better understanding of pelvic neuro-anatomy

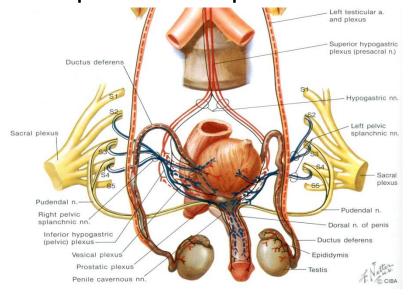
Optimize function without compromising local control

# TME with autonomic nerve preservation

- Prospective study urogenital function
- Yoshihiro Moriya
- 50 Dutch patients
  - → No urinary dysfunction

19 male patients complete nerve preservation: no sexual

dysfunction



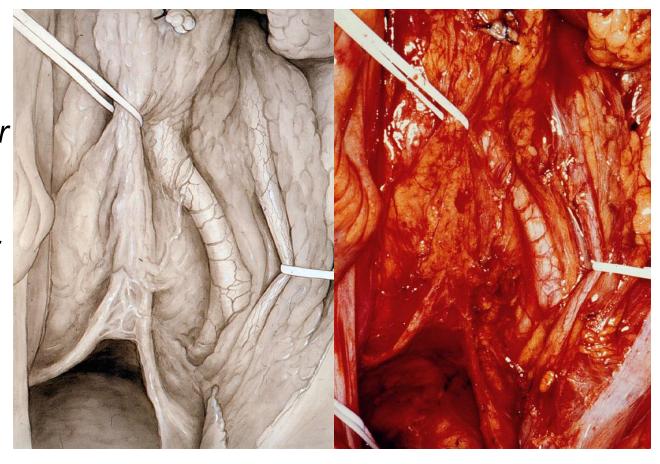
#### **Autonomic nerve preservation**

- Direct association between specific nerve damage and dysfunction
- Autonomic nerve preservation is achievable
- However, excellent results of experts have not been reproduced in large trials

### Autonomic nerve preservation

'We only see
what we look for
and
we only look for
what we know'

Walsh



Maas CP, Moriya Y, van de Velde. Lancet 1999;354:772-3

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### **Robotic Surgery**

- Aims to eliminate many of the technical difficulties
- Rectal cancer: few studies.
  - Not established a benefit over standard laparoscopic surgery in terms of:
    - Technical, functional or oncological outcomes



### Randomized trial – Robotic-assisted Tumor-specific mesorectal excision

• April 2006 – February 2007, *n* = 36

- Robotic versus laparoscopic surgery for rectal cancer
- → No difference observed in operative times, conversion rates, or the quality of mesorectal excision

→ Length of hospital stay significantly shorter in robotic surgery

# Robot-assisted Tumor-specific Mesorectal Excision

- June 2006 December 2010, n = 370 rectal cancer patients
- Clinicopathologic and follow-up data recorded prospectively and analyzed retrospectively

#### Results

- 3-year overall survival rate 93.1%
- 3-year disease-free survival rate 79.2%
- 3-year cumulative local recurrence rate 3.6%
- → Robot-assisted tumor-specific mesorectal excision feasible and safe in terms of oncologic outcomes according to these data

### **Ongoing clinical trial - ROLARR**

- Randomised controlled trial, n = 400 (planned)
- Laparoscopic surgery vs. robotic assisted laparoscopic surgery for rectal cancer
- Primary outcome measure:
  - Rate of conversion to open surgery
- Secondary outcome measure:
  - Oncological outcome (CRM positivity, 3-year local-recurrence rate)
- Other outcome measures:
  - Complications, 30-day mortality, 3-year disease-free and overall survival, sexual dysfunction assessment, QoL

# Improvement in surgery for locally advanced rectal cancer

#### **Options:**

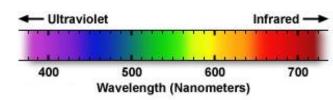
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### NIR fluorescence imaging

- NIR fluorescence imaging has the potential to improve patient management
- Already feasible for a variety of intraoperative applications (>500 patients included in over 25 clinical studies)
  - 1. SLN mapping
  - 2. Tumor identification
  - 3. Identification of vital structures
- Future goals:
  - Improved (laparoscopic) imaging systems
  - Identify Biomarkers for imaging
  - Optimized NIR fluorescent probes

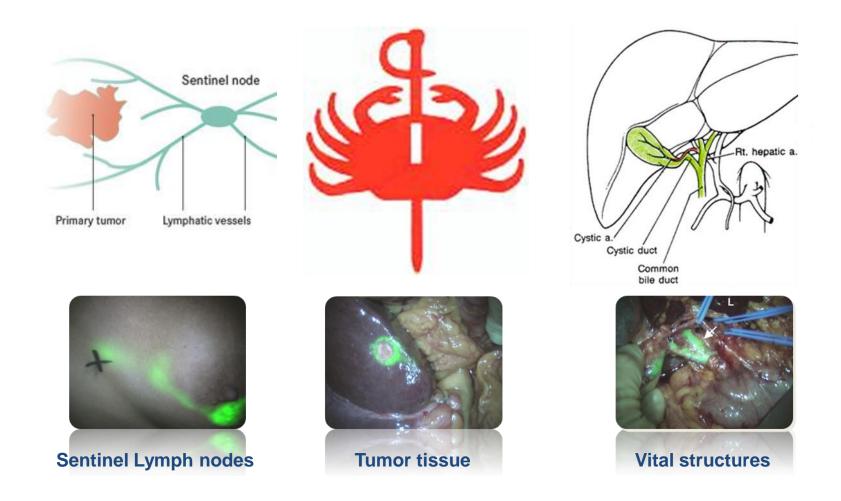
### Why optical imaging?

- Fast: acquisition in milliseconds
  - Real-Time and intraoperatively
- Invisible to the human eye
  - No alteration of the surgical field
- Relatively high tissue penetration (~ 1 cm)





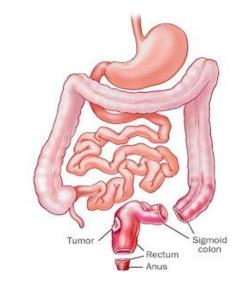
### **Focus Fluorescence-Guided Surgery**



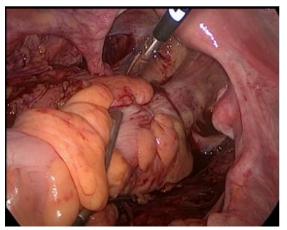
> 500 patients in more than 25 clinical trials

### Tumor marking and SLN visualization in rectal cancer

- ICG injection endoscopically
- Fluorescence HD laparoscope
- Tumor "guidance" during resection
- Ex-vivo SLN mapping



<u>Color</u> <u>NIR Fluorescence</u>







**Ex-Vivo SLN** 

# Improvement in surgery for locally advanced rectal cancer

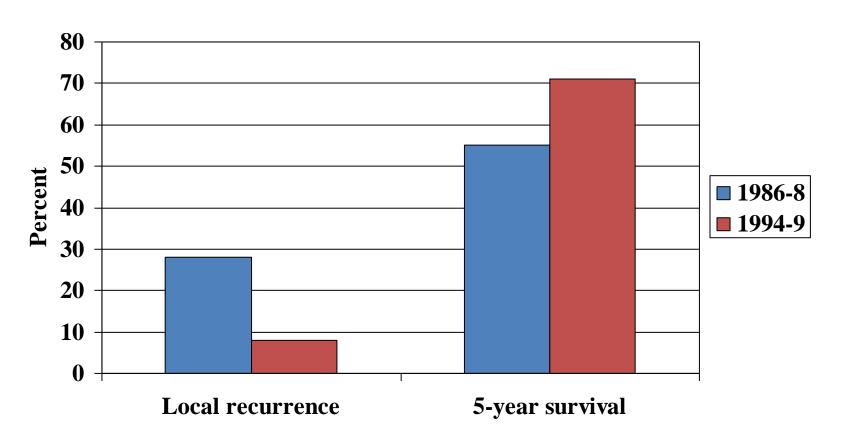
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#### **Audit**

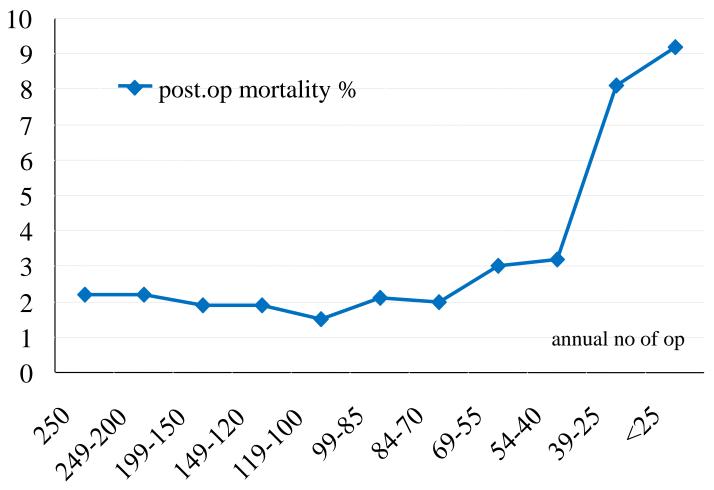
A quality instrument that collects detailed clinical data from different health care providers, which can be adjusted for baseline risk and subsequently fed back to individual hospitals or MDT's

# Norwegian Quality Assurance Program – Rectal cancer



The impact of hospital volume on the outcome of rectal cancer surgery (1995-2003)

### Sweden

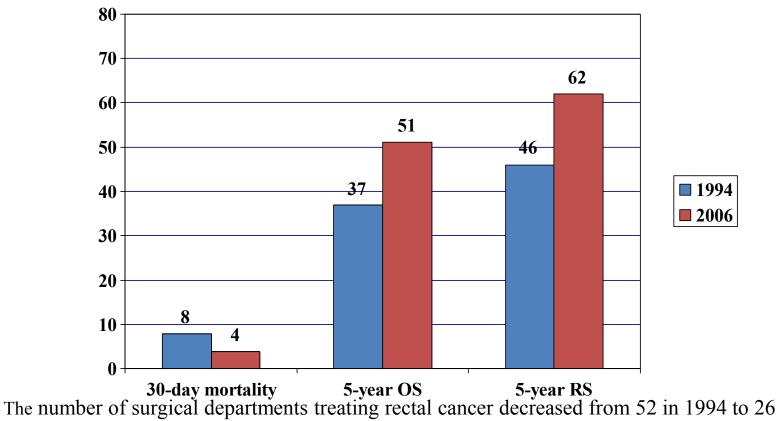


Swedish cancer registry 2006

### Sweden Variability

	High-volume team	Low-volume team	p-value
Mean no. of operations / year	>12	0-12	
Curative surgery	245 (78)	277 (82)	
Median (range) of follow-up (months)	41 (24-59)	43 (24-59)	
Local recurrence	9 (4)	27 (10)	0.02
Distant metastasis	39 (16)	54 (19)	0.33
Rectal cancer death	26 (11)	51 (18)	0.007

# Improvements by Danish audit



The number of surgical departments treating rectal cancer decreased from 52 in 1994 to 26 by the end of 2006

### **Audit**

Excellent results of national and regional audits

However, differences in outcome between European countries remain

### **EURECCA European Registration of Cancer care**



- In 2007 initiated by ESSO/ECCO
- Foundation

- Legal entity
- Independent
- Non-profit

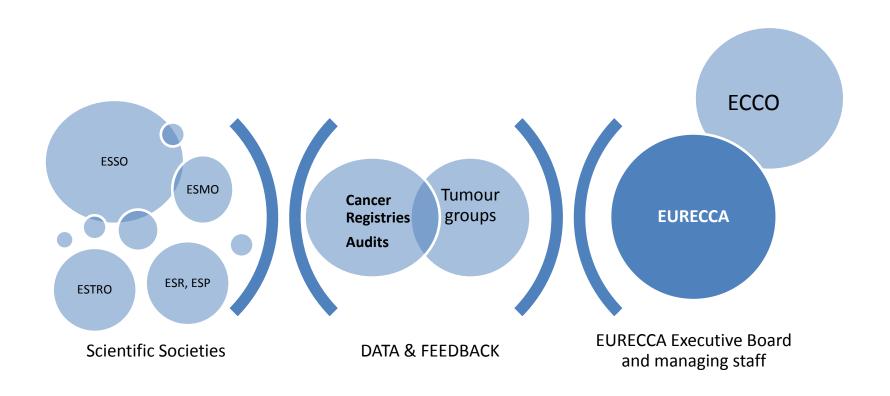
#### **EURECCA** – multidisciplinary cancer care



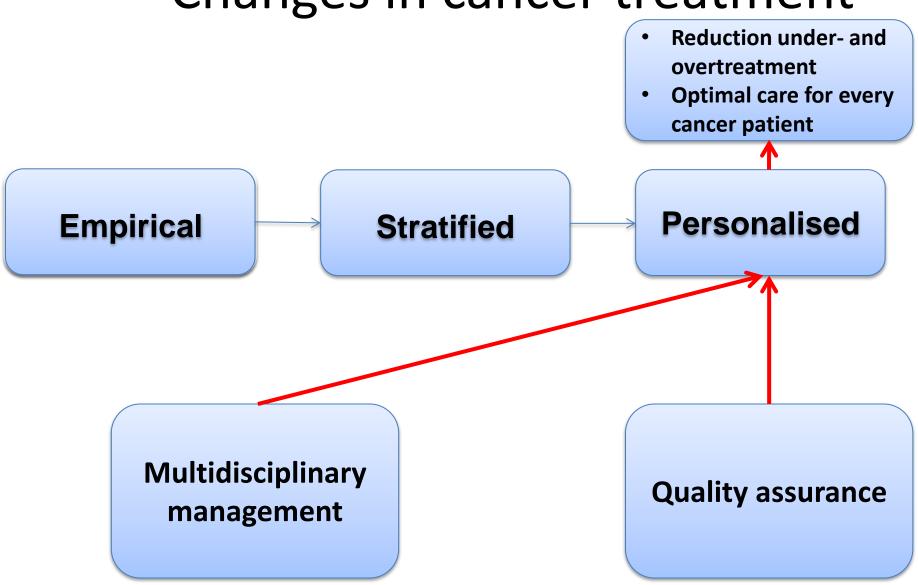
- Large database registry
- Observational population-based studies
- Data comparison: audit and quality assurance
- Identifying and communicating about 'best practices'
- Consensus meeting, educational material and workshops

## **EURECCA**Frame of collaboration





### Changes in cancer treatment



# Change neoadjuvant treatment instead of intensifying surgery?

#### **RAPIDO** trial – inclusion criteria:

- Good quality MRI
- •(T 3 c/d), T4 a/b
- •EMVI+
- •N2
- •N+ (outside the fascia plane)
- •MRF +

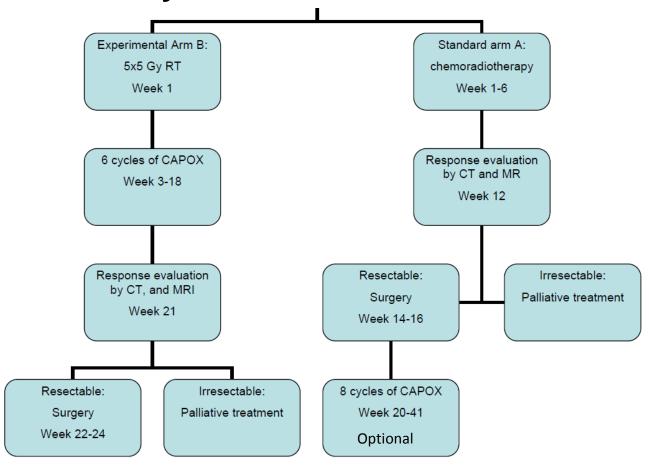
#### **RAPIDO** trial

### Experimental arm: previous experience M1 Study

- 50 patients M1 (75% T3/4N+)
   5x5 Gy + XELOX + Bevacizumab (6 cycles) + surgery
- 83% received all chemo (90% <u>></u>4 cycles)
   Low/acceptable toxicity
- pCR in 26% of specimens
   'No progression was seen on chemotherapy'

### RAPIDO Trial – current status: 450 patients included

#### **Locally advanced Rectal Cancer**



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### Potential benefits of preoperative chemoradiation in rectal cancer

- Downstaging of the tumour
- Decreasing rates of positive surgical margins
- Improving local control
- Increasing sphincter-saving procedures
- May offer the possibility of sparing patients from postoperative morbidity associated with radical rectal surgery

### Pathological outcome

Complete remission!

### **Triumph or Tragedy?**

Is it possible to avoid unneeded resections?

#### Habr-Gama – Watch and Wait Most recent publication

Median FUP: 60 months

• 49% cCR after CRT (90/183 patients)

- 31% local recurrences (28/90 patients)
  - 26/28 salvage therapy, 2/28 patients not amenable to salvage

### Observation after chemoradiation

Review

Critical appraisal of the 'wait and see' approach in rectal cancer for clinical complete responders after chemoradiation

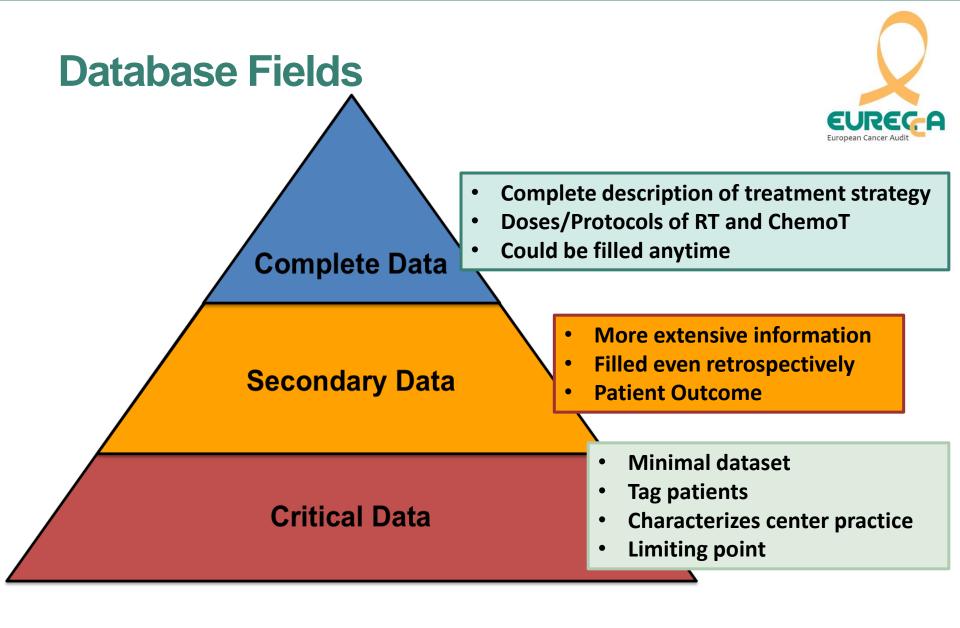
R. Glynne-Jones and R. Hughes

Centre for Cancer Treatment, Mount Vernon Hospital, Northwood HA6 2RN, UK Correspondence to: Dr R. Glynne-Jones (e-mail: rob.glynnejones@nhs.net)

- Habr-Gama series: low loco-regional failure rate (4.6%)
- Supported by study of Maas et al.
- Higher recurrence rates in other retrospective studies
- Heterogeneous studies in staging, inclusion criteria, study design and rigour of follow-up after CRT
- Inconsistent definition of cCR

### Why the need of an international organ preservation database?

- Limited number of centers / patients
- No homogeneous staging, treatment or surveillance protocols
- Need for a network of interested clinicians & scientists
- Identify best practice patterns



# Relevance prospective organ preservation database

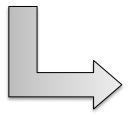
To study the concomitant risks-benefits

#### Per

- Age groups
- Comorbidity groups
- Tumour characteristics
- Chemoradiotherapy specifics
- Other adjustments

#### Relevance organ preservation database

- Provide evidence
- Help in protocol implementation
- Quality of care assessment
- Auditing
- Unit benchmarking



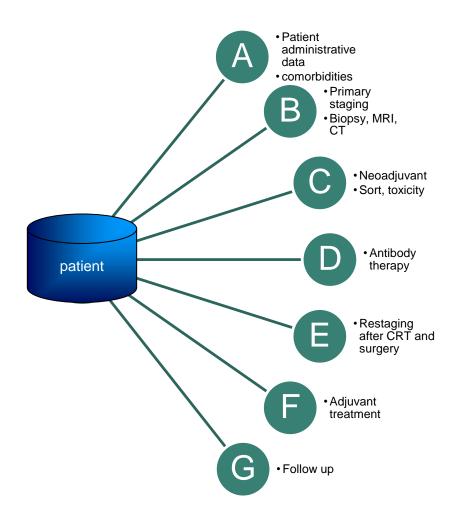
**Educational Feedback** 

**Data for Future Consensus Meetings** 

**Incorporating W&W in Standard of Care** 

### Per patient, 7 sections





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