

**6. ULUSAL CERRAHI ONKOLOJİ KONGRESİ**  
 24 - 27 Şubat 2022 | Gloria Golf Resort - ANTALYA

**Neoadjuvan kemoterapinin kolon kanserinde yeri?**

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**Percent of Cases by Stage**

- Localized (37%)  
 Confined to Primary Site
- Regional (36%)  
 Spread to Regional Lymph Nodes
- Distant (22%)  
 Cancer Has Metastasized

5%  
22%  
36%  
37%

<https://seer.cancer.gov/statfacts/html/colorect.html>

**5-Year Relative Survival**

Stage	Percent
Localized	90.6%
Regional	72.2%
Distant	14.7%
Unknown	

Neoadjuvan kemoterapi? Kime? Ne? Nasıl?  
 Rezektabl metastatik hastalıkta neoadjuvan?

<https://seer.cancer.gov/statfacts/html/colorect.html>

**Neden neoadjuvan?**

- 5-FU/lev superior to surgery alone
- 5-FU/LV superior to surgery alone
- 5-FU/LV superior to 5-FU/lev
- 6- and 12-month treatment cycles equivalent
- LV5-FU2 and monthly bolus equivalent
- Lev unnecessary
- High-dose and low-dose LV equivalent
- Monthly and weekly treatment equivalent

1990 1994 1998 2002

Moslefi et al. Ann Intern Med. 1995;122:321  
 Francis et al. Gastroenterol. 1994;106:899  
 Wolmark et al. Proc Am Soc Clin Oncol. 1996;15:205. Abstract  
 O'Connell et al. J Clin Oncol. 1998;16:295.  
 Haller et al. Proc Am Soc Clin Oncol. 1998;17:268a. Abstract 852  
 Andre et al. Proc Am Soc Clin Oncol. 2002. Abstract 529

**Neden neoadjuvan?**

Improved Overall Survival With Oxaliplatin, Fluorouracil, and Leucovorin As Adjuvant Treatment in Stage II or III Colon Cancer in the MOSAIC Trial

2004

Mikrometastazlar iyi tedavi edilemiyor mu?  
 DFS/ OS için ek birşeyler yapabilir miyiz?

**FOLFOX- 5y DFS %73.3**

Probability of survival at 5 years (%)	Hazard ratio (95% CI)	P
FL (304 events)	0.64	.003
FL + oxaliplatin (304 events)	0.80 (0.68 to 0.93)	

J Clin Oncol. 2009 Jul 1;27(19):3109-16

**Neden neoadjuvan?**

• Rektum, mide, meme, akciğer, sarkom....neoadjuvan etkinlik tecrübesi

CLINICAL STAGE

T3, N any involved + threatens CRM (by T4, N any or Locally unresectable or medically inoperable

Chemotherapy (12-16 weeks) + FOLFOX or CAPEOX + Consider FOLFOXIRI (for T4 N1)

Leucovorin or Infusional 5-FU or Short-course RT<sup>14</sup>

Restaging<sup>14</sup>

Restaging<sup>14</sup>

6. Ulusal CERRAHI ONKOLOJİ KONGRESİ

10-12 Eylül 2021 | İstanbul Tıp Fakültesi - İstanbul

• Postoperatif morbidite nedeniyle tedavi alamama ihtimalini ortadan kaldırabilir

• Kemoterapi duyarlılığını test etmek kıymetli

Dig Surg. 2020;37 (4):292-301. doi:10.1159/000503446

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10-12 Eylül 2021 | İstanbul Tıp Fakültesi - İstanbul

Neoadjuvant olumsuz yöneri

• Neoadjuvant tedavi alırken acil cerrahi ihtiyacı olabilir

Outcomes	Nonemergency (n = 25,710)	Emergency (n = 5,083)	p Value
Mortality	492 (1.9)	780 (15.4)	<0.0001*
Inpatient	133 (27.0)	110 (14.1)	
Outpatient	359 (73.0)	670 (85.9)	
Morbidity	6,174 (24.0)	2,451 (48.2)	<0.0001

• "Overtreatment"  
Klinik/radyolojik olarak lokal ileri (T3-T4 veya N+) **Olmayabilir**

J Am Coll Surg. 2010 Feb;210(2):155-65

Accuracy of radiological staging in identifying high-risk colon cancer patients suitable for neoadjuvant chemotherapy: a multicentre experience

Radiologist T-stage	Pathologist T-stage			Total
	T2	T3	T4	
T2	6	3	1	10
T3	4	40	15	59
T4 (adjacent organs)	1	6	4	11
T4 (peritoneal)	1	8	5	14
Grand total	12	57	25	94

T3- T4 saptamada- Sensitivite %95  
Spesifisite %50

Lenf nodu pozitif – Sensitivite %68  
Spesifisite %42

Colorectal Dis. 2012 Apr;14(4):438-44

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10-12 Eylül 2021 | İstanbul Tıp Fakültesi - İstanbul

• Kemoterapi toksisitesi ile cerrahiye ulaşamama ihtimali

• Postoperatif morbidite artabilir

Characteristic	Sundar et al. [12]	Pretorius et al. [13]	Rosa et al. [14]	Current study
Grade 3 or 4 leucocytosis	1 (3.7)	4 (10.6)	0 (0)	2 (7.1)
Anemia	0 (0)	-	0 (0)	0 (0)
Leukopenia	4 (14.8)	11 (29.0)	1 (2.1)	3 (10.7)
Neutropenia	3 (11.1)	8 (20.8)	1 (2.1)	1 (3.6)
Thrombocytopenia	-	-	0 (0)	0 (0)
Abdominal discomfort	-	-	0 (0)	0 (0)
Anorexia	-	3 (7.9)	0 (0)	0 (0)
Constipation	0 (0)	-	0 (0)	0 (0)
Diarrhea	1 (3.7)	3 (11.5)	0 (0)	0 (0)
Fatigue	-	3 (7.9)	0 (0)	1 (3.6)
Nausea and vomiting	0 (0)	4 (10.5)	0 (0)	2 (7.1)
Mucositis	-	4 (10.5)	0 (0)	0 (0)
Peripheral neuropathy	-	6 (15.8)	2 (4.3)	3 (10.7)
Peripheral edema	-	-	0 (0)	0 (0)
Hypokalemia	0 (0)	-	0 (0)	0 (0)

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Ya, progrese olursa? Evre atlarsa?

• 6 haftalık FOLFOX tedavisi altında progresyon ihtimali <%5

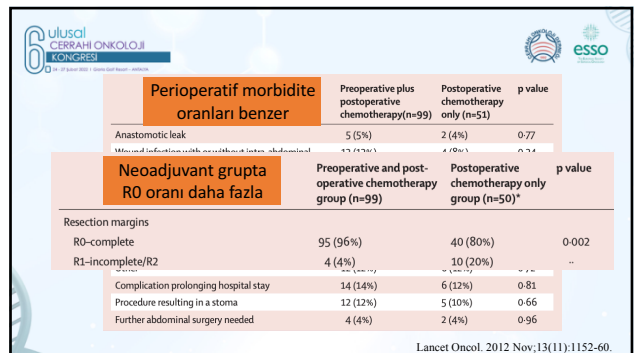
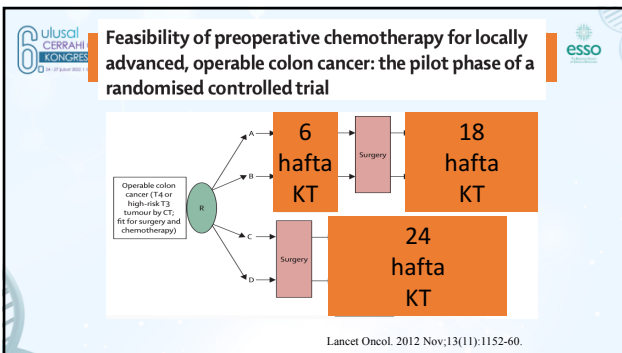
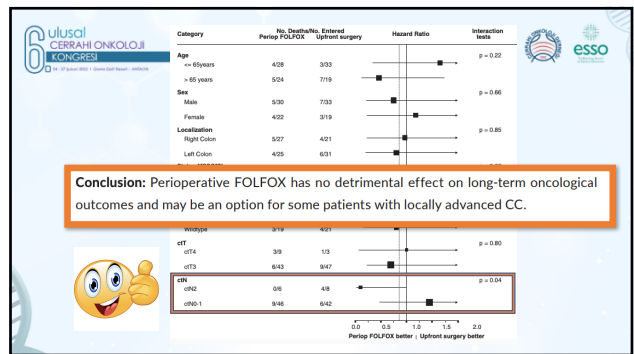
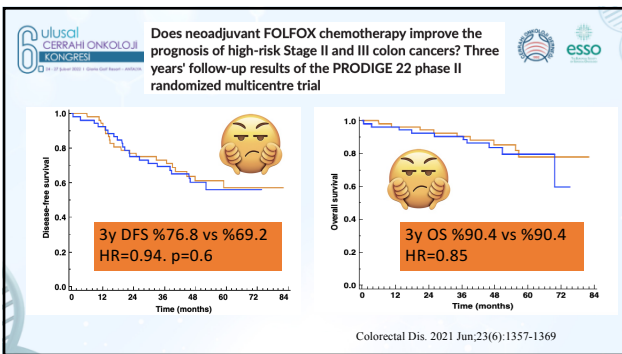
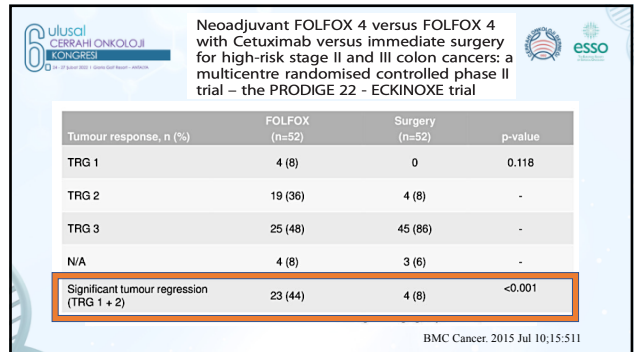
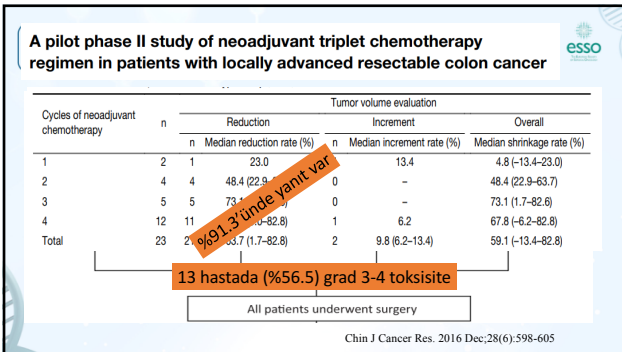
6. Ulusal CERRAHI ONKOLOJİ KONGRESİ

10-12 Eylül 2021 | İstanbul Tıp Fakültesi - İstanbul

Neoadjuvant chemotherapy in locally advanced colon cancer. A phase II trial

3 yıllık DFS %94 vs %63 (p=0.005).

Acta Oncol. 2015 Nov;54(10):1747-53



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ESMO Congress

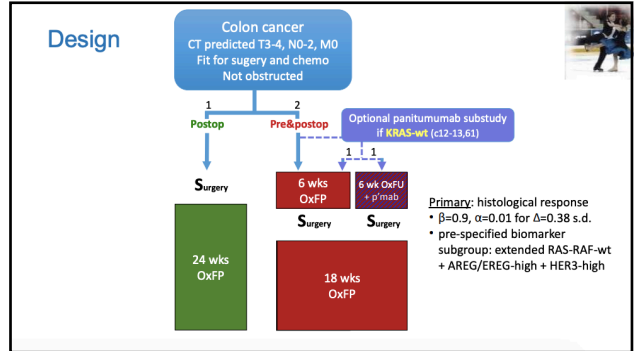
CANCER RESEARCH UK

NCRI

## FOxTROT:

an international randomised controlled trial in 1052 patients evaluating neoadjuvant chemotherapy for colon cancer.

Presented on behalf of the FOxTROT collaborators of UK, Denmark and Sweden



### Neoadjuvant kemoterapi alanlarda R0 rezeksiyon oranı daha yüksek

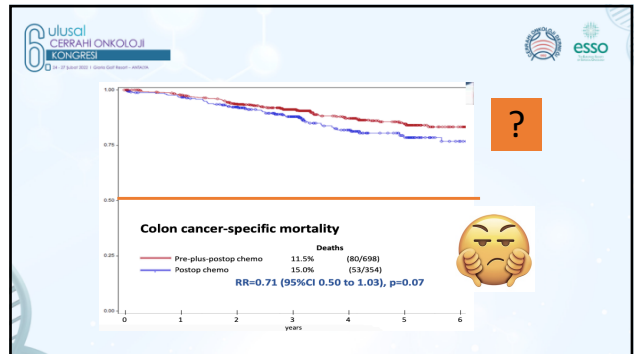
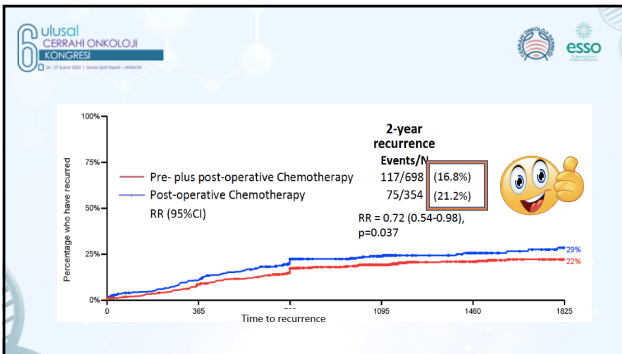
Local pathologist score*	neoadjuvant chemotherapy n=689	Straight to surgery n=353
Did not proceed to surgery	0.6%	0.6%
Surgery but no resection	0.3%	1.1%
R2 - macroscopically incomplete	4.2%	8.8%
R0 - microscopically complete	93.1%	88.4%

**Inkomplet rezeksiyon %4.8 vs. %11.1**

p=0.001 (MH)

### Neoadjuvant kemoterapi alanlarda major cerrahi komplikasyonlar daha az

	Pre&post n=684	Post n=351	
Underwent surgery			
Procedure involved a stoma	11.7%	9.0%	p=0.18
Wound infection	8.5%	8.9%	p=0.85
Bronchopneumonia	1.8%	3.1%	p=0.16
PE ± DVT	1.6%	0.6%	p=0.18
Anastomotic leak or intra-abdo abscess	4.7%	7.4%	p=0.07
complication requiring further surgery	4.3%	7.1%	p=0.05
complication prolonging hospital stay	11.6%	14.3%	p=0.21
Death within 30 days	0.6%	0.6%	p=0.98



Ulusal CERRAHI ONKOLOJİ KONGRESİ

pre&post n=698 post n=354

Attempted curative resection	98.2%	97.7%	p=0.54	
no attempt at curative resection	Died before surgery	0.4%	0.3%	p=0.72
	Inoperable or metastatic disease	1.3%	2.0%	p=0.39
Did not receive chemotherapy	4%	27%	p<0.0001	

**Radyoloji hasta seçiminde mükemmel değil**  
(Bir grup düşük riskli bulunması nedeniyle KT almıyor)\*%24

Ulusal

**Neoadj KT ile önemli oranda yanıt var**

91% scored blind by central pathologist  
9% scored by local pathologists

	neoadjuvant chemo n=666	straight to surgery n=332	
Complete Response (TRG4)	3.5%	0%	p<0.0001 MH
Marked Regression (TRG3)	4.1%	0%	
Moderate Regression (TRG2)	12.3%	0.6%	
Little Regression (TRG1)	43.9%	16.7%	
No regression (TRG0)	33.9%	78.8%	

**1/3'ü FOLFOX'tan fayda görmüyor**

- Kimler fayda görmüyor?
- Daha farklı tedavi seçenekleri?

Ulusal CERRAHI ONKOLOJİ KONGRESİ

**FOXTROT**

- Neoadjuvant FOLFOX ile
  - RFS avantajı
  - Güvenli, az postop komplikasyon
  - Inkomplet rezeksiyonları azaltıyor
- Bazı düşük riskli hatsalarda neoadjuvant KT alabilir
  - Kontrol grubunda %24'ünde "düşük riskli hastalık"
- Yanıtızlara post- op kemoterapi??

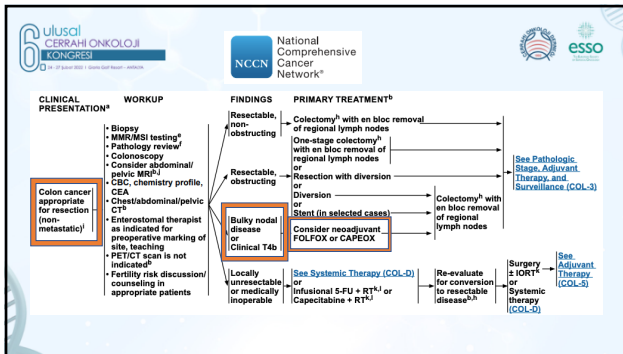
**\*\*\*Radyoloji önemli\*\*\***

**RADIOLOGY**  
YOU POSE - WE EXPOSE

Ulusal

**Kolon Ca'da neoadjuvant verelim mi?**

- Radyolojik değerlendirme
- Seçili vakalarda verelim
- Daha beklemeye gerek yok, Herkese neoadjuvant verelim
- Sağkalım datası yok



Ulusal CERRAHI ONKOLOJİ KONGRESİ

**Neoadjuvantta biyolojik ajanlar?**

91% scored blind by central pathologist  
9% scored by local pathologists

	Preop OxFU alone n=134	Preop OxFU + p/mab n=140	
Complete Response (TRG4)	3.7%	0.7%	p=0.30 MH
Marked Regression (TRG3)	4.5%	2.2%	
Moderate Regression (TRG2)	14.3%	13.9%	
Little Regression (TRG1)	39.8%	48.2%	
No regression (TRG0)	37.6%	35.0%	

### Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers

**study design**

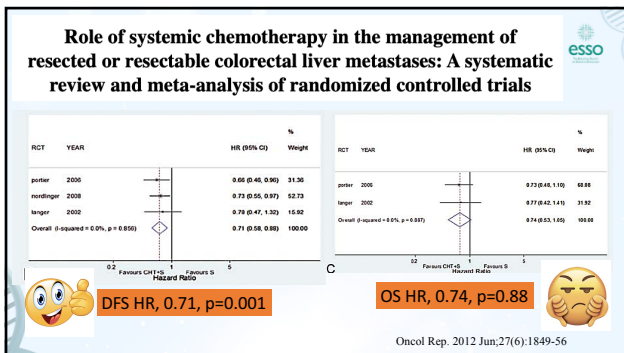
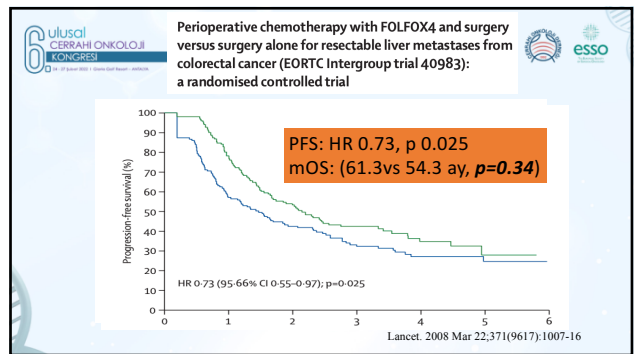
- dMMR'de
  - 20/20 patolojik yanıt+
  - 12/20 patolojik tam yanıt
- pMMR'de
  - 4/15'inde patolojik yanıt+

Nat Med. 2020 Apr;26(4):566-576

**LOADING**

Trial Number	Intervention	Population	Status	Phase	Accrual Grad.	Location(s)	Primary Endpoint
NCT0128940	CAPOX v4 → surgery → CAPOX v4 vs. surgery → CAPOX v4	LACC	Recruiting	III	1570	China	3-year DFS
NCT0426894	neoadjuvant FOLFOX v4 → surgery → adjuvant FOLFOX v4 vs. surgery → adjuvant FOLFOX v4 × 12	LACC	Recruiting	III	560	Korea	RFS
NCT0194827	neoadjuvant CAPOX v3 → surgery → adjuvant CAPOX (if indicated based on pathology) vs. surgery → adjuvant CAPOX v4 × 4	LACC	Recruiting	III	250	Denmark, Sweden, Norway	2-year DFS
NCT0207241 (NAACOG)	colonic stent → FOLFOX v5 or CAPOX v2 → surgery → FOLFOX v5-9 or CAPOX v4-4 vs. surgery → FOLFOX v5-9 or CAPOX v4-4	LACC	Recruiting	II	248	China	DFS
NCT04018158 (ELICA)	colonic stent → surgery → FOLFOX v6-12 or CAPOX v6-8 vs. neoadjuvant CAPOX v3 → surgery → adjuvant CAPOX v5 vs. surgery → adjuvant CAPOX v8	LACC	Recruiting	II	238	Spain	2-year DFS
NCT01675999 (ECKON3)	neoadjuvant FOLFOX v4 × 4 or capecitabine → surgery → adjuvant FOLFOX v4 × 4 or capecitabine	LACC	Recruiting	II	186	France	Tumor response by TRC
NCT0302140 (NCS3)	surgery → adjuvant FOLFOX v12 vs. ipilimumab + nivolumab + celecoxib → surgery	Stage I-III CC	Not yet recruiting	II	60	Netherlands	Safety
NCT0421526	pentostatin → surgery vs. surgery	LACC	Not yet recruiting	II	46	USA	Feasibility
NCT0368891	toripalimab (anti-PD-1) → FOLFOX v6 → surgery → same vs. FOLFOX v6 → surgery → FOLFOX v6	LACC	Not yet recruiting	III	40	China	pCR rate, pCR rate, OS
NCT0464935	FOLFONIRI v4 → surgery vs. FOLFONIRI v4 → surgery	LACC	Not yet recruiting	II	30	China	Tumor downstaging

### Metastatik rezektabl kolon kanserinde neoadjuvant tedavi?

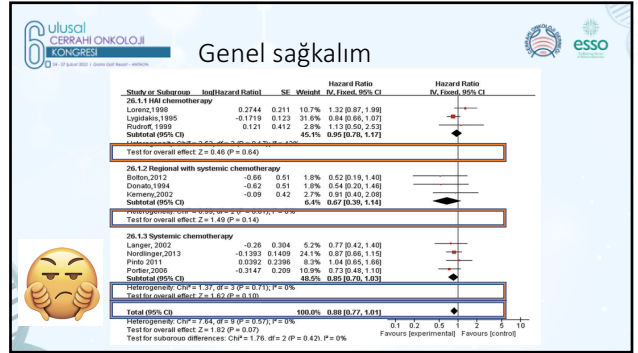
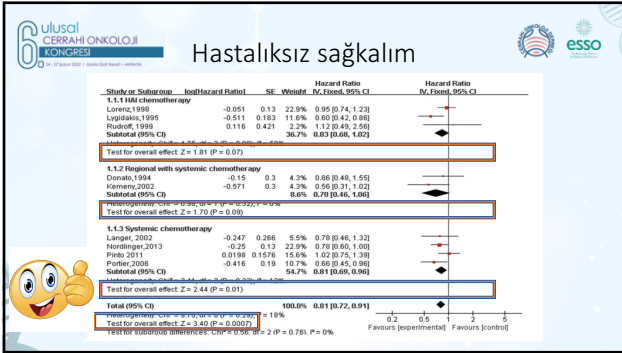


### Peri-operative chemotherapy for patients with resectable colorectal hepatic metastasis: A meta-analysis

First author	Therapy regimen	Patients analyzed (n)	Chemotherapy/control	Number of metastases	Comparative outcomes	Follow-up (Months)	Design	Quality score
Nordlinger 2013 <sup>13</sup>	FOLFOX4, systemic	364	182/182	1-4	PFS <sup>a</sup> ; OS <sup>a</sup>	122	RCT	25
Bolton 2012 <sup>19</sup>	HAI, FUDR, systemic	49	36/13	1-2	OS <sup>a</sup>	66	Prospective	17
Pinto 2011 <sup>21</sup>	5-FU, systemic	676	334/342	1-6	DFS <sup>a</sup> ; OS <sup>a</sup>	60	Retrospective	19
Pontier 2006 <sup>22</sup>	5-FU, systemic	171	86/85	1-4	DFS <sup>a</sup> ; OS <sup>a</sup>	87.4	RCT	23
Kemeny 2002 <sup>10</sup>	FUDR,HAI, 5-FU, systemic	109	53/56	1-3	RFS <sup>a</sup> ; OS <sup>a</sup>	51	RCT	17
Langer 2002 <sup>23</sup>	5-FU, systemic	107	52/55	1-4	DFS <sup>a</sup> ; OS <sup>a</sup>	n.r.	RCT	18
Rudloff 1999 <sup>7</sup>	5FU, HAI	30	14/16	1-4	RFS <sup>a</sup> ; OS <sup>a</sup>	144	RCT	18
Lorenz 1998 <sup>8</sup>	5-FU, HAI	226	113/113	1-6	DFS <sup>a</sup> ; OS <sup>a</sup>	18	RCT	23
Lygidakis 1995 <sup>9</sup>	5-FU, HAI	40	20/20	n.r.	DFS <sup>a</sup> ; OS <sup>a</sup>	n.r.	RCT	16
Donato 1994 <sup>20</sup>	5-FU, regional; systemic	124	40/62	1-4	DFS <sup>a</sup> ; OS <sup>a</sup>	n.r.	Retrospective	15

HAI: Hepatik arterial infuzyon

Eur J Surg Oncol. 2015 Sep;41(9):1197-203.



### TREATMENT

Resectable synchronous liver and/or lung metastases only

Synchronous or staged colectomy<sup>a</sup> with liver or lung resection (preferred) and/or local therapy<sup>b</sup>

or

Neoadjuvant therapy (for 2-3 months) FOLFOX (preferred) or CAPEOX (preferred) or FOLFIRI (category 2B) or FOLFOXIRI (category 2B) followed by synchronous or staged colectomy<sup>a</sup> and resection of metastatic disease

or

Colectomy<sup>a</sup> followed by chemotherapy (for 2-3 months) FOLFOX (preferred) or CAPEOX (preferred) or FOLFIRI (category 2B) or FOLFOXIRI (category 2B) and staged resection of metastatic disease

or

Consider (Nivolumab ± ipilimumab) or pembrolizumab (preferred) (IMMUNOS-H only)<sup>ca</sup> followed by synchronous or staged colectomy<sup>a</sup> and resection of metastatic disease

### ADJUVANT TREATMENT<sup>a</sup> (UP TO 6 MO PERIOPERATIVE TREATMENT) (resected metastatic disease)

### \*Take home message

- Kolon kanserinde neoadjuvant tedavi ile
  - RFS avantajı
  - Daha az postop komplikasyon
  - Daha az inkomplet rezeksiyon
- İlk değerlendirmede radyolojik yanlış "overstaging" ile lüzensüz KT alabilir hastalar
- Oligometastatik/ rezektabl olgularda seçilmiş vakalarda neoadjuvant PFS avantajı sağlayabilir

### \*Take home message

- Hasta ve ilaç seçimi
- Sağkalım etkileri?
- Evreleme için daha iyi tetkikler neler?
- Neoadjuvant İmmünoterapi?
- .....

## Uzun takip verisi Yeni klinik çalışmalar

