Actualización en el manejo de Cáncer de Recto

Dra. Mayte Lima Pérez
Unidad de Tumores Digestivos HHA
mayte.lima@infomed.sld.cu

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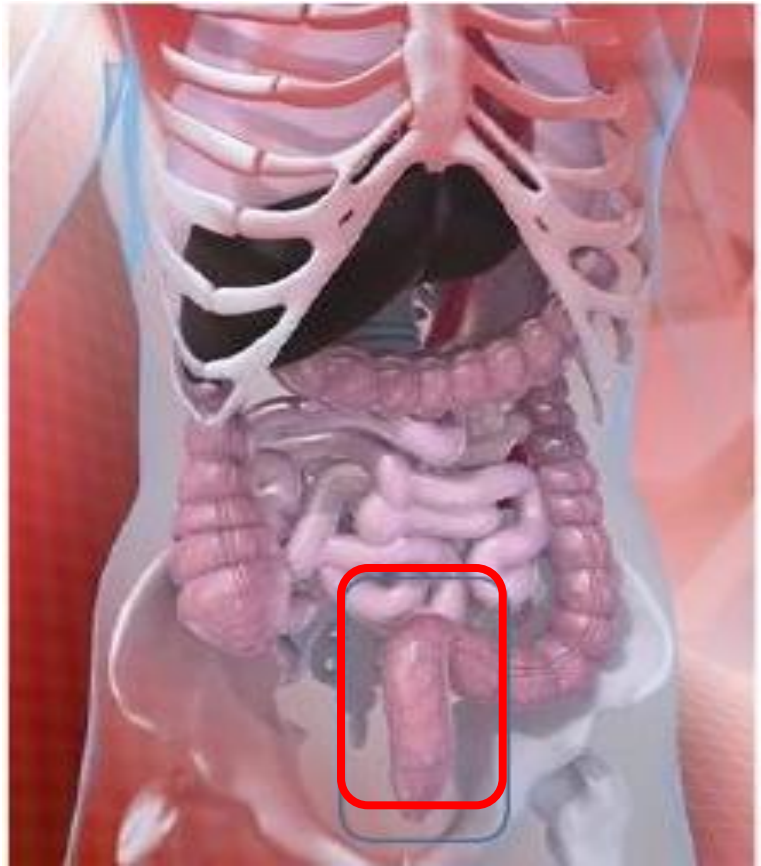

SUMARIO

- Antecedentes históricos
- Papel de la clasificación TNM y de Patología
- Que ha pasado con la cirugía
- Manejo de la enfermedad localmente avanzada y Metastásica
- Lo mas comentado……..

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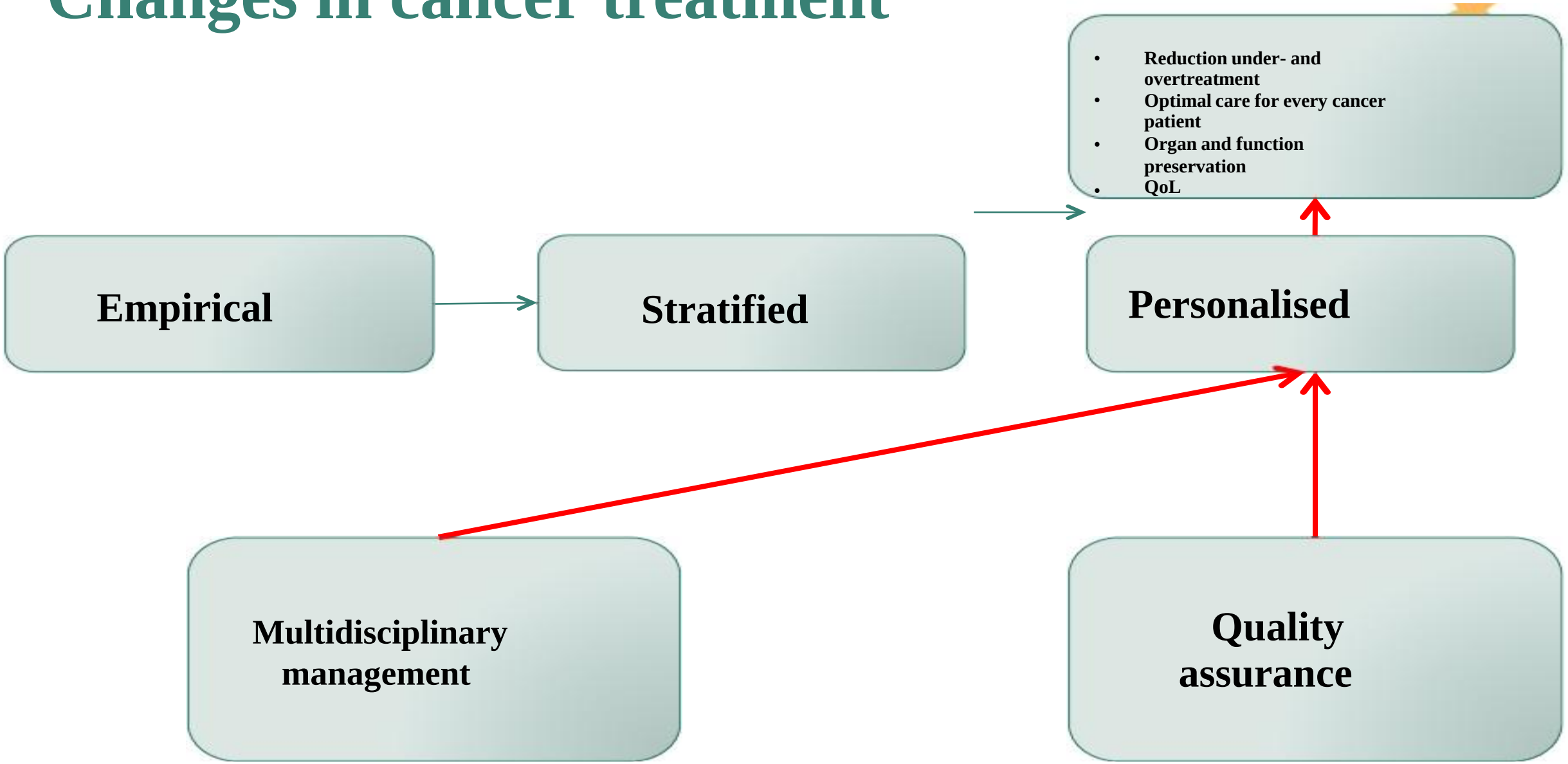
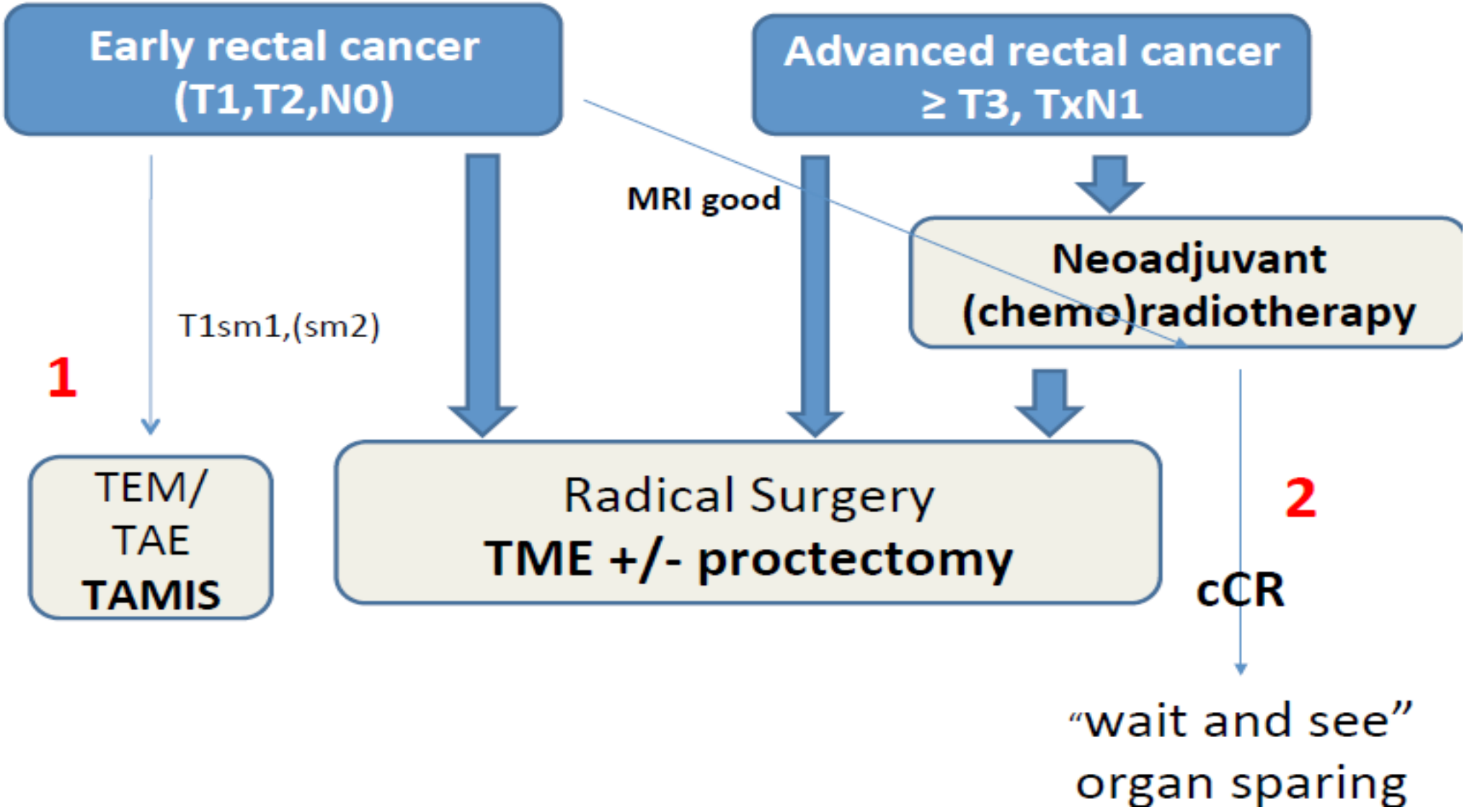
Changes in cancer treatment



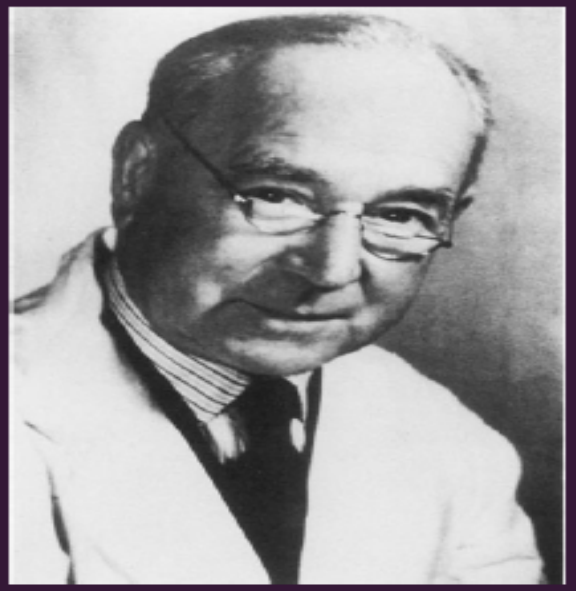
Tratamiento Actual del C. Recto



Historia……

The Royal Marsden

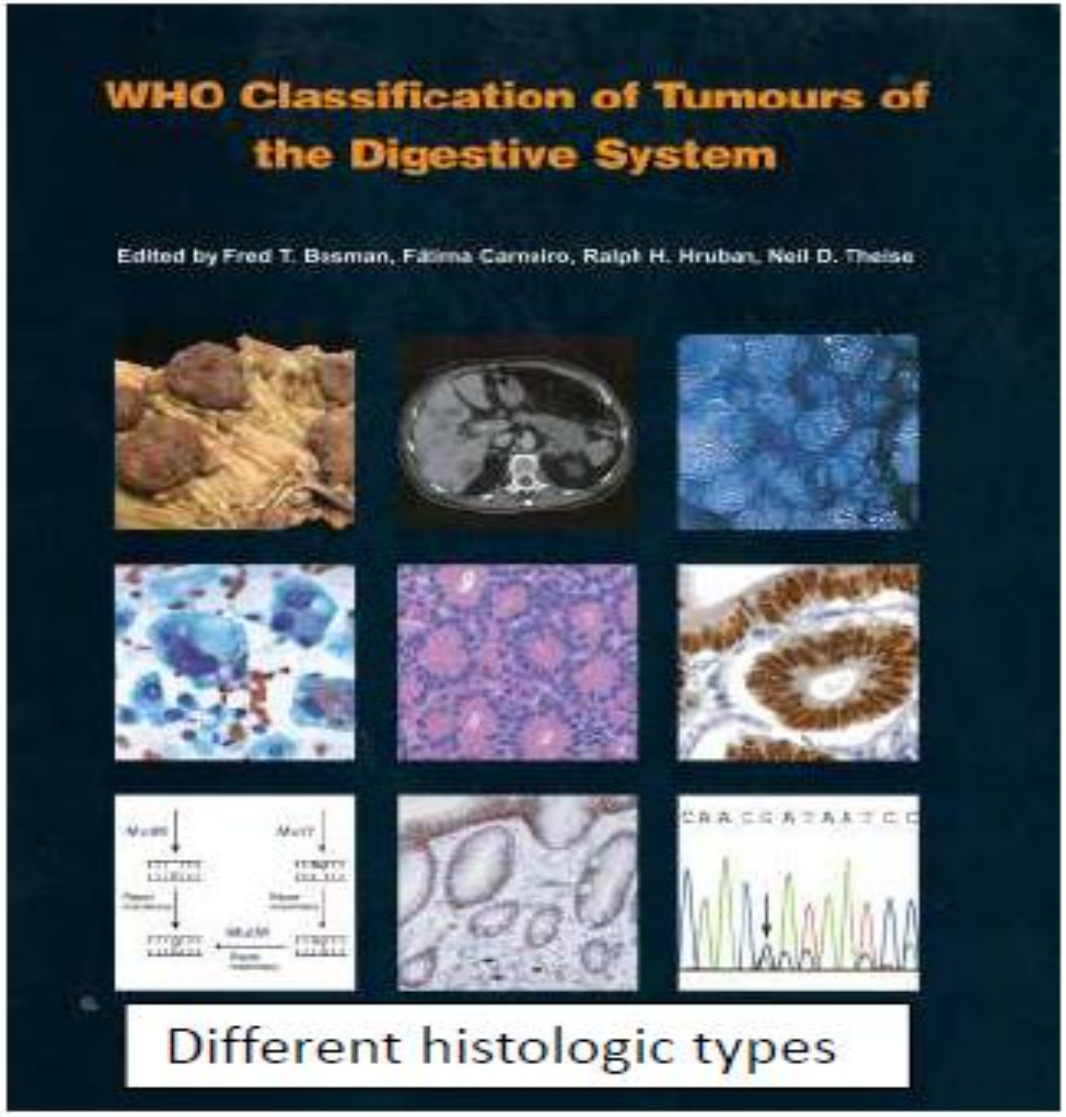
Cuthbert Dukes 1932: Nodes as a prognostic factor



- *A cases* - carcinoma is limited to the wall of the rectum, no extension into the extra-rectal tissues and no metastases in lymph nodes.
- *B cases* - carcinoma has spread by direct continuity to the extra-rectal tissues but has not yet invaded the regional nodes,
- *C cases* - metastases are present in the regional lymph nodes.
- system predicted **prognosis** and became a gold standard: Three-year survival after surgery was 80%, 73% and **7%** for A,B and C respectively.

NHS

Cáncer Colo rectal es una enfermedad Heterogénea



ESMO guidelines

Treatment algorithm for localised rectal cancer

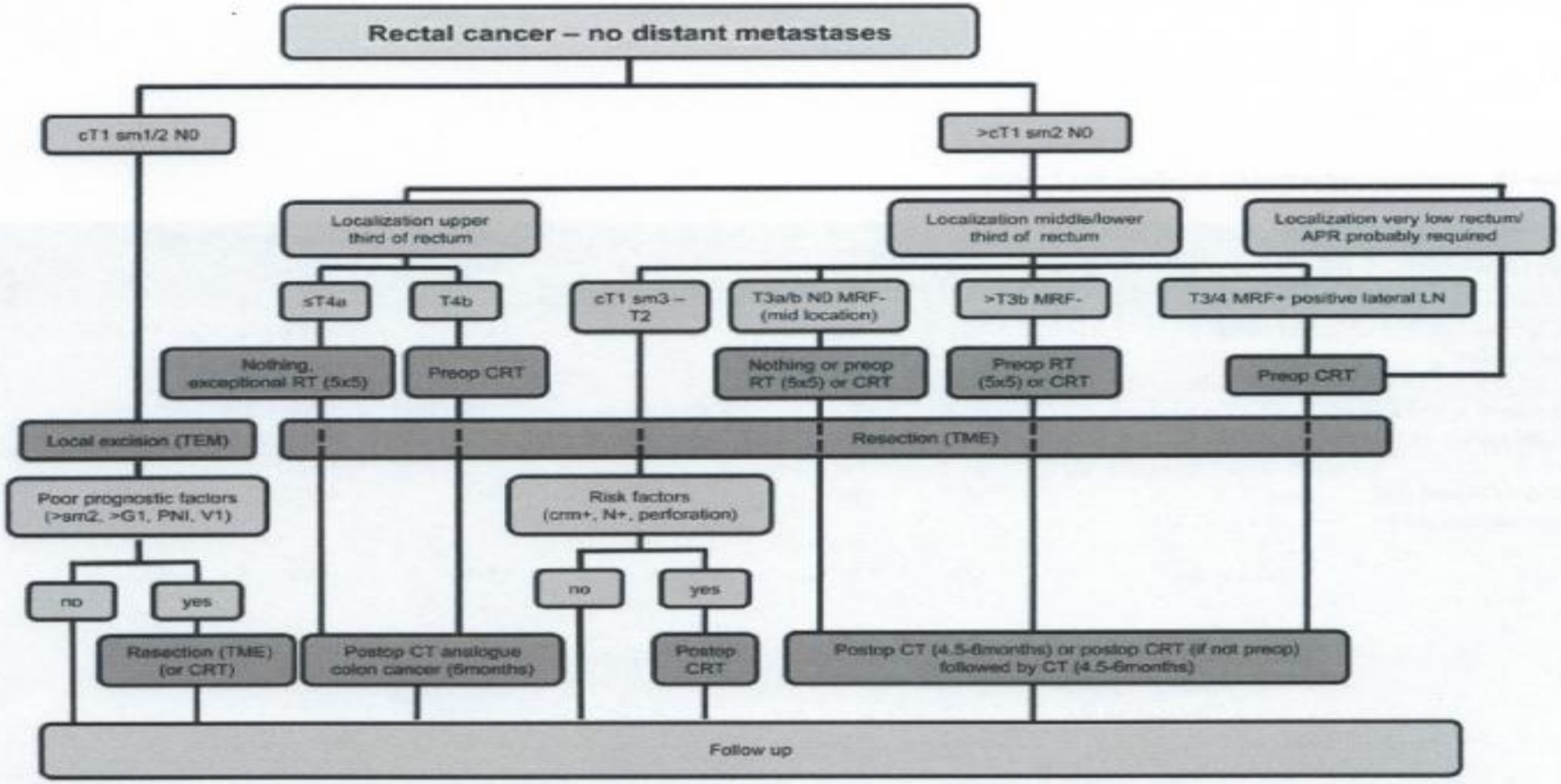
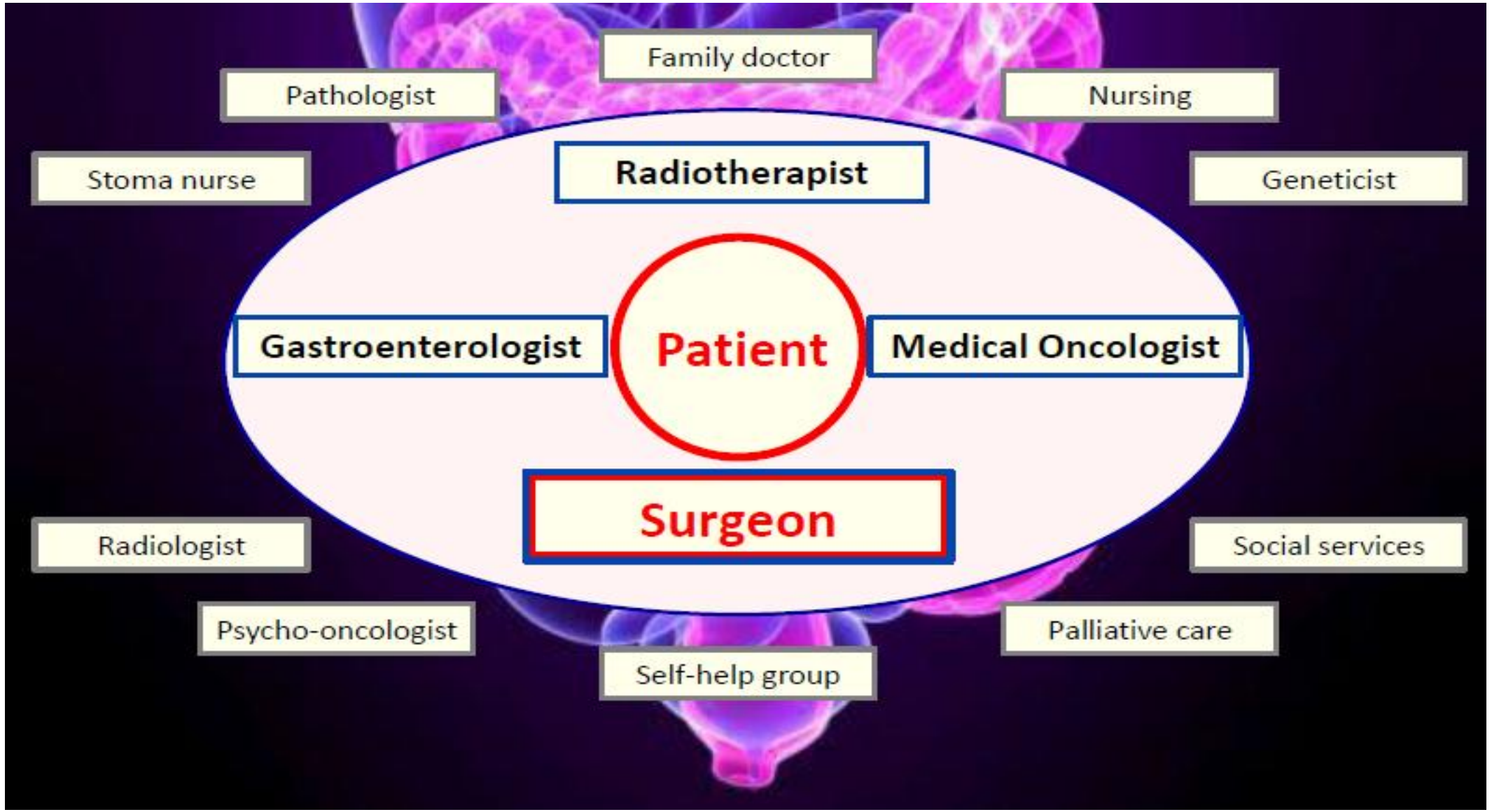


Figure 1. Treatment algorithm for localized rectal cancer. (Lateral LN: drainage of the a rectalis media (if present) or along the obturatorius or internal iliac vessels).

Armas terapéuticas

- ✓ **Cirugía**
- ✓ **Quimio – Radioterapia Neoadyuvante**
- ✓ **Tratamientos sistémicos para la enfermedad metastásica e Irresecable**

Indispensable el Grupo Multidisciplinario



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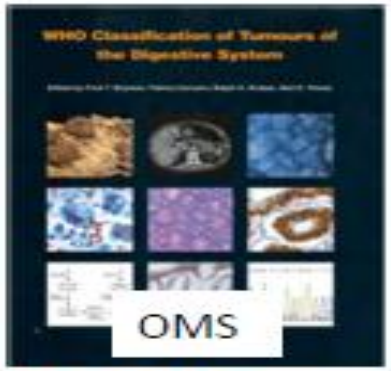
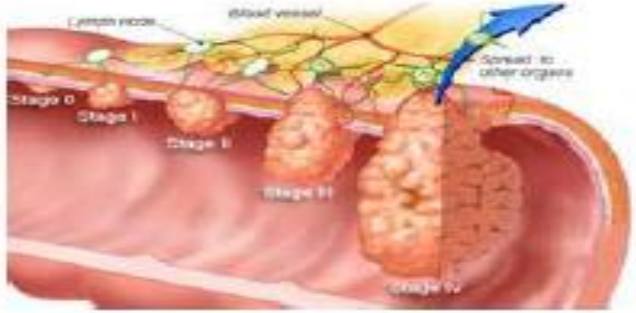
Elementos claves de la Patología

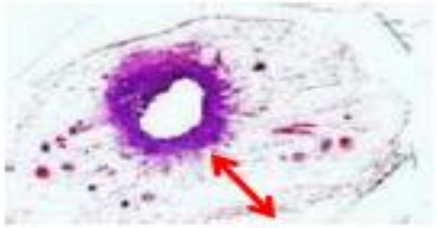


Histologic type

Differenciation
(Grade)



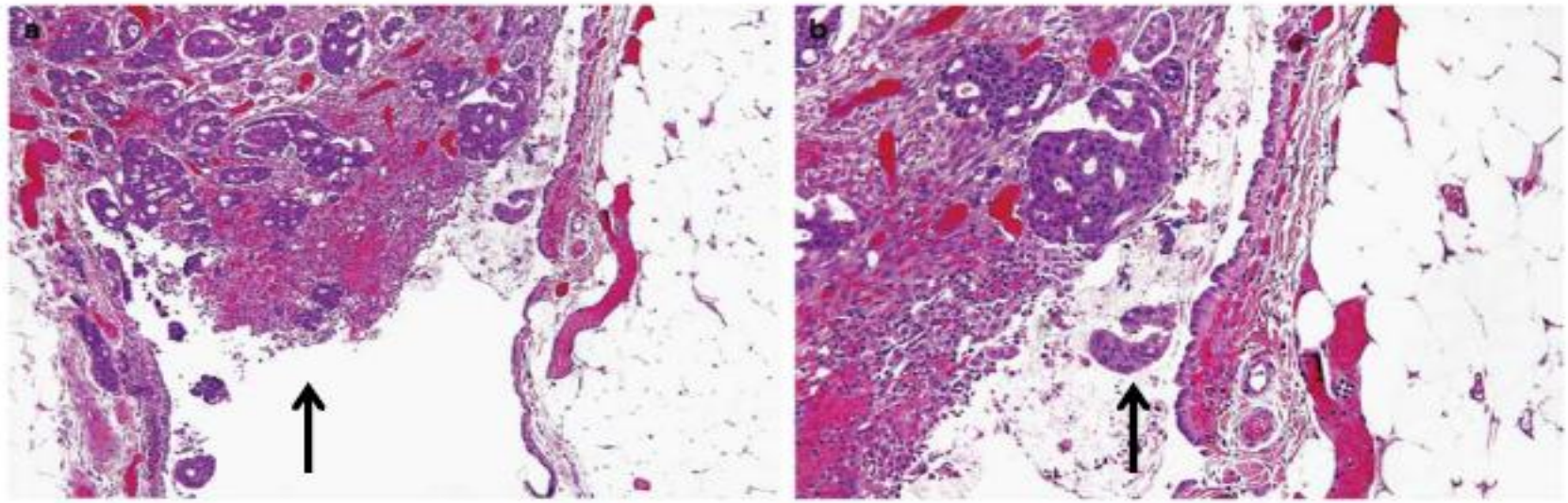
Extension
- Tumour (**pT**)
- Lymph node (**pN**)



Margins
- Distal/proximal
- Circumferential (Rectum)

Vasculo-lymphatic and perineural invasions

Serosal involvement



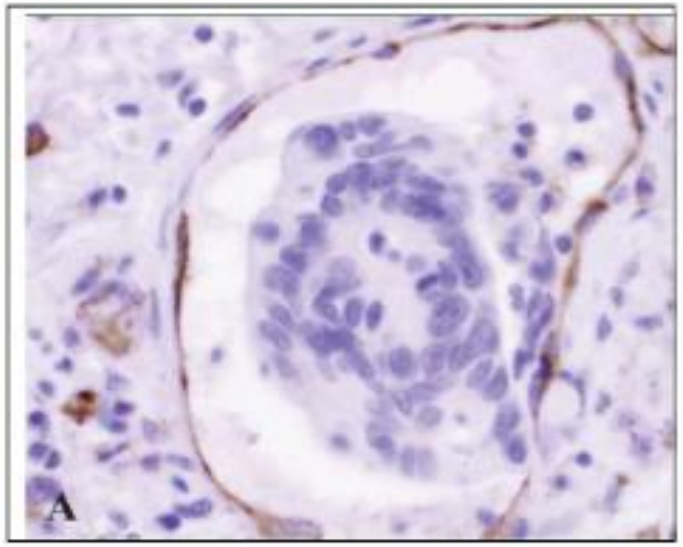
pT4a

7th TNM UICC 2009 classification

Frankel et al. Mod Pathol 2015

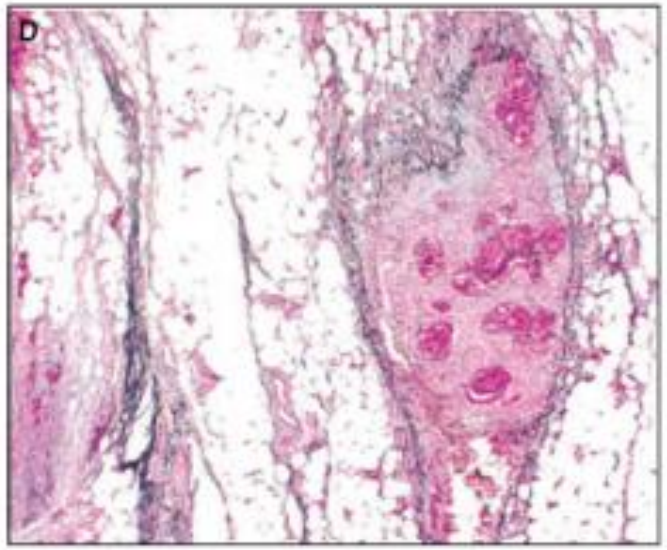
Distant extension : VELIPI*

Lymphatic invasion



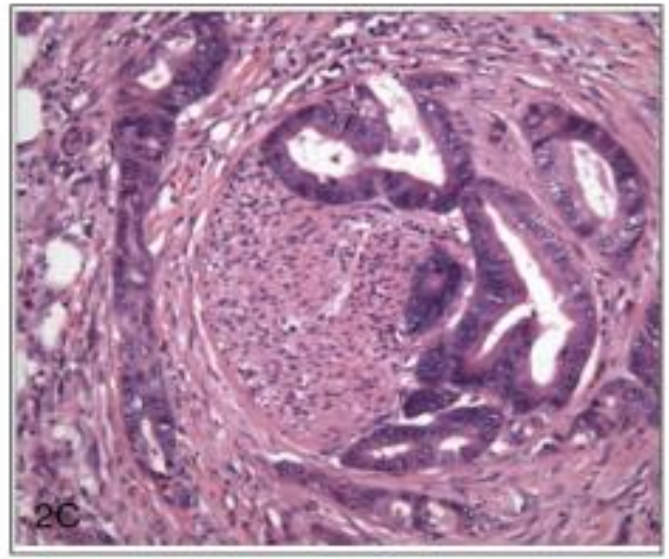
Harris et al, Am J Surg Path 2008

Venous invasion



Mori et al. Histopathology 2009

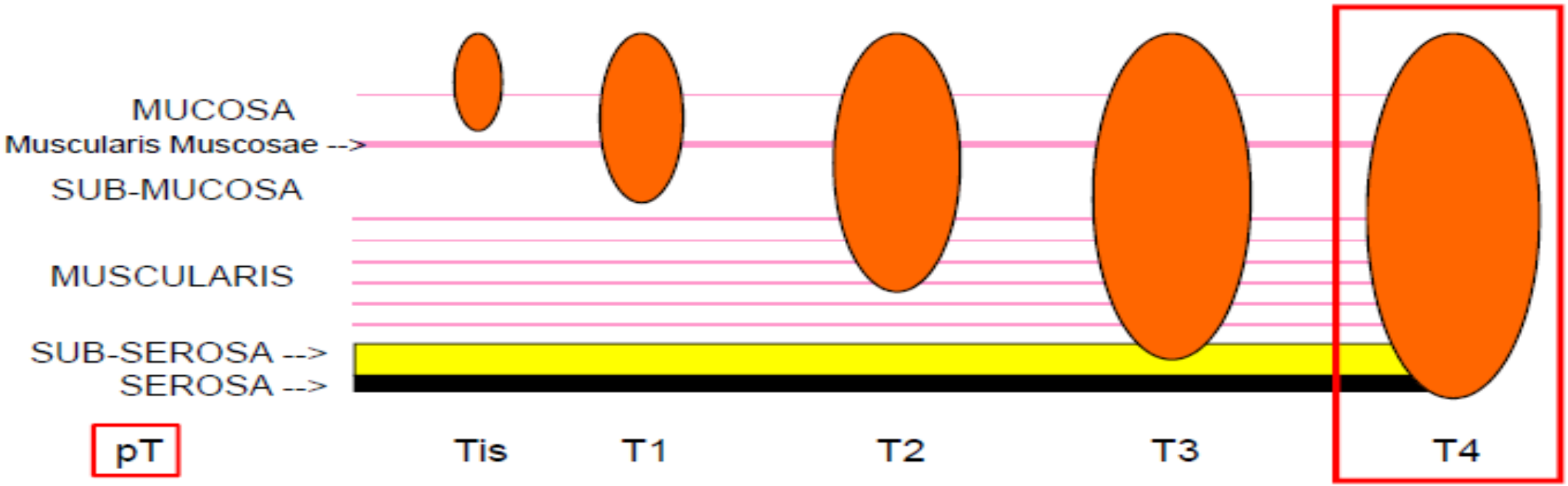
Perineural invasion



Liebig et al J Clin Oncol 2010

**Venous emboli and lymphatic and perineural invasion*

pTNM classification



Organe infiltration and / or visceral peritoneal perforation

pN

N0 : no positive lymph node (LN)
N1 : ≤ 3 positive LN
N2 : ≥ 4 positive LN

pM

M0 : No distant metastasis
M1 : Distant metastasis

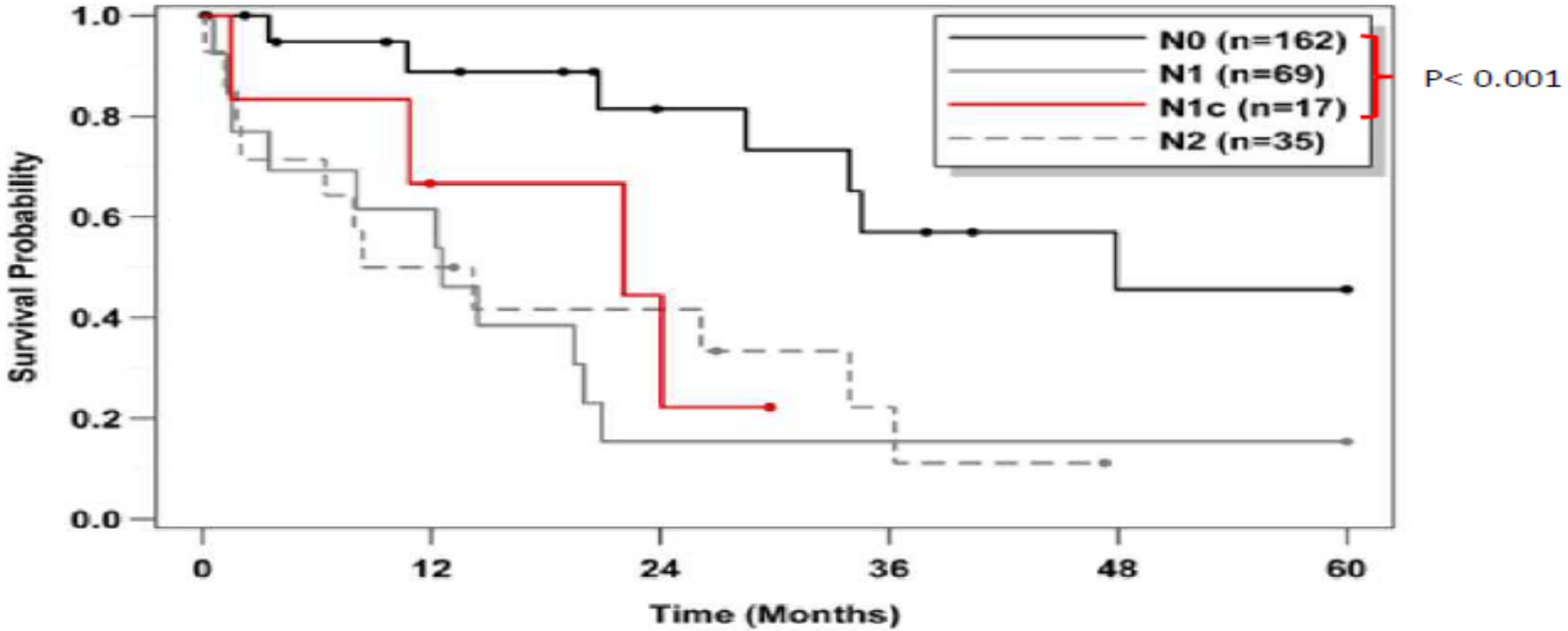
TNM UICC 2009 7th Classification

Distant extension : tumour deposits

Nx	Statut ganglionnaire non évaluable
N0	No positive regional lymph node
N1	Metastase(s) in 1-3 regional lymph node(s)
• **N1a**	1 positive lymph node
• **N1b**	➢ 2-3 positive regional lymph node
• **N1c**	➢ Tumour deposits, satellites, in the sub-serosa or peri-rectal or peri-colic non peritonised tissue, without regional metastatic lymph node
N2	≥ 4 or more positive regional lymph nodes
• **N2a**	• ≥ 4-6 regional positive lymph nodes
• **N2b**	• ≥ 7 regional positive lymph nodes

TNM UICC 2009 7thClassification

Impact of « tumour deposits » (N1c)



Jin et al. Am J Surg Path 2014

Distant extension: lymph nodes

Recommendations > 12

But...

Recovered lymph nodes	Total number of specimens	Percent of specimens with a lymph node metastasis
1–5	462	6.49%
6–10	596	8.89%
11–15	334	41.62%
16–20	138	31.16%
>= 21	112	80.36%

Goldstein et al. Am J Surg Pathol 2002

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The “Swedish” study (1997, updated 2002)

13 years follow-up
1168 patients
Surgery v Surgery after pre-op RT (25Gy / 5 fractions)

	S + RT	S	
Local recurrence	9%	26%	p<0.001
Cancer specific survival	72%	62%	p=0.03
Overall survival	38%	30%	p=0.008

Benefits to all Dukes stages

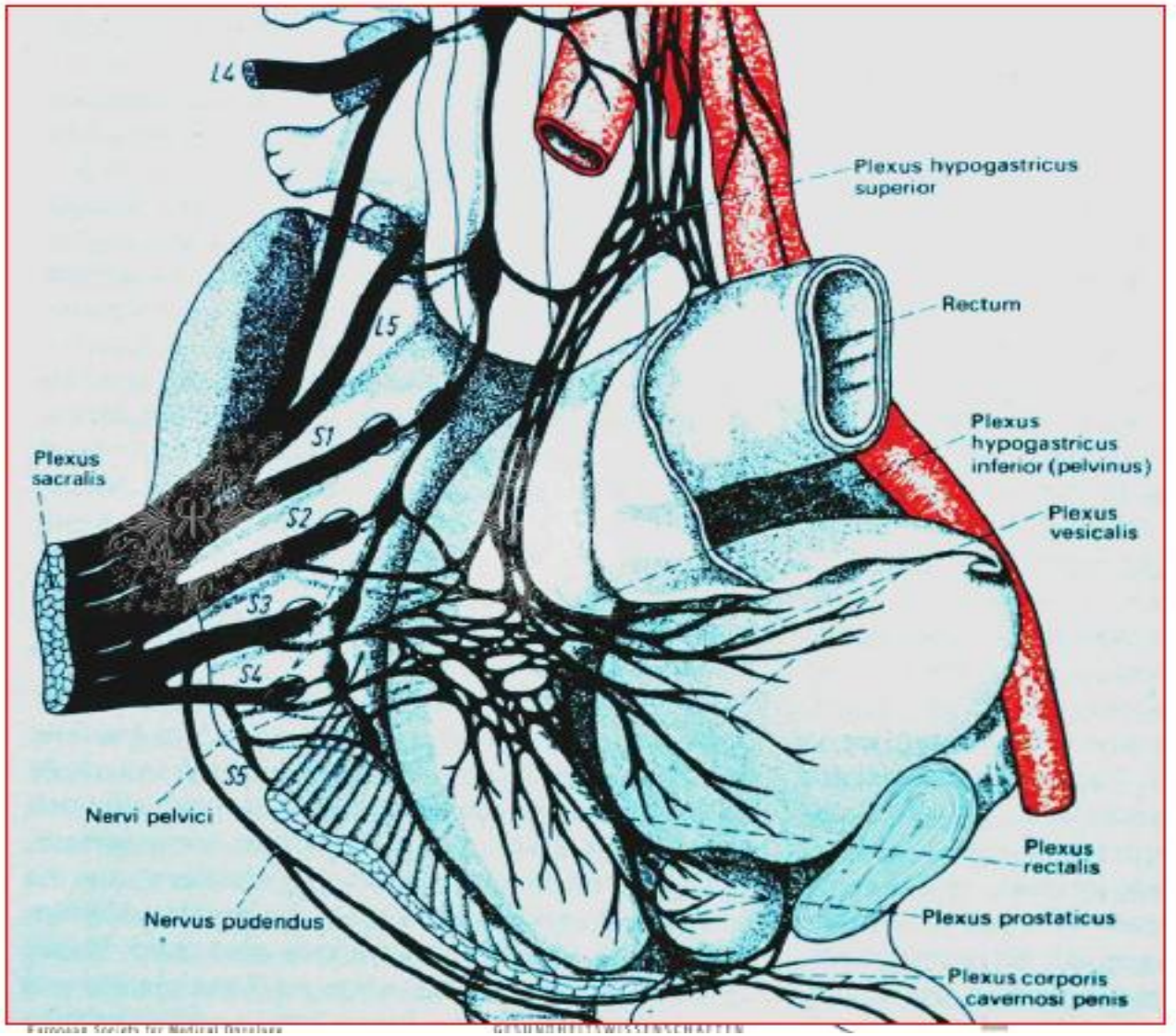
(Folkesson et al, JCO 23, 24: 5644 - 5650)

Situación Anatómica de la Pelvis Menor

- Many organs close together

- Bowel, bladder, prostate/vagina, nervs, ureter etc.

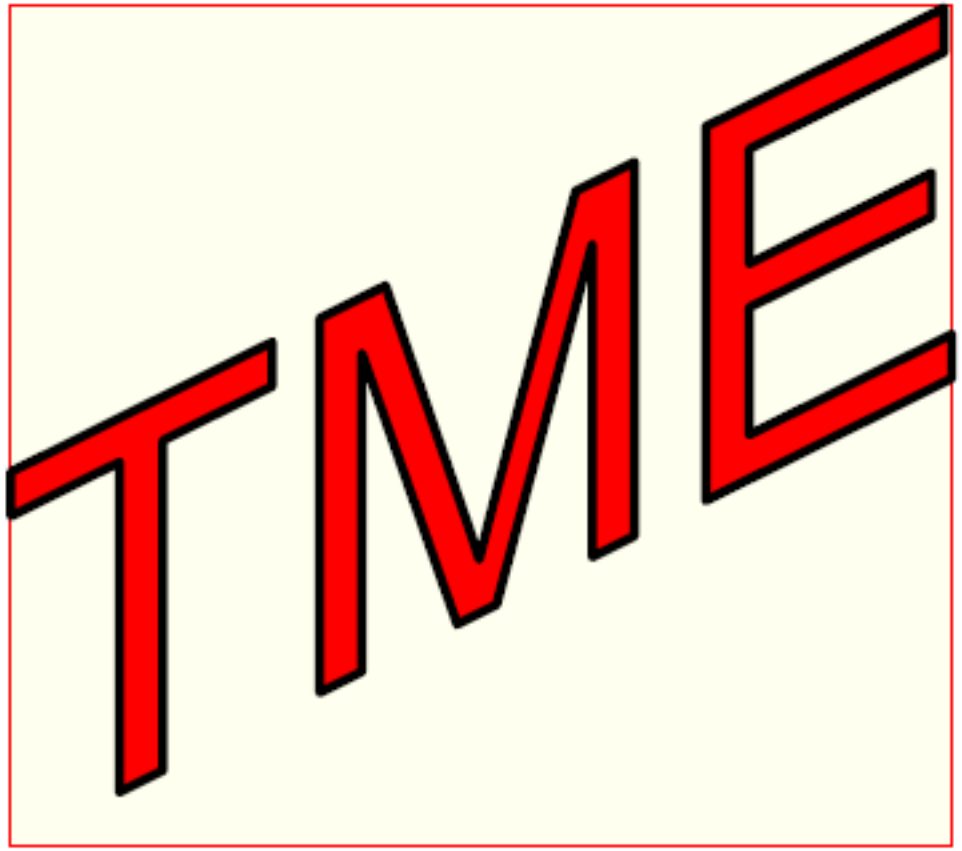
- Function-preserving but radical procedure



Cáncer de Recto

Operative technique:

The catchphrase of the last twenty years was...



- TME alone is not sufficient

- TME has to be understood as a synonym for

→ **Standardized radical surgery =**

- Resection of tumor, lymph nodes (TME) radices, borderline layers, and if applicable neighboring organs
  en bloc in a standardized technique.

- In most cases nowadays
  by laparoscopic surgery

Estandarización de la Cirugía Radical en C. Rectal

- Local recurrence rate <5% (2-3%) !

→ Do we still need (neo-) adjuvant therapy?

Si…!!!!

- Surgery has no influence on distant metastases as first event!
- Local recurrence rate can still be improved, even after excellent surgery!
- Rate of sphincter preservation is higher after neoadjuvant therapy!

Principios de la Cirugía Rectal

Surgery of colorectal cancer

is ...

- a surgery of lymph nodes
- a surgery of radices
- a surgery of safety distances
- a surgery of borderline layers

➔ Always a mono-bloc surgery

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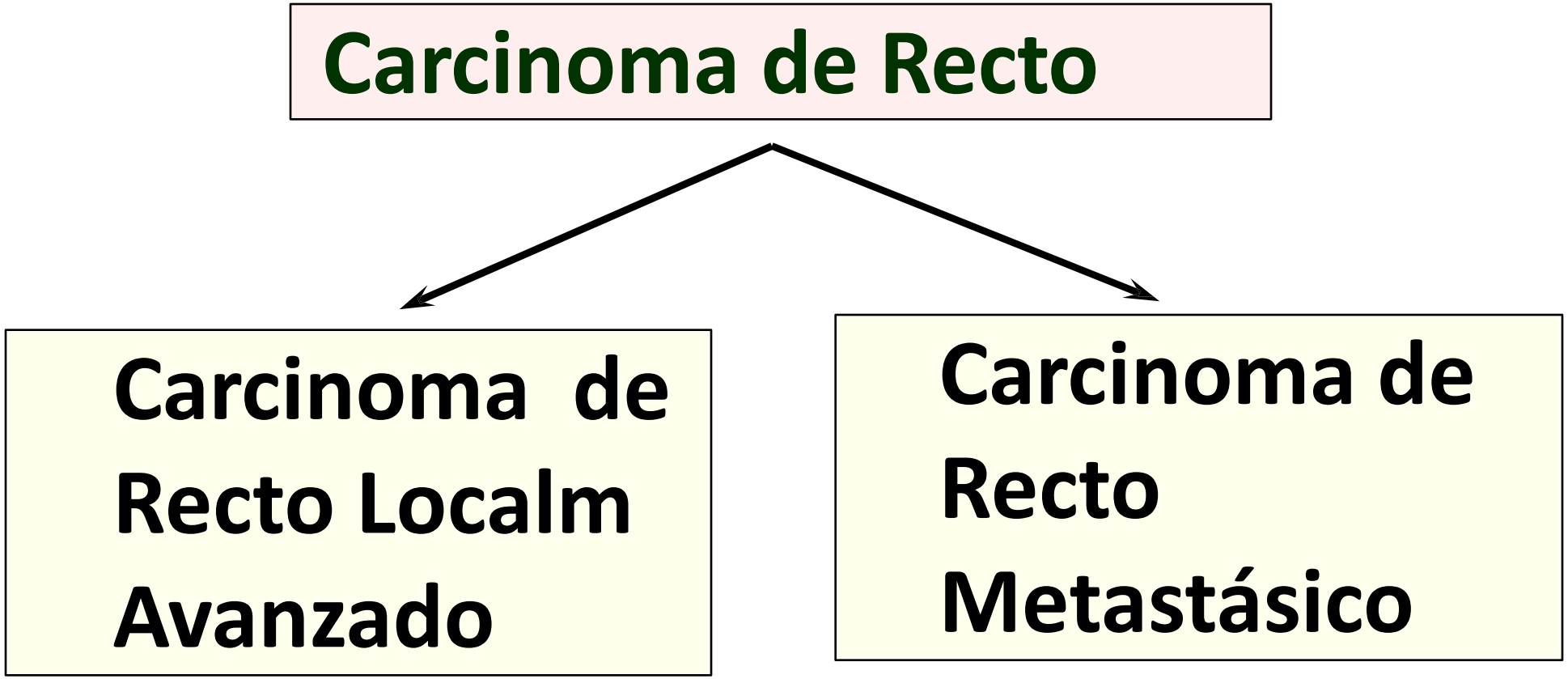
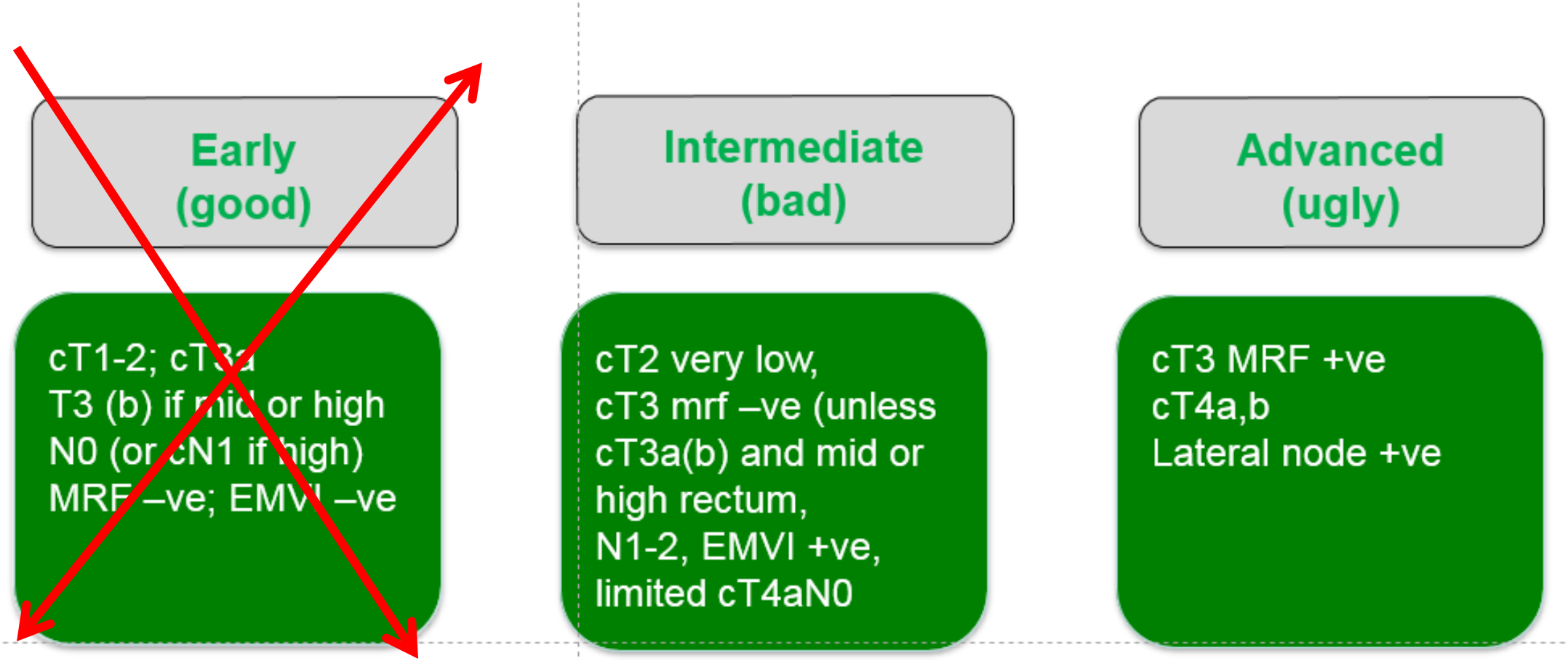
Presentación del C Rectal al debut



Rectal Cancer: ESMO Clinical Practice



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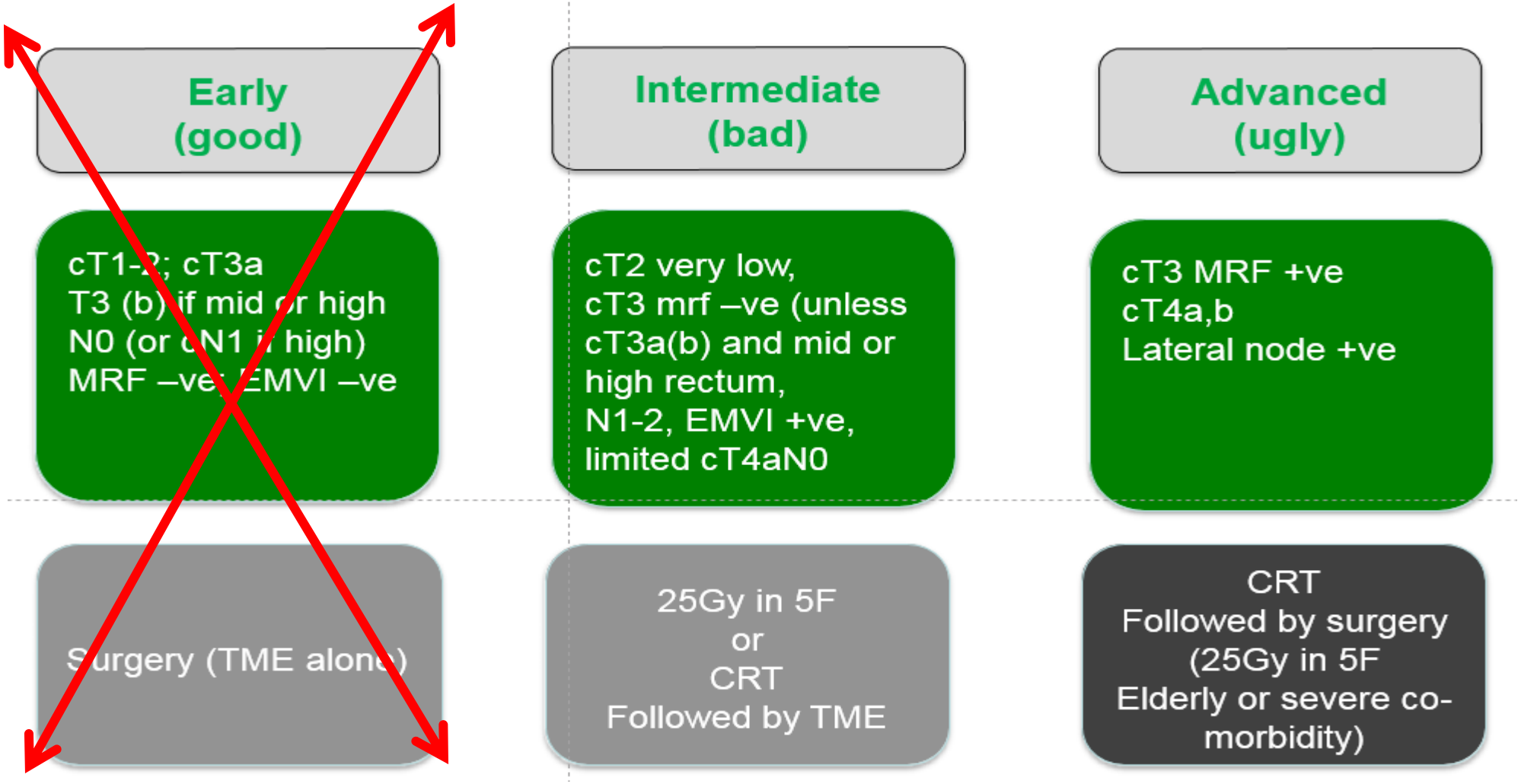


Efectos de la QT Y la RT Neoadyuvante

may induce significant tumor regression:

- Reduction in tumor **size** (downsizing)
- Reduction in depth of penetration (downstaging)
- Nodal sterilization
- **Pathological complete response** (**pCR**)

Estrategia en C Rectal en etapa IV (Hígado)

R0-resection of both, the primary tumor and the liver metastases offers the only chance of cure!

Therapeutic strategies

- **in potentially curative situations:**

⇨ **increasing resectability**

⇨ **lowering the risk for local and systemic recurrence**

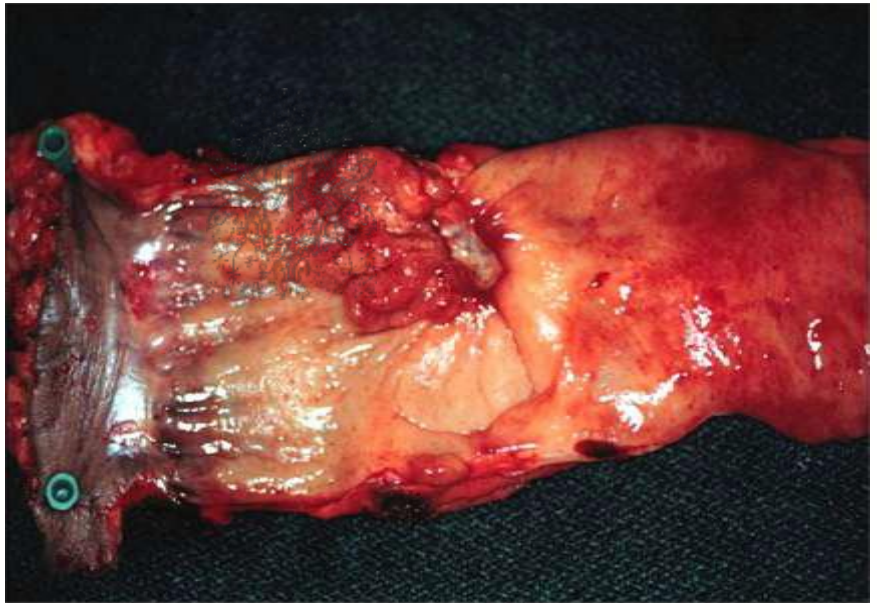
- **in case of non-curable disease: prolongation of survi**

⇨ **improvement of quality of life**

⇨

No randomized studies!

Case report Hannover 1991



30 year old man:

Rectal cancer with synchronous

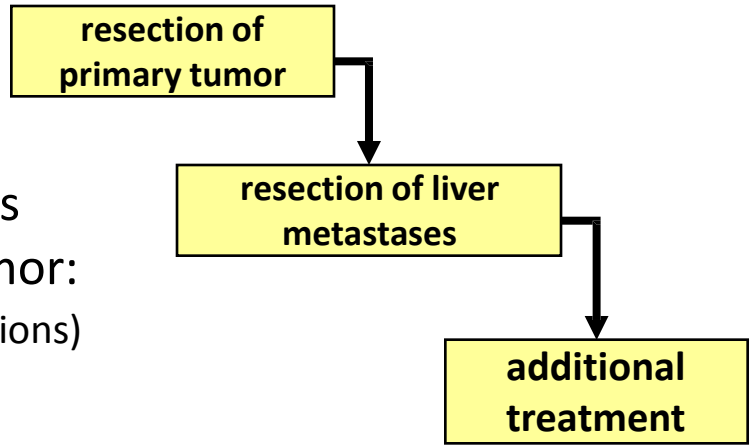
- **huge liver metastasis**
- **infiltration of diaphragm**

- **rectal extirpation; simultaneous extended right hepatectomy**
- **postoperative chemotherapy with 5-FU**
- **died of the disease after 1 year**

Estrategia en C Rectal en etapa IV (Hígado)

Rational for traditional approach (primary first)

- Treatment of tumor related symptoms
- Prevention of tumor related symptoms
- Primary tumor is source and „motor“ of mets
- Recovery time after resection of primary tumor:
  - „selection period“ (to avoid unneccessary liver resections)

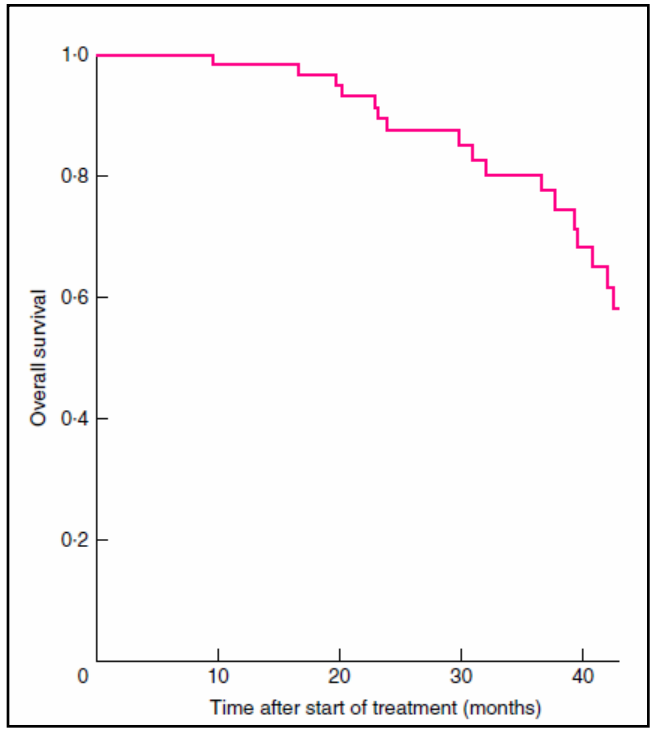


Rational for liver first

- liver metastases determine prognosis
- „better“ condition for RCTx (rectal cancer)
- Recovery time after liver resection:
  - Selection period (to avoid unneccessary colorectal resections)

Liver-first approach

Outcome of surgery in patients with rectal cancer and simultaneous liver metastases



Overall survival (OS) all groups (n=57)

5 years 38%

Group 1 (n=29)

Primary tumor first

5-year OS 28%

Group 2 (n=8)

Simultaneous resection

5-year OS 73%

Group 3 (n=20)

Liver-first-approach

5-year OS 67%

Van der Pool et al., Br J Surg 2010

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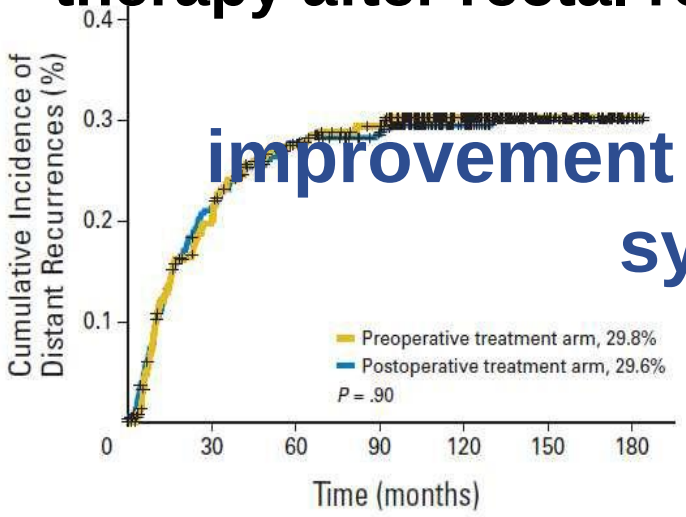
QTP- RT C. Rectal

- **5-Fu/Oxaliplatin; 50,4 Gy**
- **Under treatment of liver metastases**
- **German rectal cancer study:**
  - **only about 50% of patients received adjuvant therapy after rectal resection**



improvement of survival by intensifying systemic therapy !

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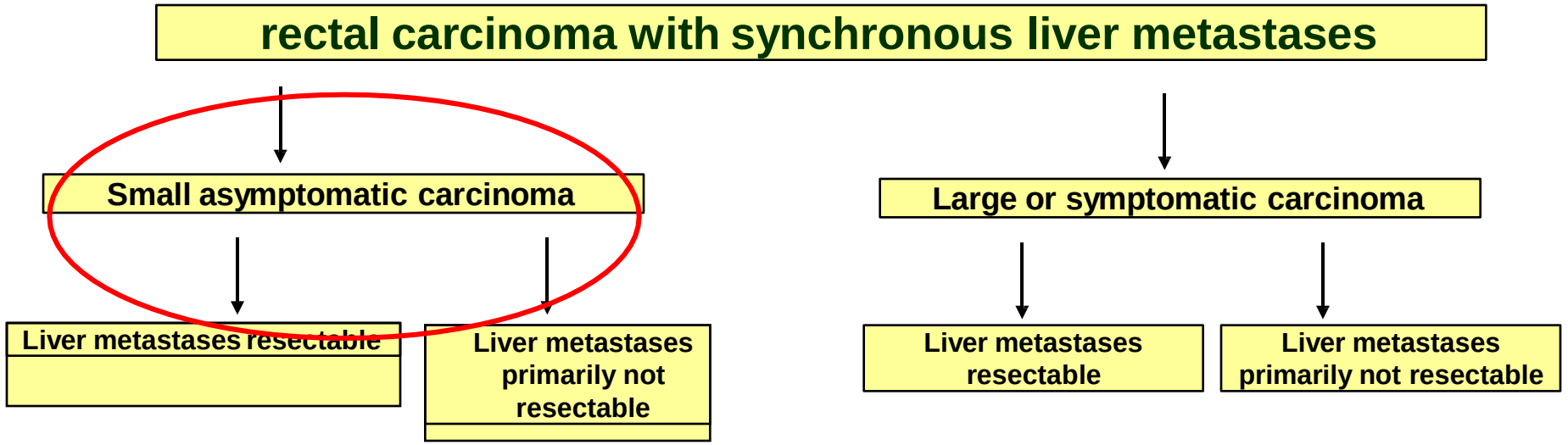
Strategy in rectal carcinoma stage IV (liver only)



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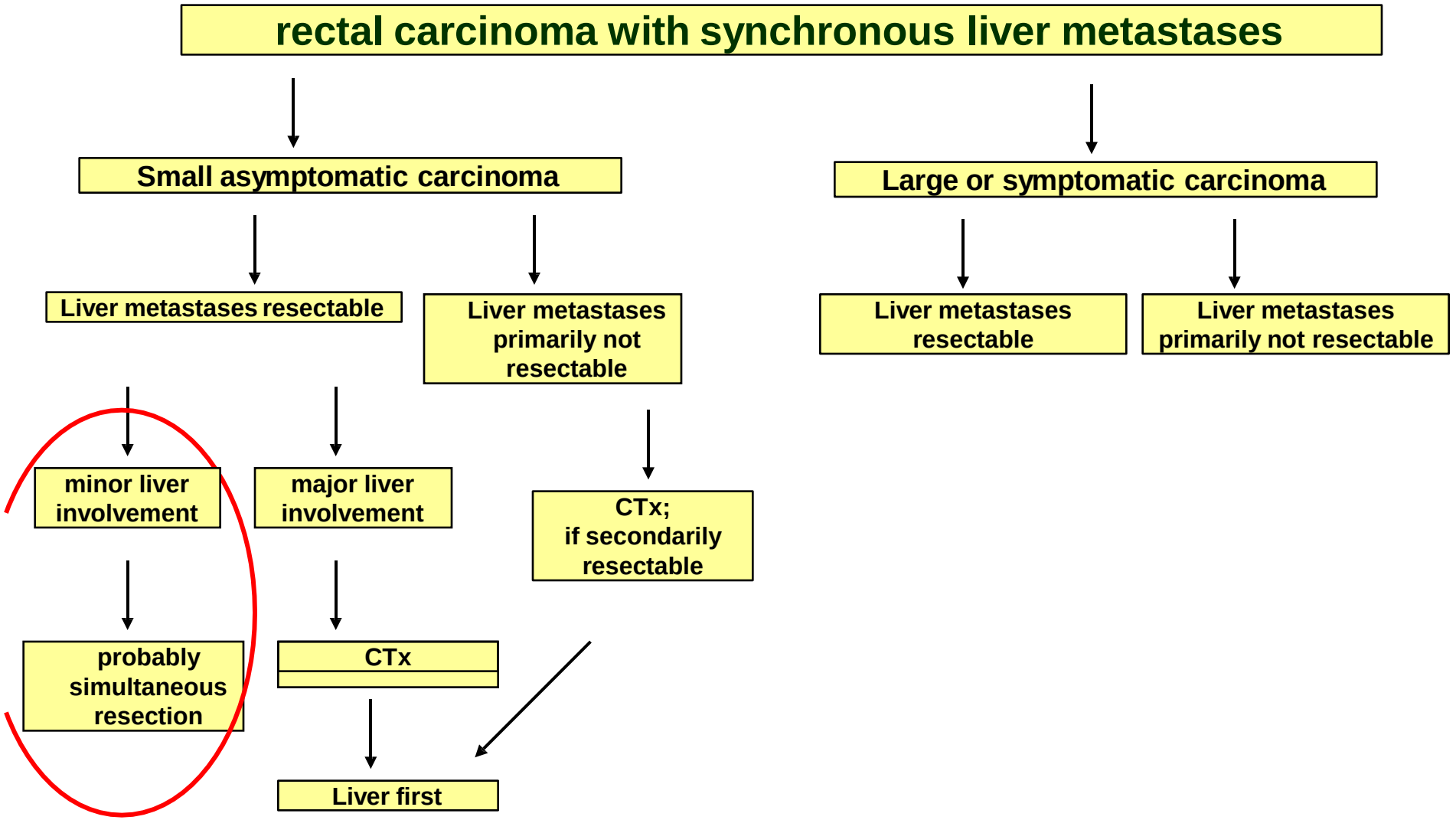

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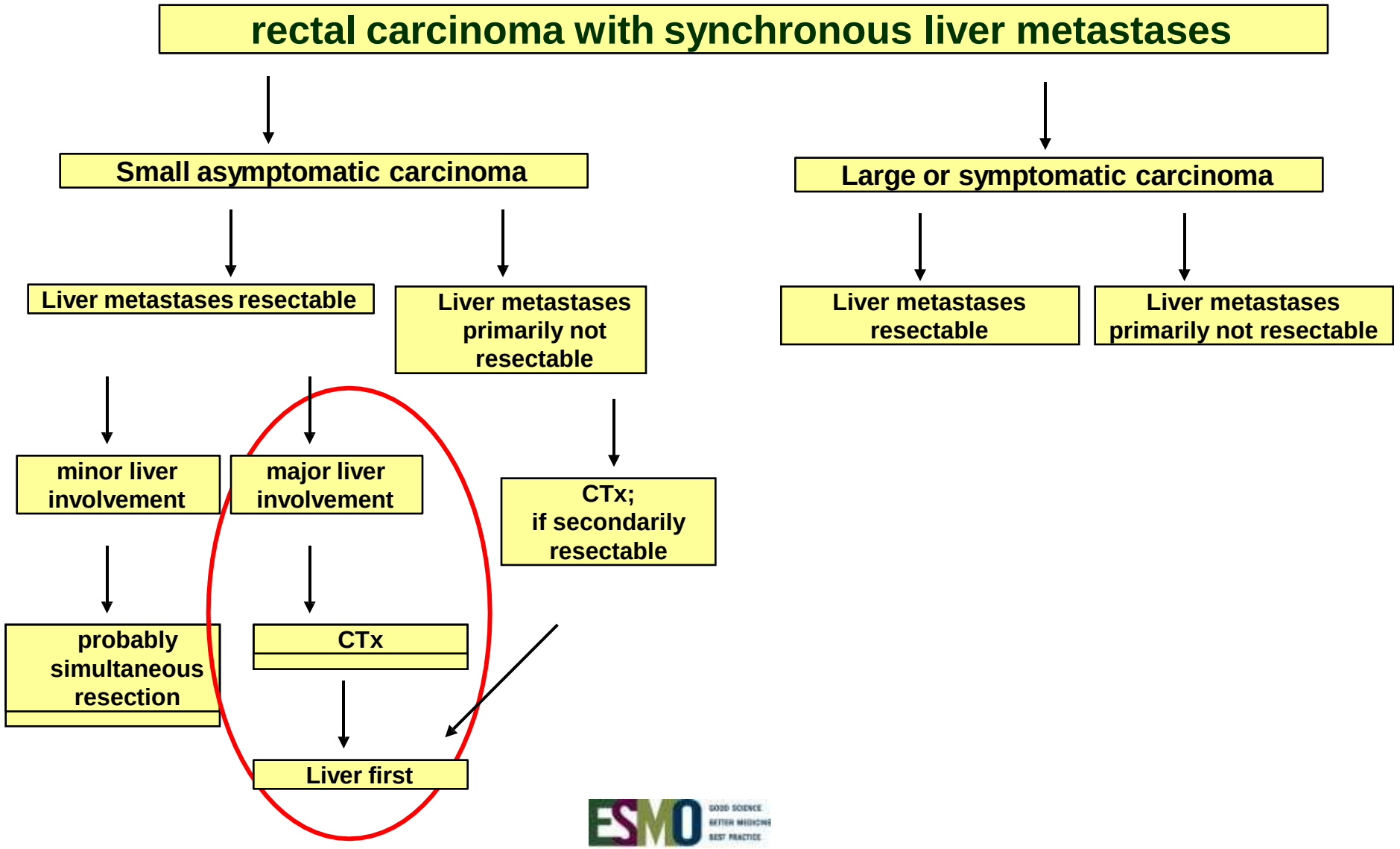

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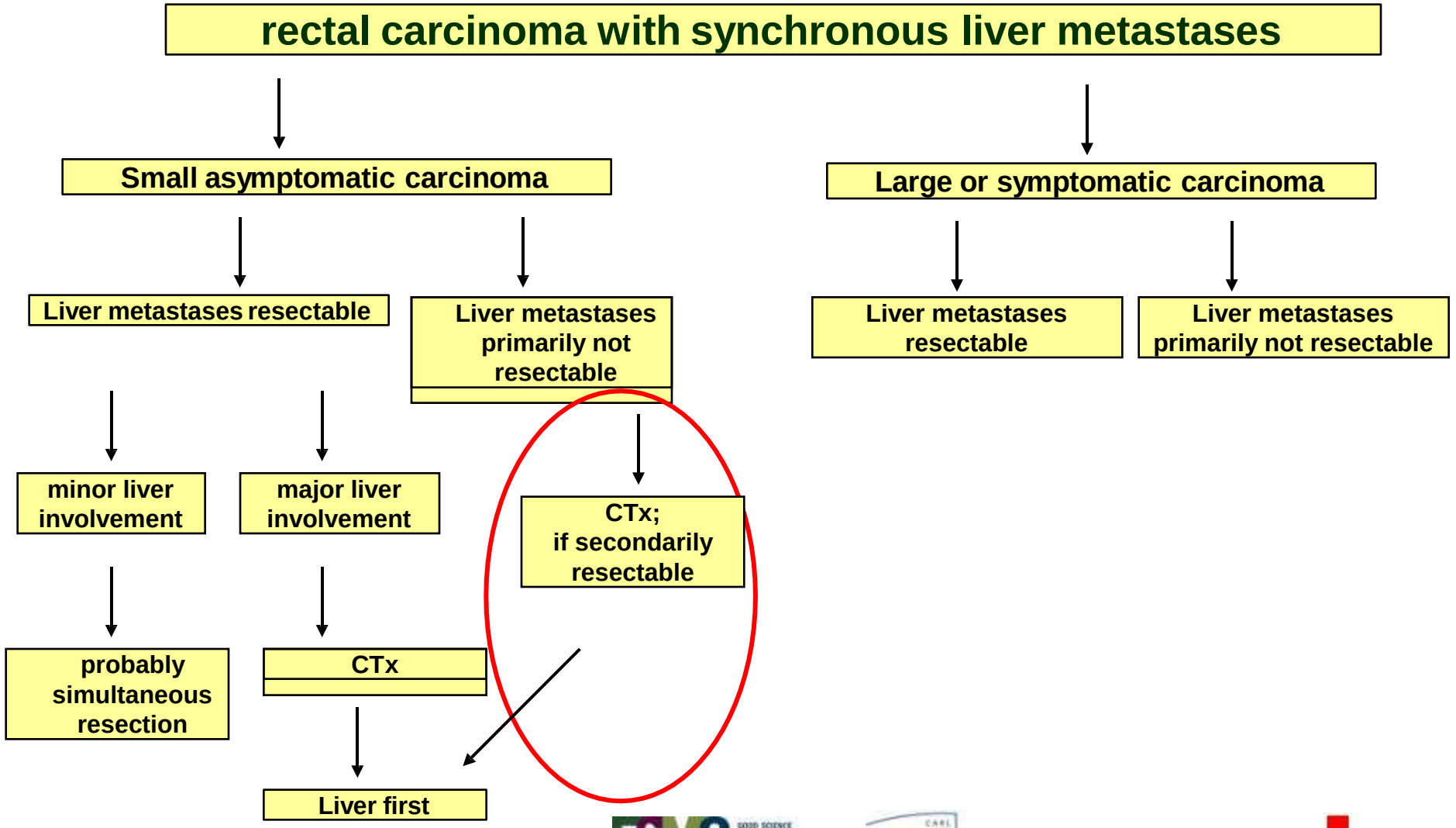
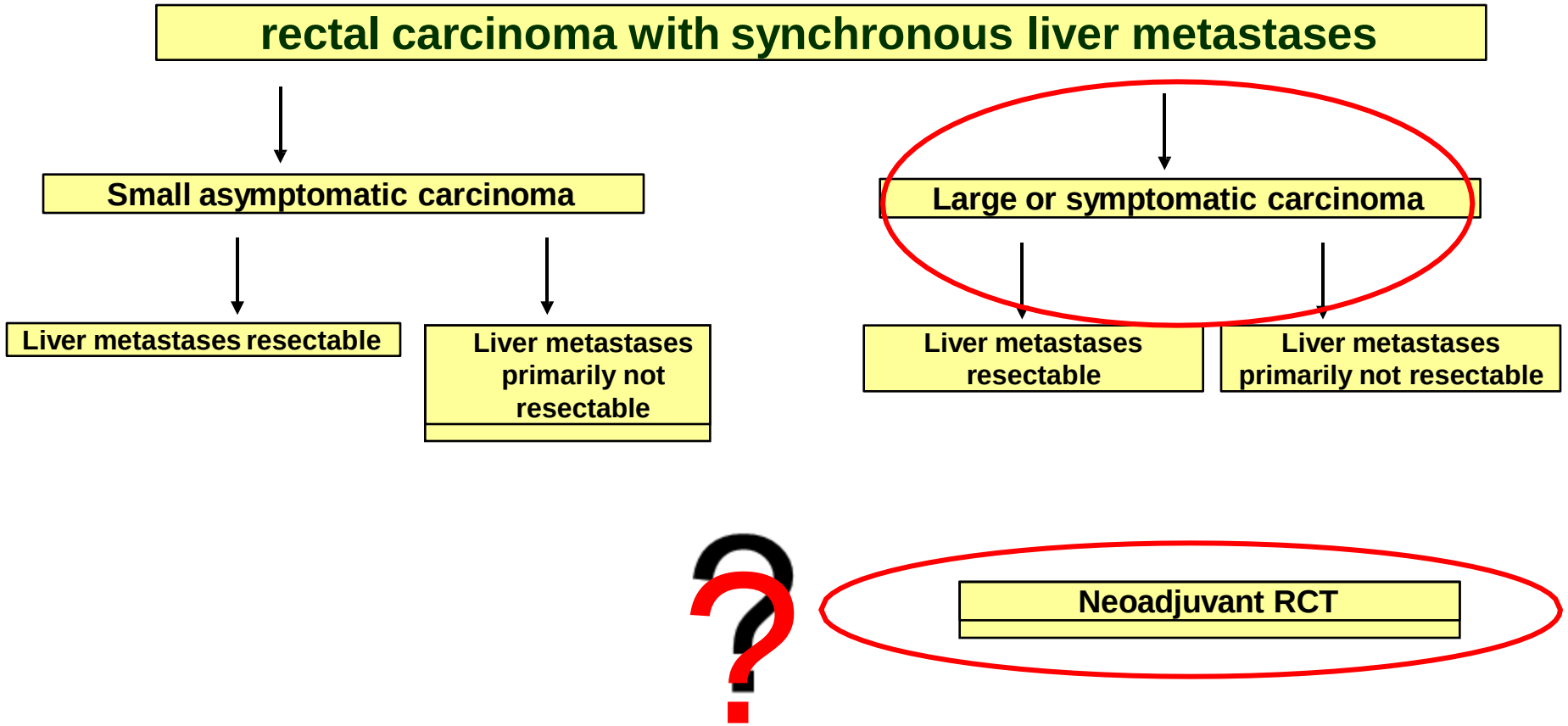
Strategy in rectal carcinoma stage IV (liver only)



Strategy in rectal carcinoma stage IV (liver only)



ESMO Guidelines Package

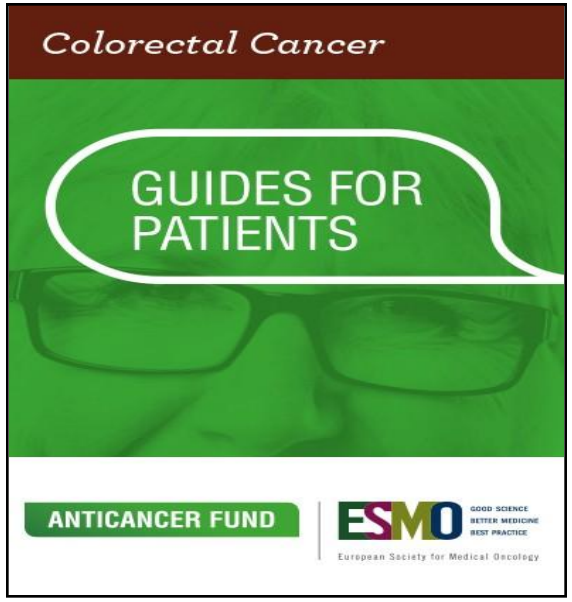
clinical practice guidelines

Annals of Oncology 00 (0): iii1–iii9, 2014
doi:10.1093/annonc/mdu260

Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

E. Van Cutsem[1], A. Cervantes[2], B. Nordlinger[3] & D. Arnold[4], on behalf of the ESMO Guidelines Working Group*

[1]Digestive Oncology, University Hospitals Leuven, Leuven, Belgium; [2]Department of Hematology and Medical Oncology, INCLIVA, University of Valencia, Valencia, Spain; [3]Department of General Surgery and Surgical Oncology, Hôpital Ambroise Paré, Assistance Publique – Hôpitaux de Paris, Paris, France; [4]Klinik für Tumorbiologie, Freiburg, Germany



special article

Annals of Oncology 23: 2479–2516, 2012
doi:10.1093/annonc/mds236

ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making

H. J. Schmoll[1*], E. Van Cutsem[2], A. Stein[3], V. Valentini[4], B. Glimelius[5,6], K. Haustermans[7], B. Nordlinger[8,9], C. J. van de Velde[10], J. Balmana[11], J. Regula[12], I. D. Nagtegaal[13], R. G. Beets-Tan[14], D. Arnold[3], F. Ciardiello[15], P. Hoff[16,17], D. Kerr[18], C.H. Köhne[19], R. Labianca[20], T. Price[21], W. Scheithauer[22], A. Sobrero[23], J. Tabernero[24], D. Aderka[25], S. Barroso[26], G. Bodoky[27], J. Y. Douillard[28], H. El Ghazaly[29], J. Gallardo[30], A. Garin[31], R. Glynne-Jones[32], K. Jordan[1], A. Meshcheryakov[31], D. Papamichail[33], P. Pfeiffer[34], I. Souglakos[35], S. Turhal[36] & A. Cervantes[37]

[1]Department of Oncology/Haematology, Martin Luther University Halle, Germany; [2]Digestive Oncology Unit, University Hospital Gasthuisberg, Leuven, Belgium; [3]Hubertus Wald Tumor Center, University Comprehensive Cancer Center, Hamburg-Eppendorf, Germany; [4]Department of Radiotherapy, Policlinico Universitario "A. Gemelli," Catholic University, Rome, Italy; [5]Department of Radiology, Oncology and Radiation Sciences, Uppsala University, Uppsala; [6]Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden; [7]Department of Radiation Oncology, University Hospitals Leuven Campus Gasthuisberg, Leuven, Belgium;

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Treatment of metastatic disease

Drivers for decison making in 1st line treatment

Table 4. Treatment drivers for first-line treatment

Tumour characteristics	Patient characteristics	Treatment characteristics
Clinical presentation: Tumour burden Tumour localisation	Age	Toxicity profile
Tumour biology	Performance status	Flexibility
RAS mutation status	Organ function	Socio-economic factors
BRAF mutation status	Comorbidities	Quality of life, patient expectation and preference

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Local and ablative treatment (including surgery)

Unresectable CLM with "conversion" as treatment goal

- Any patient with liver (+/- lung) limited disease should be considered a **candidate for potential secondary resection**
- In patients receiving conversion therapy, response to chemotherapy is a strong prognostic indicator
- **Resectability is to be evaluated after only 2 months of (optimal) treatment** so that the opportunity for resection is not missed
- R0 resection of lung metastases is recommended whenever feasible

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Local and ablative treatment (including surgery)

Recommendation: Conversion therapy

- In potentially resectable disease (where conversion is the goal) a regimen associated with a high response rate / best tumour size reduction is recommended
- There is uncertainty on the best combination:
  - **RAS mutant**: FOLFOXIRI *± bevacizumab or acytotoxic doublet*
  - **RAS wild type**: *doublet (FOLFOX/FOLFIR) plus an anti-EGFR antibody*

    seems to have the best benefit/risk ratio,

    although the *combination of FOLFOXIRI ± bevacizumab* may also be considered

Re-evaluate regularly to not overtreat resectable patients

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Local and ablative treatment (including surgery)

Recommendation: oligometastatic disease (omd)

- In patients with (unresectable) CLM only or omd, **local ablation techniques** such as RFTA, thermal ablation or high conformal radiotherapy (e.g. SBRT, HDR-brachytherapy) as well as embolization techniques can be **considered in addition to systemic therapy**
- In patients with CLM only or omd, resection and/or ablative high conformal radiotherapy, thermal ablation and others may be considered **in addition to resection** if this is limited by comorbidity, the extent of parenchyma resection, or other factors.
- The decision on the appropriate technique of the **"toolbox of ablative techniques"** should be taken in a MDT decision - based on local experience, tumour location / disease characteristics, patient preference

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- Papel de la clasificación TNM y de Patología
- Que pasa con la cirugía
- Manejo de la enfermedad localmente avanzada y Metastásica
- Lo más comentado……..

"Watch and wait" – subgroup from Manchester

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Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis

Andrew G Renehan, Lee Malcomson, Richard Emsley, Simon Gollins, Andrew Maw, Arthur Sun Myint, Paul S Rooney, Shabbir Susnerwala, Anthony Blower, Mark P Saunders, Malcolm S Wilson, Nigel Scott, Sarah T O'Dwyer

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See Comment page 125

Institute of Cancer Sciences, Manchester Academic Health Science Centre

Summary

Background Induction of a clinical complete response with chemoradiotherapy, followed by observation via a watch-and-wait approach, has emerged as a management option for patients with rectal cancer. We aimed to address the shortage of evidence regarding the safety of the watch-and-wait approach by comparing oncological outcomes between patients managed by watch and wait who achieved a clinical complete response and those who had surgical resection (standard care).

Methods Oncological Outcomes after Clinical Complete Response in Patients with Rectal Cancer (OnCoRe) was a propensity-score matched cohort analysis study, that included patients of all ages diagnosed with rectal adenocarcinoma

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Es la mejor Evidencia??????

Son necesarios mas estudios que así lo demuestren……

2016

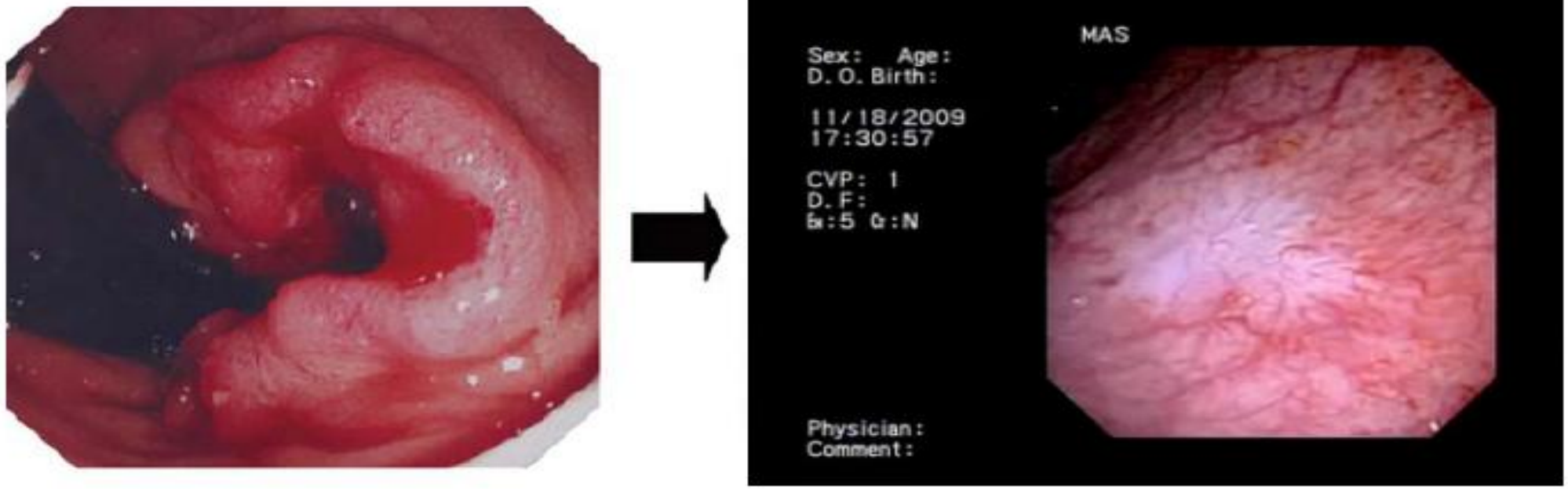
TME after neoadjuvant chemoradiation
ypT0N0 (ypCR)

T2-4, N+ rectal cancer, n = 3105

	Prevalence	pCR
cT2	4%	28%
cT3	83%	16%
cT4	12%	12%

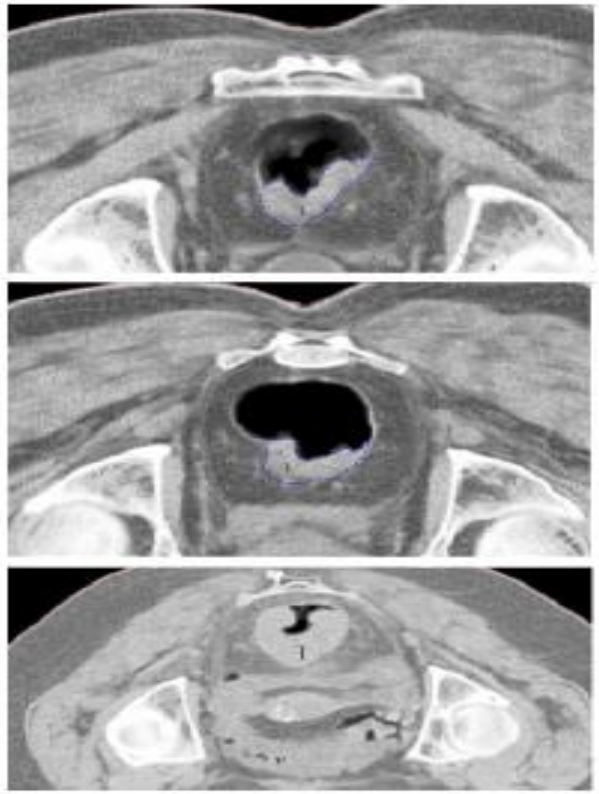
Maas et al. *Lancet Oncol* 2010; 11:835-41

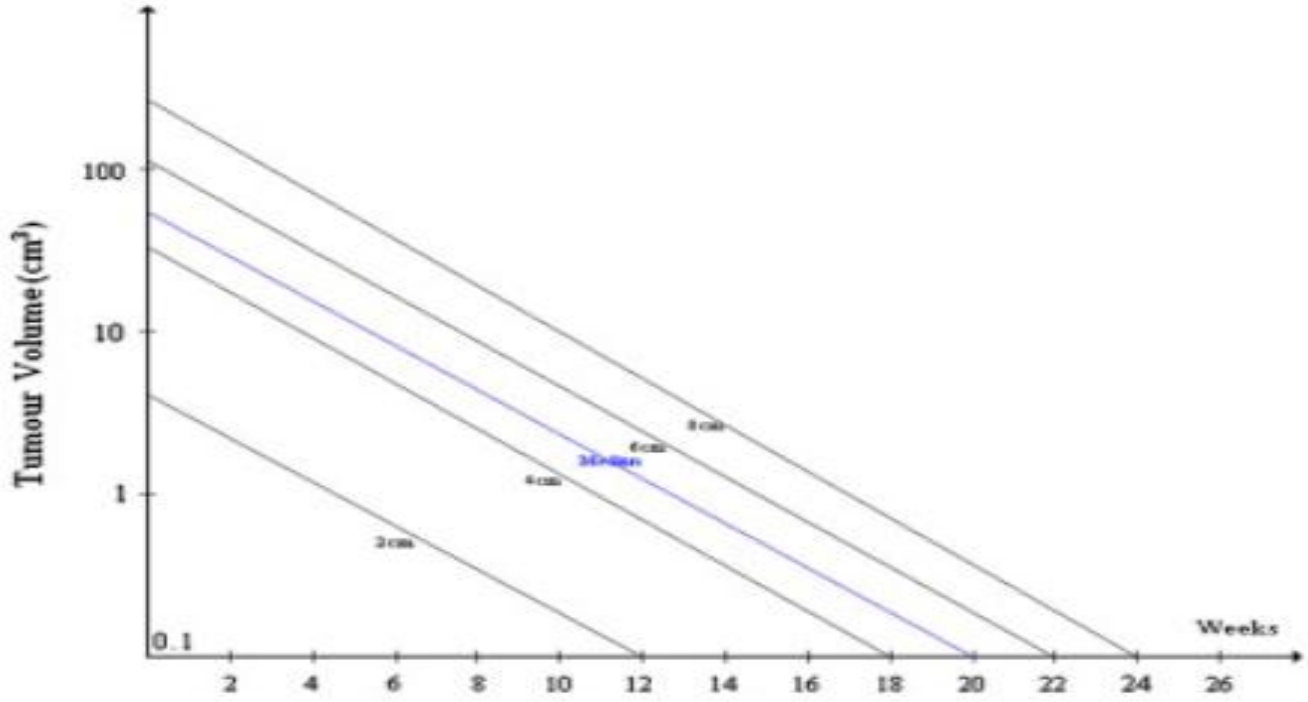
Can we avoid radical surgery in good responders after chemoradiotherapy?



concept of sustained clinical complete response

Radiation induced necrosis (apoptosis) is time-dependent

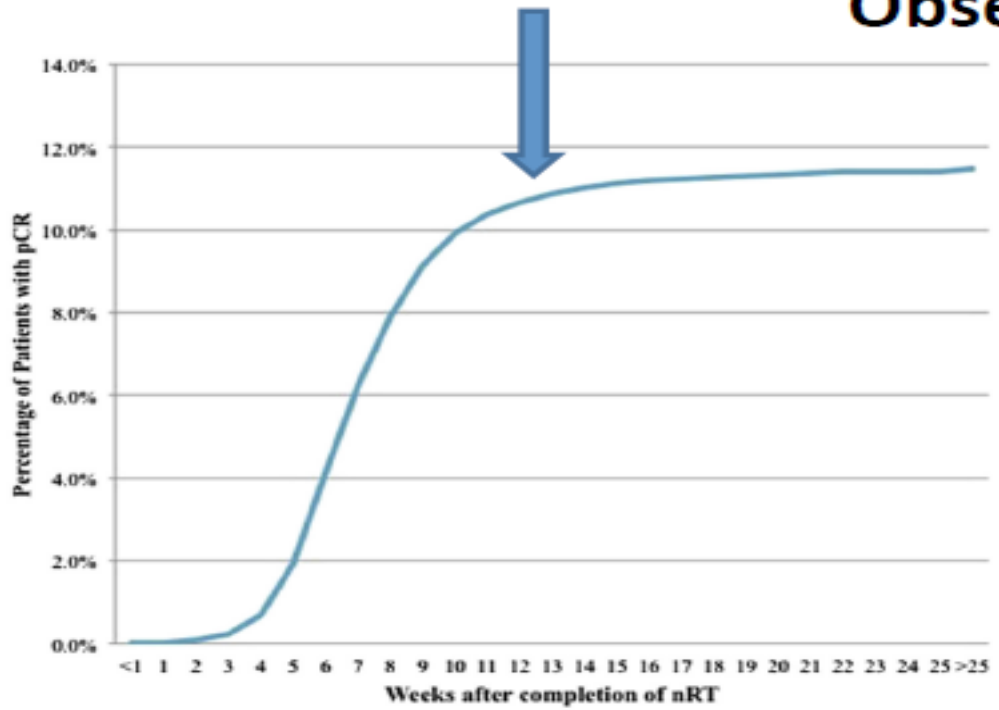




Dhadda A.S. *Clinical Oncology* 2009; **21**:23-31

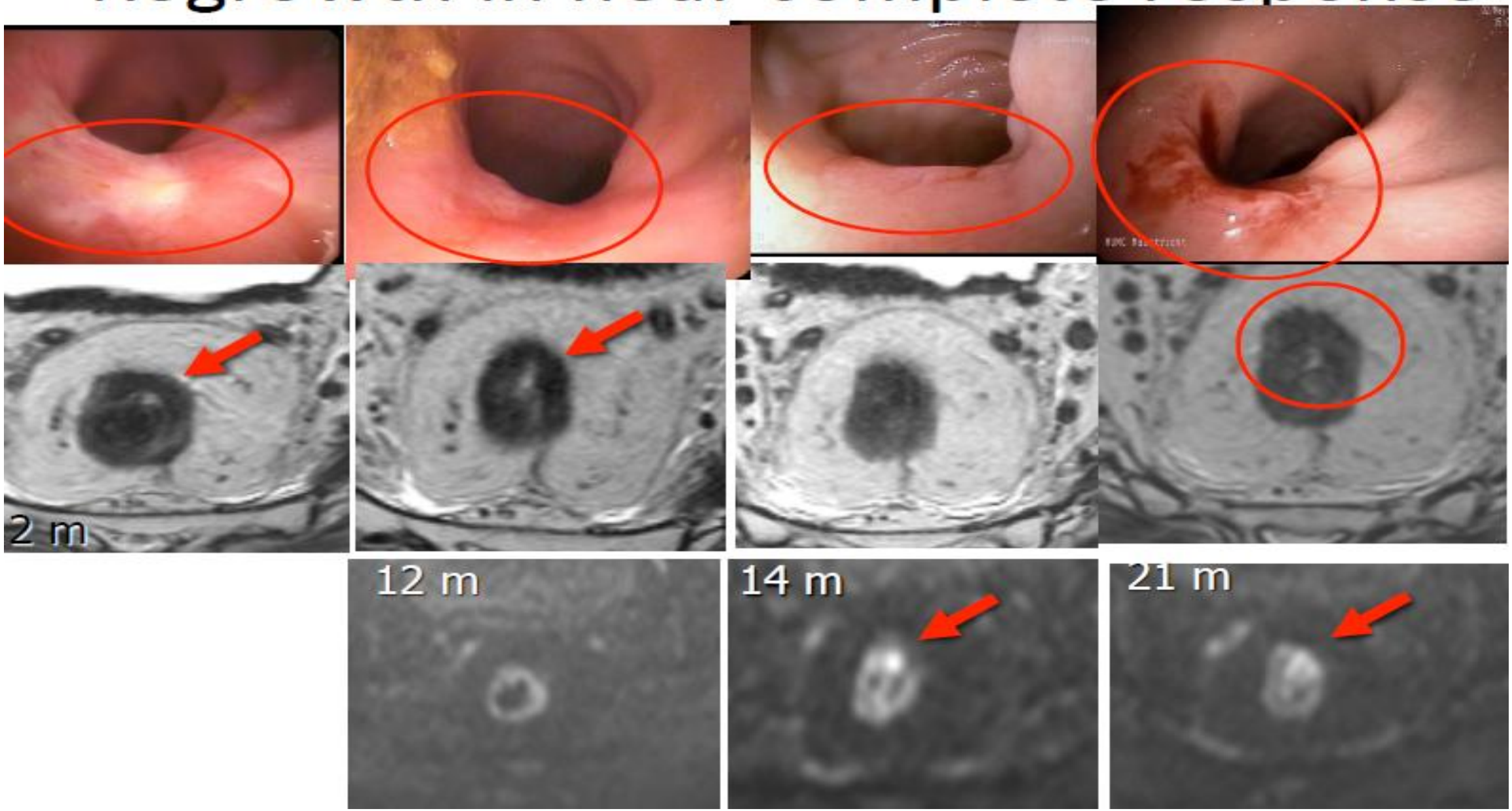
12 weeks: the new standard?

Observational



Probst CJ Am Coll Surg 2015;221:430-440

Regrowth in near complete response



“wait and see protocols”

- lack of clarity to **define** clinical complete response (**cCR**)
  - clinical criteria
  - imaging
  - punch biopsy – TEM (excisional biopsy)

- 20% - 30% fail the first year (**early regrowth**)
  - outcome early salvage

- uncertainty in regard to long-term efficacy (**late failure**)
  - rational, consistent follow-up programme
  - selection of patients
  - outcome late salvage

Conclusion

non-operative treatment **not accepted paradigm yet** (but appealing)

optimal neoadjuvant thearpy to be determined

multimodal-defined cCR improves accuracy

longer follow-up needed (>5 yrs.)

Conclusiones

- ✓ La Cirugia EMT es la opción estándar en C Recto
- ✓ El resultado de la anatomía patológica confirma la calidad quirúrgica
- ✓ Papel del uso de la QT/ RT Preoperatoria
- ✓ Integrar el manejo del paciente en equipos multidisciplinarios
- ✓ Saber interpretar el beneficio del tratamiento preoperatorio
- ✓ El manejo de la enfermedad L Avanz y metastásica es posible n

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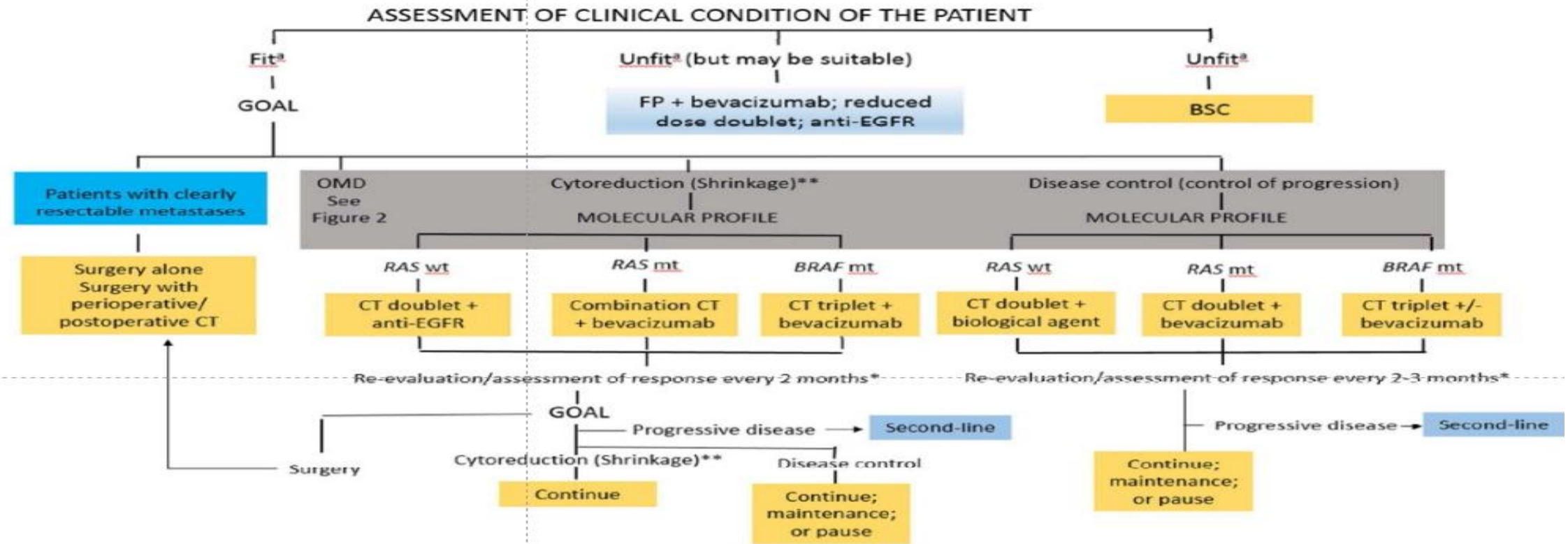
European Society for Medical Oncology

Treatment of metastatic disease

Figure 4. Zurich treatment algorithm



BSC, best supportive care; CT, chemotherapy; EGFR, epidermal growth factor receptor; FP, fluoropyrmidine; mt, mutant, NED, no evidence of disease; OMD, oligometastatic disease; wt, wild-type.

Gracias!!!!!!!!!