NIO Hannover

Fallvorstellung

W.R. 1964

5/12 Coloncarcinom re Flexur pT3d pN2b (13/83) M0, R0
muzinöses Adenokarzinom G2, L1)
Ausfall der MSH2 + MSH6-Expression -
MSH2: Heterozygotie für c.1786_1788del (p.Asn596del)
Krankheitsassozierte Variante

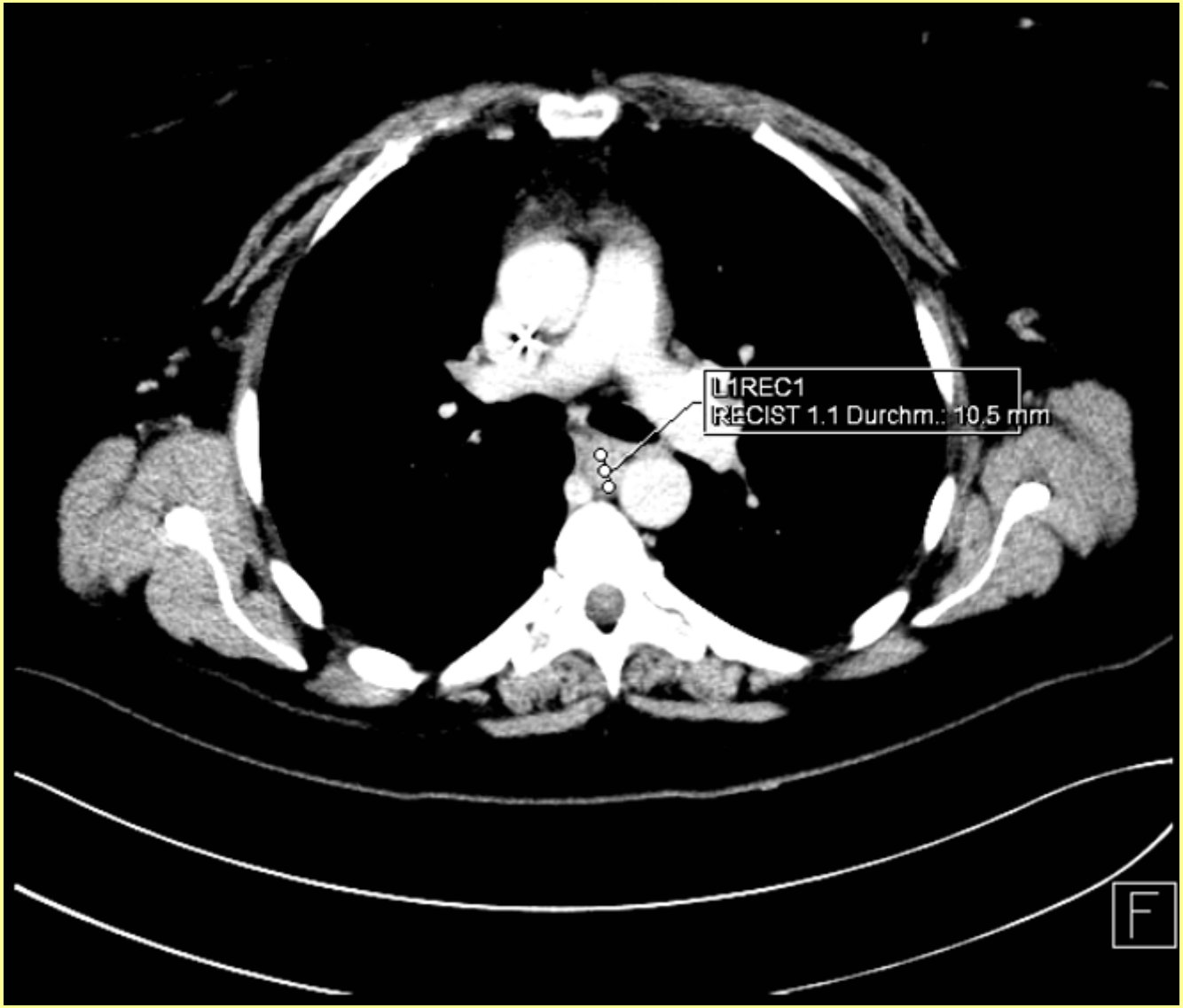
ND: Diabetes mellitus Typ II;

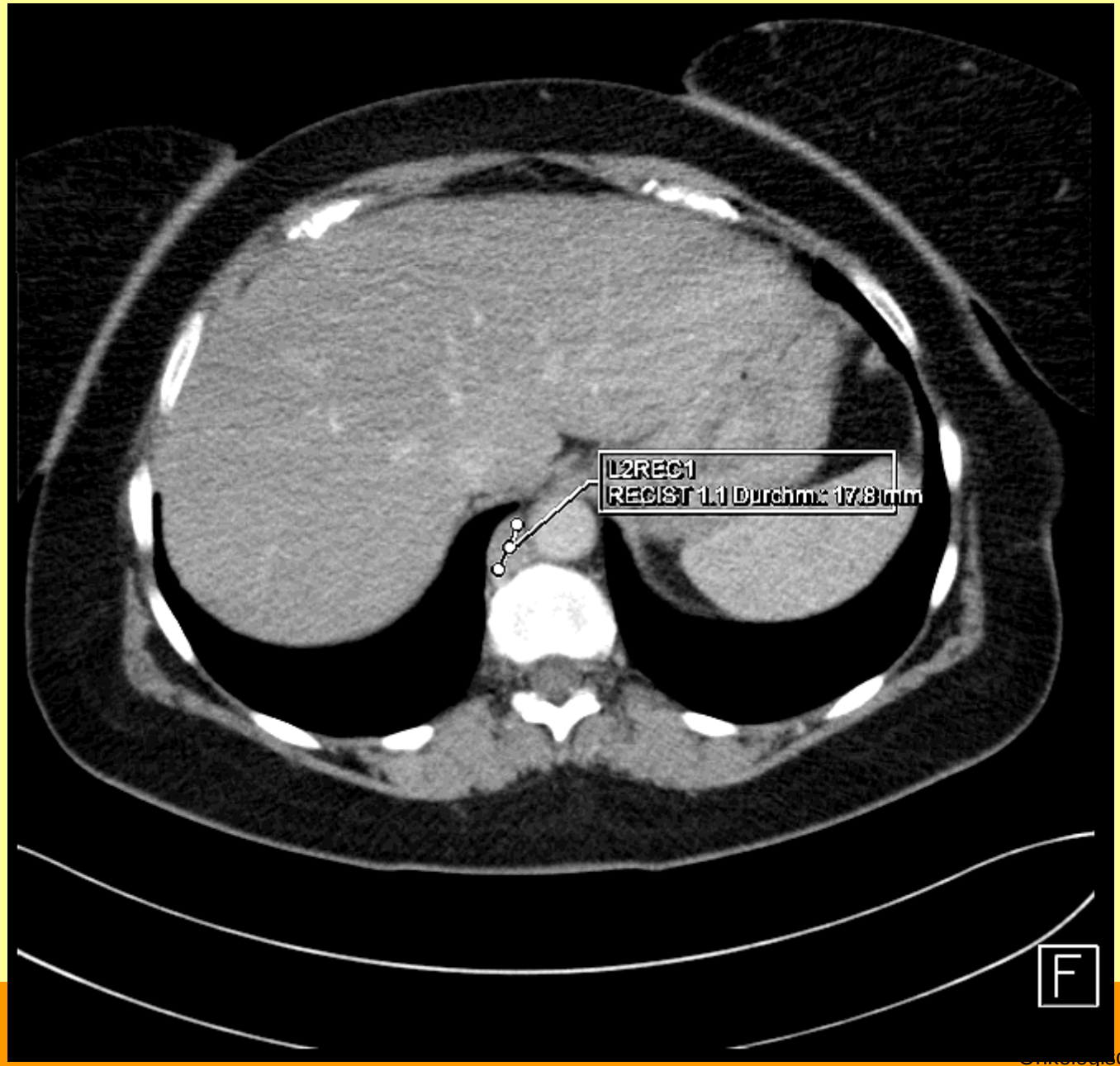
- Depression
- Restless legs-Syndrom
- Asthma bronchiale
- Nikotinabusus

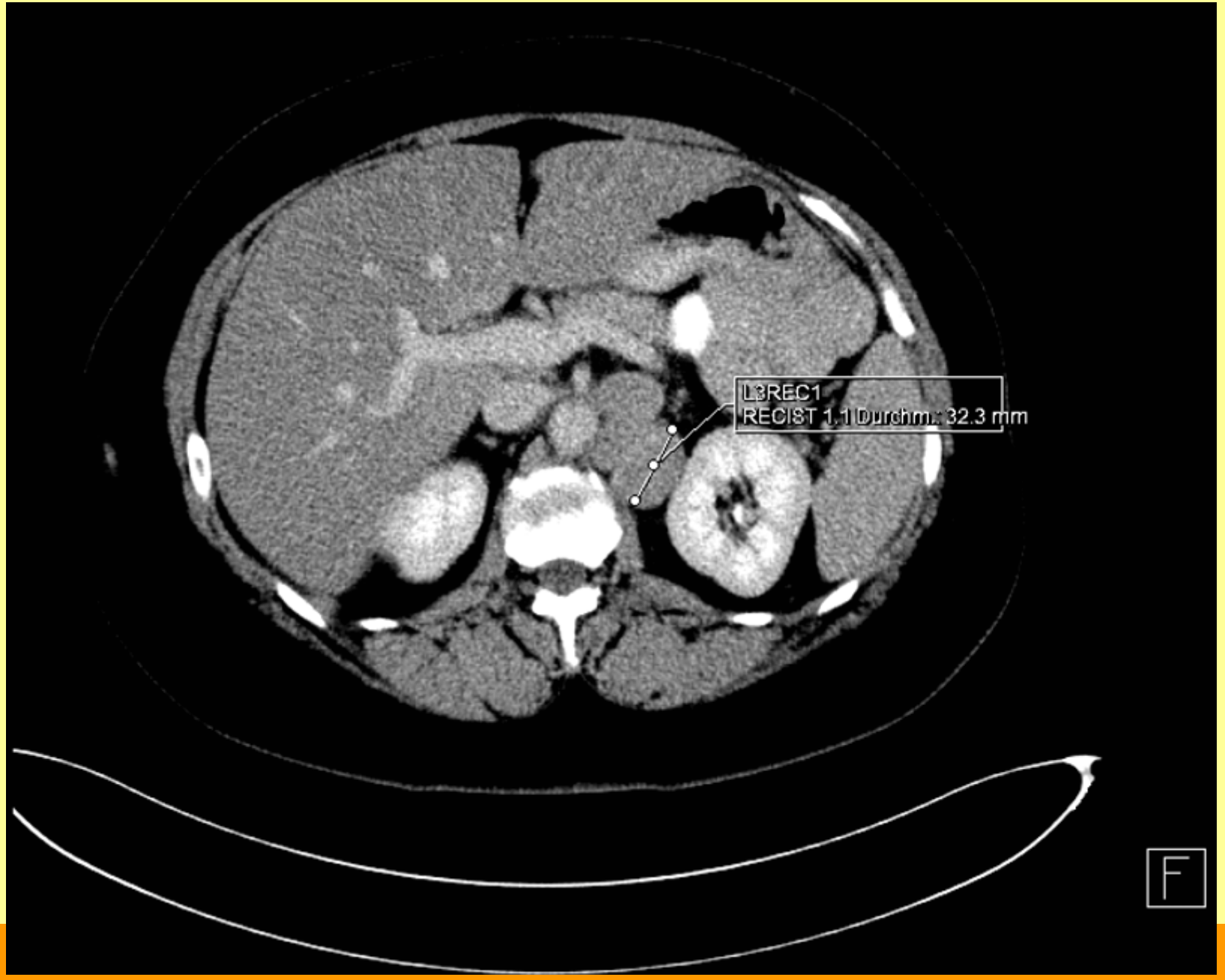
05/12 **Hemicolektomie re, terminoterminaler Ileodescendosstomie, Lymphadenektomie**

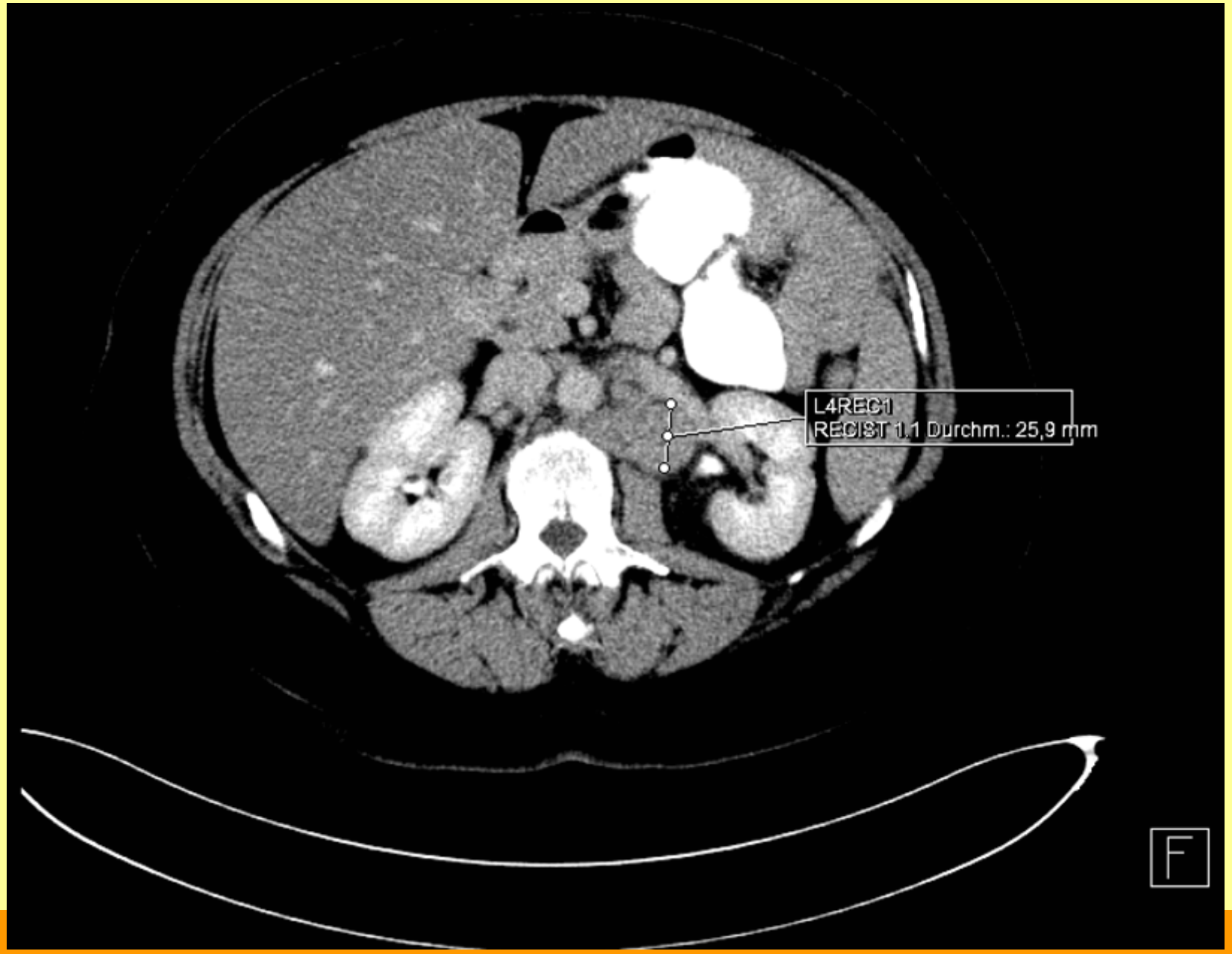
- 06/12 Portimplantation
- 06-9/12 Oxaliplatin, Folinsäure, 5-FU
- 09/12 Phlebothrombose V. jugularis interna, subclavia
- li Abbruch der Chemotherapie über den Port
- 9-11/12 Capecitabine, Oxaliplatin
- Rückbildung der Phlebothrombose - postthrombotisches
- Syndrom li II°
- 12/12 unklare RF Ösophagus mittleres Drittel –zytologisch o.B.

- 12/13 mesenteriale und retroperitoneale LK mit Einwachsen ins
- Duodenum Pars III
  (Adenocarcinom G2 Ausfall der MSH2 + MSH6 IHC)
  KRAS und NRAS WT
- 06/14 weitere Therapie


L1REC1
RECIST 1.1 Durchm.: 10,5 mm
F


L2REC1
RECIST 1.1 Durchm.: 17.8 mm
F


L3REC1
RECIST 1.1 Durchm.: 32.3 mm
F


L4REC1
RECIST 1.1 Durchm.: 25,9 mm
F

Weiters Vorgehen

- Chirurgie

Chemotherapie bei HNPCC

Kein Vorteil von 5-FU in vitro

MSS Tumore mit 5-FU besseres OS in Stad. II+III mit 5-FU als ohne ($p \leq .05$

MSI-H : kein OS Differenz mit oder ohne 5-FU Therapie p= .52

Carethers et al.: Mismatch repair proficiency and in vitro response to 5-fluorouracil. Gastroenterology. 1999

Ribic C M, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N Engl J Med. 2003

Metanalyse

Stad. II + III adj. Therapie mit 5-FU

- 1027 Pat.
- Kein Vorteil für dMMR (HR 2.3 bzw. 1,0)
- Kein Vorteil für MSS und Stad. II
- Nur Vorteil für MSS und Stad. III (HR 0.64, p=0.001)

Sargent DJ et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol. 2010;28:3219–3226.

Widersprüchliche Studien

- Elsaleh H, Iacopetta B. Microsatellite instability is a predictive marker for survival benefit from adjuvant chemotherapy in a population-based series of stage III colorectal carcinoma. Clin Colorectal Cancer. 2001;1(2):104–
- Hemminki A, Mecklin J P, Järvinen H, Aaltonen L A, Joensuu H. Microsatellite instability is a favorable prognostic indicator in patients with colorectal cancer receiving chemotherapy. Gastroenterology. 2000;119(4):921–928

Zeigen Vorteil bei adj. 5-FU haltiger Therapie

- G, Southward K, Handley K. et al. Value of mismatch repair, KRAS, and BRAF mutations in predicting recurrence and benefits from chemotherapy in colorectal cancer. J Clin Oncol. 2011;29(10):1261–127

- Colangelo L H, et al. National Cancer Institute. Prognostic and predictive roles of high-degree microsatellite instability in colon cancer: a National Cancer Institute-National Surgical Adjuvant Breast and Bowel Project Collaborative Study. J Clin Oncol. 2007;25(7):767–772

MSI-H gleich wie MSS bei 5-FU haltiger Therapie

Stad. II+III Vorteil von 5-FU?

- In summary, data remain conflicting regarding the potential benefits from 5-FU chemotherapy in the adjuvant setting in patients with MSI colorectal cancer. Several of the studies that supported the concept of a lack of benefit from adjuvant 5-FU in MSI-H tumors directly compared patients with MSI-H tumors who received adjuvant 5-FU versus observation.6,8,9,13 However, the other studies that suggested a benefit from adjuvant 5-FU did not do a similar comparison except for the study by Hutchins et al. Rather, they looked at differences in outcome between MSI and MSS patients who received chemotherapy. The better outcome in MSI patients may have been secondary to better prognosis in those patients and not necessarily a benefit from treatment. Prospective trials are needed to evaluate the role of 5-FU in MSI patients in the adjuvant setting.

Stad. IV

Retrospektiv: (n=46):

	RR	OS
MSI-H	**72 %**	**33 Mo**
MSS	41 %	19 mo

W M, Moesch C, et al. Relationship between microsatellite instability, response and survival in palliative patients with colorectal cancer undergoing first-line chemotherapy. Anticancer Res. 2003;23(2C):1773–1777.

Prospectiv (n=244) HD-5FU/FA vs Observation

	OS: 5-FU	OB	RR 5-FU	
MSI-H	**24 Mo OS**	**7 Mo**	**65%**	
MSS	**19 Mo OS**	7 Mo	43%	

Liang J T. et al. Int J Cancer. 2002;101:519–525

Fragen

OS Verbesserung in MSI-H durch generell bessere Prognose ??

Bessere Prognose bei sporadischen MSI-H durch bessere Chemosensitivität

vergleichbar zu verminderter biologischer Aggressivität bei dMMR

Cave: es liegen nicht genug Daten vor, die eine verminderte Wirkung von 5-FU bei MSI-H Tumoren belegen

Oxaliplatin

- MMR deficiant Zellen sind nicht resistent

  Vaisman A, Cancer Res. 1998;58(16):3579–

- Keine Korrelation von MSI-H Status und PFS+ OS

  Müller C I et al. A report of the AIO Colorectal Study Group. Int J Colorectal Dis. 2008;23(11):1033–1039

  Kim S T, Lee J, Park S H. et al. Clinical impact of microsatellite instability in colon cancer following adjuvant FOLFOX therapy. Cancer Chemother Pharmacol. 2010;66(4):659–667

Schlechteres Ansprechen von MSI-H 50% disease controll rate

Non –MSI-H 90%

Irinotecan

In CALGB 89803 Stad. III IFL vs FU/LV

- nur 13% dMMR/MSI-H
  - Kein Unterschied OS
  - Aber DFS war besser in IFL vs FU/LV (HR.76 vs .57)

    Bertagnolli M M et al. J Clin Oncol. 2009;27(11):1814–1821.

Stad. IV:

82 Pat: bessere RR in MSHI-H vs non MSI-H

Bendardaf R Tumour Biol. 2007;28(4):212–220

Fazit