M1 hepáticas sincrónicas de cáncer de recto

19 de diciembre 2022
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Caso clínico

Mujer de 62 años. 1º síntoma: Tenesmo rectal.

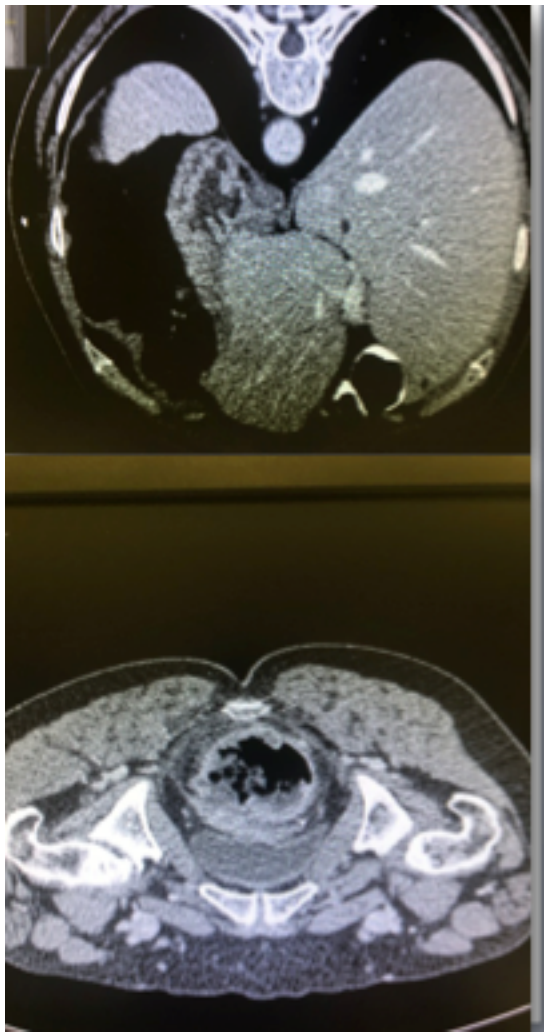
-Colonoscopia: Lesión en recto medio no estenosante.

-Adenocarcinoma de tipo intestinal.

-TC: Recto medio-alto cT3d-4aN+Mx.

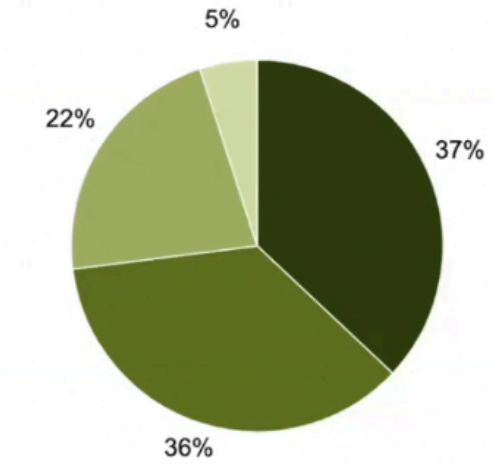
Lesión focal en seg V hepático de 10 mm.

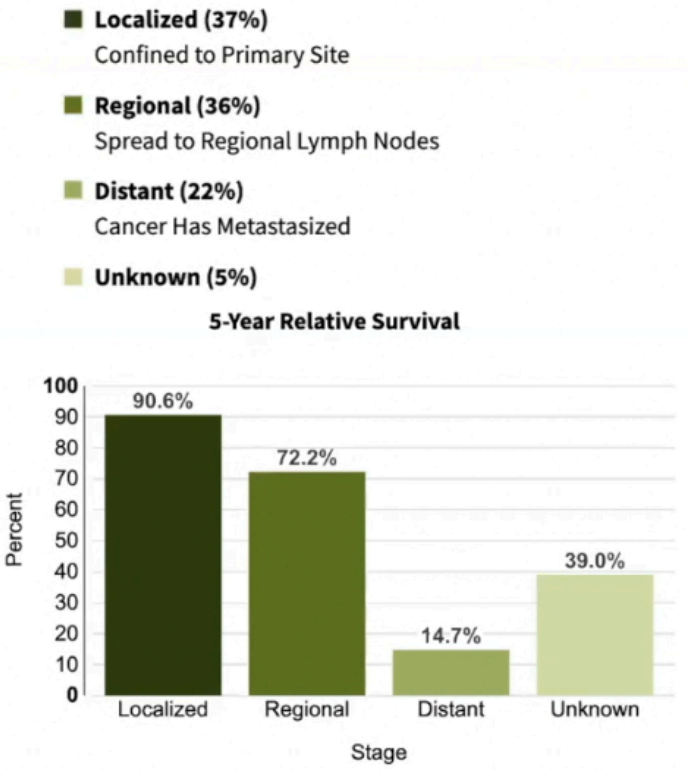
→ Presenta pérdida de expresión de PMS2.



Epidemiología

- 15% pac. tienen M1 hepáticas Sincrónicas.
- 15% pac tendrán M1 metacrónicas hepáticas.
  - 4% Estadio I
  - 13% estadio II
  - 30% estadio III
- >50% de las muertes en CRC son por M1 hepáticas.





Manfred et al. Ann Surg 2006; Helling et al. Ann Surg Onc 2014

Definición M1 sincrónicas

¿A qué nos referimos con metástasis hepáticas sincrónicas?

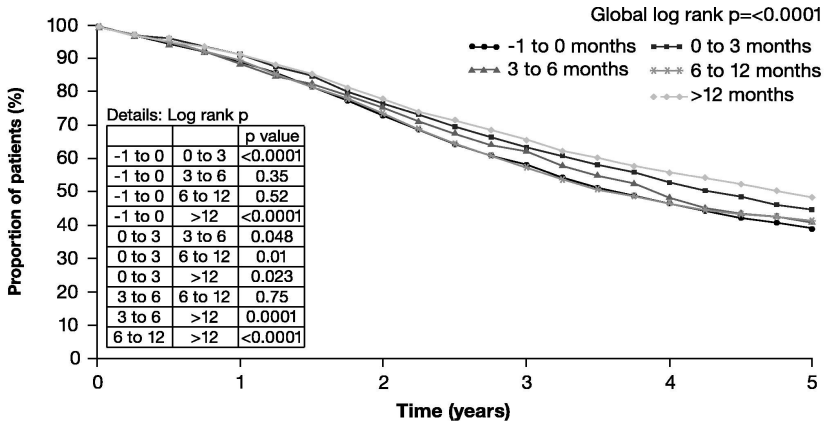
1. La mayoría de las definiciones incluyen aquellas metástasis que se detectan antes o durante el diagnóstico o cirugía del tumor primario.

2. Marcan peor pronóstico.

Adam et al. *Cancer Treatment Reviews* 2015 41729-741DOI: (10.1016/j.ctrv.2015.06.006)

Definición M1 sincrónicas

Algunos autores incluyen las que se detectan en los tres o cuatro o seis primeros meses, tras el diagnóstico del primario.



		p value
-1 to 0	0 to 3	<0.0001
-1 to 0	3 to 6	0.35
-1 to 0	6 to 12	0.52
-1 to 0	>12	<0.0001
0 to 3	3 to 6	0.048
0 to 3	6 to 12	0.01
0 to 3	>12	0.023
3 to 6	6 to 12	0.75
3 to 6	>12	0.0001
6 to 12	>12	<0.0001

Survival %

Diagnosis of metastases	1 year	2 years	3 years	4 years	5 years
-1 to 0 months	89%	73%	58%	46%	39%
0 to 3 months	91%	77%	64%	53%	44%
3 to 6 months	89%	75%	62%	48%	41%
6 to 12 months	90%	74%	57%	46%	41%
>12 months	92%	78%	66%	56%	48%

Number of exposed patients

	Total	1 year	2 years	3 years	4 years	5 years
-1 to 0 months	5272	3456	2259	1429	896	572
0 to 3 months	2783	1901	1294	840	542	341
3 to 6 months	1339	871	581	382	220	151
6 to 12 months	1913	1256	832	525	327	229
>12 months	4912	3346	2282	1550	1028	704

Adam et al. *Cancer Treatment Reviews* 2015 41729-741DOI: (10.1016/j.ctrv.2015.06.006)

JAMA Network Open

Original Investigation | Oncology

Incidence and Survival in Synchronous and Metachronous Liver Metastases From Colorectal Cancer

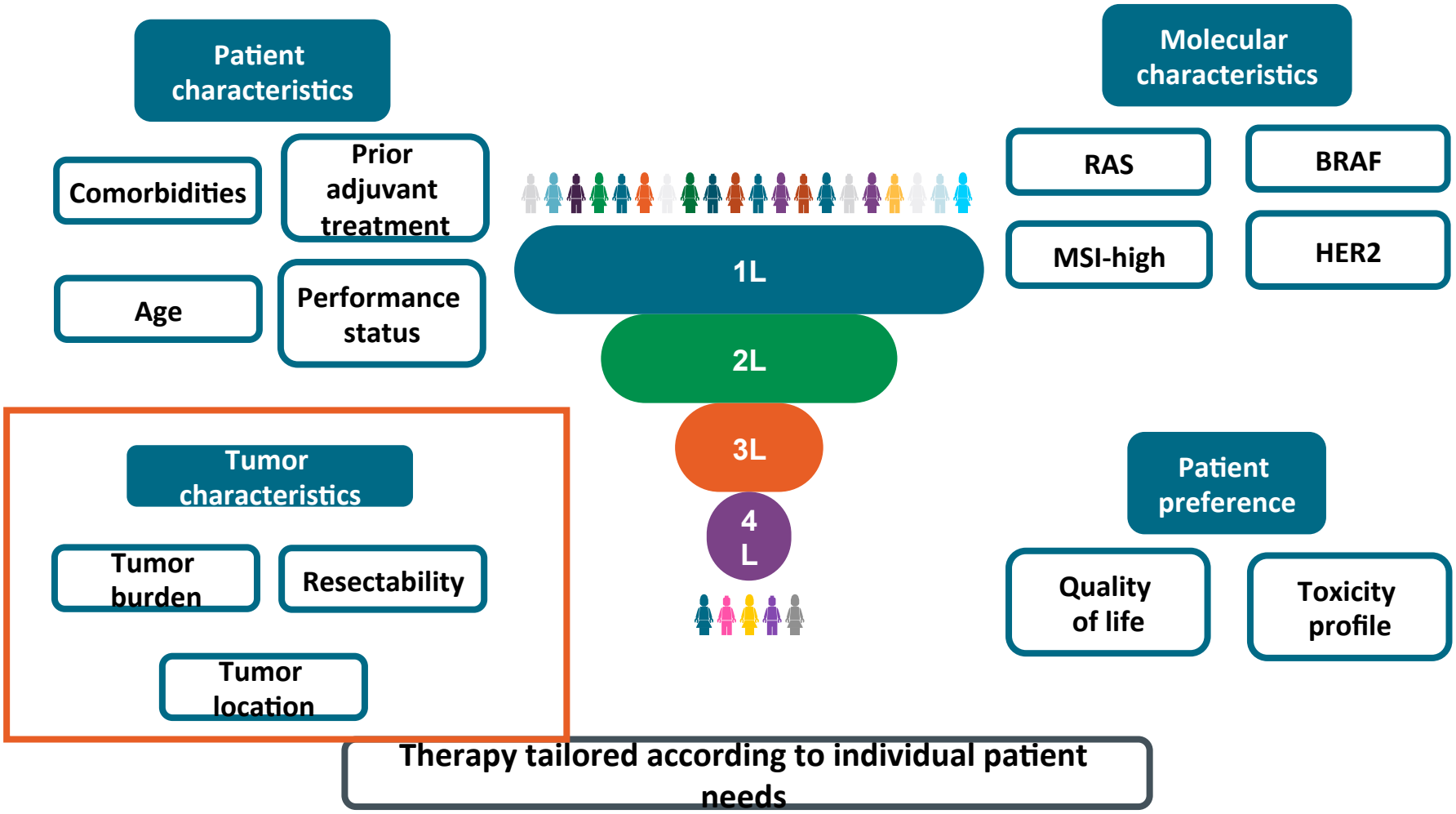
Noémi Reboux, MD; Valérie Jooste, PhD; Juste Goungounga, MD, PhD; Michel Robaszkiewicz, MD, PhD; Jean-Baptiste Nousbaum, MD, PhD; Anne-Marie Bouvier, MD, PhD

What are the **differences** in patterns of **incidence and outcomes** over time between **synchronous and metachronous** liver metastases from colorectal cancer?

- De 26 813 pac CRC 4546 (17.0%) presentaron LM(liver M1) sincrónicas.
- La tasa de incidencia de LM sincro es 6.9 por 100.000 hab en hombres y 3.4 por 100.000 hab en mujeres, sin variación desde el 2000.
- La incidencia acumulada de LM meta pasó de un 18,6% de 1976-1980 a un 10% en el periodo 2006-2011.
- Supervivencia a un año: 41.8% en LMsincro VS 49,9% en LM meta
- Supervivencia a 5 años, es de 6.2% para LMsincro VS 13.2% para LMmeta.

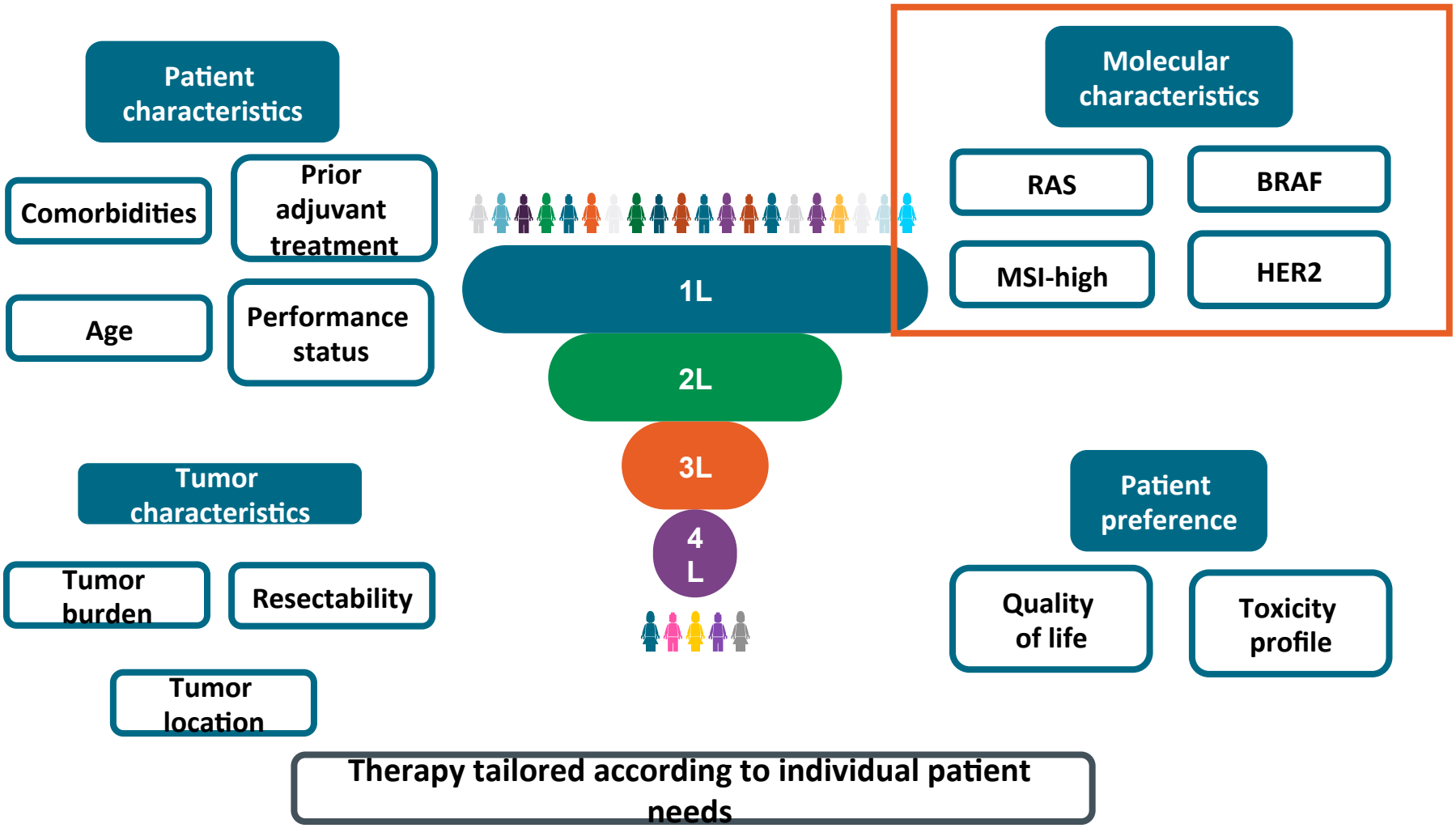
Reboux N. et al. JAMA Network Open. 2022

¿Elección del tratamiento de un paciente con mCRC?



Modified from Van Cutsem. Ann Oncol. 2016;27:1386.

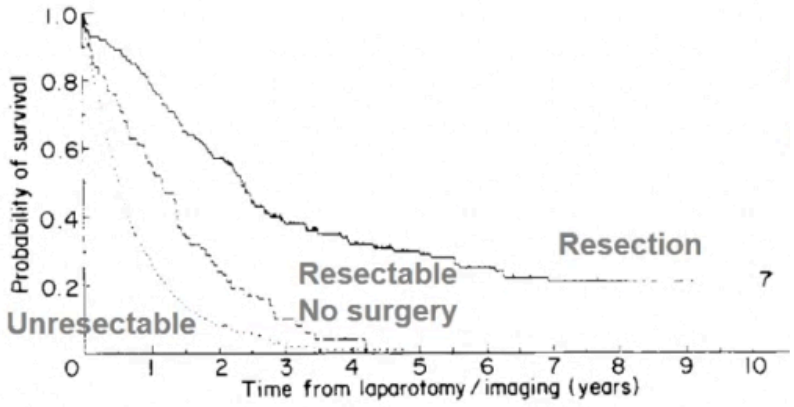
¿Elección del tratamiento de un paciente con mCRC?

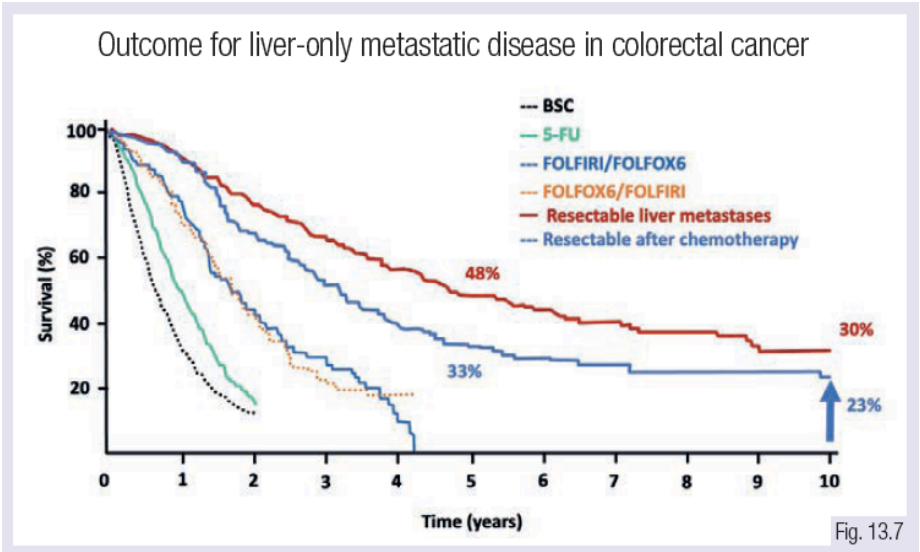


Modified from Van Cutsem. Ann Oncol. 2016;27:1386.

Enfermedad metastásica hepática.

- Las M1 hepáticas representan la principal causa de morbi-mortalidad en los pacientes con ADC colorrectal.
- La supervivencia tras la cirugía R0 es de aprox 30-50% y a 10 años de un 20%.
- El 12,5 % de los pacientes con M1 hepáticas irresecables, pueden ser convertidos a resecables, tras tratamiento sistémico basado en quimioterapia.





1.Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectablecolorectal liver metastases downstaged by chemotherapy: a model topredict long-term survival. Ann Surg 2004;240:644–57. discussion 657-648. 2. Adam R, Avisar E, Ariche A, et al. Five-year survival following hepaticresection after neoadjuvant therapy for nonresectable colorectal. AnnSurg Oncol 2001;8:347–53.

Clinical risk scores for patients with colorectal liver metastases

	Criteria (1 point assigned for each risk factor)	Risk groups
Fong[1]	1. Disease-free interval <12 months 2. Number of metastases >1 3. Preoperative CEA level >200 ng/mL 4. Largest liver metastasis >5 cm 5. Lymph node positive primary tumor	Low: 0 to 2 points High: 3 to 5 points
Nordlinger[2]	1. Age >60 2. Serosal invasion of the primary tumor (>pT3) 3. Lymph node positive primary tumor 4. Disease-free interval <24 months 5. Number of liver metastases >3 6. Largest liver metastasis >5 cm	Low: 0 to 2 points Intermediate: 3 to 4 points High: 5 to 6 points
Nagashima[3]	1. Serosal invasion of primary tumor (>pT3) 2. Lymph node positive primary tumor 3. Number of liver metastases ≥2 4. Largest liver metastasis >5 cm 5. Resectable extrahepatic metastases	Low: 0 to 1 points Intermediate: 2 to 3 points High: ≥4 points
Konopke[4]	1. Number of liver metastases ≥4 2. CEA ≥200 ng/mL 3. Synchronous liver metastases	Low: 0 points Intermediate: 1 point High: ≥2 points

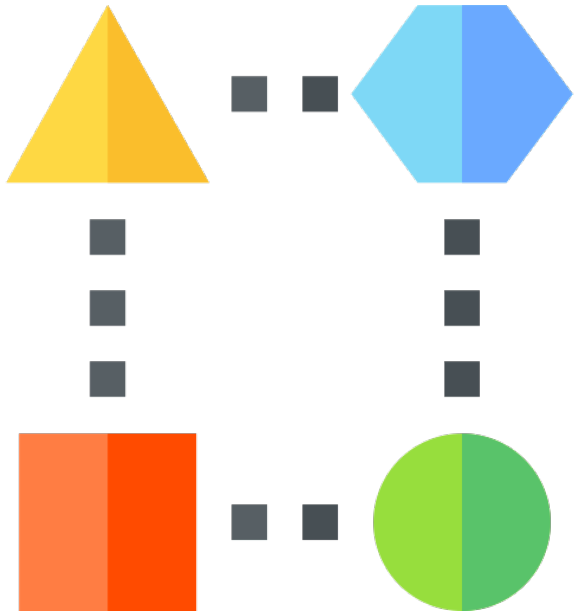
SYNCHRONOUS RECTAL PRIMARY AND METASTASES

" Control of disease in the pelvis can have important implications for patient quality of life; therefore, combined modality therapy, including radiation, chemotherapy, and in some cases palliative surgery, can be appropriate, especially when extrapelvic metastatic disease is small volume and the patient´s prognosis is favorable enough that pelvic complications could be anticipated as a long-term problem."

Pag 837 , Capítulo 60; De Vita 10º edición

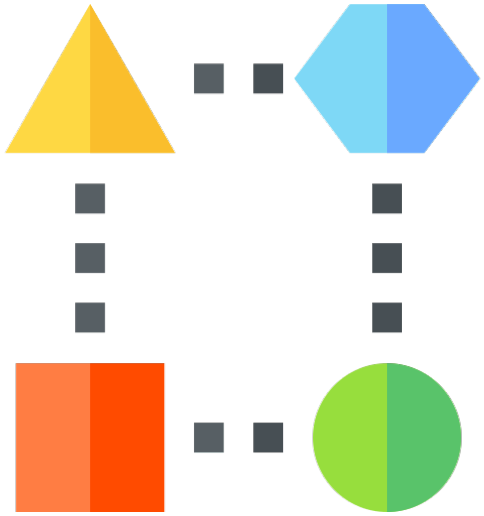
Entonces, ¿ por donde empezamos?

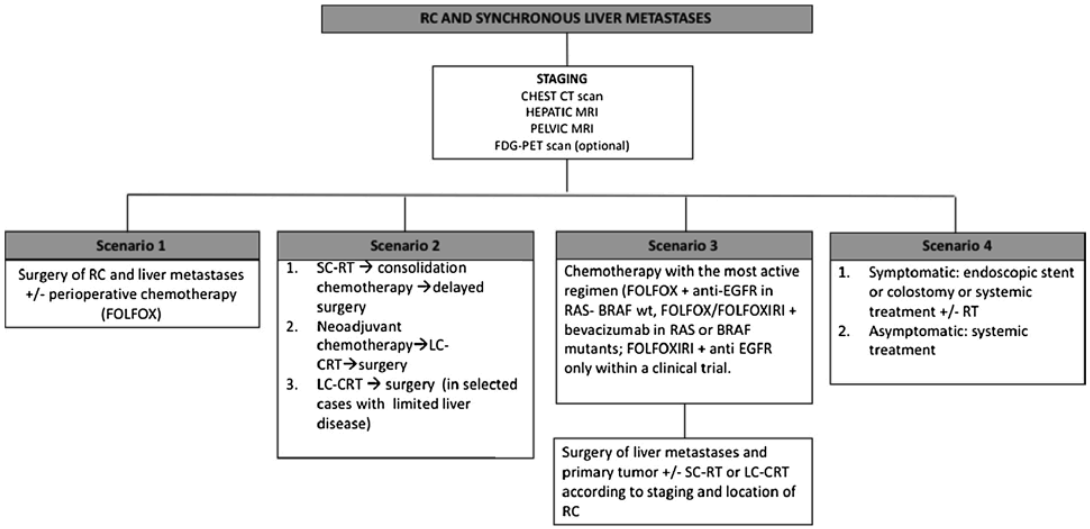
- Pues, depende…



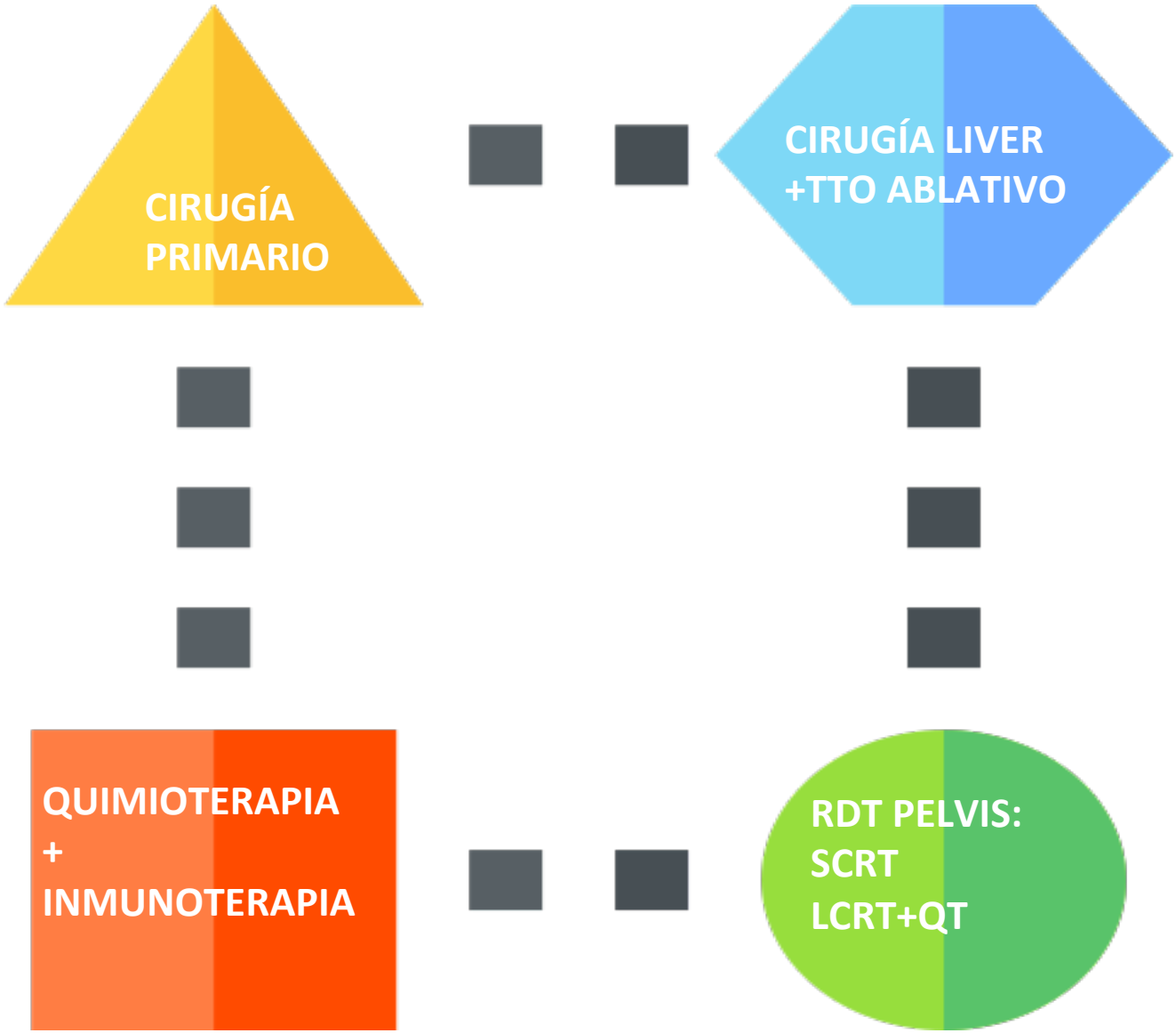
Entonces, ¿ por donde empezamos?

- Pues, depende…
- Tumor primario
  - ✧ Recto alto,medio,bajo
  - ✧ cTN; Fascia mesorrectal
  - ✧ Irresecable
- M1 hepáticas:
  - ✧ Resecables fácil
  - ✧ Bordeline
  - ✧ Irresecables
  - ✧ Bilobares





Elementos del tratamiento



Comité multidisciplinar

Comité multidisciplinar.
Tratamiento sistémico: QT

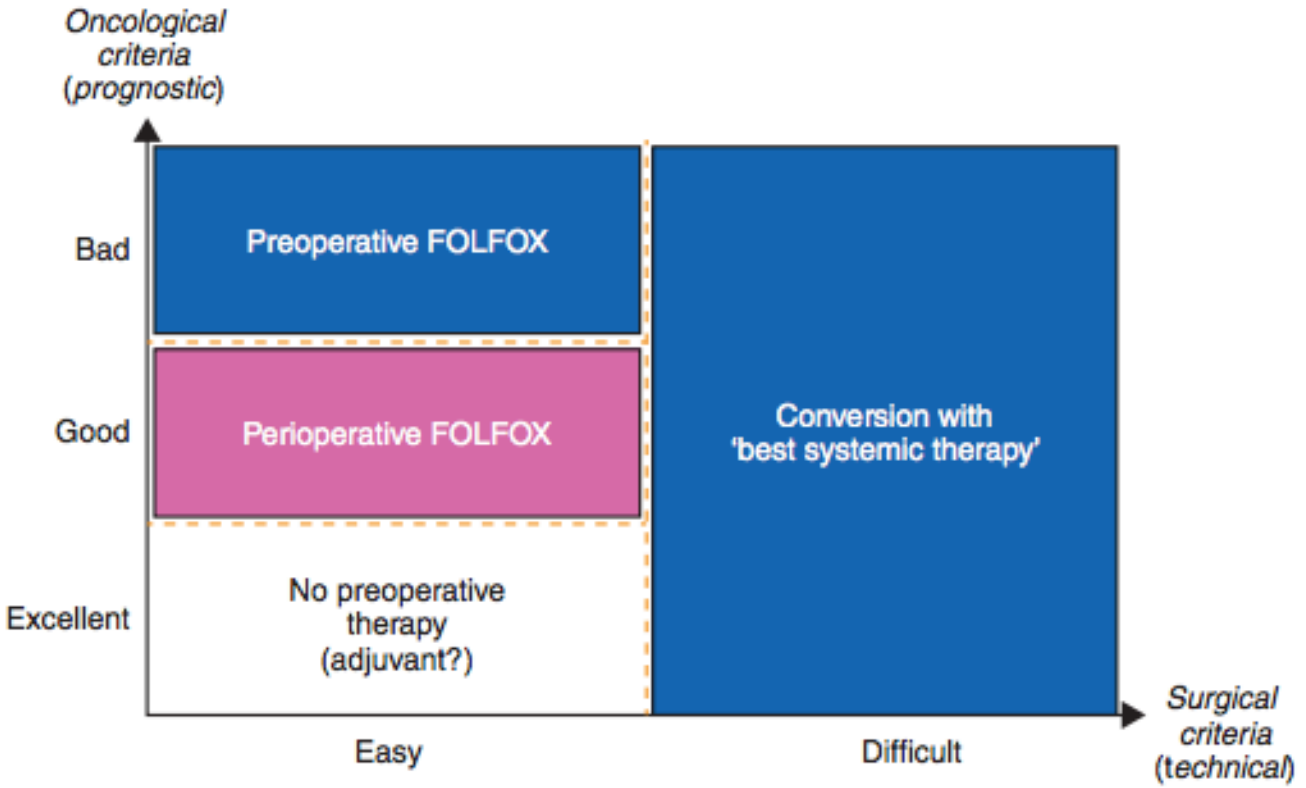


Figure 2. Categorisation of patients according to technical and oncological criteria. FOLFOX, infusional 5-fluorouracil, leucovorin, oxaliplatin.

Annals of Oncology 25 (Supplement 3): iii1–iii9, 2014 doi:10.1093

TUMOR PRIMARIO EN RECTO

¿ que tenemos en cuenta?

Low-risk

T2 T3a-b / Nx
< 4 cm

Up-front TME
Rectal preservation ?
CRT

Intermediate-risk

> 4 cm
T2 T3/ Nx
CRM > 2mm

TNT
RT-free strategy?
CT alone

High-risk

T3 T4/ Nx
Lateral LN+
EMVI+
CRM < 1mm

TNT
Survival without metastases

Estrategias de tratamiento del cáncer de recto localmente avanzado

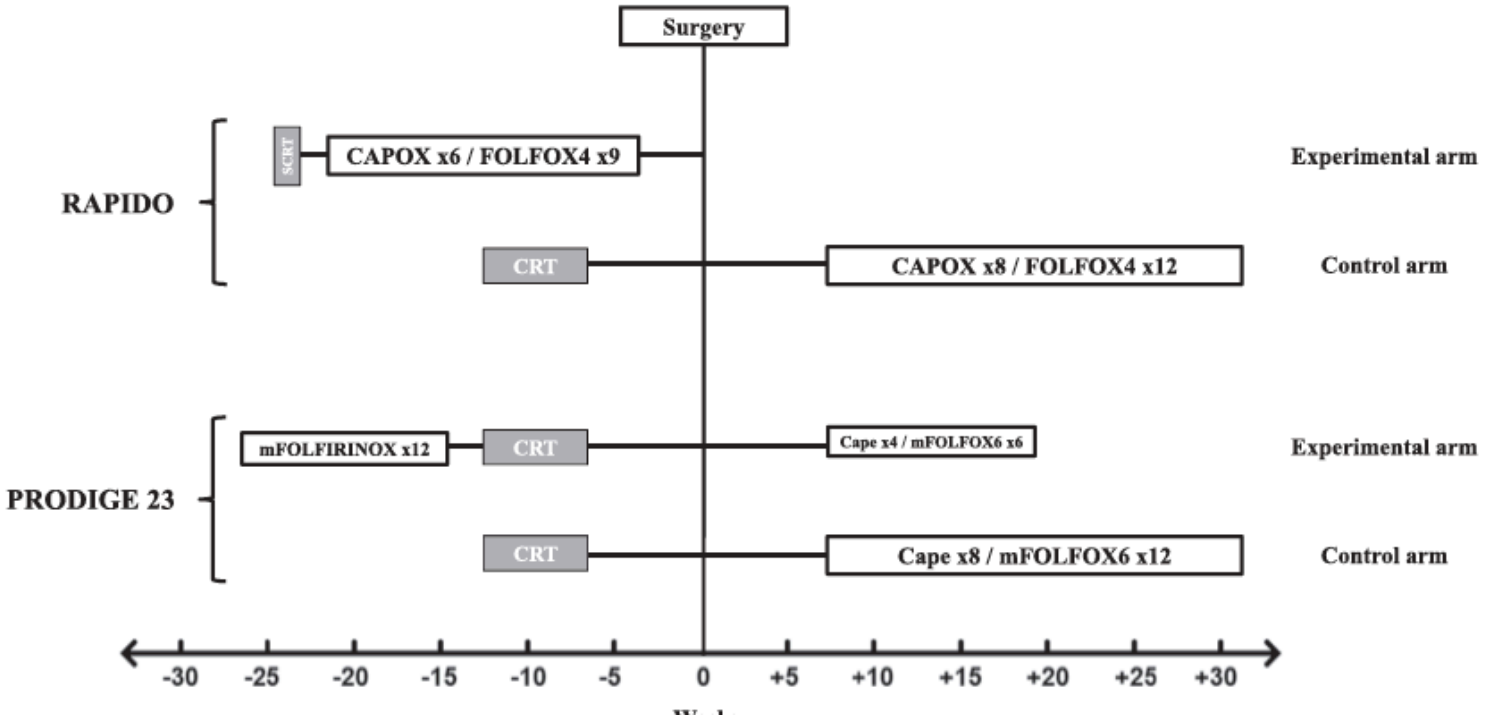
Traditional "Sandwich" Approach

LCCRT or SCRT → Surgery → Adjuvant Chemo

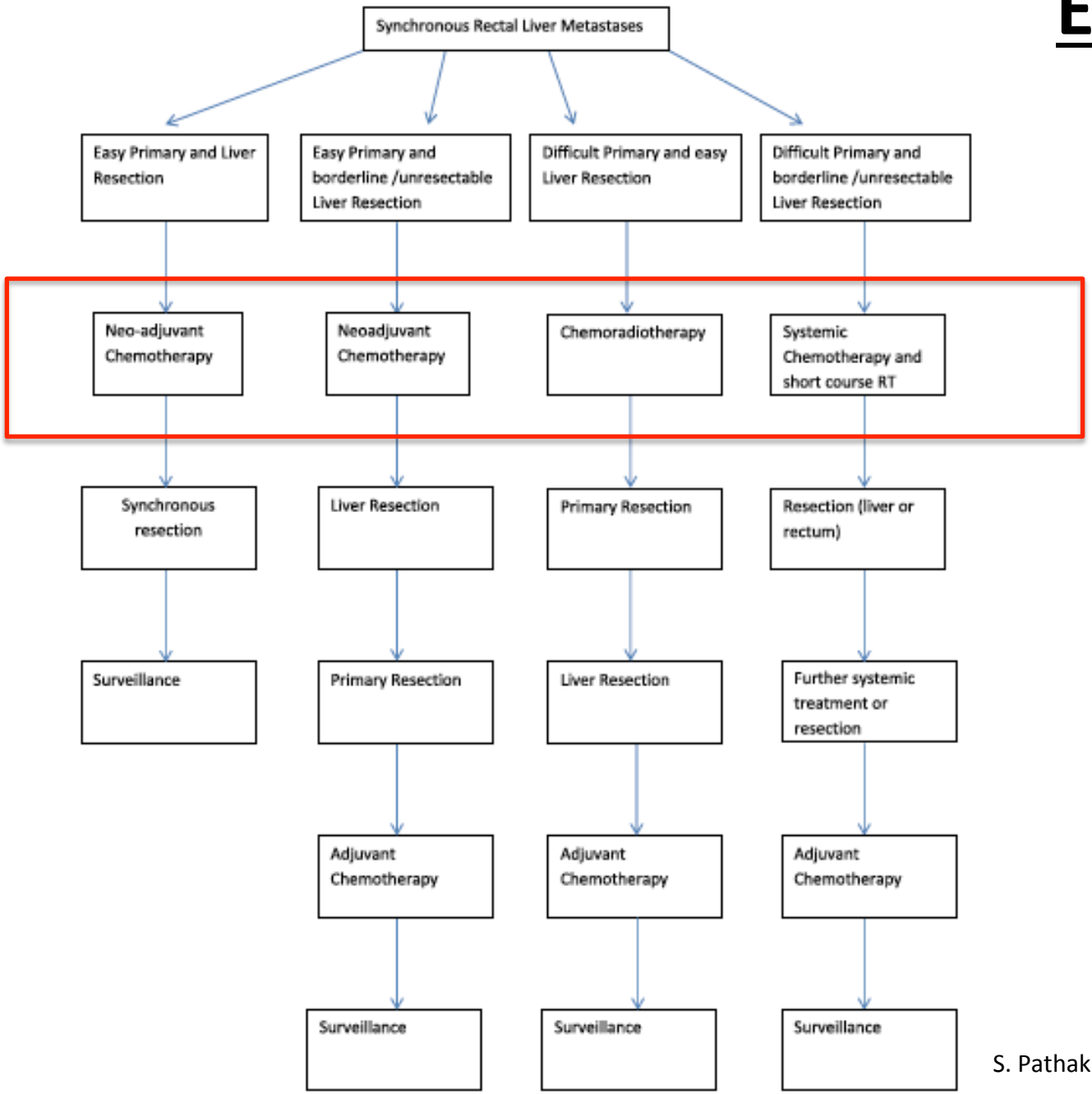
Total Neoadjuvant Therapy

Chemo → LCCRT or SCRT → Surgery

LCCRT or SCRT → Chemo → Surgery



Escenarios

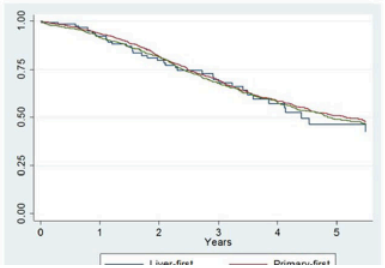


TRATAMIENTO SISTÉMICO FIRST

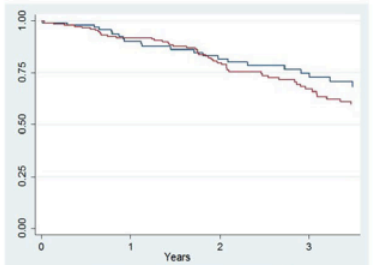
S. Pathak et al. / EJSO 41 (2015) 1570e1577

Estrategia/tiempo qgco.
Liver first.

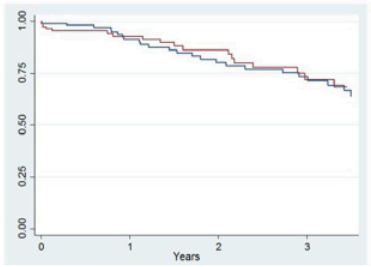
Whole population



Liver-first vs. Primary-first after PSM

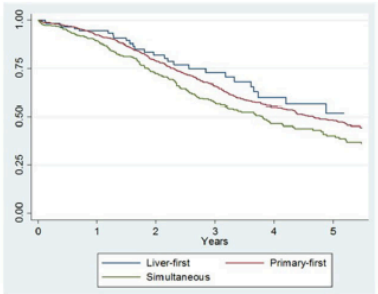


Liver-first vs. Simultaneous after PSM

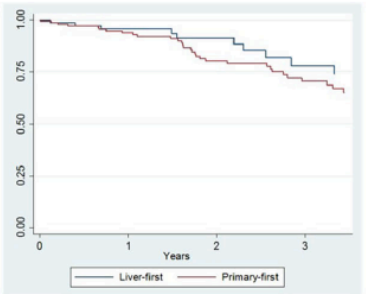


LM solitary

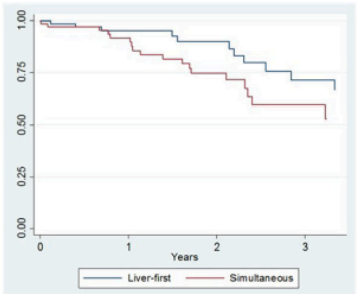
Whole population



Liver-first vs. Primary-first after PSM

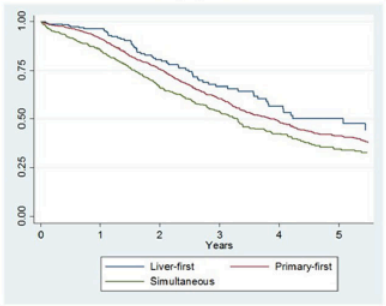


Liver-first vs. Simultaneous after PSM

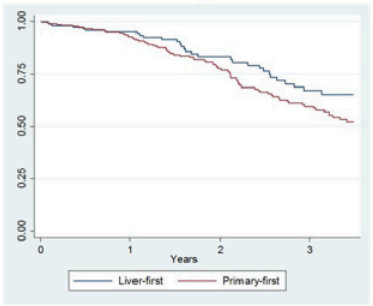


LM unilobar

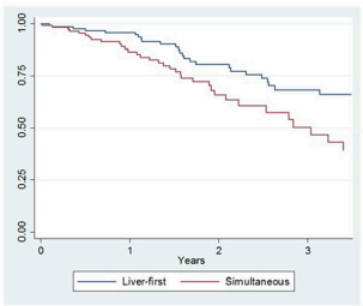
Whole population



Liver-first vs. Primary-first after PSM



Liver-first vs. Simultaneous after PSM



LM bilobar

	0	1 years	2 years	3 years	4 years	5 years
Primary-first	1644	1110	757	491	316	214
Liver-first	252	172	99	62	36	22

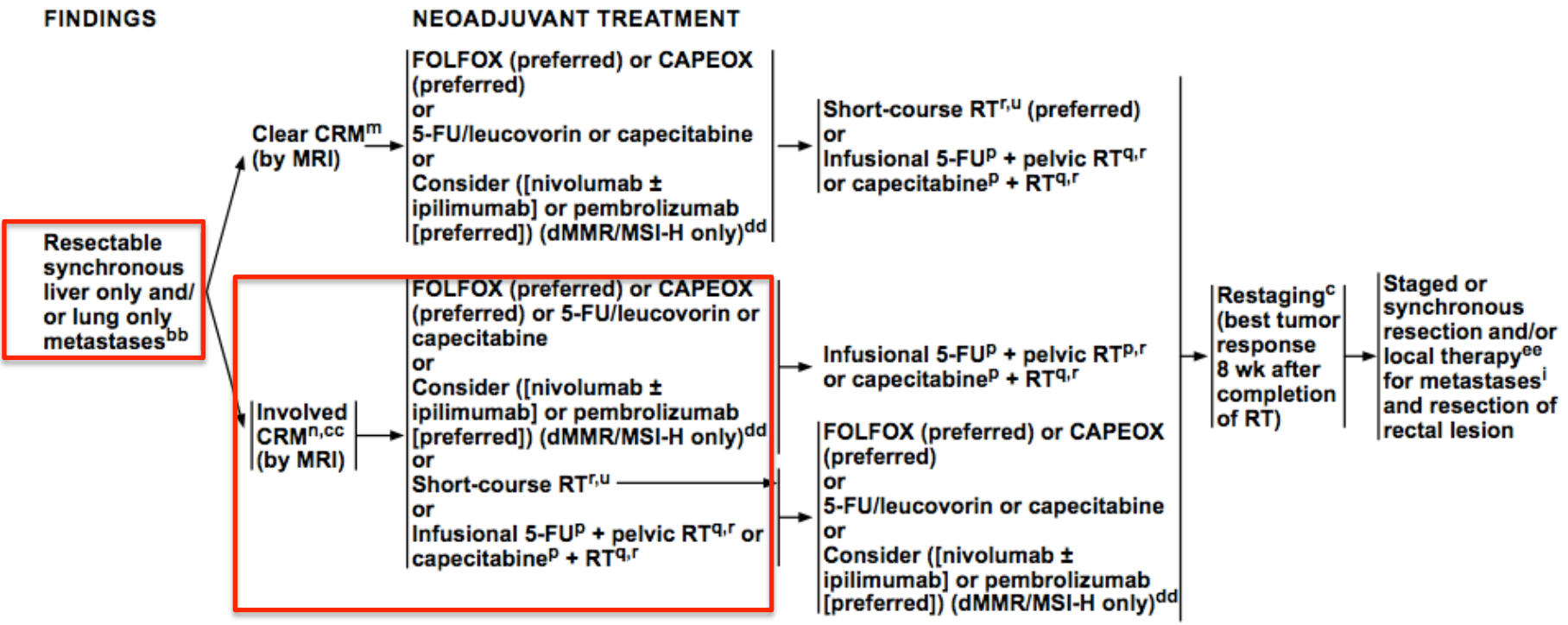
	0	1 year	2 years	3 years
Primary-first	326	194	123	71
Liver-first	163	111	66	40

	0	1 year	2 years	3 years
Liver-first	135	93	52	34
Simultaneous	135	71	31	15

Giuliante F, et al. Ann Surg Oncol (2021) 28:8198–8208

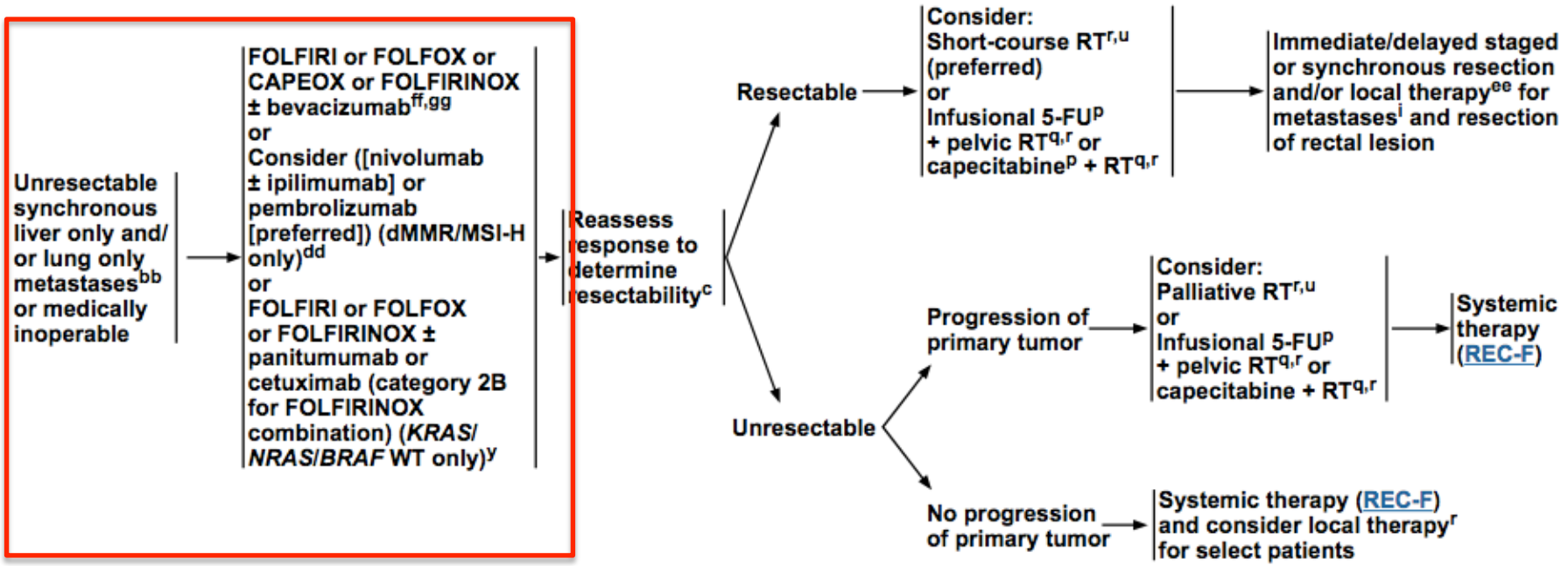
¿Qué dicen las guías?

There is NCCN Member Institutional variation in the choice of neoadjuvant therapy approach for resectable synchronous metastases. Standard practice at some institutions is to start with chemotherapy and then to stratify further treatment based on the degree of metastatic disease and the response to initial therapy. If the risk of distant failure is deemed to be the greater concern, resection would be the next course of treatment. If local failure appears more likely, then RT would be given before surgery.



[c] Principles of Imaging (REC-A).
[i] Principles of Surgery (REC-C).
[m] CRM measured at the closest distance of the tumor to the mesorectal fascia. Clear CRM: Greater than 1 mm from mesorectal fascia and levator muscles and not invading into the intersphincteric plane.
[n] CRM measured at the closest distance of the tumor to the mesorectal fascia. Involved CRM: within 1 mm of mesorectal fascia; or, for lower third rectal tumors, within 1 mm from levator muscle; or, for anal canal lesions, invasion into or beyond the intersphincteric plane.
[p] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[q] Principles of Perioperative Therapy (REC-D).
[r] Principles of Radiation Therapy (REC-E).
[u] Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity.
[bb] If obstructing lesion, consider diversion or resection (see REC-10).
[cc] There are limited data regarding available treatment options.
[dd] Data are limited and the risk of early progression may be higher than with chemotherapy. Andre T, et al. N Engl J Med 2020;383:2207-2218.
[ee] Resection is preferred over locally ablative procedures (eg, image-guided ablation or stereotactic body radiation therapy [SBRT]). However, these local techniques can be considered for liver or lung oligometastases (REC-C and REC-E).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[c] Principles of Imaging (REC-A).
[i] Principles of Surgery (REC-C).
[p] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[q] Principles of Perioperative Therapy (REC-D).
[r] Principles of Radiation Therapy (REC-E).
[u] Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity.
[y] Principles of Pathologic Review (REC-B 5 of 9) - *KRAS*, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.

[bb] If obstructing lesion, consider diversion or resection (REC-10).
[dd] Data are limited and the risk of early progression may be higher than with chemotherapy. Andre T, et al. N Engl J Med 2020;383:2207-2218.
[ee] Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (REC-C and REC-E).
[ff] There should be at least a 6-week interval between the last dose of bevacizumab and elective surgery, and re-initiation of bevacizumab should be delayed at least 6 to 8 weeks postoperatively. There is an increased risk of stroke and other arterial events, especially in those aged 65 years or older. The use of bevacizumab may interfere with wound healing.
[gg] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

Note: All recommendations are category 2A unless otherwise indicated.
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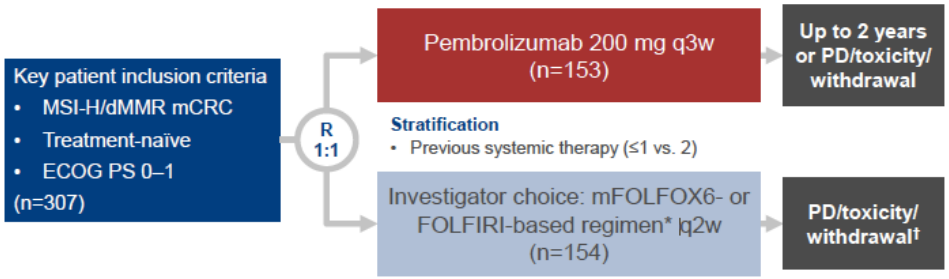
Unas palabras…….

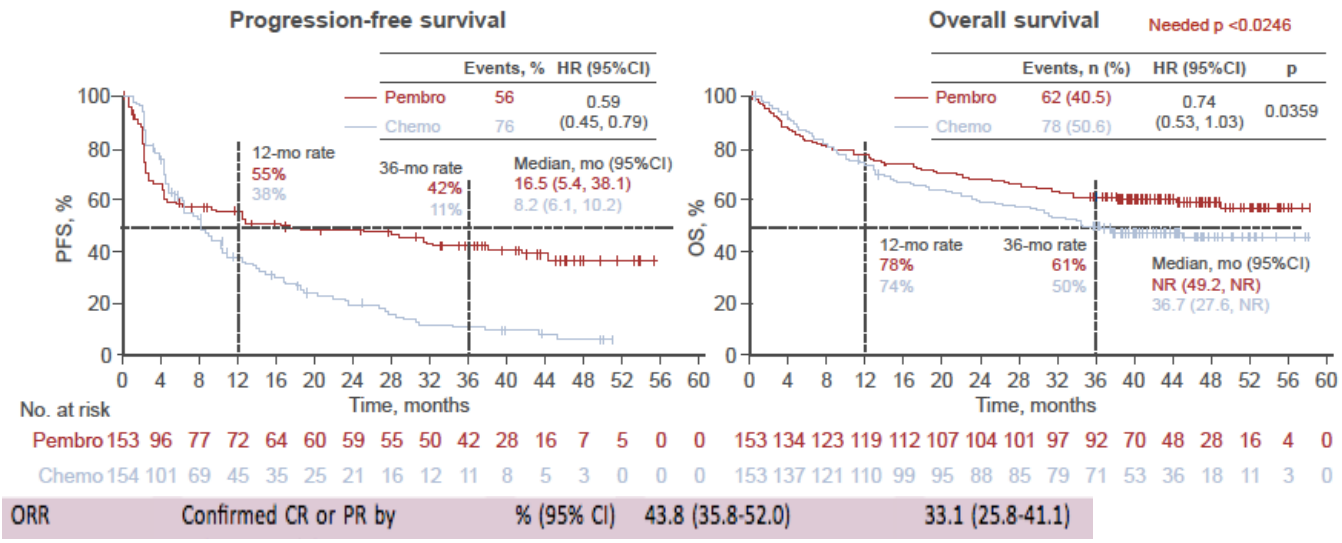
Inmunoterapia 1ºL

Study objective

- To evaluate the final OS of 1L pembrolizumab vs. standard of care chemotherapy in patients with MSI-H/dMMR mCRC in the KEYNOTE-177 study



Key results



Andre T, et al. J ClinOncol2021;39(suppl):abstr3500

The NEW ENGLAND JOURNAL of MEDICINE

Single agent PD-1 blockade as curative-intent treatment in mismatch repair deficient locally advanced rectal cancer.

Abstract LBA5

ORIGINAL ARTICLE

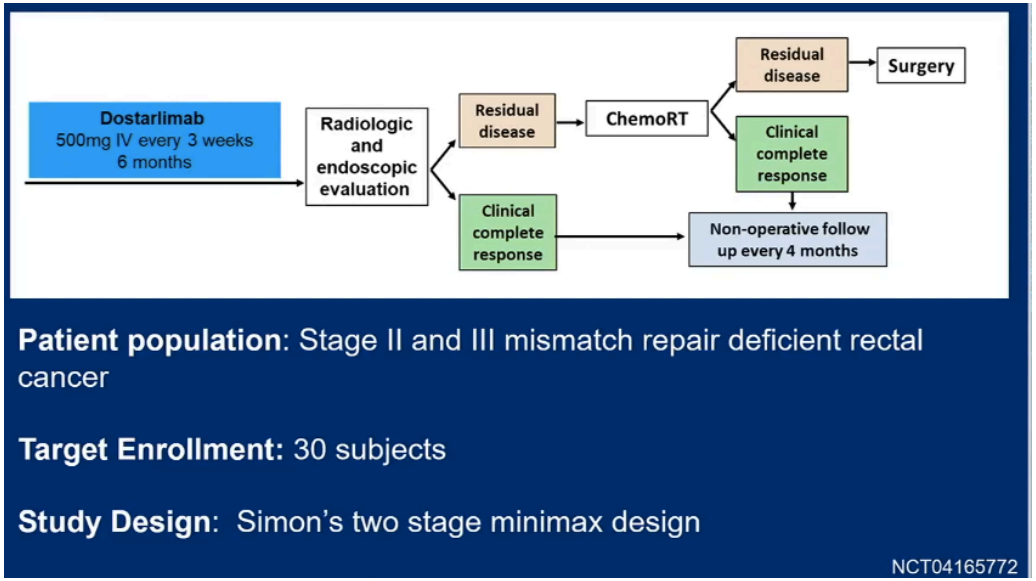
PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

Fase II prospectivo un F .
Dostarlimab x 6 m c3w→ RDT-QT→ cirugía
16 pacientes
Obj Primario: OOR y cCR /pCR 12 m del tto.

Mismatch repair deficient rectal cancer

- Approximately 5-10% of rectal cancers are mismatch repair deficient
- Relatively resistant to chemotherapy
- Checkpoint blockade is highly effective in metastatic mismatch repair deficient cancers with a complete response rate ~10%

Cercek A, Clin Cancer Res 2020
Andre T, N Engl J Med 2020
Le DT, N Engl J Med 2015



Patient population: Stage II and III mismatch repair deficient rectal cancer

Target Enrollment: 30 subjects

Study Design: Simon's two stage minimax design

NCT04165772

Demographic and disease characteristics of the patients at baseline

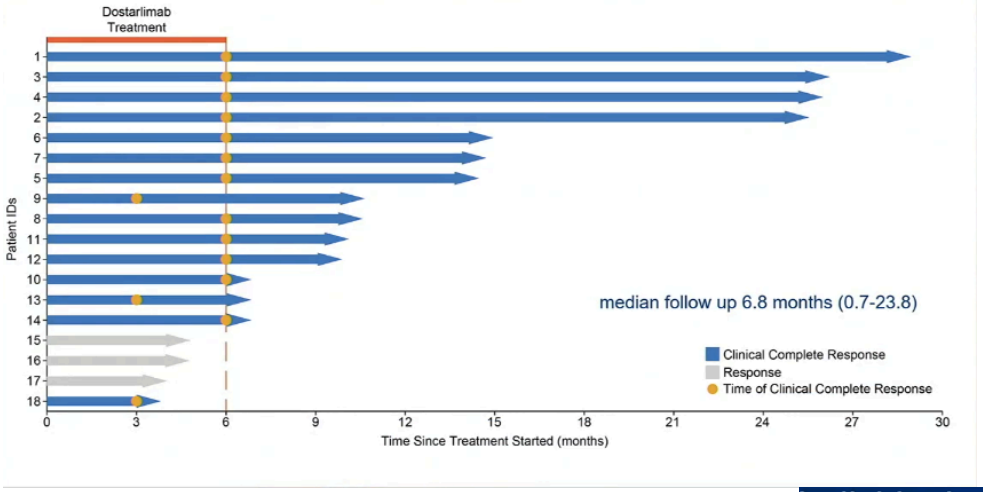
	Value (%)
Sex	
Male	6 (33)
Female	12 (67)
Age, median (range)	54 (26-78)
Race/Ethnicity	
White non-Hispanic	11 (61)
Hispanic	1 (6)
Black or African American	3 (17)
Asian-Far East/Indian Subcontinent	3 (17)
Tumor Staging	
T1/2	4 (22)
T3, T4	14 (78)
Nodal Staging	
Node-positive	17 (94)
Node-negative	1 (6)
Germline Mutation Status n=17	
MSH2, MLH1, MSH6, or PMS2	10 (59)
Negative	7 (41)
BRAF V600E wild type	18 (100)
Tumor Mutational Burden (mut/Mb), mean (range)	67 (36 -106)

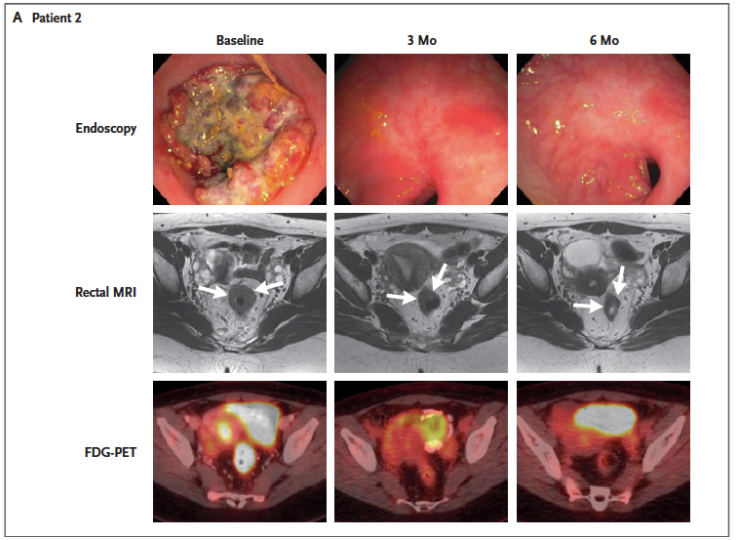
Neoadyuvancia recto : inmunoterapia.

Single agent PD-1 blockade as curative-intent treatment in mismatch repair deficient locally advanced rectal cancer.

Abstract LBA5

Duration of response





Individual responses to PD-1 blockade with dostarlimab

Patients who completed 6-months of dostarlimab

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response 100%
1	38	T4	N+	23.8	CR	CR	CR	cCR
2	30	T3	N+	20.5	CR	CR	CR	cCR
3	61	T1/2	N+	20.6	CR	CR	CR	cCR
4	28	T4	N+	20.5	CR	CR	CR	cCR
5	53	T1/2	N+	9.1	CR	CR	CR	cCR
6	77	T1/2	N+	11.0	CR	CR	CR	cCR
7	77	T1/2	N+	8.7	CR	CR	CR	cCR
8	55	T3	N+	5.0	CR	CR	CR	cCR
9	68	T3	N+	4.9	CR	CR	CR	cCR
10	78	T3	N-	1.7	CR	CR	CR	cCR
11	55	T3	N+	4.7	CR	CR	CR	cCR
12	27	T3	N+	4.4	CR	CR	CR	cCR
13	26	T3	N+	0.8	CR	CR	CR	cCR
14	43	T3	N+	0.7	CR	CR	CR	cCR

Conclusiones

- Las M1 hepáticas sincrónicas de CRC implican peor pronóstico, que las metacrónicas.
- La valoración por un equipo multidisciplinar es fundamental para optimizar la evolución.
- El manejo dependerá de la resecabilidad y los síntomas derivados del tumor primario y las M1 hepáticas.