HUMANITAS
GAVAZZENI

Ordine dei Medici Chirurghi
e Odontoiatri
della provincia di Bergamo

MERCOLEDÌ 21 SETTEMBRE 2022

DIAGNOSI E TERAPIA DEL CANCRO DEL RETTO: COSA FARE NEL 2022

www.humanitasedu.it

RESPONSABILE SCIENTIFICO

Prof. Giovanni Dapri
Direttore Chirurgia Mini-Invasiva Generale e Oncologica, Humanitas Gavazzeni, Bergamo

PROGRAMMA

ore 19:30 **REGISTRAZIONE DEI PARTECIPANTI**

ore 19:50 **SALUTI ISTITUZIONALI**
Emilio Bombardieri, Guido Marinoni, Giovanni Dapri

ore 20:00 **PRESENTAZIONE DEL MEDICO DI FAMIGLIA**
Ivan Carrara

ore 20:15 **RUOLO DEL GASTROENTEROLOGO**
LOCALIZZAZIONE DEL POLIPO CANCERIZZATO, BIOPSIA E STADIAZIONE TRANSMURALE CON L'ECOENDOSCOPIA
Nicola Gaffuri

ore 20:30 **RUOLO DEL PATOLOGO**
ANALISI E STADIAZIONE TN
Paola Spaggiari

ore 20:45 **RUOLO DEL RADIOLOGO**
STADIAZIONE TAC ADDOMINO-TORACICA LINFONODALE E A DISTANZA. STADIAZIONE RMN LOCALE DEL TUMORE (T) E DEI LINFONODI PERIRETTALI (N)
Alessandro Zanello

Dott.ssa Paola Spaggiari
paola.spaggiari@humanitas.it
02 8224 4759

HUMANITAS
RESEARCH HOSPITAL

Pathology report

Local excision
Surgical specimens

Sequenza adenoma-carcinoma: classificazione delle lesioni

Adenomi di tipo convenzionale

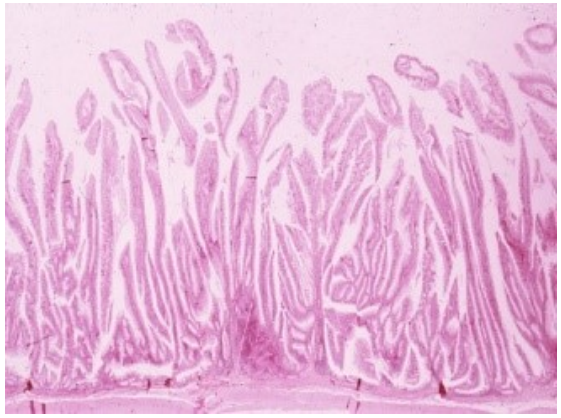
"Adenoma avanzato"

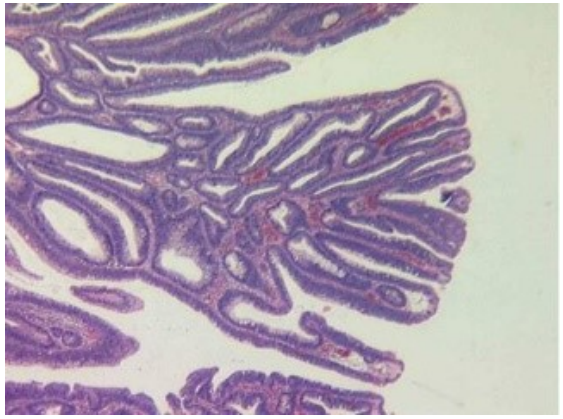
> 10 mm o
con displasia di alto grado o
con componente villosa

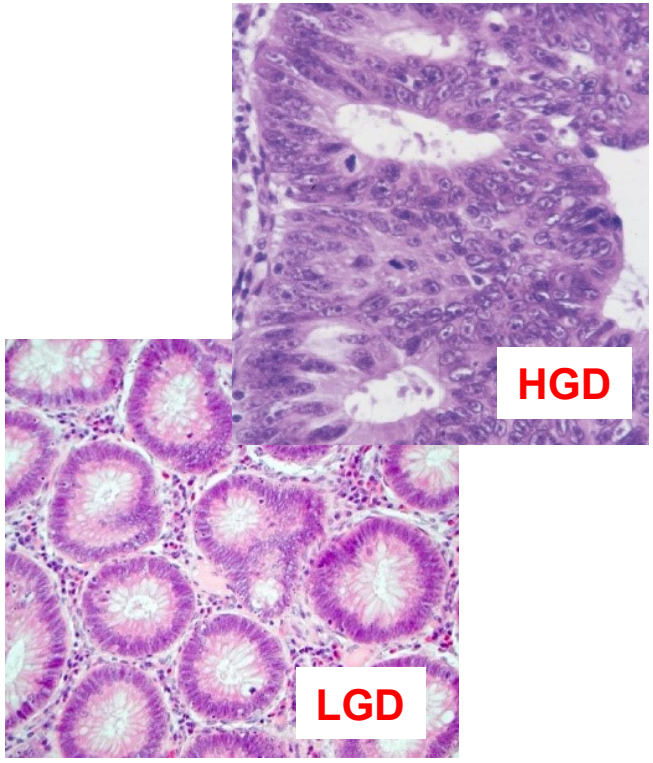
-Dimensione

-Villosità

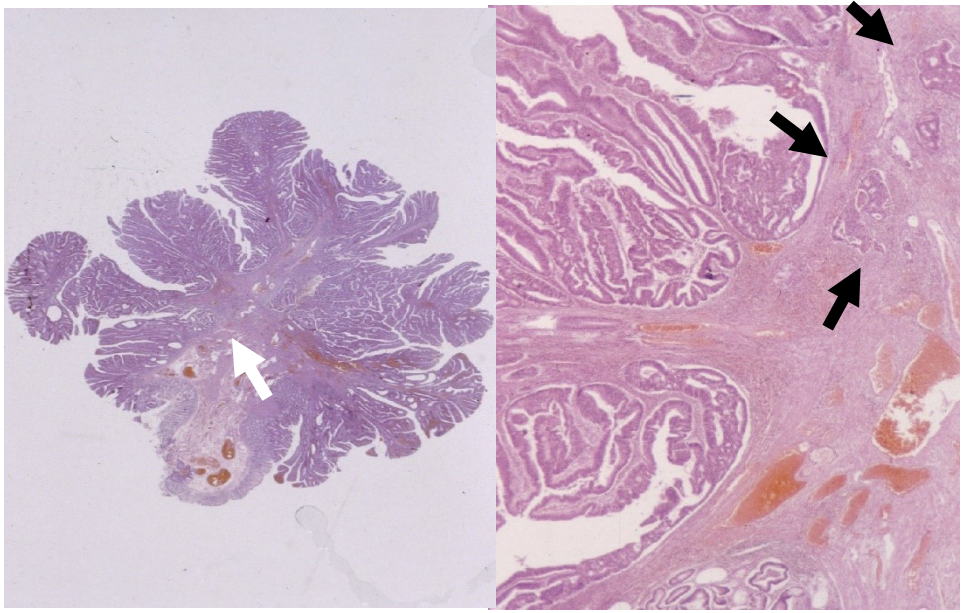
-Grading della neoplasia







'Polipo cancerizzato' = invasione della sottomucosa Adenocarcinoma pT1



WHO, colon-retto:
"***adenocarcinoma"*** = invasione della sottomucosa attraverso la m mucosae

WHO, colon-retto:
"***neoplasia intraepiteliale di alto grado"*** (anziché adenocarcinoma intramucoso)
(ex displasia di alto grado)

TNM:
-prevede ***pTis***, non contemplato nella classificazione di Vienna
-**pT1**: invasione della sottomucosa

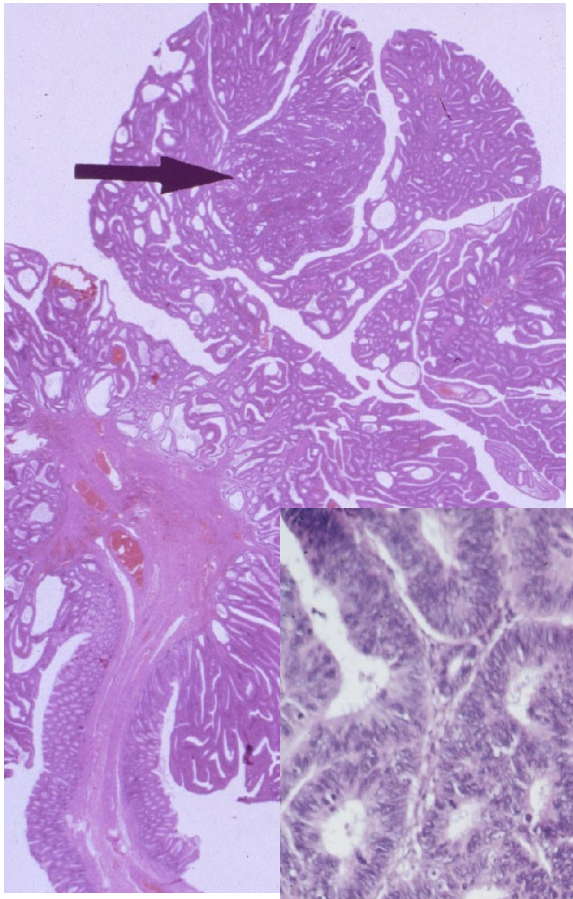
~~pTis~~

overtreatment di pT1
erroaneamente diagnosticato

Morbilità/mortalità
post-operatoria

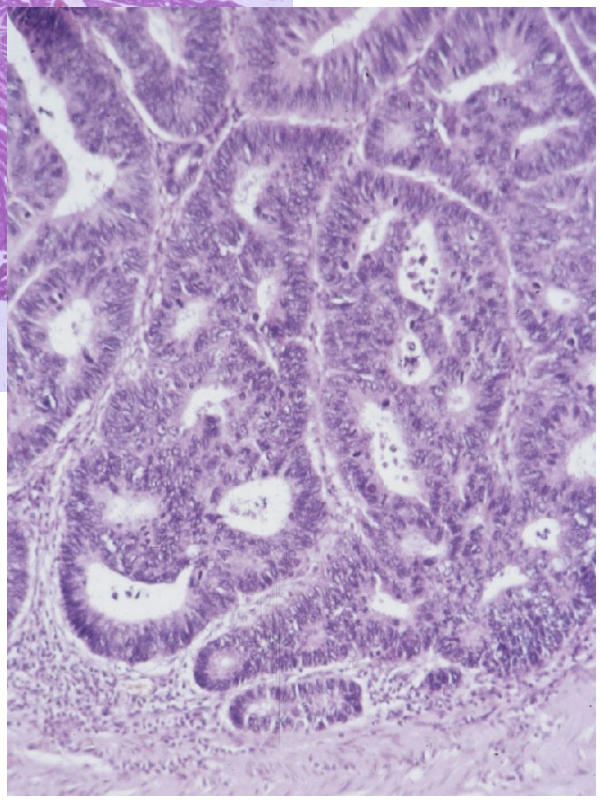
CARCINOMA IN SITU
CONFINED TO EPITHELIUM

invasion and metastatic potential absent
Excellent prognosis



INTRAMUCOUS CARCINOMA
CONFINED TO MUCOSA

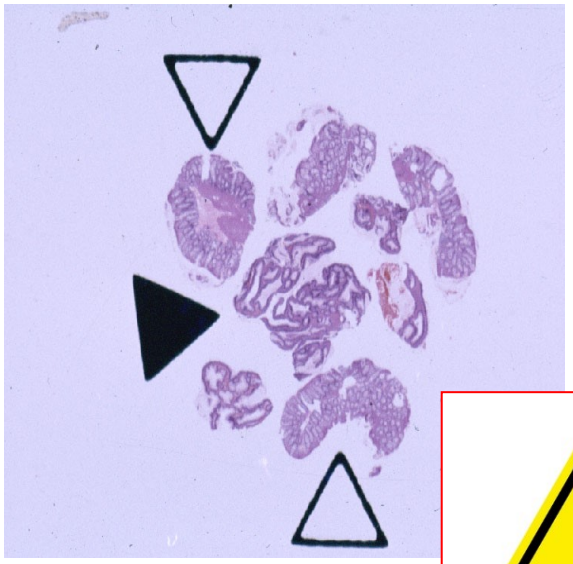
metastatic potential absent
Excellent prognosis

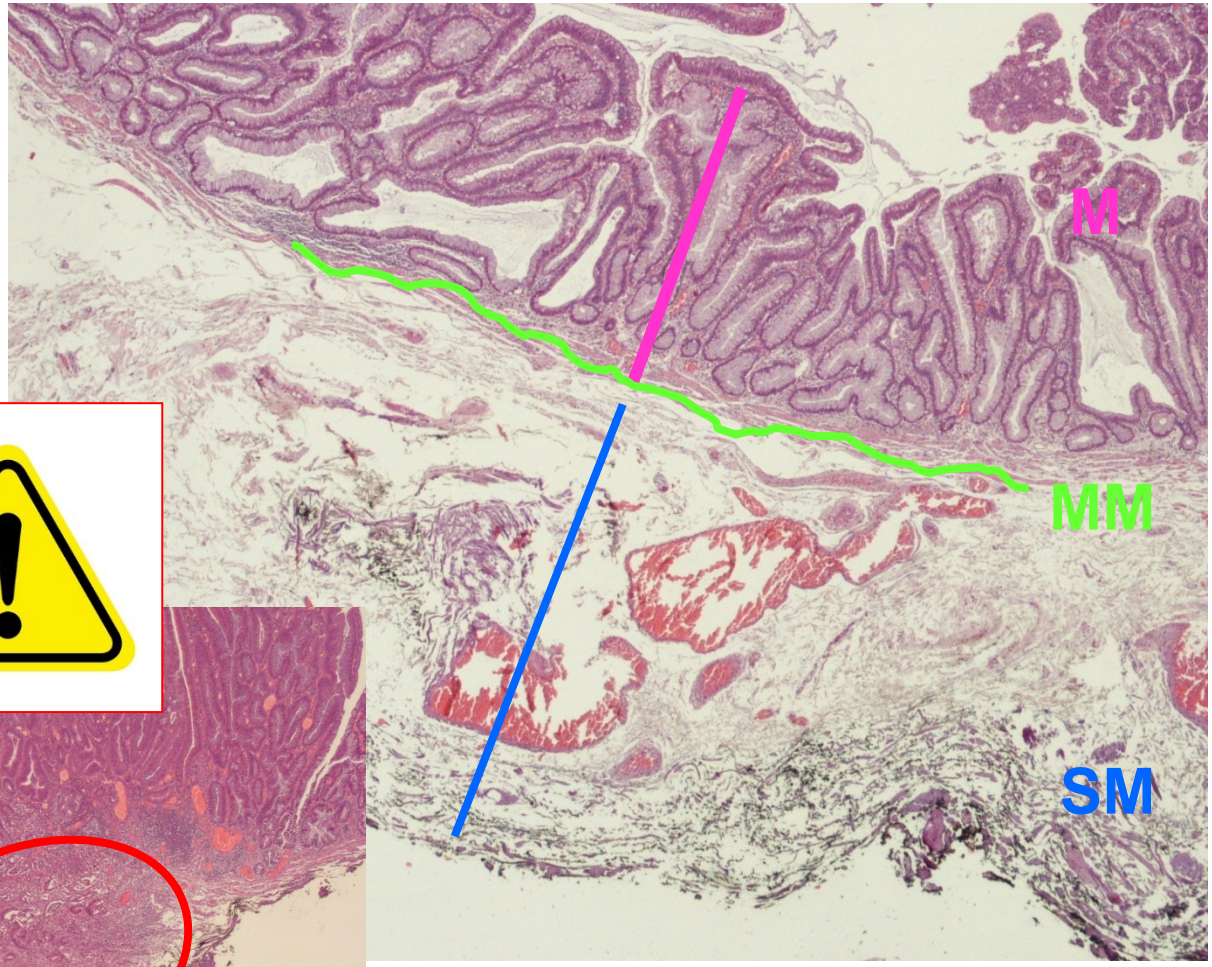


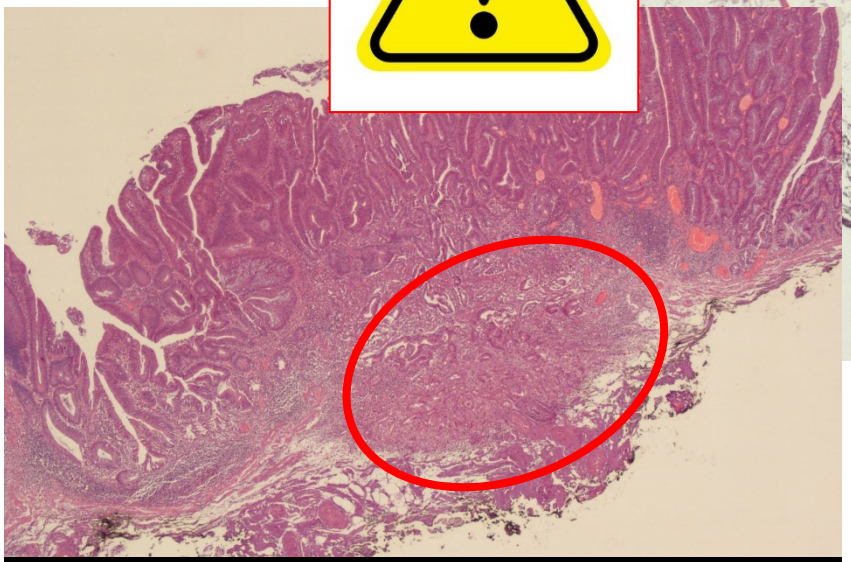
Metastatic potential absent

‘high grade dysplasia’

Frammentarietà del campione!





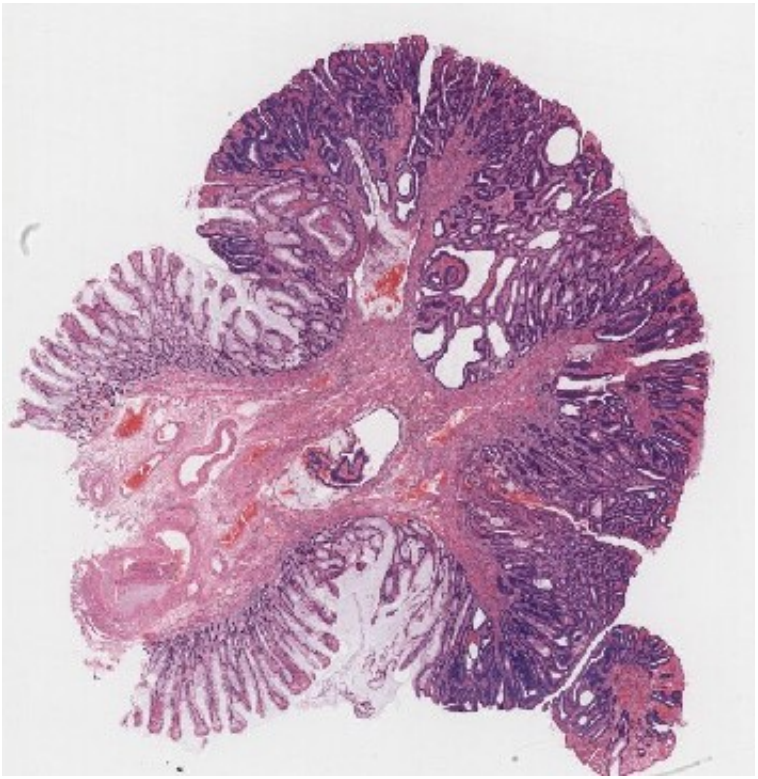


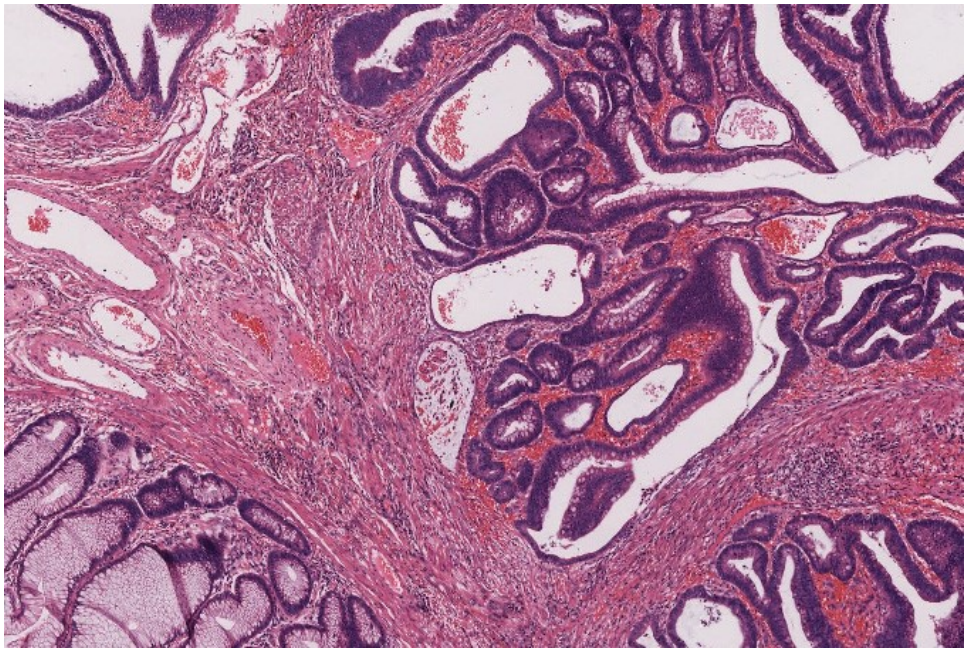
Componente infiltrante (pT1)

‘Psedoinfiltrazione’

“one of the most difficult areas of pathological diagnostic practice in FOBT screening”

Esito di torsione del peduncolo

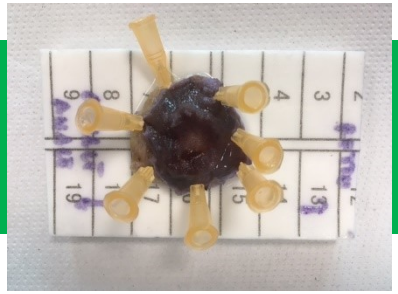




-flogosi
-ghiandole circondate da connettivo tipo ‘lamina propria’
-macrofagi captanti emosiderina
-laghi mucosi
-flogosi aumenta le modificazioni citoarchitetturali

Se dubbi: second opinion

Early cancer



“pathology affects the decision to undergo further local and/or a major resections or surveillance after screening”

European Guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition

Virchows Arch (2011) 458:1–19
DOI 10.1007/s00428-010-0977-6

REVIEW AND PERSPECTIVE

Quality assurance in pathology in colorectal cancer screening and diagnosis—European recommendations

Phil Quirke · Mauro Risio · René Lambert · Lawrence von Karsa · Michael Vieth

Virchows Arch (2011) 458:21–30
DOI 10.1007/s00428-010-0997-2

REVIEW AND PERSPECTIVE

Annex to Quirke et al. Quality assurance in pathology in colorectal cancer screening and diagnosis: annotations of colorectal lesions

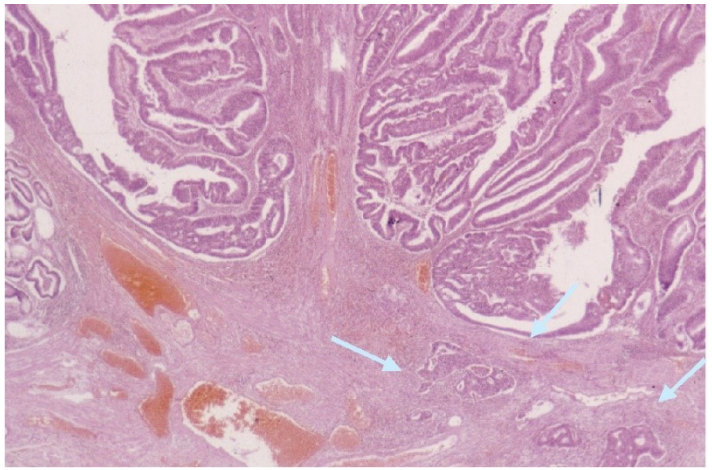
Michael Vieth · Phil Quirke · René Lambert · Lawrence von Karsa · Mauro Risio

Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

Authors Pedro Pimentel-Nunes[1], Mário Dinis-Ribeiro[1], Thierry Ponchon[2], Alessandro Repici[3], Michael Vieth[4], Antonella De Ceglie[5], Arnaldo Amato[6], Frieder Berr[7], Pradeep Bhandari[8], Andrzej Bialek[9], Massimo Conio[10], Jelle Haringsma[11], Cord Langner[12], Søren Meisner[13], Helmut Messmann[14], Mario Morino[15], Horst Neuhaus[16], Hubert Piessevaux[17], Massimo Rugge[18], Brian P. Saunders[19], Michel Robaszkiewicz[20], Stefan Seewald[21], Sergey Kashin[22], Jean-Marc Dumonceau[23], Cesare Hassan[24], Pierre H. Deprez[17]

Institutions Institutions listed at end of article

Adenocarcinomi pT1 ad alto rischio



-Grading	*-G3*
-Invasione linfo-vascolare	*-presente*
-Substaging	*-Haggitt/Kikuchi/Ueno/Parigi >sm1*
-Margine	*-R1 (verticale/orizzontale), < mm1*
-"Budding" tumorale	*-Bd2 e Bd3*

Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

<table>
<tr><th></th><th colspan="3">VM0</th><th>VM1</th></tr>
<tr><td rowspan="2">En bloc HM0</td><td colspan="3">R0</td><td rowspan="2">R1</td></tr>
<tr><td>No submucosal invasion</td><td>< Cutoff*,
L0 & V0,
Well moderately differentiated</td><td>> Cutoff*, or
L1 or V1, or
Poorly differentiated</td></tr>
<tr><td colspan="2">Low-risk resection
(endoscopic follow-up is enough)</td><td>High risk resection
(i.e. surgery +/– adjuvant treatment recommended)</td><td>High risk resection
(i.e. surgery +/– adjuvant treatment recommended)</td></tr>
<tr><td rowspan="2">En bloc HM1c
En bloc HM1d
Piecemeal</td><td colspan="3">RX</td><td>R1</td></tr>
<tr><td colspan="2">Local-risk resection
(endoscopic follow-up and putative therapy may be possible)</td><td>High risk resection
(i.e. surgery +/– adjuvant treatment recommended)</td><td>High risk resection
(i.e. surgery +/– adjuvant treatment recommended)</td></tr>
</table>

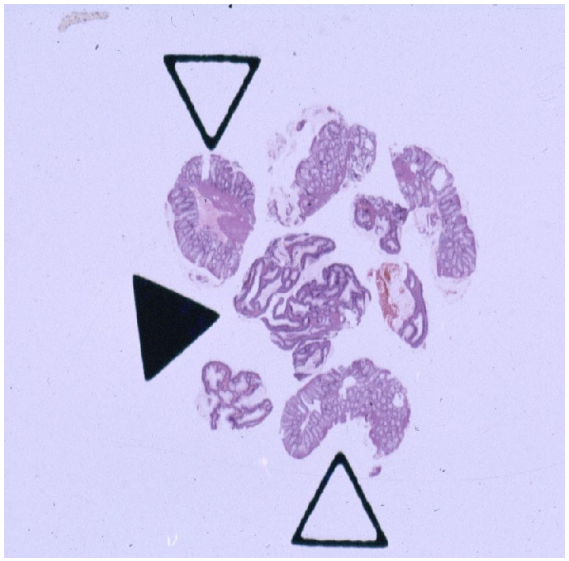
Notation: VM, vertical margin; HM, horizontal margin; R. resection; L, lymphatic invasion; V, vascular invasion; c, carcinoma; d, dysplasia

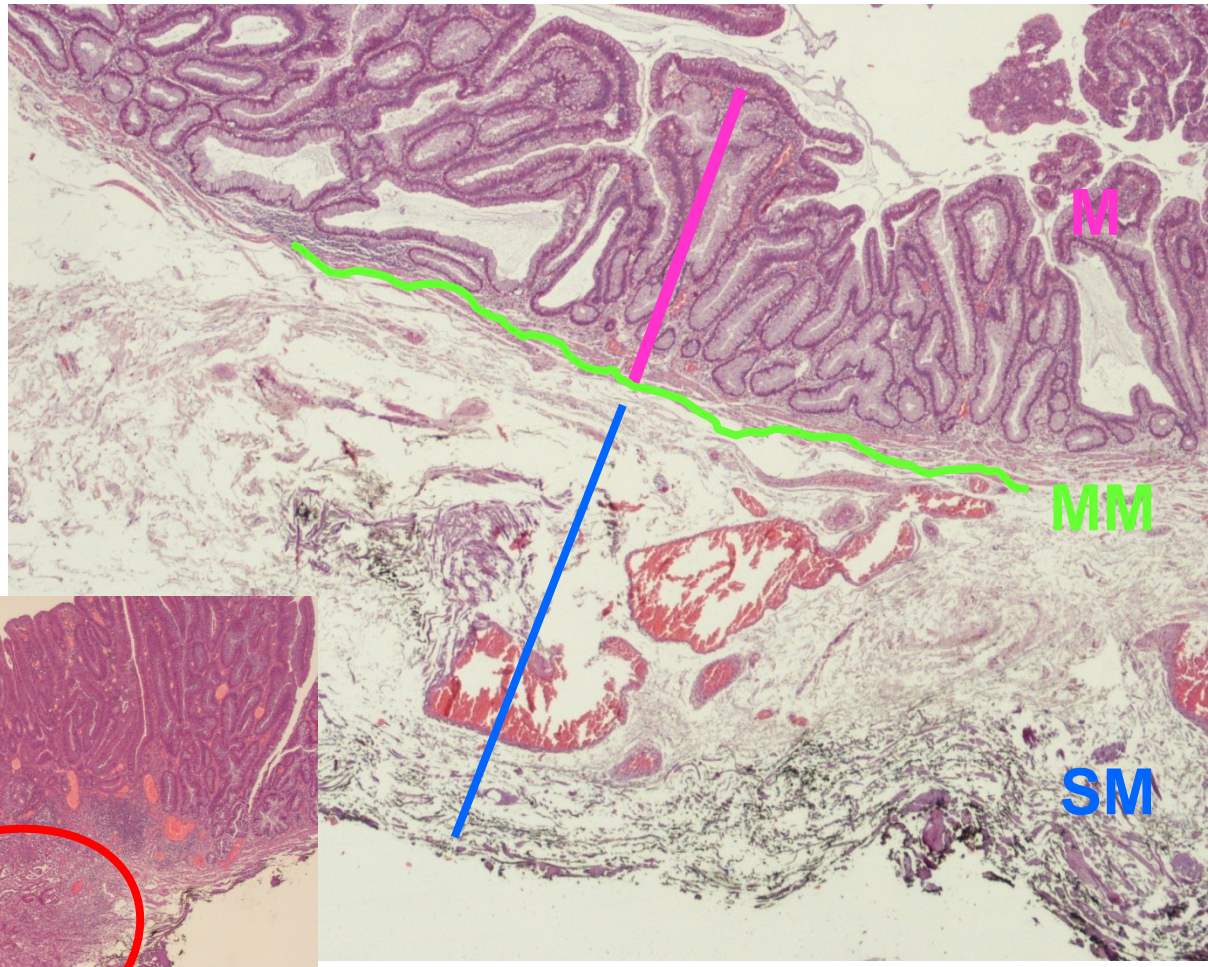
Fig. 2 Pathological criteria for determining whether to consider the resection as low risk, local risk (risk of local recurrence), or high risk (to be adjusted according to organ and size if required). * Cutoff will differ: SCC ≤ 200 µm, Barrett's or gastric adenocarcinoma ≤ 500 µm and colorectal adenocarcinoma ≤ 1000 µm

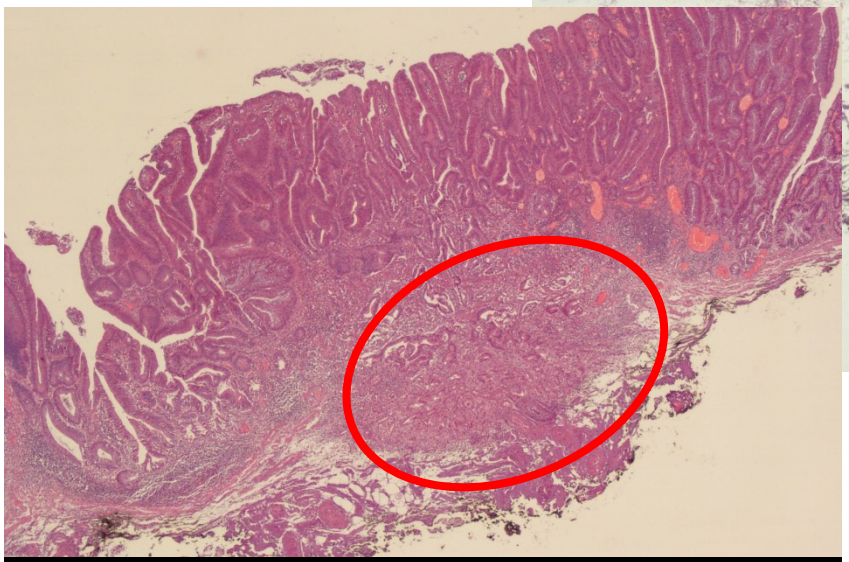
no further therapy is required
further mesaures are required

case-by-case follow-up

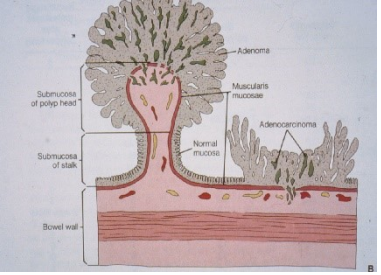
Frammentarietà del campione!





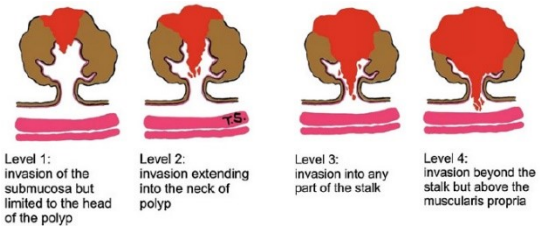


Componente infiltrante (pT1)

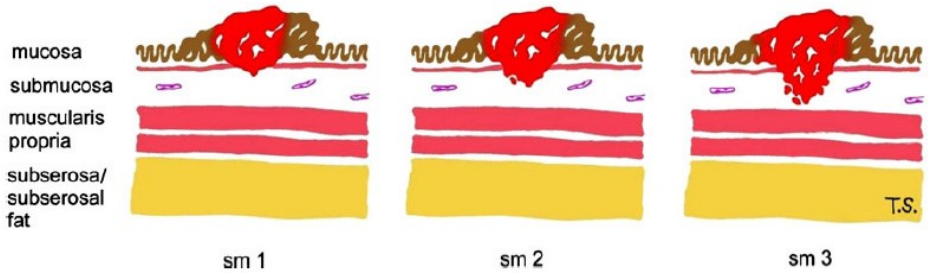


Substaging (sessili/peduncolati)

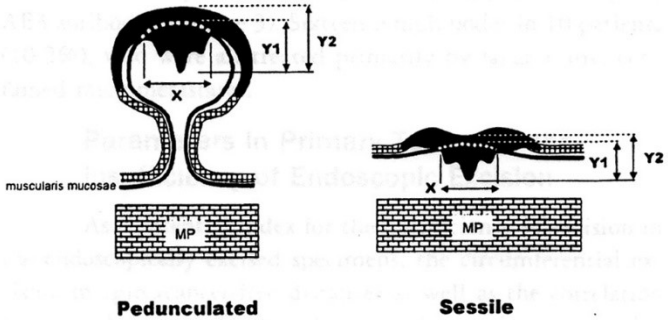
HAGGIT levels



KIKUCHI levels



Microstadiazione sec. UENO



Classificazione di Parigi

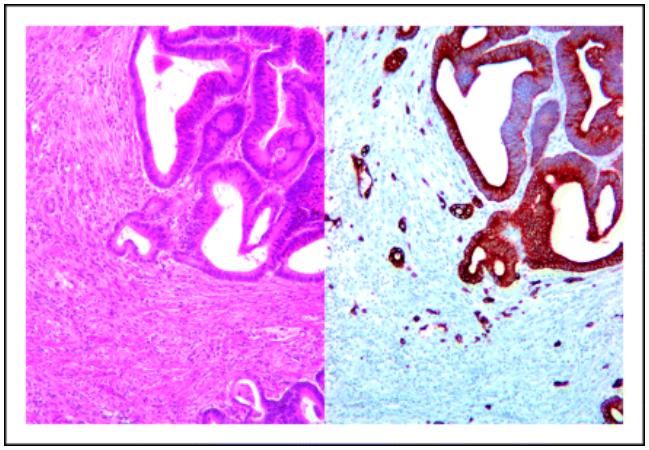
(lesioni sessili)

sm1 < 1000 micron
sm2 < 2000 micron
sm3

Tumor cell budding

"to bud" = germogliare

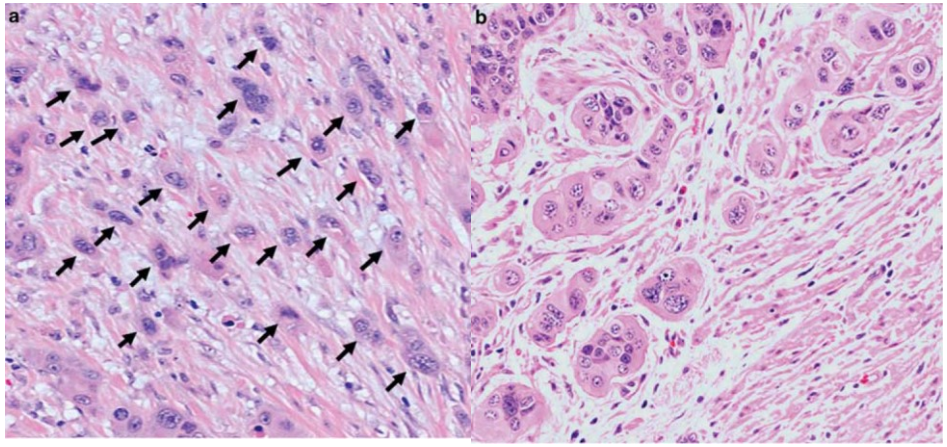
piccoli aggregati di cellule
o cellule isolate
sul fronte di invasione del tumore



MODERN PATHOLOGY (2017) 30, 1299–1311

Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016

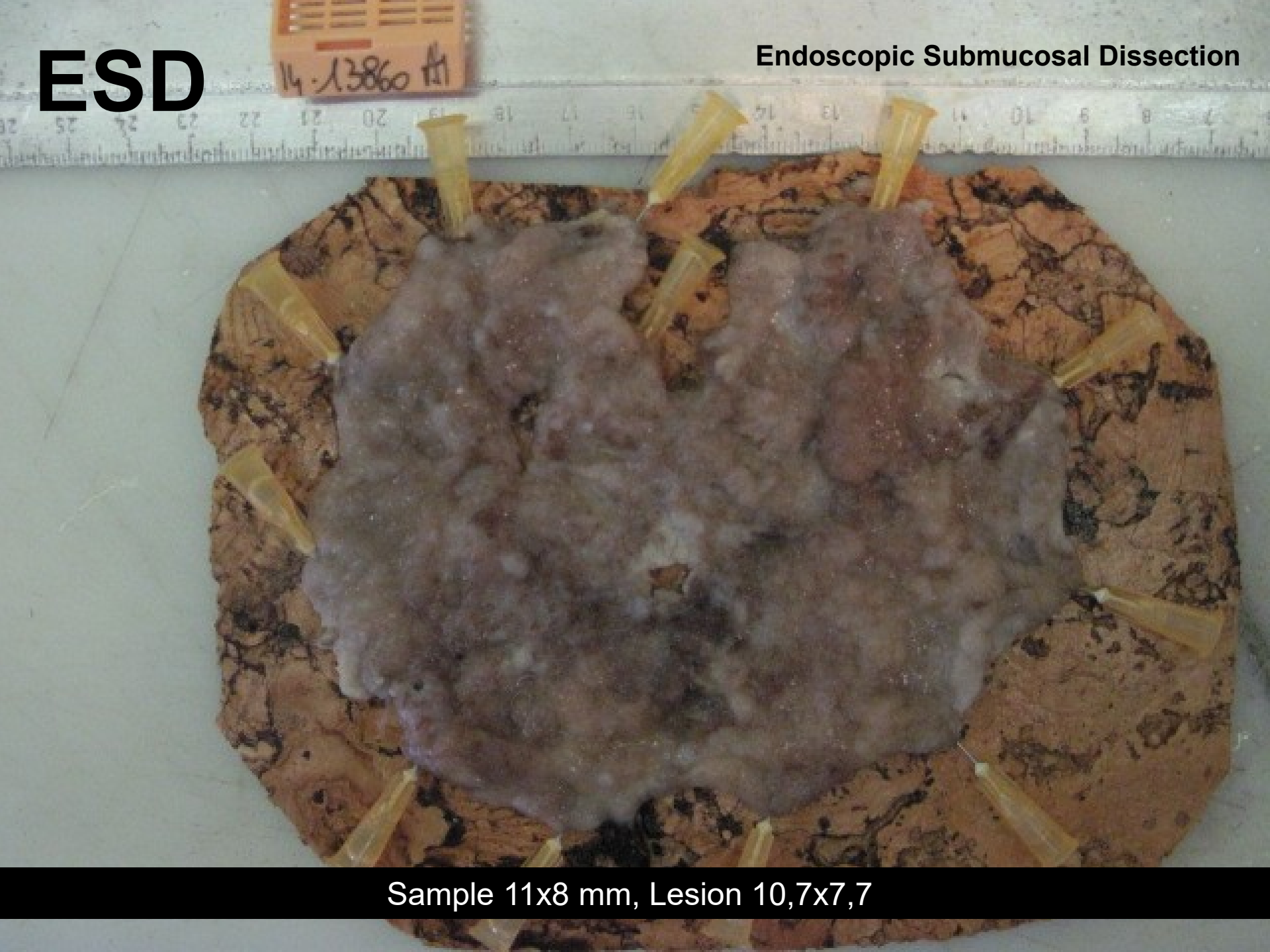
Alessandro Lugli[1,22], Richard Kirsch[2,22], Yoichi Ajioka[3], Fred Bosman[4], Gieri Cathomas[5], Heather Dawson[1], Hala El Zimaity[6], Jean-François Fléjou[7], Tine Plato Hansen[8], Arndt Hartmann[9], Sanjay Kakar[10], Cord Langner[11], Iris Nagtegaal[12], Giacomo Puppa[13], Robert Riddell[2], Ari Ristimäki[14], Kieran Sheahan[15], Thomas Smyrk[16], Kenichi Sugihara[17], Benoît Terris[18], Hideki Ueno[19], Michael Vieth[20], Inti Zlobec[1] and Phil Quirke[21]



- 0–4 buds—low budding (Bd 1).
- 5–9 buds—intermediate budding (Bd 2).
- 10 or more buds—high budding (Bd 3).

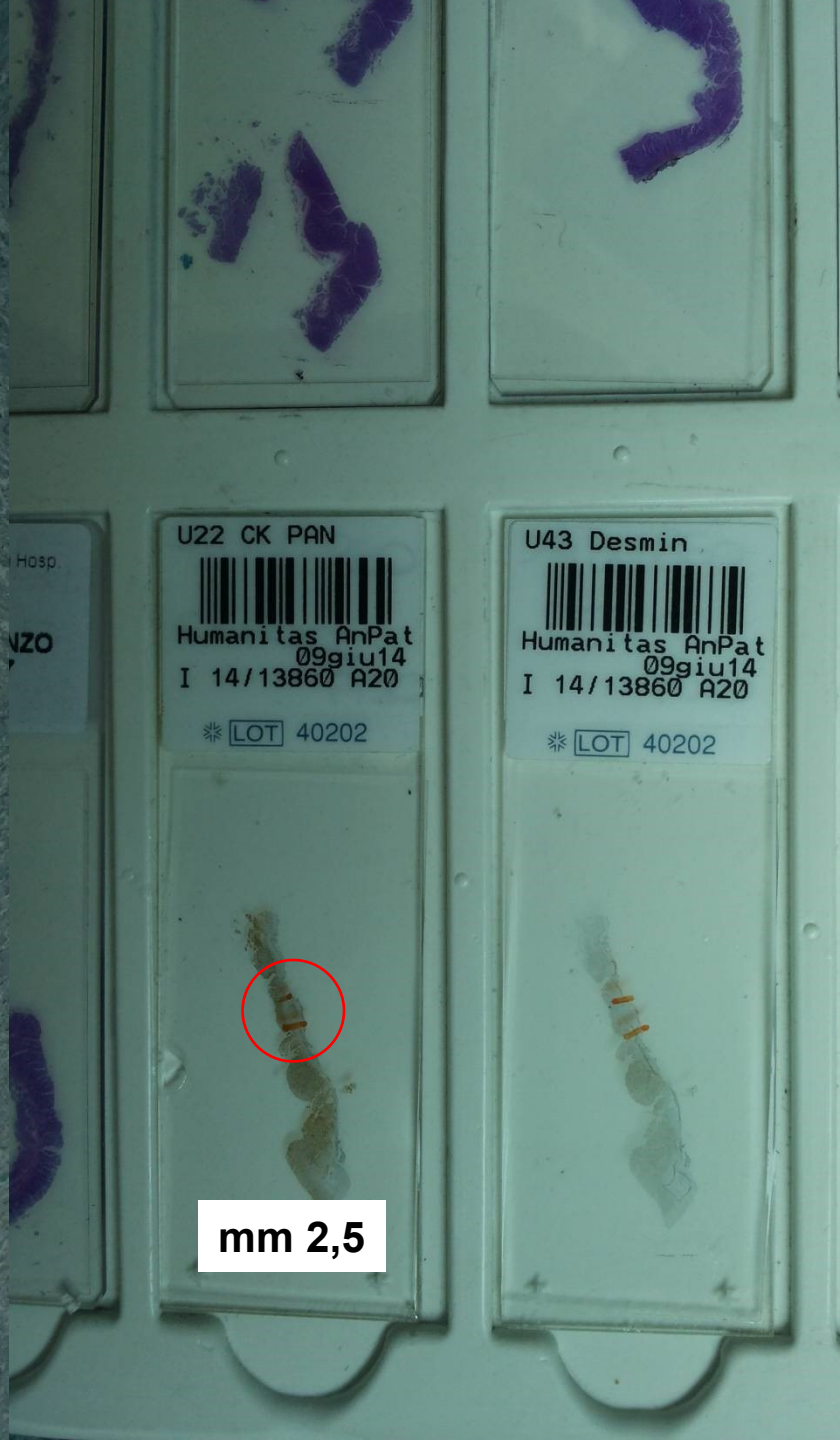
ESD

Endoscopic Submucosal Dissection

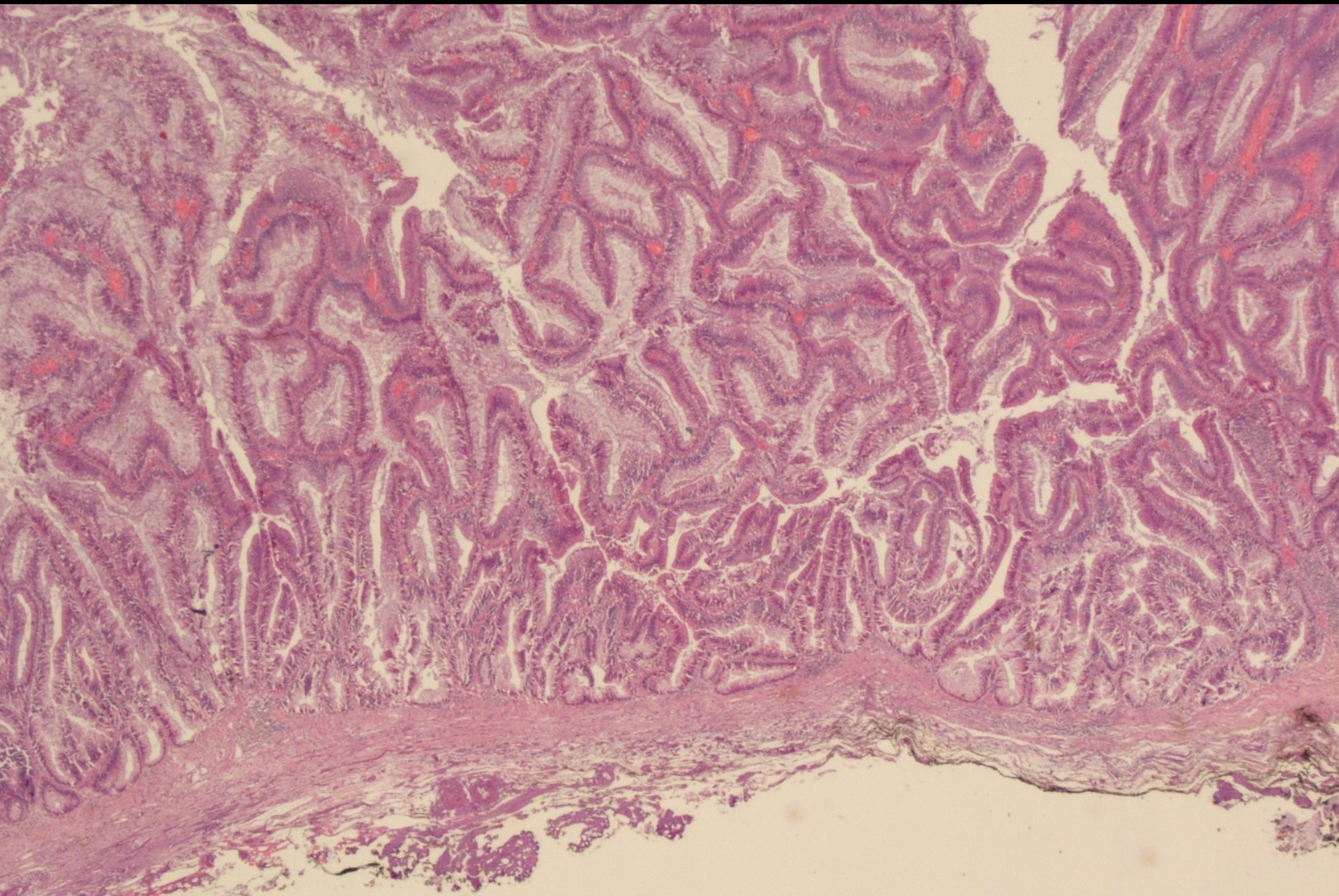


Sample 11x8 mm, Lesion 10,7x7,7

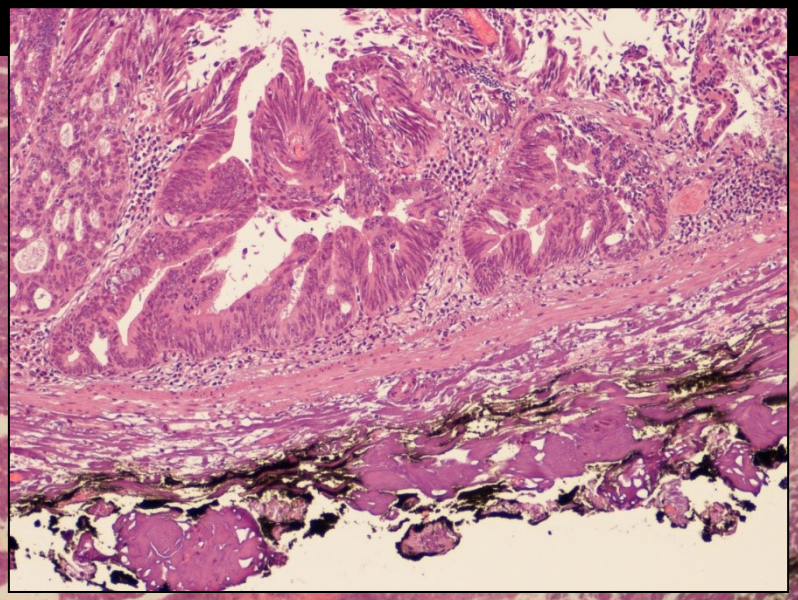

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37

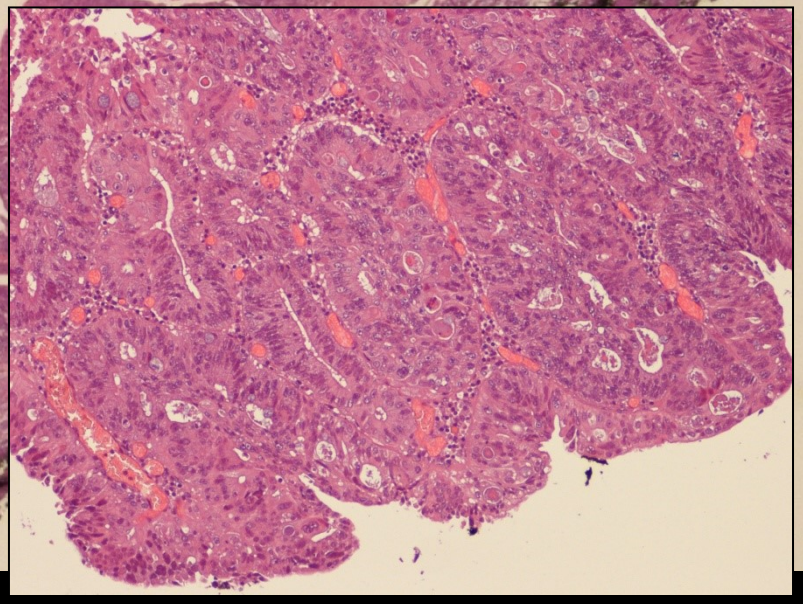

U22 CK PAN
Humanitas AnPat
09giu14
I 14/13860 A20
LOT 40202
U43 Desmin
Humanitas AnPat
09giu14
I 14/13860 A20
LOT 40202
mm 2,5

displasia di basso grado



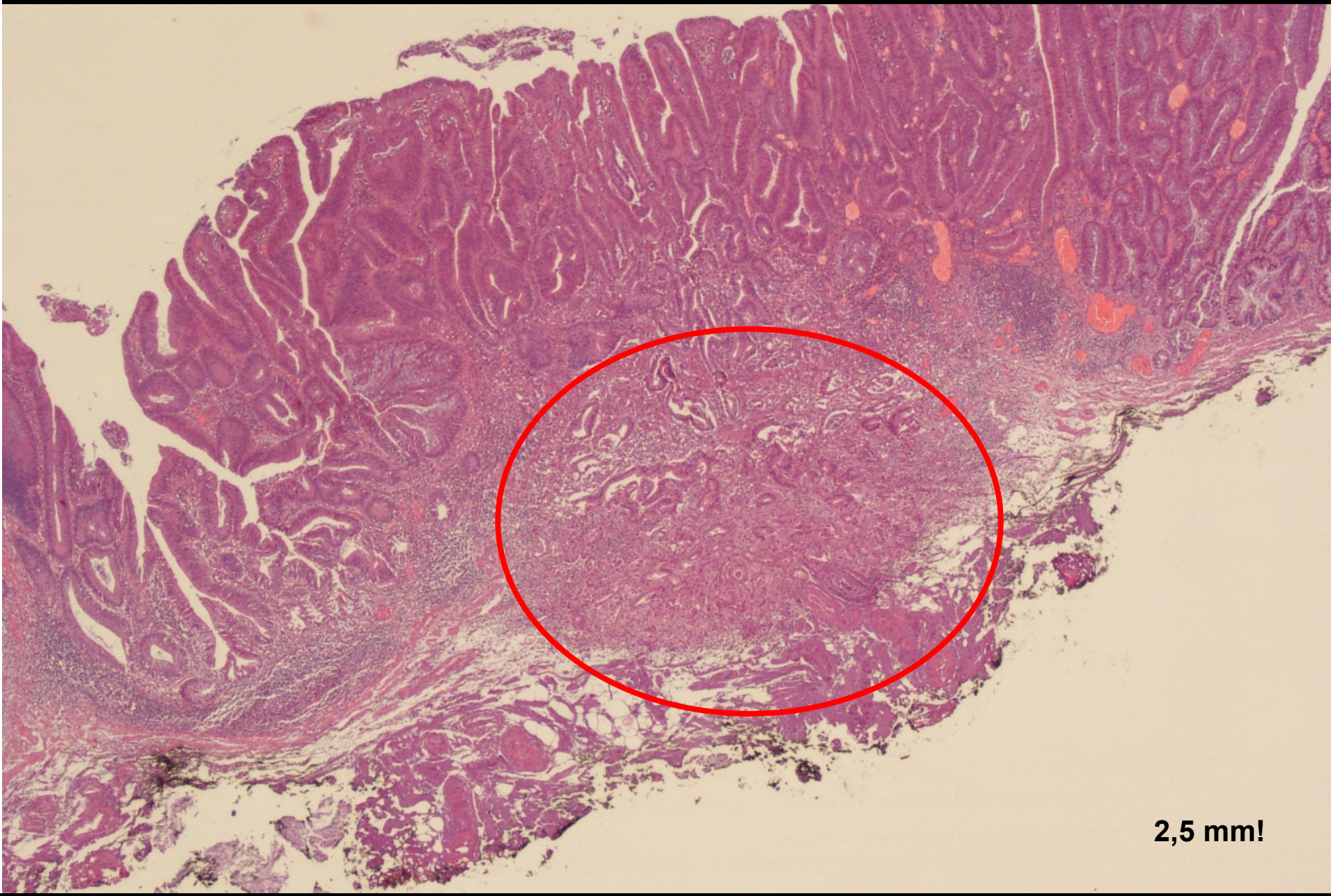
displasia di alto grado





Prelievo 22

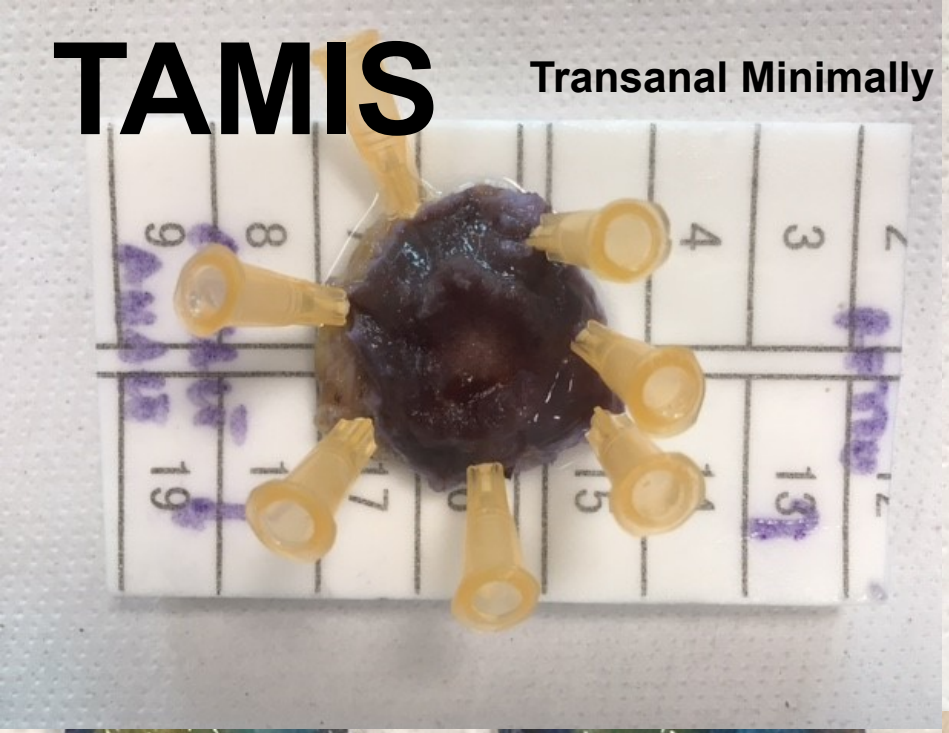
Adenocarcinoma pT1,NAS, G2, L0, V0, R0

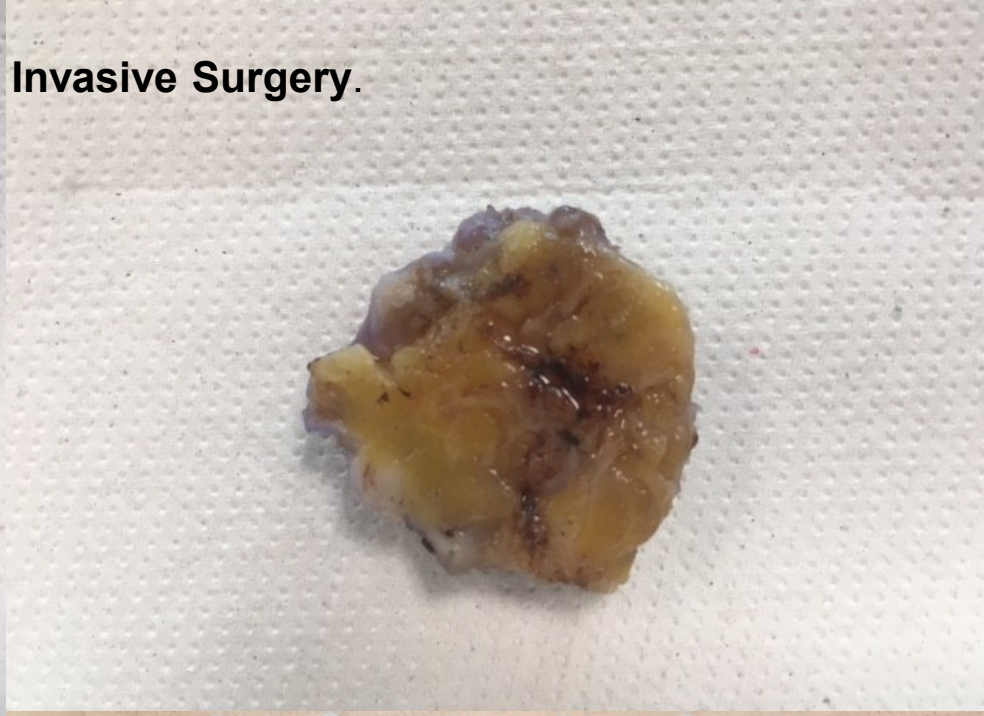


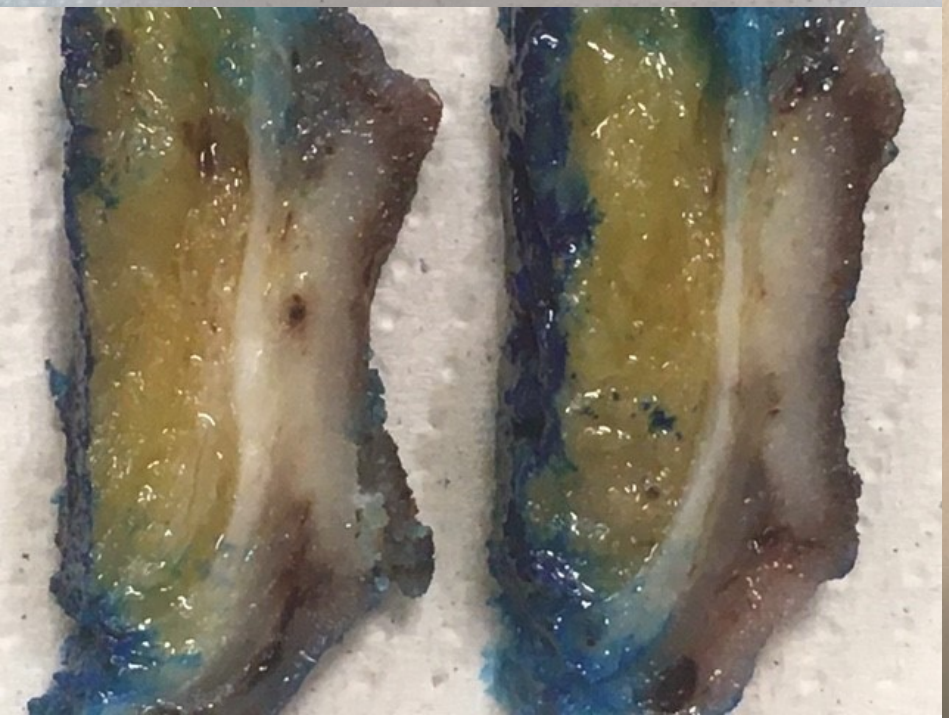
Prelievo 20

TAMIS

Transanal Minimally Invasive Surgery.







DIAGNOSI EARLY COLORECTAL CANCER (pT1)

Adenocarcinoma del grosso intestino insorto in contesto di adenoma tubulare/tubulo-villoso/villoso con displasia di basso/alto grado,
infiltrante la tonaca sottomucosa (“early colorectal cancer”).
-Grado di differenziazione: G1-G2-G3-G4, basso/alto grado (sec. WHO)
-Angioinvasione (linfatica o venosa): assente/presente/non evidente (oppure: focale/discreta/massiva)
-Stato del margine di resezione endoscopica: positivo/negativo (neoplasia a mm….dal margine). Non valutabile stante la frammentarietà del campione.
-Rapporto quantitativo tessuto adenomatoso/adenocarcinoma: %
-“Budding” tumorale (presenza di cellule di carcinoma isolate o in gruppi di meno di 5 elementi al fronte di avanzamento tumorale): presente/assente.
Grado: Bd1 (basso, 0-4 per 0,785 mmq) Bd2 (intermedio, 5-9 buds per 0,785 mmq), Bd3 (alto, > o uguale a 10 buds per 0,785 mmq)
sec. International Tumor Budding Consensus Conference, ITBCC 2016, Modern Pathology (2017) 30, 1299-1311.
-Profondità di invasione della sottomucosa: > o < 2 mm; ampiezza di invasione della sottomucosa: > o < 4 mm (sec. Ueno 2004)
-Livello di infiltrazione del peduncolo-livello di Haggitt (lesione polipoide): livello 1 di 4; 2 di 4; 3 di 4; 4 di 4. Non valutabile.
-Livello di invasione della sottomucosa-livello di Kikuchi (lesione sessile): sm1 (terzo superficiale della sottomucosa),
sm2 (terzo intermedio della sottomucosa), sm 3 (terzo profondo della sottomucosa). Non valutabile
-Profondità di infiltrazione sec. Classificazione di Parigi: sm1 (<1000 micron); sm2 (< 2000 micron); sm3)
-Studio immunoistochimico per Mismatch Repair Proteins
MLH1 positività nucleare conservata nelle cellule tumorali
PMS2 perdita della positività nucleare nelle cellule tumorali (opzionale)
MSH2
MSH6
Stadiazione istopatologica sec. TNM: pT1

Commento: adenoma cancerizzato a basso/alto rischio di diffusione metastastatica

Pathology report minimum items

- Exact location
- Paris classification
- Size (mm)
- En bloc versus piecemeal

- Grading (well/moderate vs poorly)
- Presence of lymphovascular invasion
- Substaging (sm1, sm2,sm3; Ueno)
- Resection margins status (HM, VM)
- Complete resection or not (R0,Rx,R1)

no further therapy is required

further mesaures are required

case-by-case follow-up

Low risk resection

High risk resection

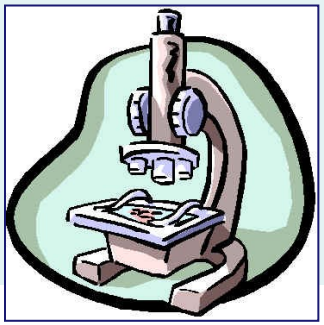
Local risk resection

Considerare la revisione istologica da patologo dedicato per pT1 ad alto rischio

Advanced cancer

Pathologic examination of CRC resection specimens

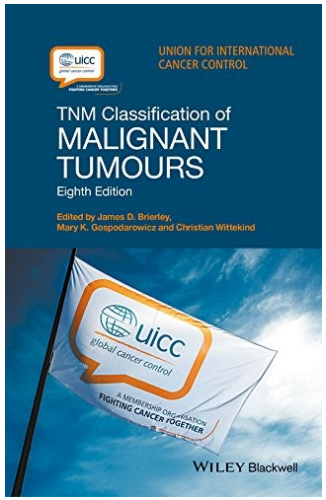
prognosis
appropriate post-operative treatment
need for genetic counseling

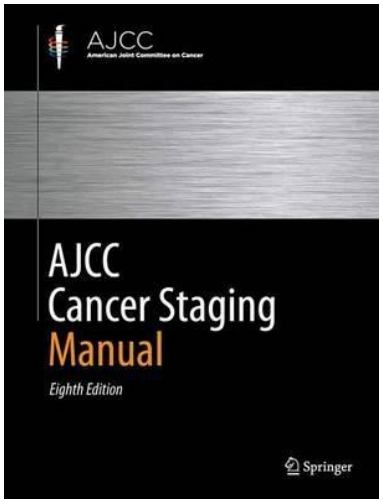


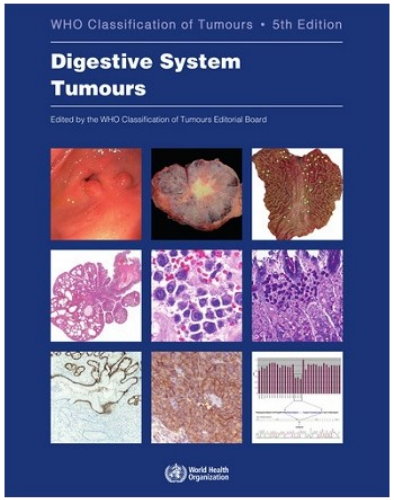
Tumour Node Metastasis (TNM) staging
non-stage-related prognostic factors
specimen quality and surgical margins
response to therapy

mismatch repair protein (MMR) immunohistochemistry
KRAS and BRAF mutational analysis

standardizing reporting of colorectal cancer







Cancer Checklists
(synoptic reporting)

standardization
completeness of pathology reporting

COLLEGE of AMERICAN PATHOLOGISTS

Protocol for the Examination of Resection Specimens From Patients With Primary Carcinoma of the Colon and Rectum

Version: 4.2.0.1
Protocol Posting Date: November 2021

The Royal College of Pathologists
Pathology: the science behind the cure

Standards and datasets for reporting cancers

Dataset for histopathological reporting of colorectal cancer

September 2018

RCPA
The Royal College of Pathologists of Australasia

REVIEW PAPER

OPEN

Dataset for Pathology Reporting of Colorectal Cancer

Recommendations From the International Collaboration on Cancer Reporting (ICCR)

Maurice B. Loughrey, MRCP, FRCPAth, MD,† Fleur Webster,‡ Mark J. Arends, MD, PhD, FRCPath,§ Ian Brown, MBBS, BGEN, FRCPA,¶ Lawrence J. Burgart, MD,‖ Chris Cunningham, BSC (Hons), MBChB, MD, FRCSEd,** Jean-Francois Flejou, MD, PhD,†† Sanjay Kakar, MD,‡‡ Richard Kirsch, MBChB, PhD, FRCPath(SA), FRCPC,§§ Motohiro Kojima, MD, PhD,¶¶ Alessandro Lugli, MD,‖‖ Christophe Rosty, MD, PhD, FRCPA,***†††‡‡‡ Kieran Sheahan, MB, FRCPI, FRCPath,§§§ Nicholas P. West, MBChB, PhD, FRCPath,¶¶¶ Richard H. Wilson, MD,‖‖‖ and Iris D. Nagtegaal, MD, PhD****✉*

internationally agreed

Annals of Surgery • Volume 275, Number 3, March 2022

Standardization
Clinicopathological communication

'Quality of pathology reporting and mutual understanding between colorectal surgeon, pathologist and oncologist are vital to patient management'

TABLE 1. Core and Non-Core Elements for Reporting

Core Items	Non-Core Items
Neoadjuvant therapy	Clinical information
Operative procedure	Plane of sphincter excision*
Tumor site	Plane of mesocolic excision*
Tumor dimensions (maximum)	Measurement of invasion beyond muscularis propria
Perforation	Tumor budding
Relation of tumor to anterior peritoneal reflection,* Plane of mesorectal excision*	Coexistent pathology
Histological tumor type	Ancillary studies
Histological tumor grade	
Extent of invasion	
Lymphatic and venous invasion	
Perineural invasion	
Lymph node status	
Tumor deposits	
Response to neoadjuvant therapy	
Margin status	
Histologically confirmed distant metastases	
Pathological staging	
Ancillary studies	

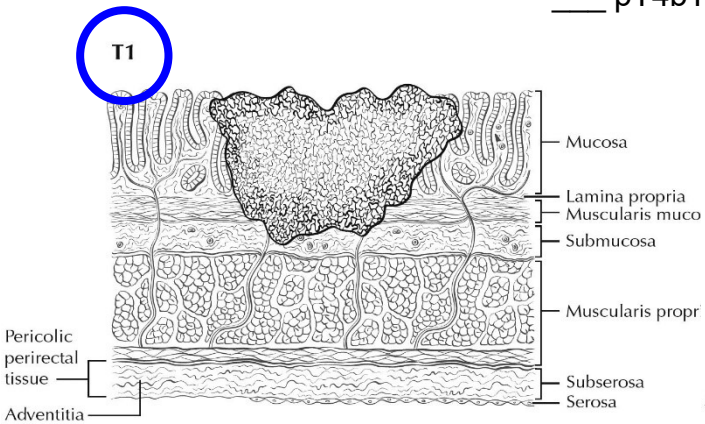
*These items are only relevant to certain specimen types—see text for details.

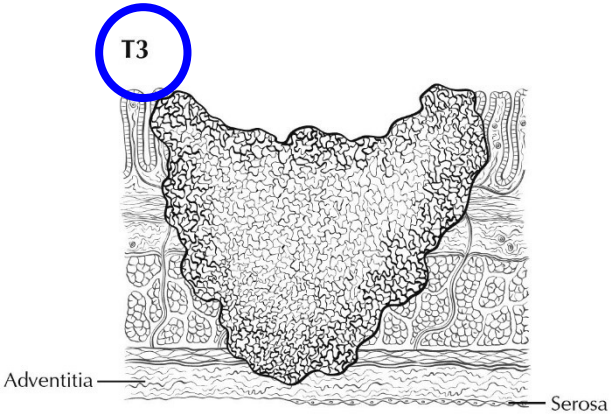
TNM, v8

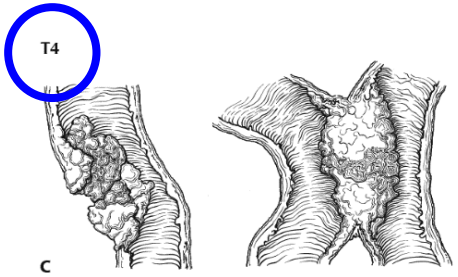
T

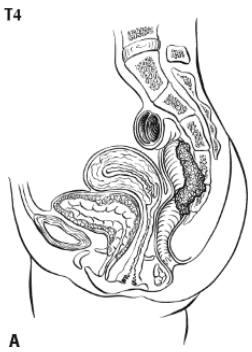
~~pTis~~

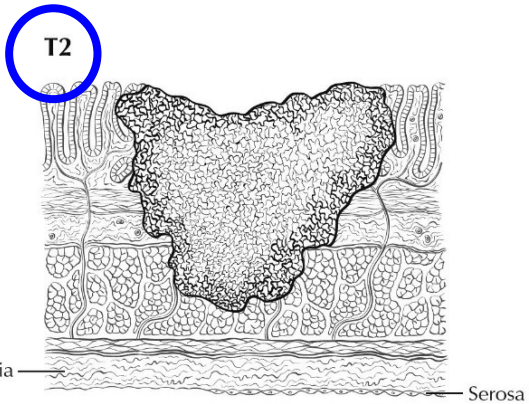
___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence of primary tumor
___ pT1: Tumor invades the submucosa
___ pT2: Tumor invades the muscularis propria
___ pT3: Tumor invades through the muscularis propria into pericolorectal tissues
___ pT4a Tumor invades through the visceral peritoneum
(including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
___ pT4bTumor directly invades# or adheres## to adjacent organs or structures

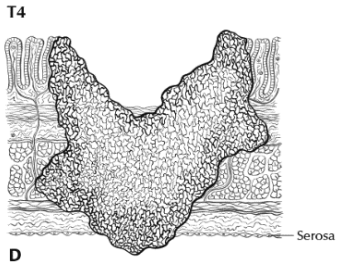


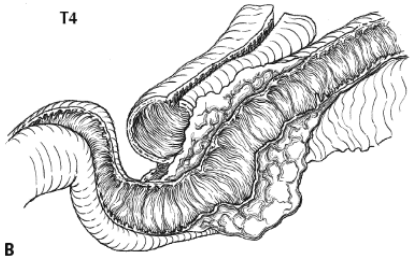






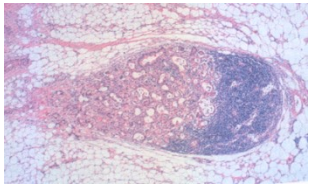




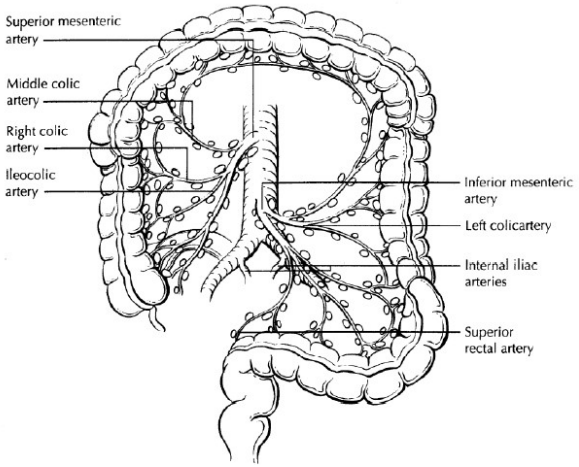


TNM v8

T



12 minimum recommended number



surgical technique, resection volume

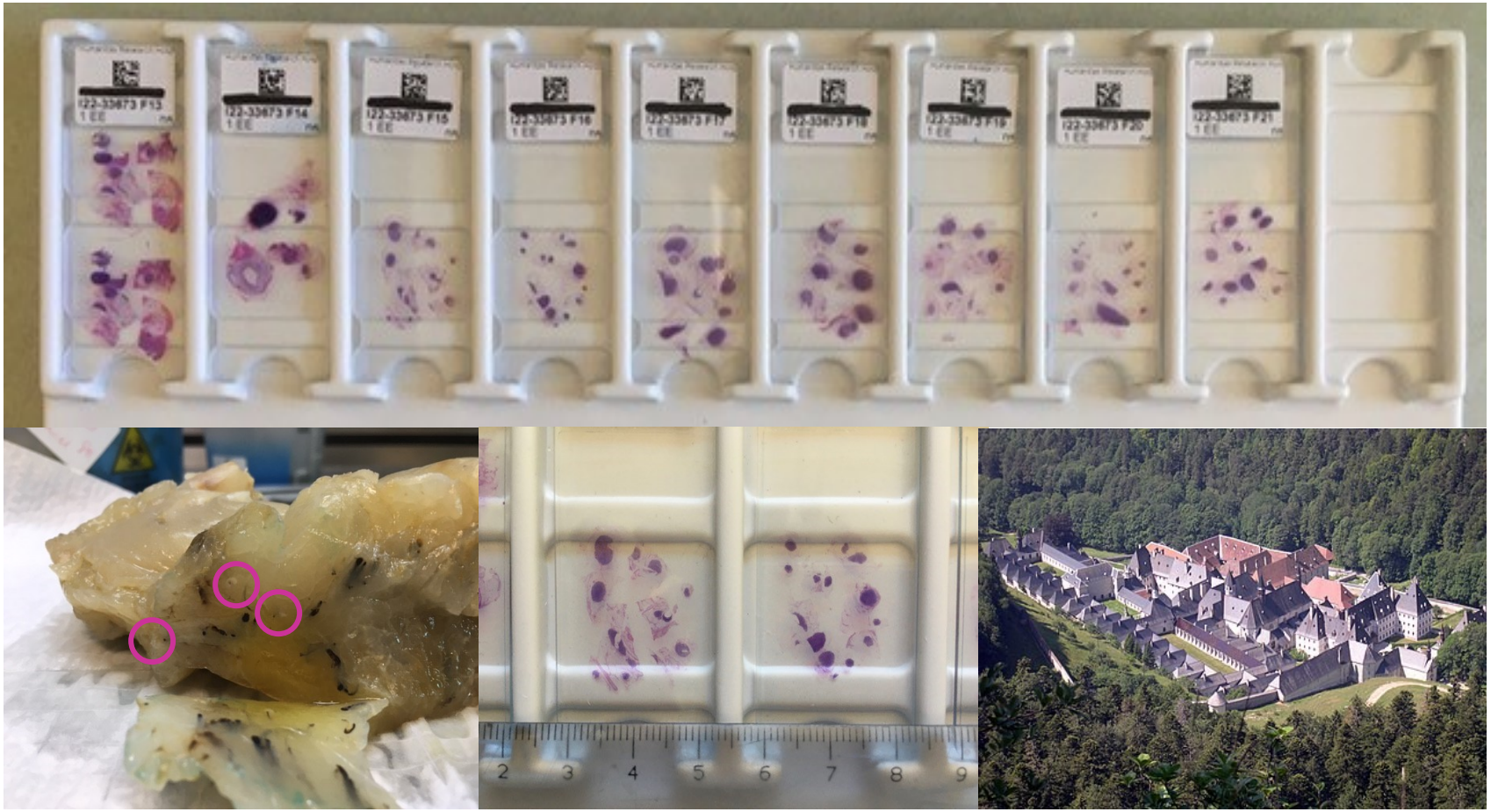
pathology technique

age, obesity, neoadjuvant therapy

Regional Lymph Nodes (pN)

___ pNX: Regional lymph nodes cannot be assessed
___ pN0: No regional lymph node metastasis (even if < 12)
___ pN1a: One regional lymph node is positive
___ pN1b: Two or three regional lymph nodes are positive
___ pN1c: No regional lymph nodes are positive, but there are tumor
___ pN2a: Four to six regional lymph nodes are positive
___ pN2b: Seven or more regional lymph nodes are positive

Il chirurgo deve rimuoverne tanti….



…. Il patologo deve trovarli tutti!

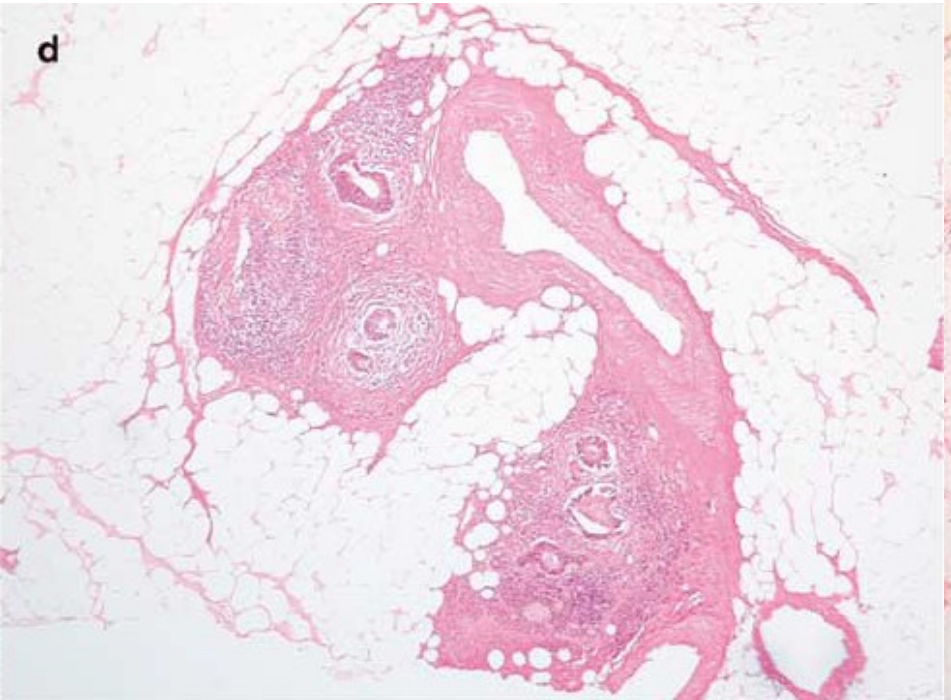
TUMOR DEPOSITS (discontinous extramural extension)

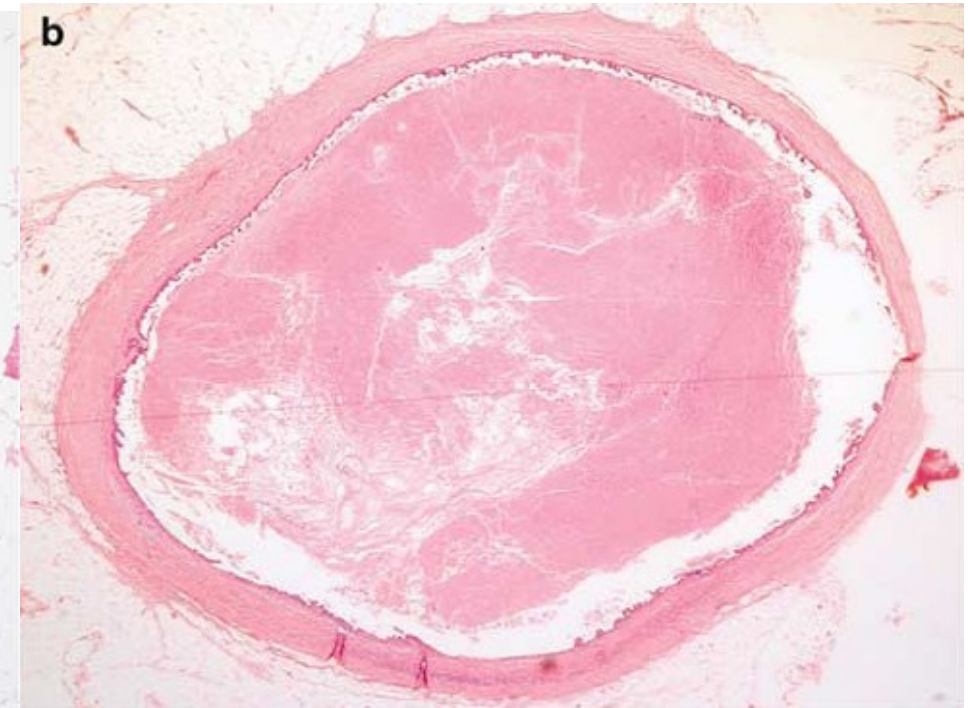
↓ recurrence-free survival
↓ overall survival

Cancer 2008;112(1):50-54
Mod Pathol.2007;20(8):843-855

Satellite nodules are discountinous spread,
(no lymph nodes mets)

TNM v8 **N1c** (with negative lymph nodes)





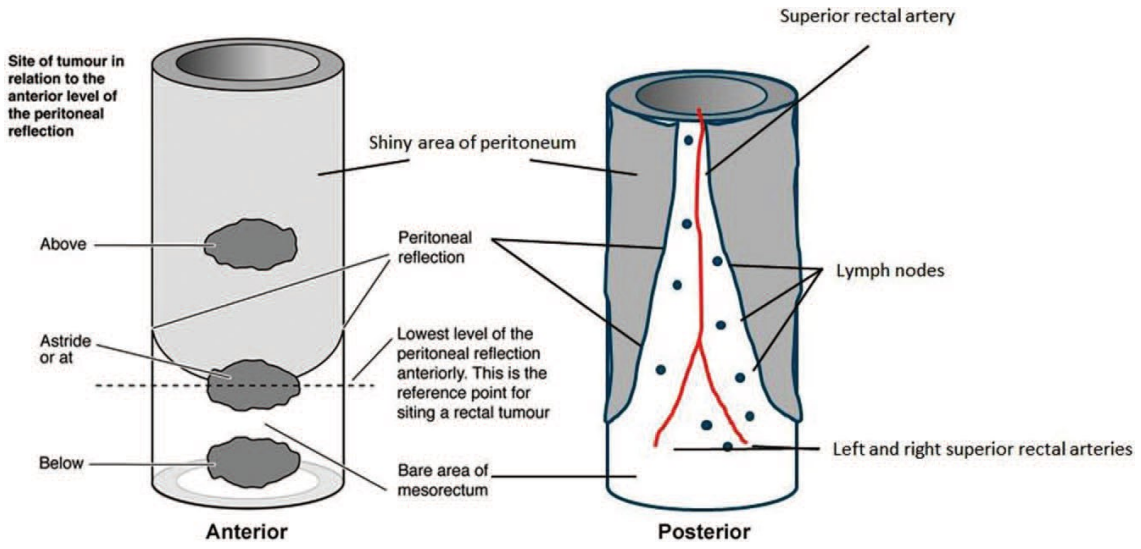
Relation of Tumor to Anterior Peritoneal Reflection

Rectal cancer

local recurrence
peritoneal recurrence

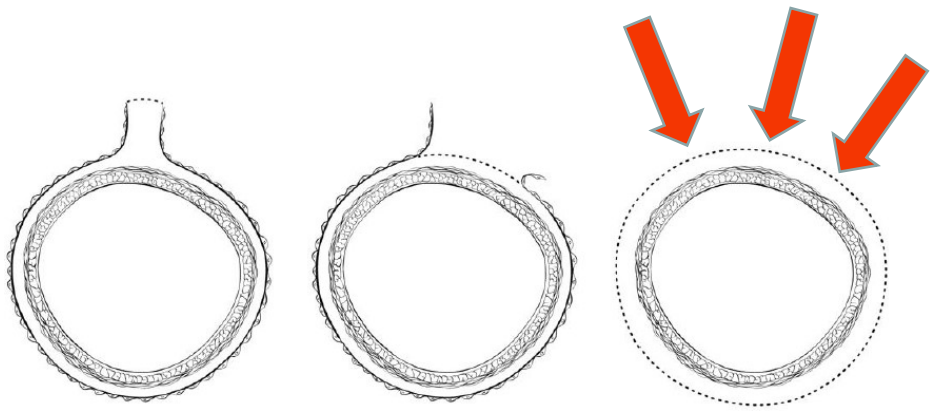
neoadjuvant therapy

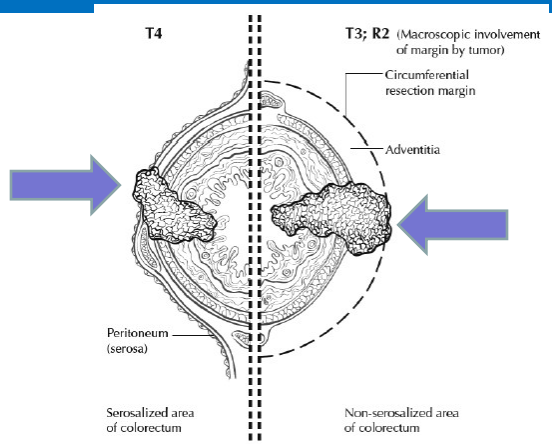
clinicopathological correlation!



Relation of Tumor to Anterior Peritoneal Reflection

Rectal cancer

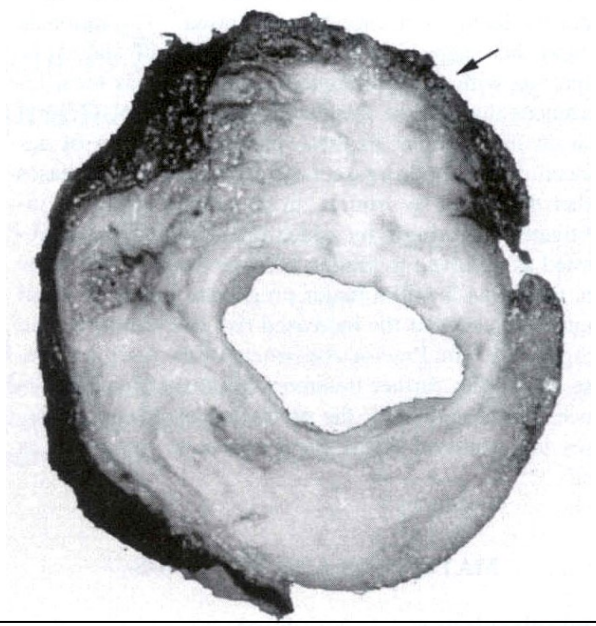




Circumferential margin

0-1 mm

Positive Margin: **R1 o R2**



'surgical clerance'

TABLE 2. *Relation of the circumferential margin and patient's prognosis**

	Local recurrence	Distant metastases	Survival (2 y)	No.
≤0.10 cm	16.4%	37.6%	69.7%	120
0.11–0.20 cm	14.9%	21.0%	84.8%	53
0.21–0.50 cm	10.3%	17.2%	87.0%	139
0.51–1.00 cm	6.0%	8.2%	91.2%	155
>1.00 cm	2.4%	10.9%	92.8%	189
	p = 0.0007	p <0.0001	p <0.0001	

* Local and distant recurrence rates and survival rates after 2-year follow-up are given. All differences are significant using log rank testing.

Am J Surg Patholol. 2002; 26(3):350-357

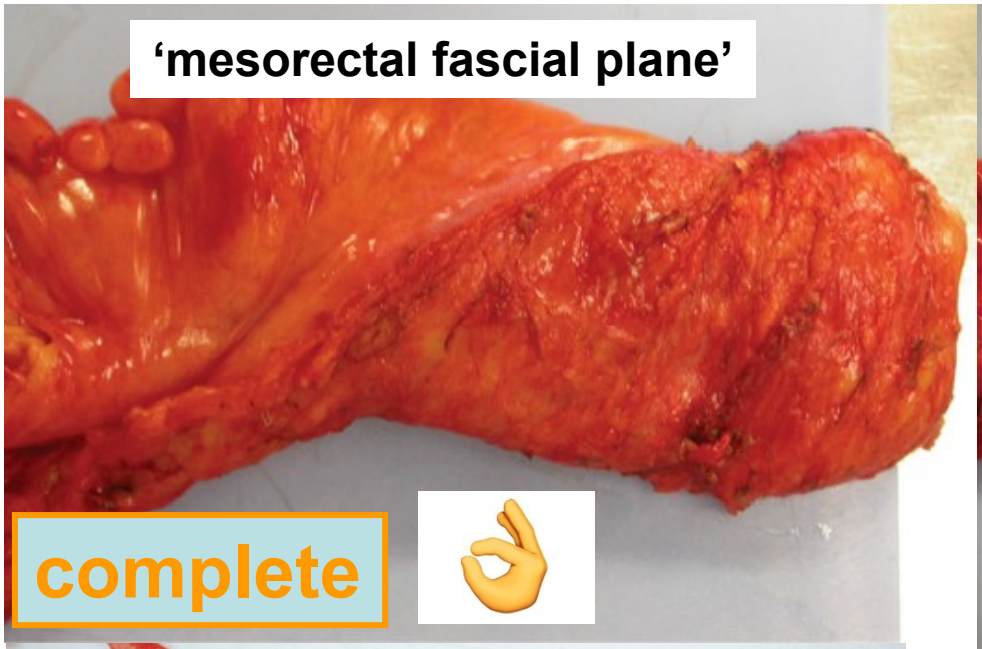
Proximal and distal margins

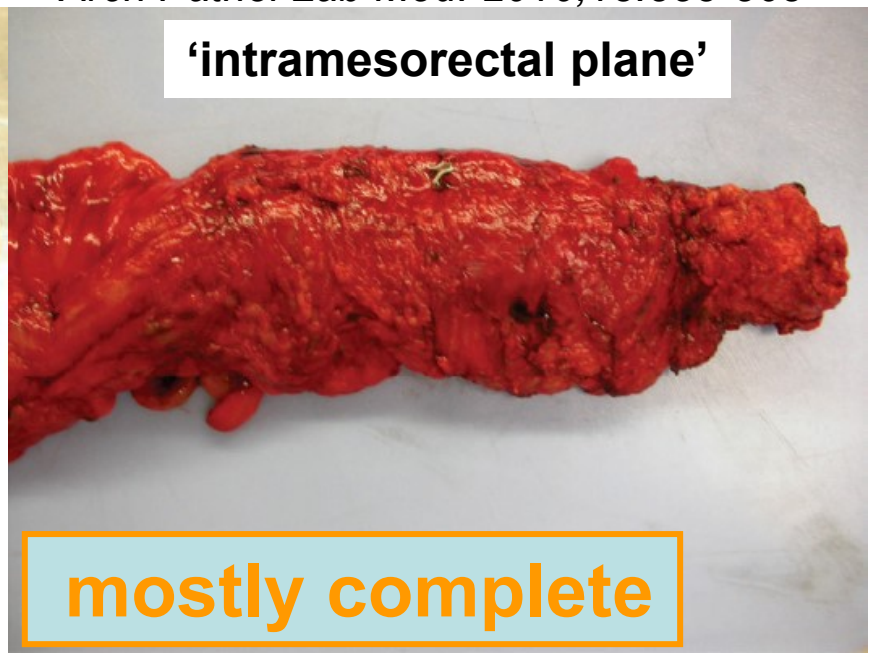
Anterior rectum resection

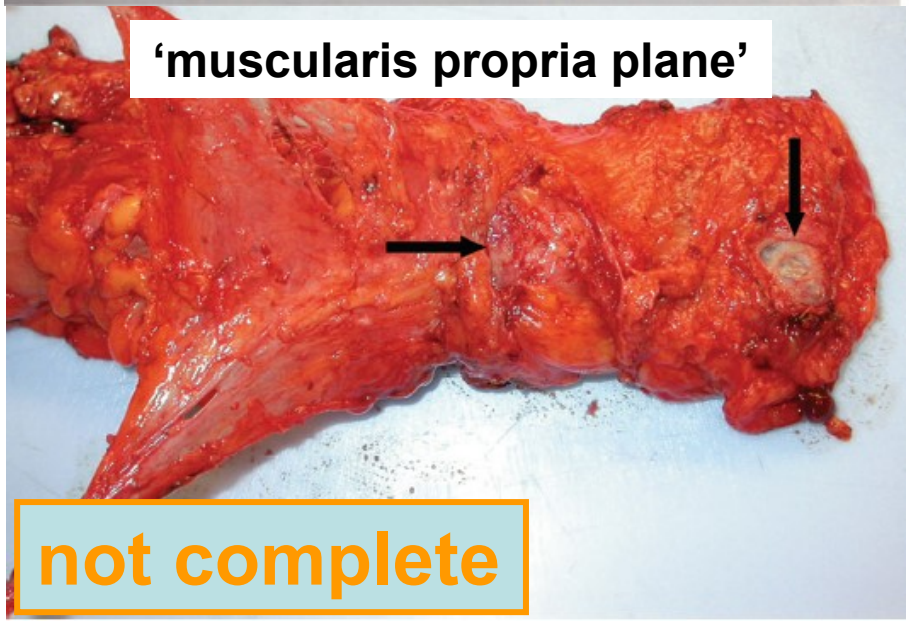
2 cm adequate distance
1 cm sufficient for T1 e T2

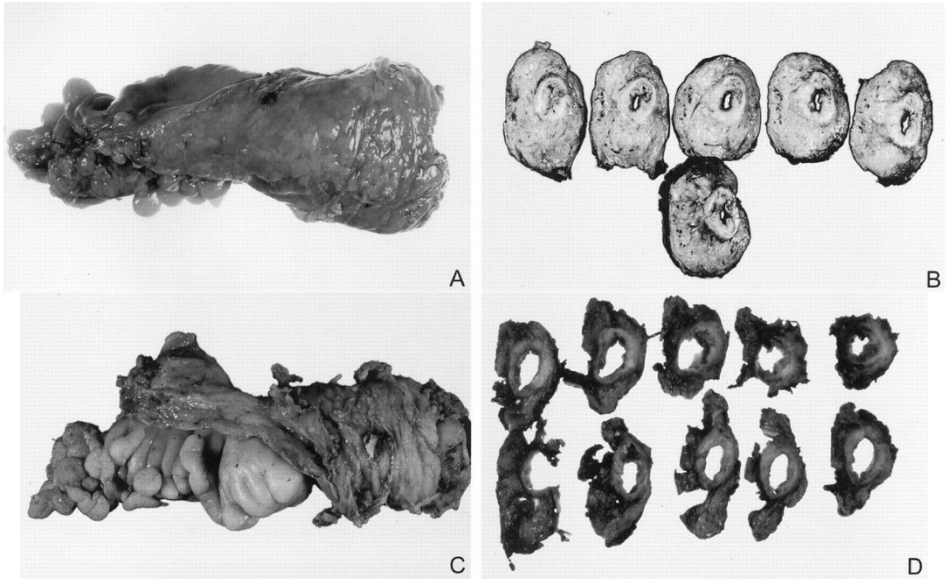
Plane of mesorectal excision

Arch Pathol Lab Med. 2010;13:853-863





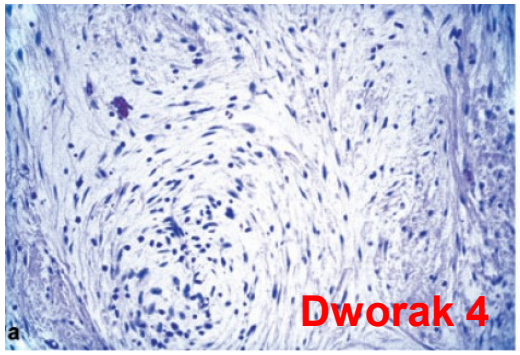


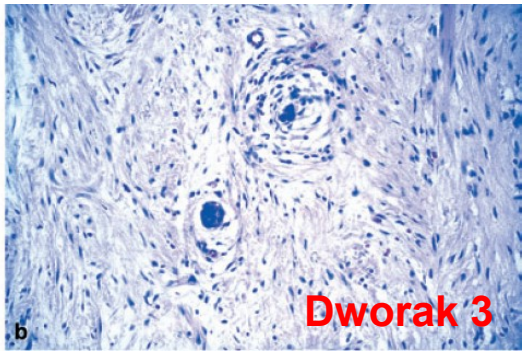


Response to neoadjuvant therapy (TRG)

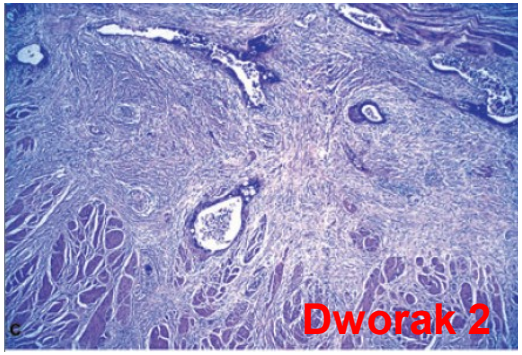
The minimal residual disease is associate to a better prognosis

Dis colon Rectum. 2005;48 (10):1851-1857



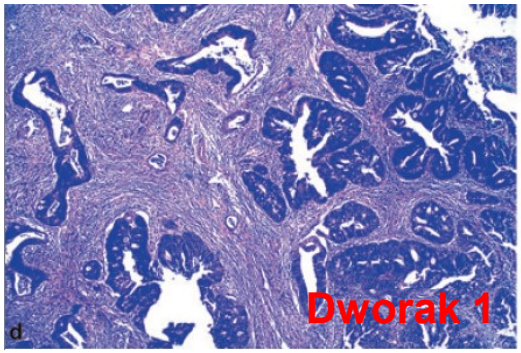


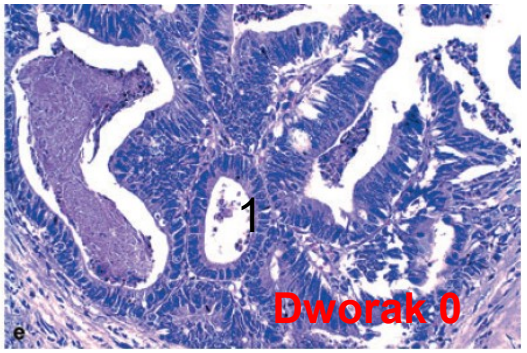
1



Tumor mass
Fibrosis
Vasculopathy

2





3

Tumor Regression Grade sec. Ryan

Table 1. Tumour regression grade

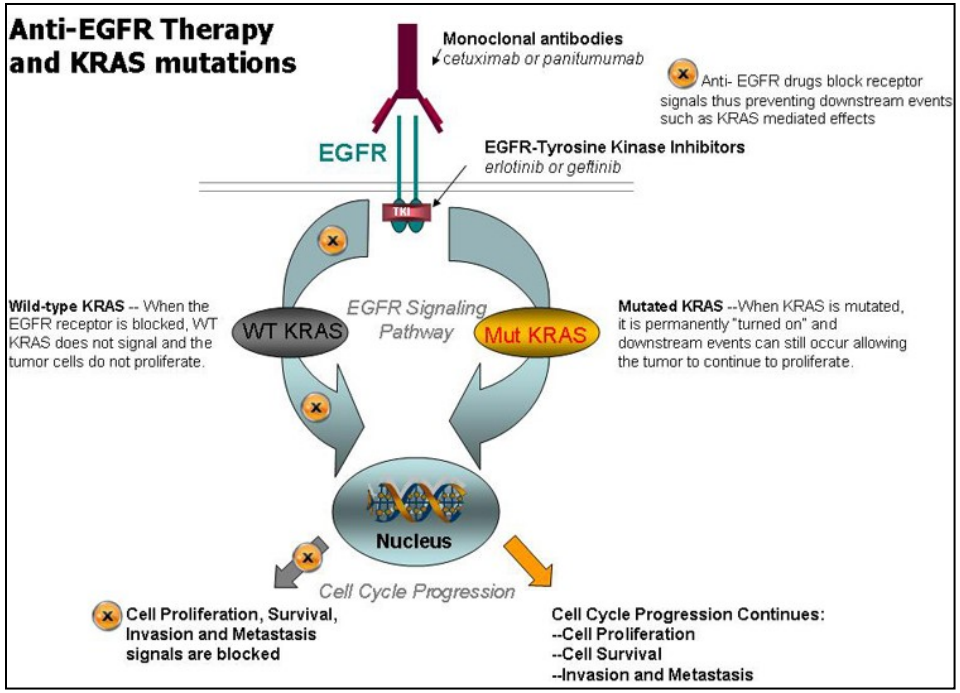
Five-point TRG	Description	Three-point TRG
1	No viable cancer cells	1
2	Single cells or small groups of cancer cells	
3	Residual cancer outgrown by fibrosis	2
4	Significant fibrosis outgrown by cancer	3
5	No fibrosis with extensive residual cancer	

ypT

Ancillary Studies (1)

For metastatic CRC

RAS mutations (KRAS and NRAS)



KRAS mutation confers resistance to anti-EGFR therapy
(CETUXIMAB OR PANITUMUMAB)

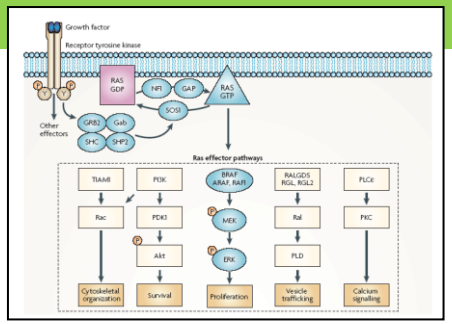
Circa 40% del CRC

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines() Colon Cancer. 2020. Available from: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed August 28, 2020.

National Institute for Health and Care Excellence. Cetuximab and panitumumab for previously untreated metastatic colorectal cancer. Technology appraisal guidance. 2017. Available from: https://www.nice.org.uk/guidance/ta439/chapter/1-Recommendations. Accessed August 28, 2020

Pietrantonio F, Petrelli F, Coinu A, et al. Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. Eur J Cancer. 2015;51:587–594.
70. Morris VK, Bekaii-Saab T. Improvements in clinical outcomes for BRAF(V600E)—mutant metastatic colorectal cancer. Clin Cancer Res. 2020;26:4435–4441.

BRAF mutations

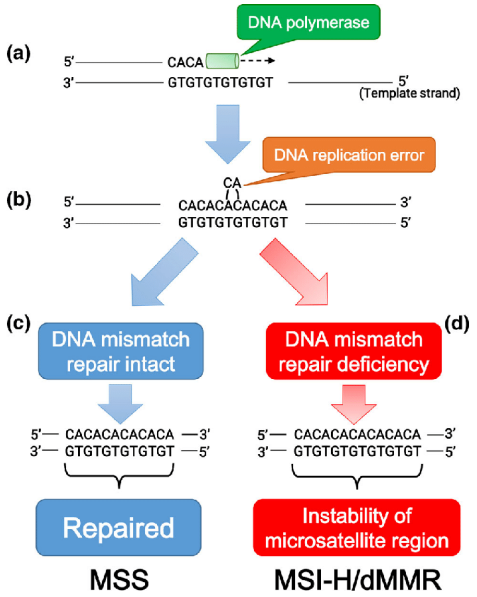


V600E BRAF mutation confers resistance to anti-EGFR therapy

Ancillary Studies (2)

Defective mismatch repair (MMR)/microsatellite instability (MSI)

14-15% CRC are defective in DNA mismatch repair complex (dMMR)



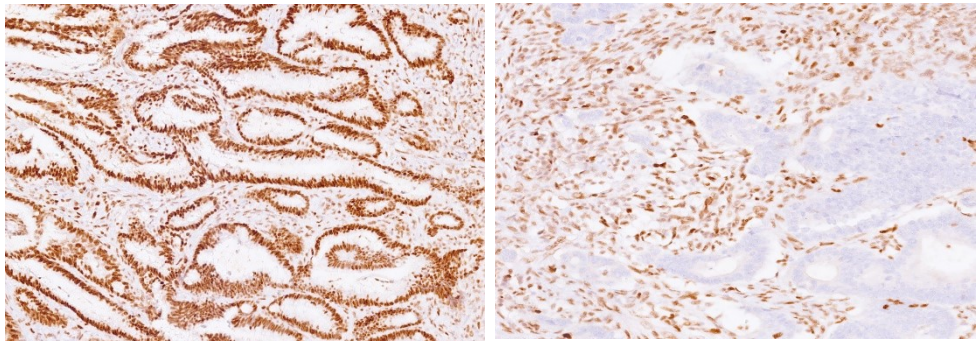
MMR

Highly conserved protein complex - recognizes and repairs erroneous short insertions, short deletions and single base mismatches that can arise during DNA replication and recombination.

Microsatellites: short repeated sequences (1-10 bases) in the coding and non coding portion of genes (including oncogenes) which lead to a higher frequence of mismatch errors

Heterodimers

- **MSH2/MSH6 identifies error**
- **MLH1/PMS2 repairs error**



Ancillary Studies (2)

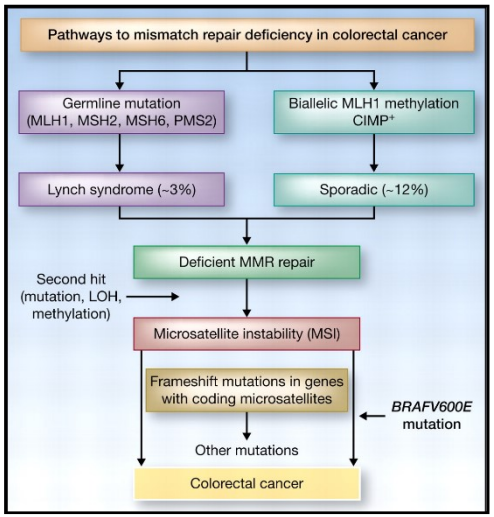
Defective mismatch repair (MMR)/microsatellite instability (MSI)

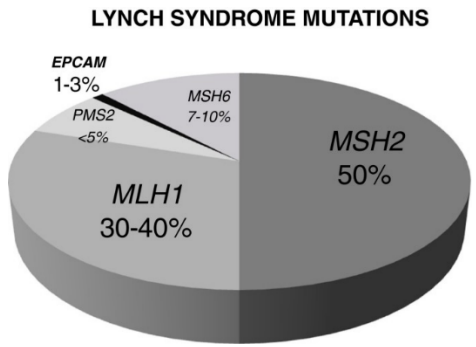
Constitutional pathogenic mutation
in one of the MMR genes

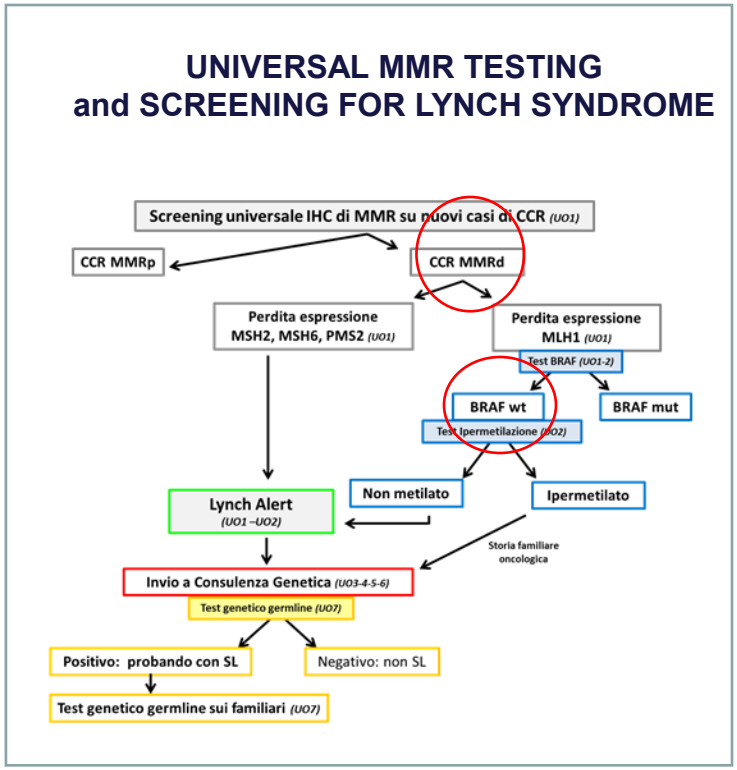
Sporadic MMR deficient CRC, usually
caused by hypermethylation
of the **MLH1** MMR gene promoter region

Patient management
-MMR deficiency good prognosis
-poorer response to 5-fluorouracil-based chemotherapy
-potential response to immune checkpoint blockade therapy

Lynch syndrome








Grazie a Tutti Voi!
HUMANITAS