Multidisciplinary approach to colorectal cancer treatment

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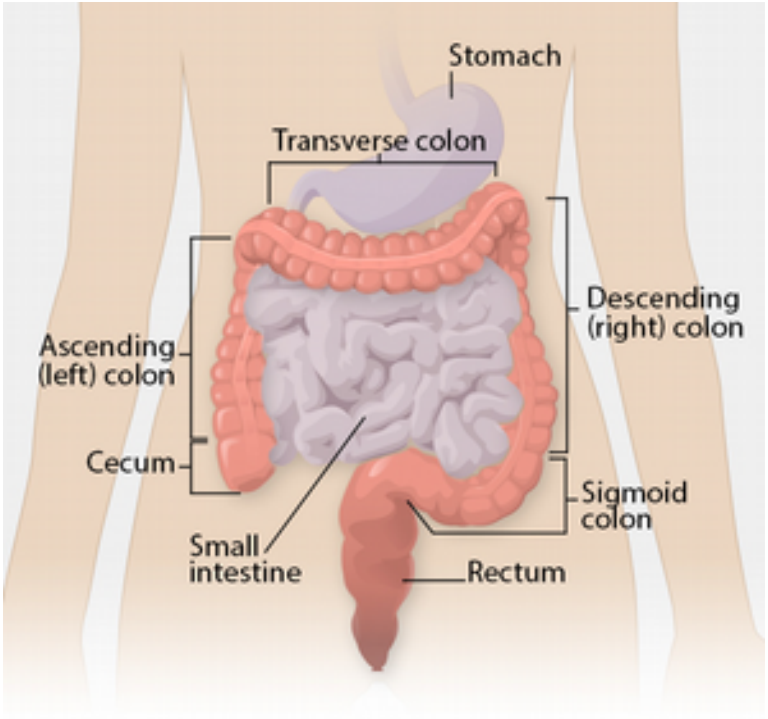
Anatomy


Stomach
Transverse colon
Descending (right) colon
Ascending (left) colon
Cecum
Sigmoid colon
Small intestine
Rectum

What we will be talking about

- Epidemiology
- Etiology and risk factors
- Prevention
- Screening
- Sings and symptoms
- Treatment
- Follow up

EPIDEMIOLOGY

- **INCIDENCE**

  - worldwide CRC is the third most common cancer, the second leading cause of cancer death. It is currently the second most common cause of cancer death in the United States for men and women combined (nearly 150,000 new cases and 50,000 deaths each year), accounting for about 10% of cancer mortality

  - Age is a major risk factor for sporadic CRC. The lifetime incidence of CRC in patients at average risk is about 5%, with 90% of cases occurring after age 50

  - the highest incidence rates in North America, Australia, and northern and western Europe; developing countries have lower rates, particularly Africa and Asia (differences in dietary and environmental exposures)

- **MORTALITY**

  - United States has one of the lowest mortality rates from CRC (61% survive 5 years)

  - China and Eastern Europe – the lowest 5-year survival rates (32 and 30%, respectively)

RISK FACTORS

- **GENETIC <5% (but up to 30% with some mutations)**

  - FAP - Familial adenomatous polyposis

  - HNPCC - hereditary nonpolyposis colorectal cancer (Lynch syndrome)

- **ENVIROMENTAL**

  - personal history of sporadic CRC (metachronous CRC)

  - personal history of large (>1 cm) adenomatous polyps and polyps with villous or tubulovillous histology (patients with an isolated small (<1 cm) tubular adenoma do not appear to be at increased risk)

  - family history of sporadic CRC

  - family history of a large (>1 cm) or histologically advanced colonic adenoma appears to carry the same significance as a positive family history of colorectal cancer

RISK FACTORS

- **ENVIROMENTAL**

  - Inflammatory bowel disease - chronic **ulcerative colitis** (mainly long lasting pancolitis), it appears that pancolitis due to **Crohn's disease** is associated with a similar relative risk of colon malignancy as extensive ulcerative colitis

  - Diabetes mellitus and insulin resistance (the risk of colorectal cancer among diabetics was approximately 30% higher than nondiabetics - hyperinsulinemia- insulin is an important growth factor for colonic mucosal cells and stimulates colonic tumor cells)

  - Obesity - also increases the likelihood of dying from colorectal cancer

  - Alcohol

  - Cholecystectomy? (proximal CRC)

RISK FACTORS

- **ENVIROMENTAL**

  - presence of coronary heart disease

  - cigarette smoking

  - ureterocolic anastomoses after extensive bladder surgery

  - long-term consumption of red meat or processed meats

  - history of radiation therapy for prostate cancer

Prevention

Diet

- high in fruits and vegetables, garlic
- fiber ? folic acid ?
- Vitamin B6 (pyridoxine)
- calcium ?
- magnesium

Physical activity

- Chemoprevention
  - Vitamins C and E
    - mixed results
  - Calcium intake
    - Modestly decreased risk
  - **NSAIDs**
    - Decreased risk, but…
    - Side effects
  - Postmenopausal HRT
    - Decreased risk, but…
    - Increased risk of other carcinomas

Survival

- **Improvement in recent years**
- Multifactor:
  - Wider surgical resection
  - Modern anesthetic techniques
  - Improved supportive care
  - Better staging
  - Screening
  - Improvement in neo-/adjuvant chemotherapy and radiotherapy

Survival

TABLE 1: Five-year relative survival rates in colorectal cancer by stage at diagnosis (1995–2005)

Stage at diagnosis	5-year survival rate (%)
All stages	64
In early, localized stage	90
After spread to adjacent organs or lymph nodes	67
After spread to distant sites	10
Unstaged	35

Horner MJ et al: SEER Cancer Statistics Review 1975–2006. National Cancer Institute, Bethesda, MD. www.seer.cancer.gov/csr/1975_2006. Accessed May 29, 2010.

SCREENING FOR COLORECTAL CANCER

Screening

Adenoma-carcinoma sequence

- Most colorectal cancers arise from **adenomatous polyps** that progress from small to large (>1.0 cm) polyps, and then to dysplasia and cancer
- The progression from adenoma to carcinoma is believed to take at least ten years
- Some colon cancers arise from non-polypoid adenomas that are flat or depressed and account for 22 to 36% of identified adenomas; difficult to identify; large flat adenomas may be more likely to contain dysplastic changes or cancer than polypoid ones of comparable size
- Removal of adenomatous polyps prevents cancer

Screening

Average risk adults should have screening at age 50

Choice of modality varies by country

In Poland : colonoscopy once every 10 years

DETECTION OF INCREASED RISK

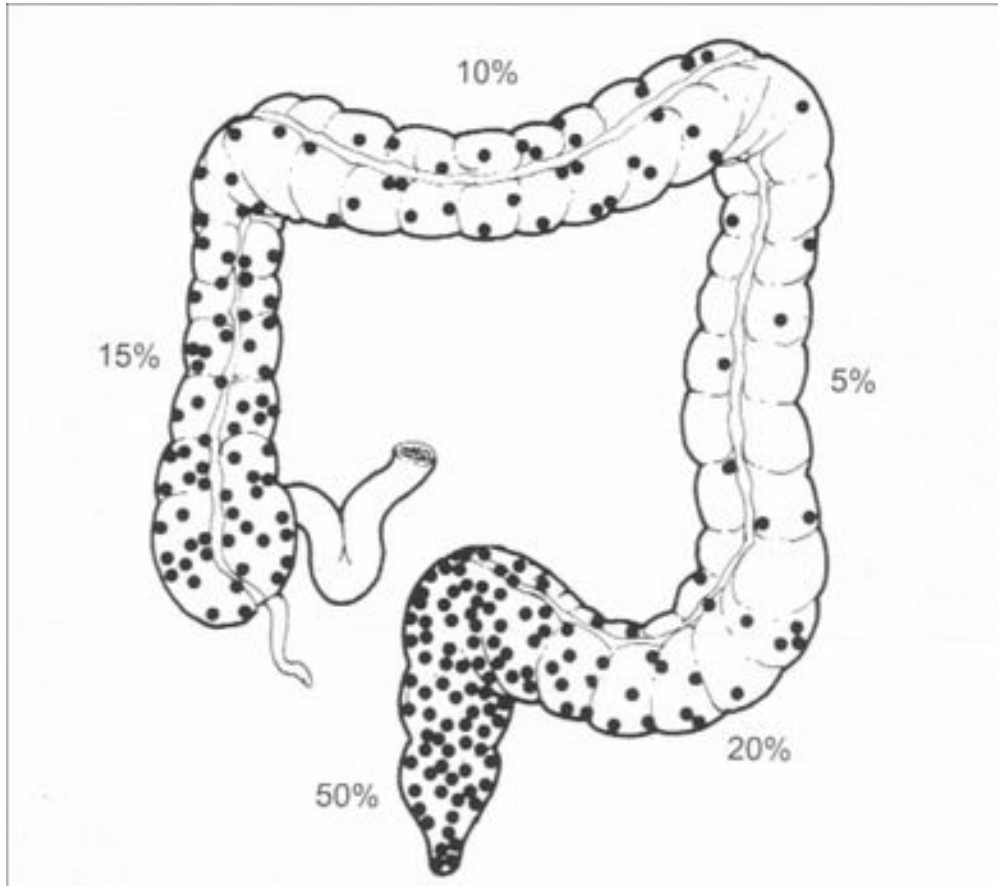
FAMILY HISTORY:

- Risk is slightly increased if any family member has had CRC, but is doubled if CRC occurred in a first-degree relative (eg, parent, sibling, or child)
- With a larger number of affected relatives and an unusually early age of onset (eg, below age 50 years) the risk is as much as six times higher
- A family history of adenomatous polyps before age 60 years also increases risk
- General rule: 1st colonoscopy 10 years before age of first CRC

Screening recommendations

Test	Interval	Comment
gFOBT and FIT	Annual	Positive test followed by colonoscopy
sDNA	?	Positive test followed by colonoscopy
Sigmoidoscopy	Every 5 yers	Positive test followed by colonoscopy
Colonoscopy	Every 10 yers	Therapeutical procedure, H-P samples
Virtual colonoscopy	Every 5 yers	If leasion > 6 mm, should be followed by colonoscopy. Visualisation of extracolonic organs
Double contrast barium enemas	Every 5 yers	If leasion > 6 mm, should be followed by colonoscopy.

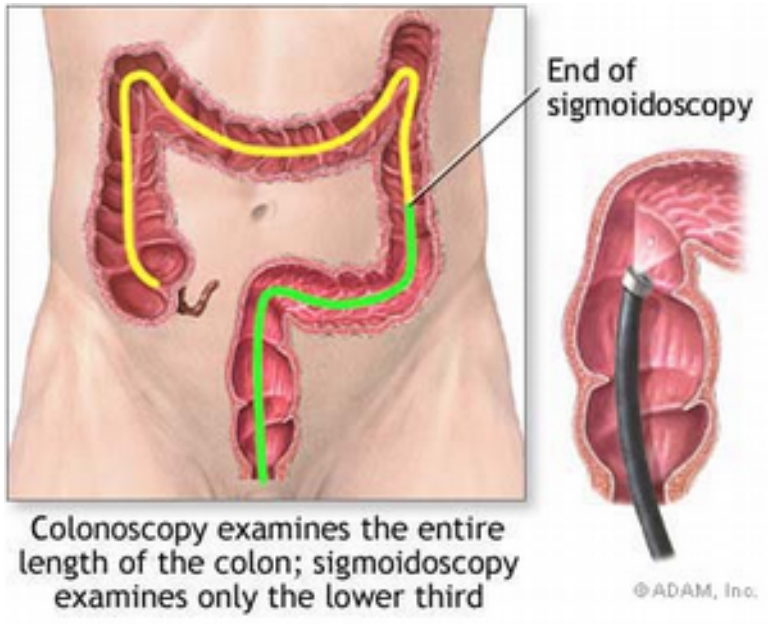
Distribution



- 30-50% of CRC can be diagnosed with sigmoidescopy
- the incidence rates for cancer of the ascending colon have increased, particularly in women
- Quality of colonoscopy!!

TESTS USED FOR SCREENING

Sigmoidoscopy



- 60 cm flexible sigmoidoscope can reach to the splenic flexure

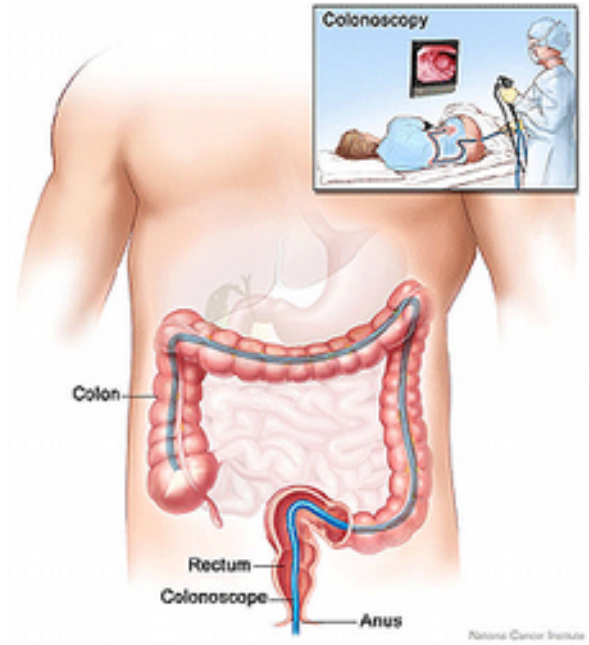
- case-control studies have found that sigmoidoscopy reduces overall CRC mortality by about one-third

- 2008 consensus guidelines recommend a five year interval for screening by flexible sigmoidoscopy (if negative) *(USPSTF guidelines recommend a combination of flexible sigmoidoscopy every 5 years with gFOBT every 3 years)*

- positive sigmoidoscopy should be followed by colonoscopy

TESTS USED FOR SCREENING

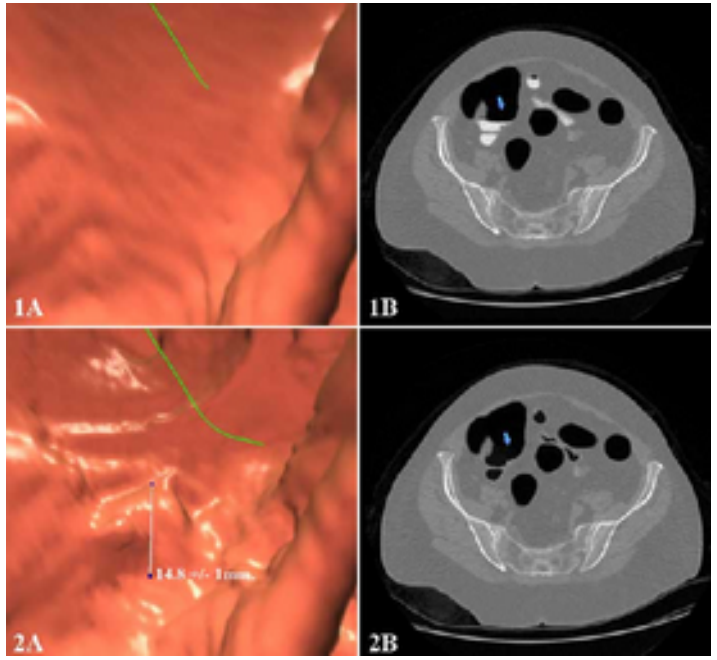
Colonoscopy



-can find most polyps and cancers - detects proximal lesions that would be missed by screening sigmoidoscopy
- lesions can be removed during the same procedure
- sensitivity for detection of adenomas and carcinomas is dependent on the experience and technique of the colonoscopist
- American College of Gastroenterology now considers colonoscopy the "preferred" screening test
- frequency of test if negative – 10 years?

TESTS USED FOR SCREENING

Computed tomographic colonography — "virtual colonoscopy"



- non-invasive (but no biopsy)

- visualizes the entire bowel

- detects large adenomas about as well as optical colonoscopy

- larger lesions need to be followed up by colonoscopy, and smaller lesions by CTC surveillance

SCREENING for colorectal cancer

INCREASED RISK PATIENTS

People with a single, small (< 1 cm) adenoma	3-6 years after the initial polypectomy	Colonoscopy*	If the exam is normal, the patient can thereafter be screened as per average-risk guidelines.
People with a large (1 cm +) adenoma, multiple adenomas, or adenomas with high-grade dysplasia or villous change	Within 3 years after the initial polypectomy	Colonoscopy*	If normal, repeat examination in 3 years; If normal then, the patient can thereafter be screened as per average-risk guidelines.
Personal history of curative-intent resection of colorectal cancer	Within 1 year after cancer resection	Colonoscopy*	If normal, repeat examination in 3 years; If normal then, repeat examination every 5 years.
Either colorectal cancer or adenomatous polyps, in any first-degree relative before age 60, or in two or more first-degree relatives at any age (if not a hereditary syndrome)	Age 40, or 10 years before the youngest case in the immediate family	Colonoscopy*	Every 5-10 years. Colorectal cancer in relatives more distant than first-degree does not increase risk substantially above the average-risk group.

Smith et al. *CA Cancer J Clin* 2003;53;27-43

Colonoscopic Polypectomy and Long-Term Prevention of Colorectal-Cancer

- In the National Polyp Study (NPS), colorectal cancer was prevented by colonoscopic removal of adenomatous polyps
- Given an estimated 25.4 expected deaths from colorectal cancer in the general population, the standardized incidence-based mortality ratio was 0.47 with colonoscopic polypectomy, suggesting a 53% reduction in mortality
- □ colonoscopic removal of adenomatous polyps prevents death from colorectal cancer □ **screening colonoscopy!!!**

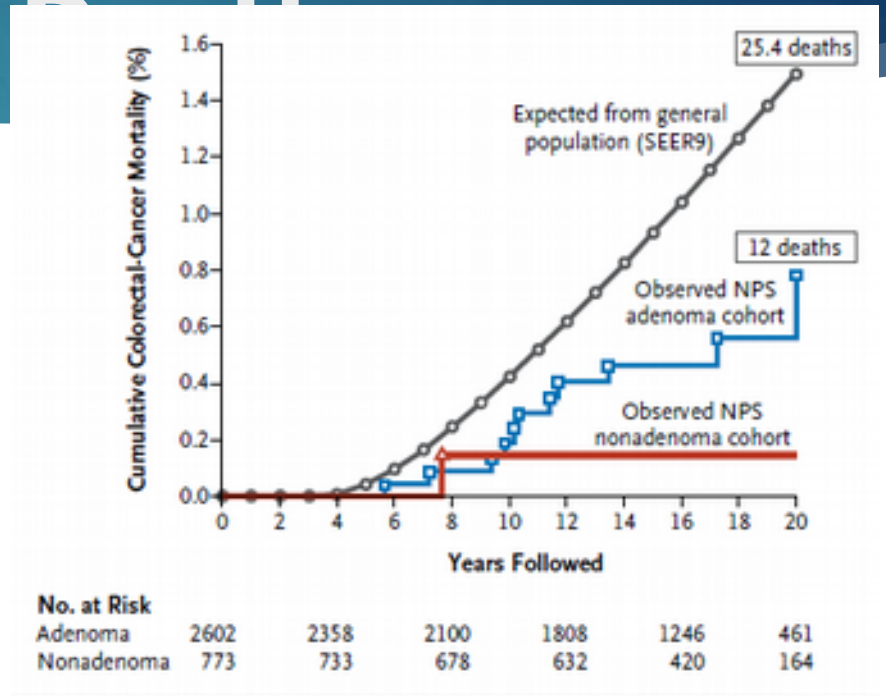


Figure 2. Cumulative Mortality from Colorectal Cancer in the General Population, as Compared with the Adenoma and Nonadenoma Cohorts.

We censored the curves at 20 years; the 12th death in the adenoma cohort was at 22 years and was included in the analysis. The numbers of deaths from colorectal cancer are given at the end of the curves for the general population (25.4 expected deaths) and the adenoma cohort (12 observed deaths). Expected deaths are based on data from Surveillance, Epidemiology, and End Results registries in nine areas (SEER9).

N Engl J Med 2012;366:687-96

Short clinical scenario

- 59 year old male patient with recent history of melena
- No weight loss
- No family history of any malignancy

- What should we do next?

Principles of treatment

- Diagnosis
- Staging
- Treatment
- Follow up

Symptoms

- Abdominal pain — 44%
- Change in bowel habit — 43%
- Hematochezia or melena — 40%
- Weakness — 20%
- Anemia without other gastrointestinal symptoms — 11%
- Weight loss — 6%
- Other possible symptoms of CRC include abdominal distention, nausea, vomiting, weight loss, and fatigue
- CRC ultimately proves to be the origin of approximately 6% of adenocarcinomas of unknown primary sites – metastasis as first symptom

Diagnosis

- **Colonoscopy is the single best diagnostic test in symptomatic individuals**

- the entire large bowel can be examined for the presence of synchronous lesions (occur in 3 to 5% of patients with colon cancer)

- If malignant obstruction precludes a full colonoscopy preoperatively, the residual colon should be checked for synchronous lesions after resection of the obstruction

Diagnosis

Obligatory: histopathologic examination

Diagnosis

- Preferred
  - **Specimen from primary tumor obtained by colonoscopy/rectoscopy**
- Also
  - Specimen from metastatic tumors
    - Core needle/FNA from distant tumors (e.g. liver or lungs)
  - Body fluids
    - Peritoneal washing

Pathology

- Adenocarcinoma (90-95% of CRC)
  - Mucinous adenocarcinoma (10% of above)
    - Large quantities of extracellular mucus
    - Tendency to spread within the peritoneum
    - Lower sensitivity for PET-CT
  - Signet-ring cell carcinoma (1% of above)
    - Large quantities of intracellular mucinous
    - Probably more aggressive
- Other
  - Squamous cell (anal cancer)
  - Small cell, carcinoid tumors, adenosquamous, GIST, sarcomas, lymphomas etc.

Metastatic spread

- Local
  - Rather radial than longitudinal
  - Intra peritoneal
- Distal
  - Liver
  - Lungs (more common in rectal cancer)
  - Bones
  - Kidneys
  - Brain
  - Any other organ

STAGING
preoperative clinical staging evaluation

- **Tumor markers: carcinoembryonic antigen (CEA)**

  - serum CEA level is not used as a screening test for colorectal cancer

  - prognostic utility - patients with preoperative serum CEA >5 ng/mL have a worse prognosis, stage for stage, than those with lower levels

  - elevated preoperative CEA levels that do not normalize following surgical resection imply the presence of persistent disease and the need for further evaluation

Low sensitivity for early tumors (almost all in stage IV, ½ in stage III and ¼ in stage II)

Staging

- T – Tumor
- N- Nodes
- M- Metastases

TNM staging system

- cTNM - clinical
- pTNM – pathological
- yTNM – after neoadjuvant
- rTNM – recurrent
- aTNM - autopsy

Staging (cTNM) Procedures

- cTN
  - CT scan of abdomen/pelvis for colon cancer
  - MRI of pelvis/ TRUS (transrectal ultrasonography) for rectum

- cM
  - CT of chest and abdomen
  - *Biopsy of any detected lesions*
  - CEA level

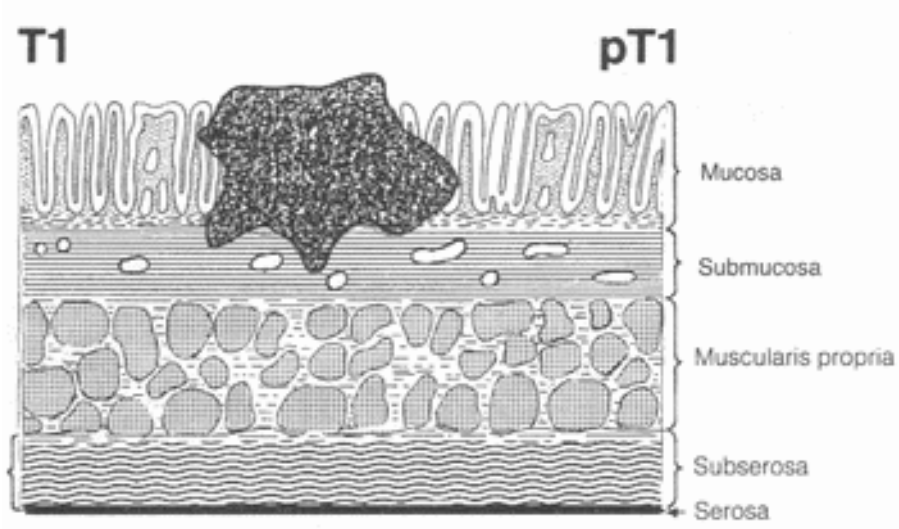
  - PET-CT – aid in equivocal situations. Body scan before radical metastasectomy

Staging

- Additional work up
  - Complete blood count
  - Liver and renal function tests
  - Urinalysis
  - Performance score assessment
  - Comorbidities

Staging

- T : depth of invasion (not: size of tumor)
- N : number of lymph nodes
- M : metastases (one organ/multiple)



Staging (pTNM)

- Pathological stage
  - Early stages – favorable prognosis
    - I – small tumor, no nodes
    - II – bigger tumor, no nodes
  - Advanced stages –
    - III – any tumor, any positive nodes
    - IV – any tumor, any distant metastases

Staging (pTNM)

- Histologic grade
  - G1 – well differentiated (5y survival = 100-56%)
  - G2 – moderately differentiated (5y survival = 80-33%)
  - G3 – poorly differentiated (5y survival = 58-11%)

Moderate impact on treatment decisions.

PROGNOSIS

The pathologic stage at diagnosis (pTNM) remains the best indicator of long-term prognosis for both colon and rectal cancer

Our patient

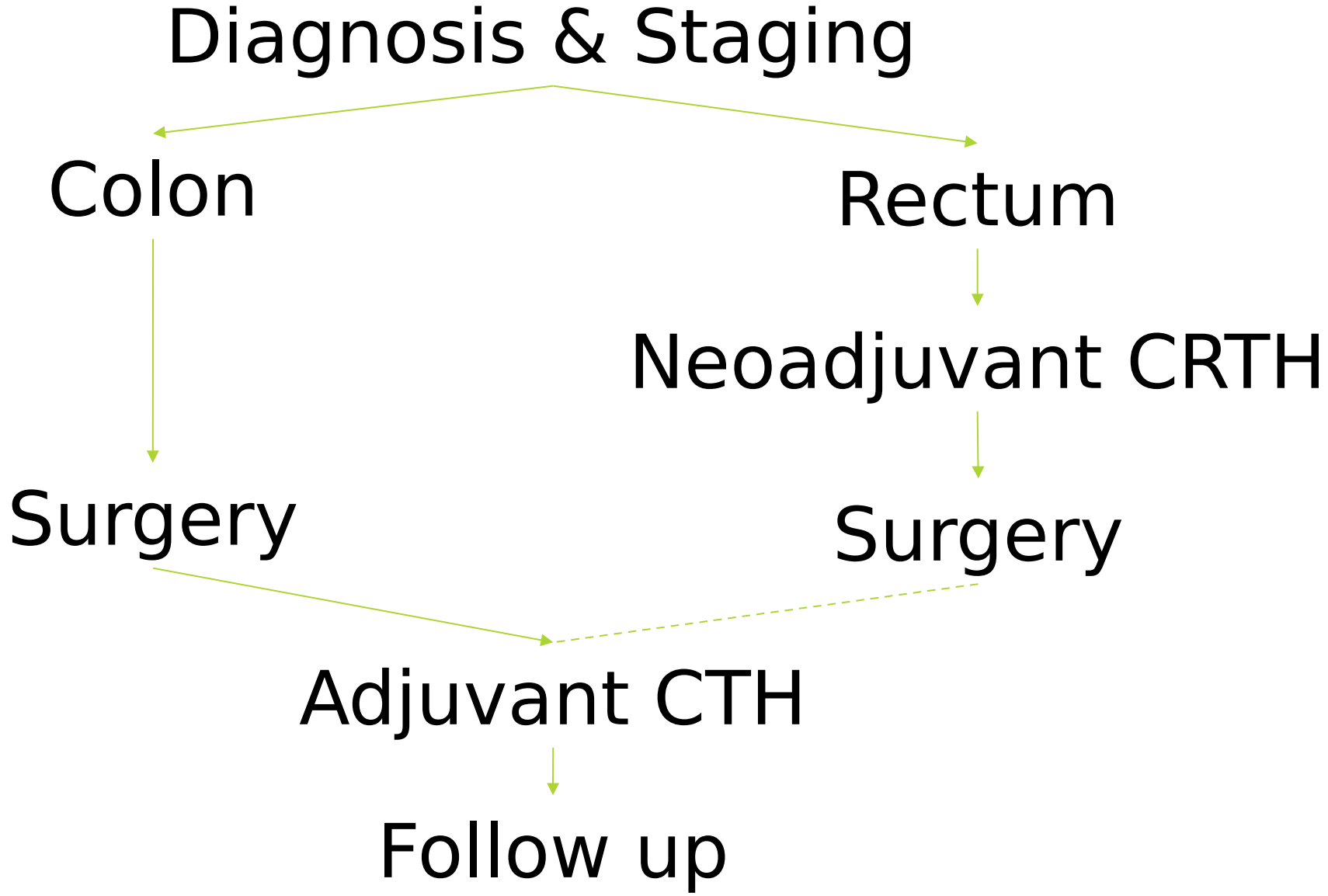
- CT of abdomen, chest and pelvis showed single lesion in liver (probably adenoma) and primary tumor in ascending colon
- CEA level is normal
- H-P: adenocarcinoma G2
- What is our stage here?

Our patient

- cTxNxM0
- PS0
- Age: 65
- No serious comorbities

- What should we do next?

Treatment algorithm (oversimplified)



Treatment

- Surgery
  - Cornerstone of every treatment
  - 99% obligatory (if feasible)
    - Early trials for observation alone after pCR (pathological complete response) after neoadjuvant chemoradiotherapy in rectal carcinoma – **not a standard approch**
- Radiotherapy
  - „Never” in colon cancer
  - Patients with rectal carcinoma
    - Neoadjuvant with chemotherapy preferred to adjuvant
- Chemotherapy
  - Adjuvant in colon cancer (all stage III, high-risk stage II)
  - Adjuvant in rectal cancer after neoadjuvant CRTH (large debate ongoing)
  - Neoadjuvant with radiotherapy in rectal cancer
  - Metastatic (standard of care)

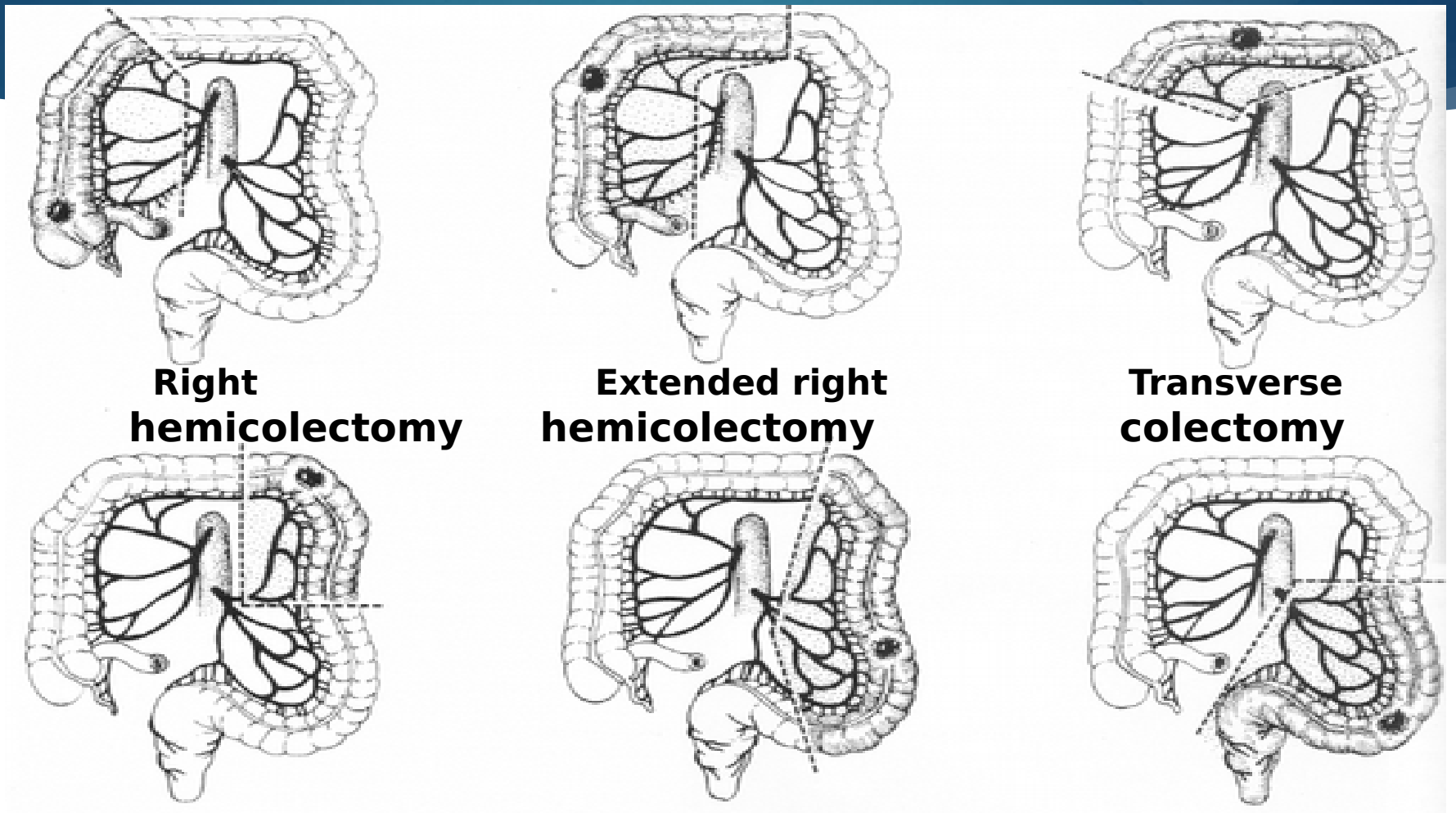
Surgery

- the only curative modality for localized colorectal cancer
- potentially curative option for selected patients with limited metastatic disease in liver and/or lung
- surgical palliation for symptoms of obstruction and bleeding from the primary tumor

Surgery
Colon cancer

- **Resection margins** — proximal and distal at least 5 cm from the tumor
- **Regional lymphadenectomy** - at least 12 lymph nodes must be assessed for adequate staging
- **SURGICAL TECHNIQUES**
  - Right hemicolectomy
  - Extended right hemicolectomy
  - Transverse colectomy
  - Left hemicolectomy
  - Sigmoid colectomy
  - Subtotal and total colectomy
  - Laparoscopic colectomy – for selected patients
  - Polypectomy – for selected patients

Surgery
Colon cancer



Right hemicolectomy

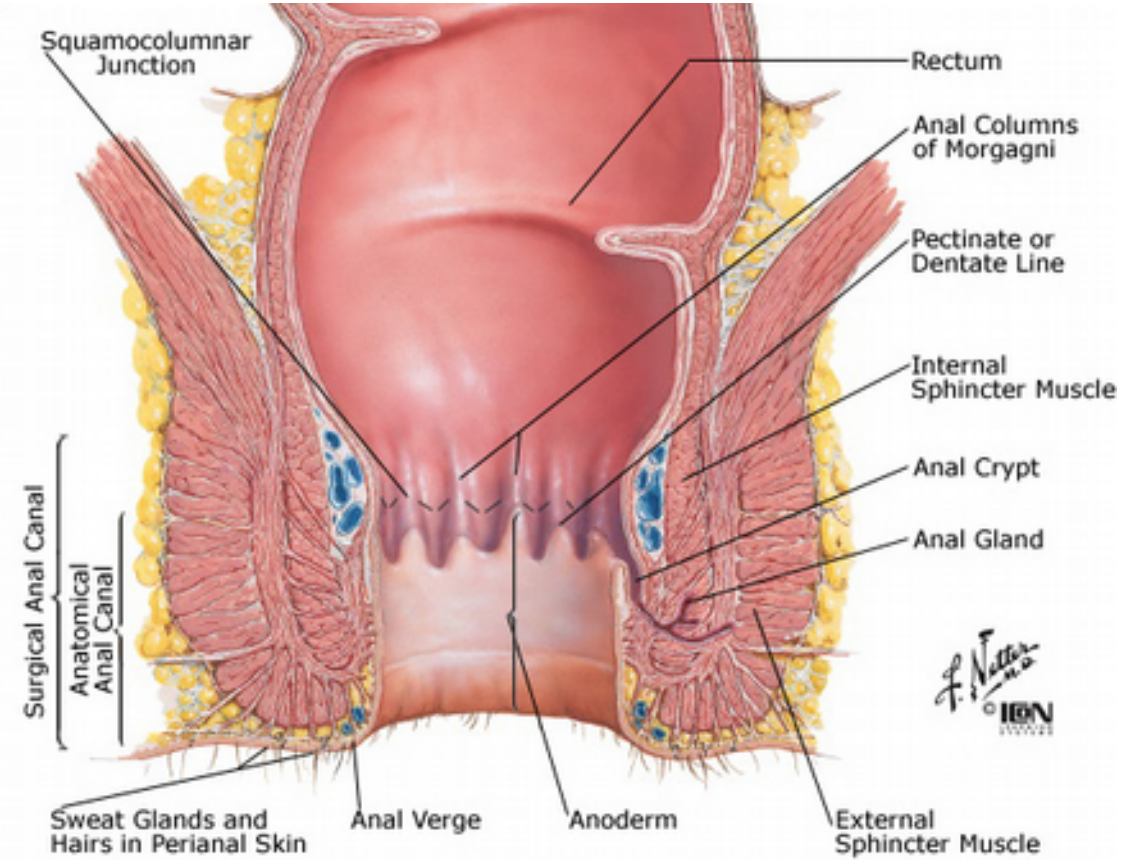
Extended right hemicolectomy

Transverse colectomy

Left hemicolectomy

Sigmoid colectomy

TREATMENT – SURGERY
RECTAL CANCER



- The upper extent of the rectum is typically defined as **12 cm** from the anal verge
- If sphincter preservation is to be achieved, the tumor has to be located high enough above the top of the anorectal ring to allow for an adequate distal margin
- preoperative chemoradiotherapy may permit sphincter preservation in some patients with low-lying tumors

TREATMENT – SURGERY
RECTAL CANCER

- removal of at least **12** lymph nodes

- complete removal of the **primary tumor** along with the adjacent **mesorectal tissue** containing the regional lymphatics and the superior hemorrhoidal artery pedicle

- status of the **distal and radial resection margins** is an important determinant of surgical outcome

  - distal margin at least 2 cm

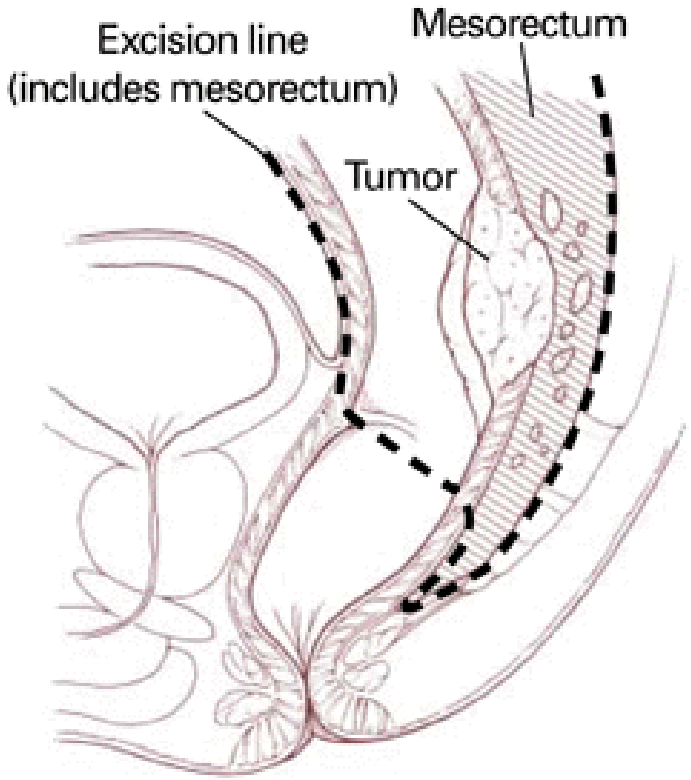
  - proximal margin – 5 cm

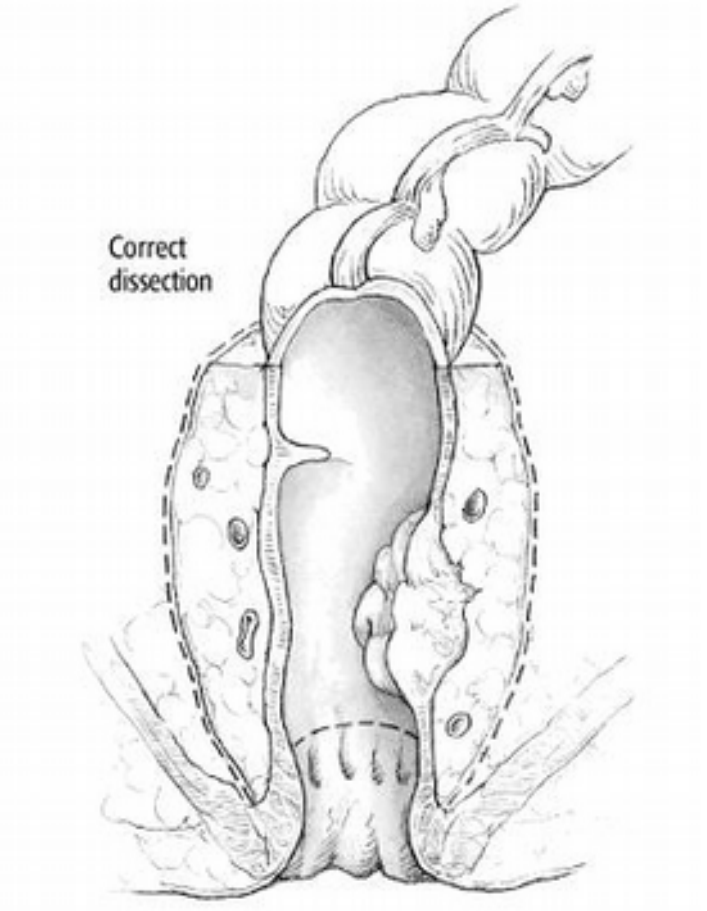
  - radial margin is more critical for local control – **TME- Total Mesorectal Excision**

TREATMENT – SURGERY

RECTAL CANCER

TME – Total Mesorectal Excision



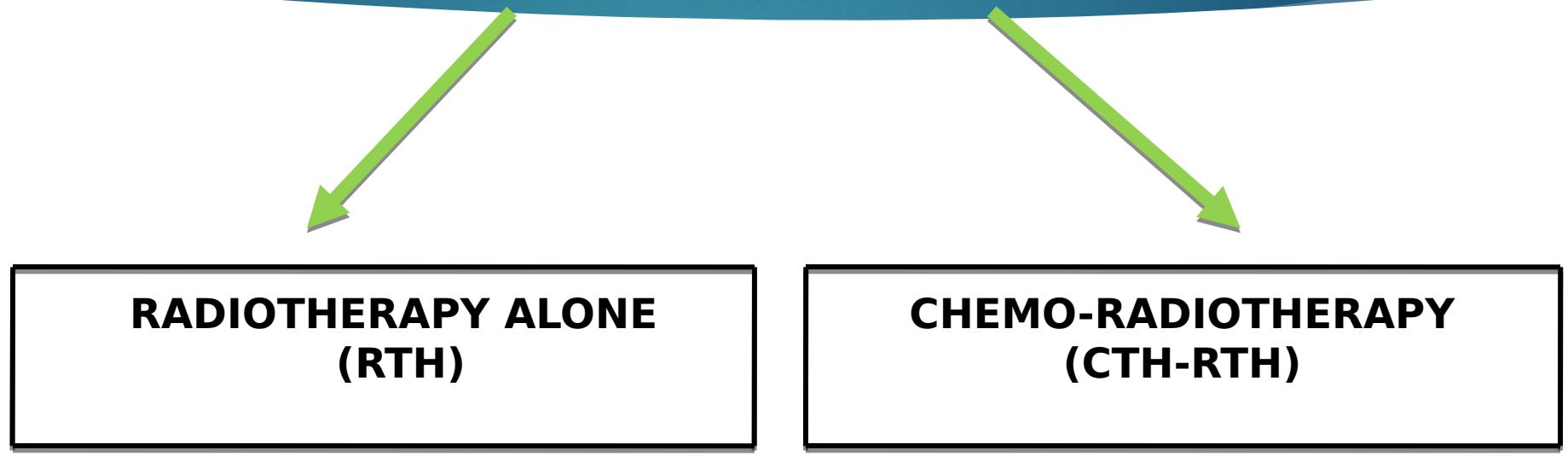


TREATMENT – SURGERY
RECTAL CANCER

SURGICAL TECHNIQUES

- **Abdominal perineal resection (APR)**
  - removal of the primary tumor along with a complete proctectomy
  - the need for a permanent colostomy
  - surgical therapy of distal rectal cancers
- **Low anterior resection (LAR)**
  - preserves the anal sphincter
  - surgical therapy for upper and mid-rectal tumors
- **Local excision** - **Transanal endoscopic microsurgery (TEM)**
  - Small, T1 tumors, G1-2
  - distal tumors

RECTAL CANCER
NEOADJUVANT TREATMENT
(preferred)



RECTAL CANCER
NEOADJUVANT CHEMORADIOTHERAPY

- **DEFINITIVE INDICATIONS**

  - T3, T4 tumors

- **RELATIVE INDICATIONS**

  - T1/2 tumors and clinically node-positive

  - distal tumors – converts surgical procedure from APR to sphincter-preserving operation

  - mesorectal fascia involvement

RECTAL CANCER

NEOADJUVANT CTH-RTH vs **ADJUVANT CTH-RTH**

German Rectal Cancer Study

- preoperative chemoradiotherapy was associated with a significantly **lower pelvic relapse** rate compared to postoperative therapy
- 5-year disease-free (68% vs 65%) and overall survival rates (76% vs 74%) were similar for preoperative and postoperative therapy
- Among 194 patients with low-lying tumors who were thought preoperatively to require APR, those undergoing preoperative chemoradiotherapy were twice as likely to undergo a **sphincter-sparing operation** (39% versus 19%)

Adjuvant treatnent Rectal Cancer

- Adjuvant CRTH
  - If neoadjuvant CRTH was not performer
- Adjuvant CTH after neoadjuvant CRTH
  - We do not know (yet…)
  - … but probably not indicated

ADJUVANT TREATMENT COLON CANCER

CHEMOTHERAPY (CTH)

- for patients who have undergone potentially curative resection, disease recurrence is thought to arise from clinically occult micrometastases that are present at the time of surgery

- the goal of postoperative (adjuvant) therapy is to eradicate these micrometastases, thereby increasing the cure rate

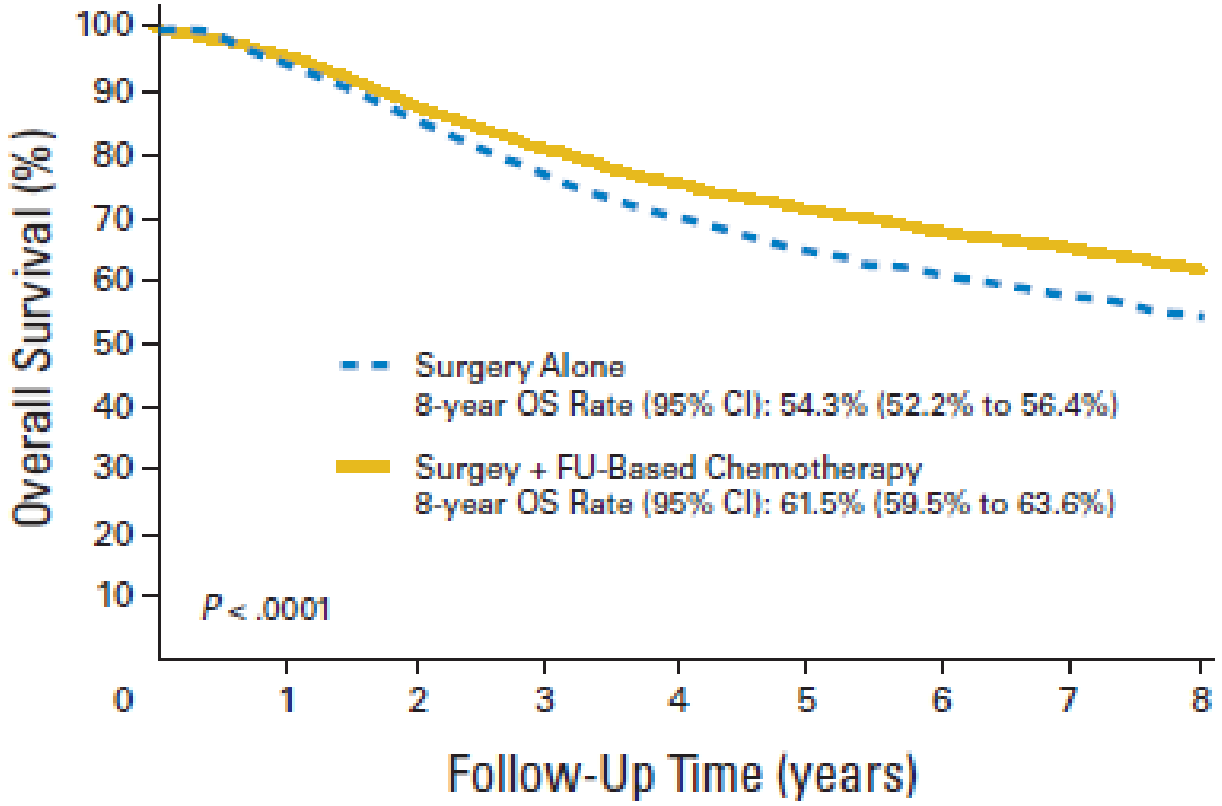
- Indicated for patients with:

  - **stage III** (N+) colon cancer

  - high-risk patients with **stage II** colon cancer (e.g. pT4, inadequate LN dissection, bowel obstructiom, bowel perforation, lymphovascular invasion, perineural invasion)

ADJUVANT TREATMENT COLON CANCER

survival benefit from adjuvant chemotherapy

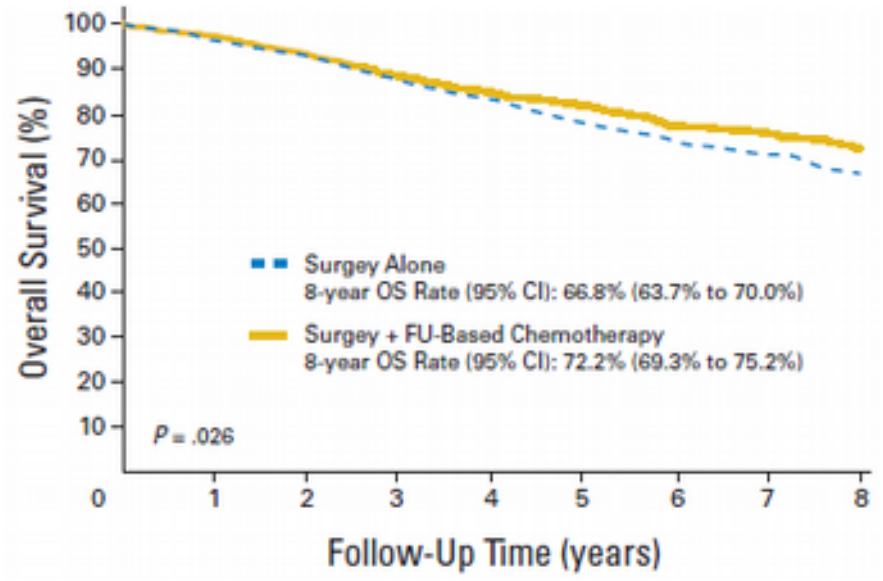


stage II and III colon cancer

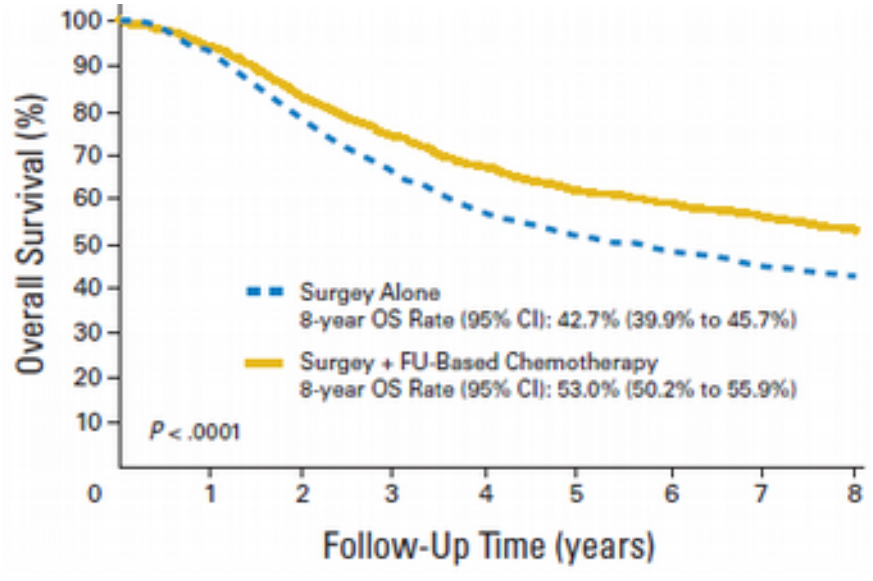
Sargent et al. *J Clin Oncol 2009; 27:872-877*

ADJUVANT TREATMENT COLON CANCER

survival benefit from adjuvant chemotherapy by stage



stage **II** colon cancer



stage **III** colon cancer (N+)

Sargent et al. *J Clin Oncol 2009; 27:872-877*

ADJUVANT TREATMENT COLON CANCER

Stage III – always

Stage II – sometimes (but should be „rarely)

ADJUVANT TREATMENT COLON CANCER

CHEMOTHERAPY (CTH)

- 6 months of adjuvant CTH
- **5-FLUOROURACIL (5FU)** BASED CTH
  - Capecytabine is oral prodrug for 5FU – similar efficacy
  - Leucovorine (folinic acid) as a „biomodulator” to enhance efficacy of 5FU
- Stage II – 5FU+leucovorine
- Stage III – 5FU + leucovorine + oxaliplatine

ADJUVANT TREATMENT COLON CANCER

CHEMOTHERAPY (CTH) - NEWER DRUGS

- **OXALIPLATIN + infusion 5FU/LV = FOLFOX regimen**

- **OXALIPLATIN + bolus i.v 5FU/LV = FLOX regimen**

  - survival benefit in stage III and high-risk stage II colon cancer (FOLFOX > FLOX)

- **OXALIPLATIN + CAPECITABINE = XELOX regimen**

FOLFOX or FLOX or XELOX regimen are recommended in stage III colon cancer

- **IRINOTECAN (IFL or FOLFIRI regimen)–** no survival benefit in adjuvant treatment

TREATMENT OF METASTATIC COLORECTAL CANCER (MCRC)
stage IV disease (M1)

mCRC TREATMENT

CURATIVE

-should be considered in patients with organ-limited metastatic disease involving the liver or lung that would allow potentially curative surgical resection (M1a disease)

-CTH + surgery of liver meta

-5-year survival about 40%

PALLIATIVE

-should be considered in patients with multiple organ involvement with the goal of increasing quality of life

-CTH alone

-not curative

-prolongs survival – 5-year survival 5-9%
-maintains quality of life

mCRC TREATMENT

ACTIVE CHEMOTHERAPEUTIC AGENTS

- **fluoropyrimidines** (5-fluorouracil [5-FU] which is usually given with leucovorin [LV], capecitabine, UFT)

- **irinotecan – FOLFIRI, IFL (irinotecan + 5FU)**

  - CapIRI=XELIRI (irinotecan + capecitabine) – high toxicity!!!

- **oxaliplatin – FOLFOX, FLOX (oxaliplatin + 5FU)**

  - XELOX (oxaliplatin + capecitabine)

ADVANCED COLORECTAL CANCER

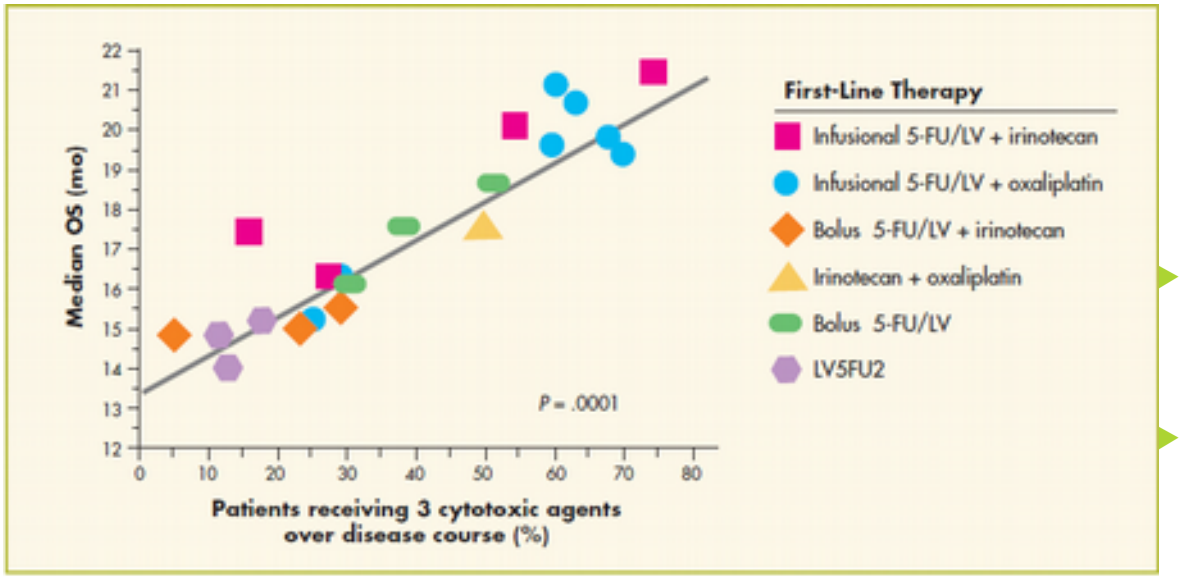


Figure 1. Regression plot of treatment and OS data extracted from 11 phase 3 trials. This plot shows the relationship between percentage of patients treated with 5-FU/LV, irinotecan, and oxaliplatin (3 drugs) and reported median OS. Grothey A, et al.[3]

- **ACTIVE DRUGS:**

- fluoropirymidine (5FU, capecitabine, tegafur)
- oxaliplatin
- irinotecan

- in clinical trials, median OS was significantly correlated with the percentage of patients who received all three drugs in the course of their disease.
- Patients who receive a doublet first-line, like FOLFOX or FOLFIRI, have a much higher chance to receive the third drug as the next step than patients who have to go through 3 steps.
- So, in clinical practice, first-line doublets are standard of care

Grothey et al. *J Clin Oncol 2004; 22:1209-1214*

ADVANCED COLORECTAL CANCER

First line → Second line → Third line

Improvement of overall survival from 6 months to 2-3 years

ADVANCED COLORECTAL CANCER

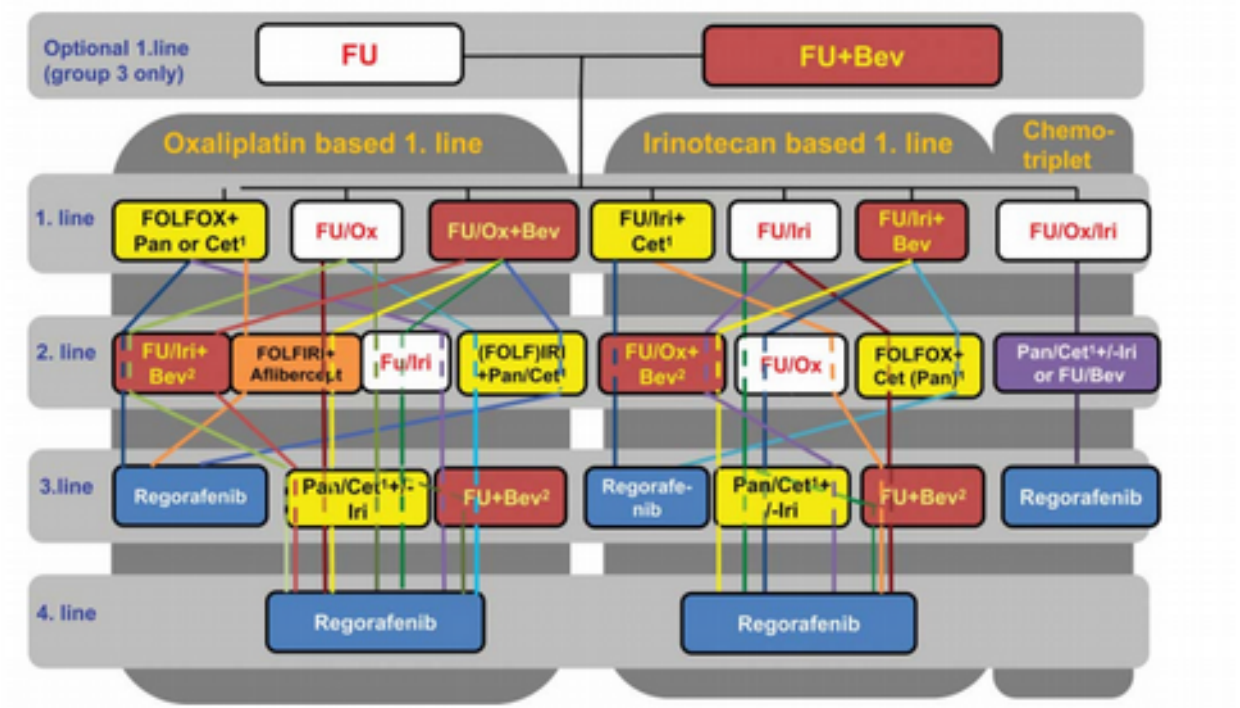
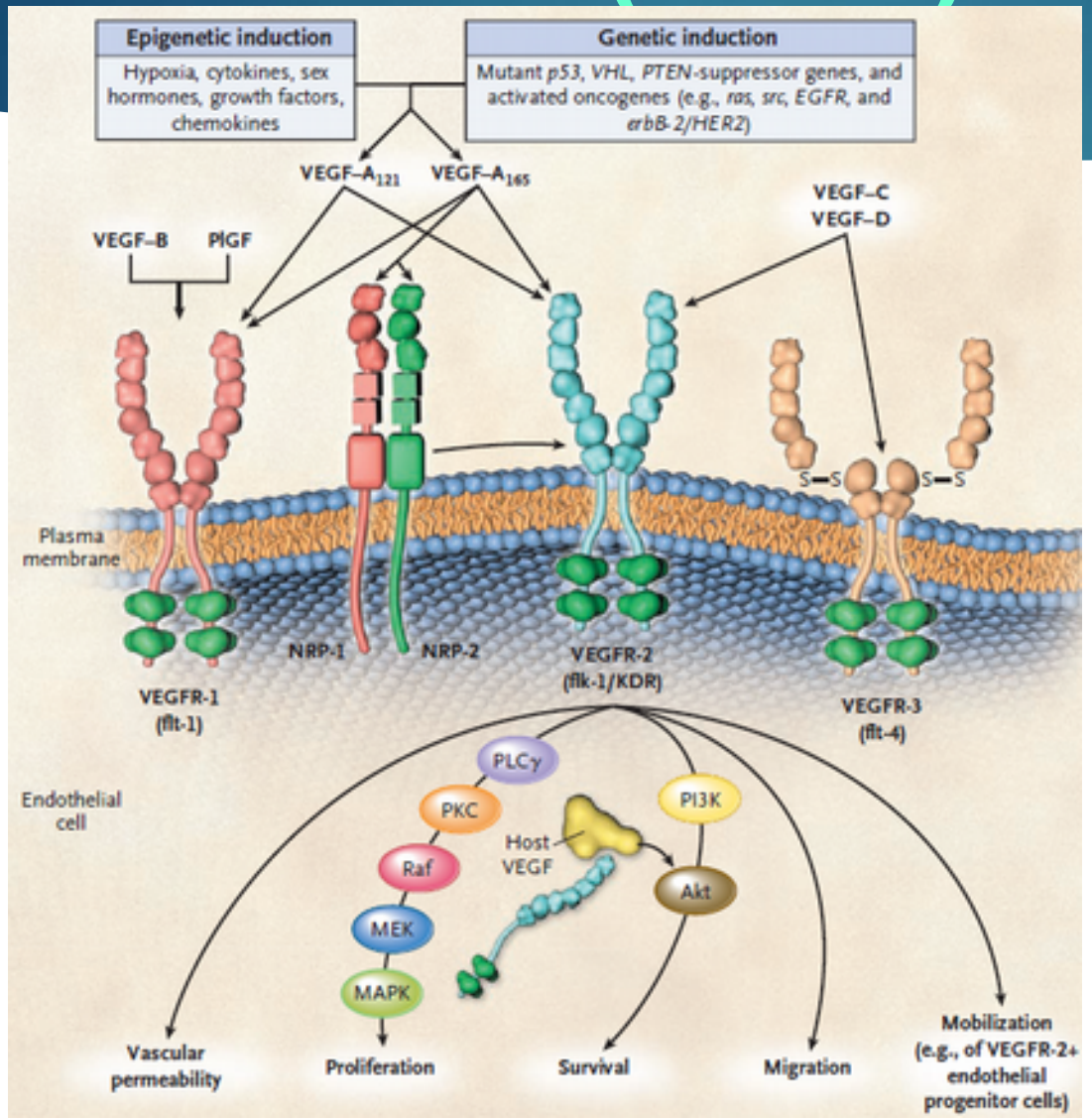


Figure 8. Proposal for sequence of salvage-chemotherapy. (1) only KRAS wt; (2) continuation of Bev not beyond second line, in case of optional first line and first line both with Bev; FU, fluoropyridmidines; Iri, irinotecan; Ox, oxaliplatin; Bev, bevacizumab; Afli, aflibercept; Cet, cetuximab; Pan, panitumumab.

TARGETED THERAPY

MONOCLONAL ANTIBODIES (M_oA_b)

MONOCLONAL ANTIBODIES (MoAb)



BEVACIZUMAB (AVASTIN)-

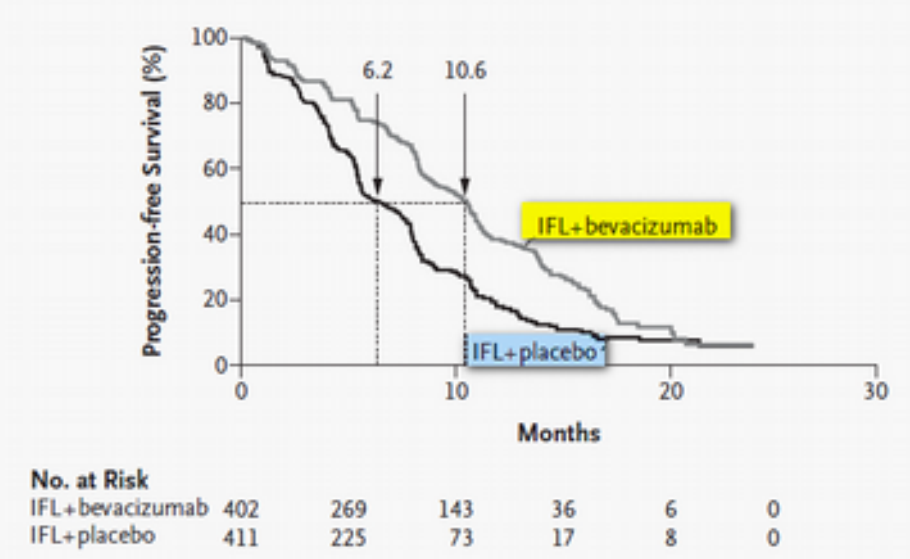
a humanised monoclonal antibody that binds VEGF prior to its attachment to its natural receptors.

Concerns Regarding Hypertension

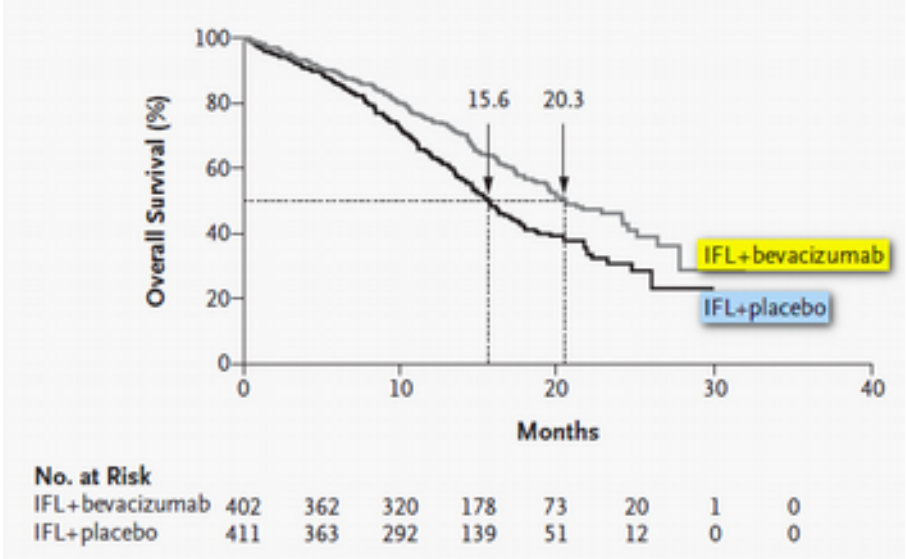
- Bevacizumab: anti-VEGF monoclonal antibody
  - Associated with increased incidence (10% to 15%) of grade 3/4 hypertension
  - Should not be used in mCRC patients with uncontrolled or severe hypertension
  - Associated with increased risk of stroke and/or other arterial thromboembolic events
    - Especially in patients 65 yrs of age or older

- Bevacizumab is also associated with risk of
  - Bleeding complications
  - Wound healing complications
  - GI perforations
  - Proteinuria, nephrotic syndrome

BEVACIZUMAB in metastatic colorectal cancer – pivotal trial



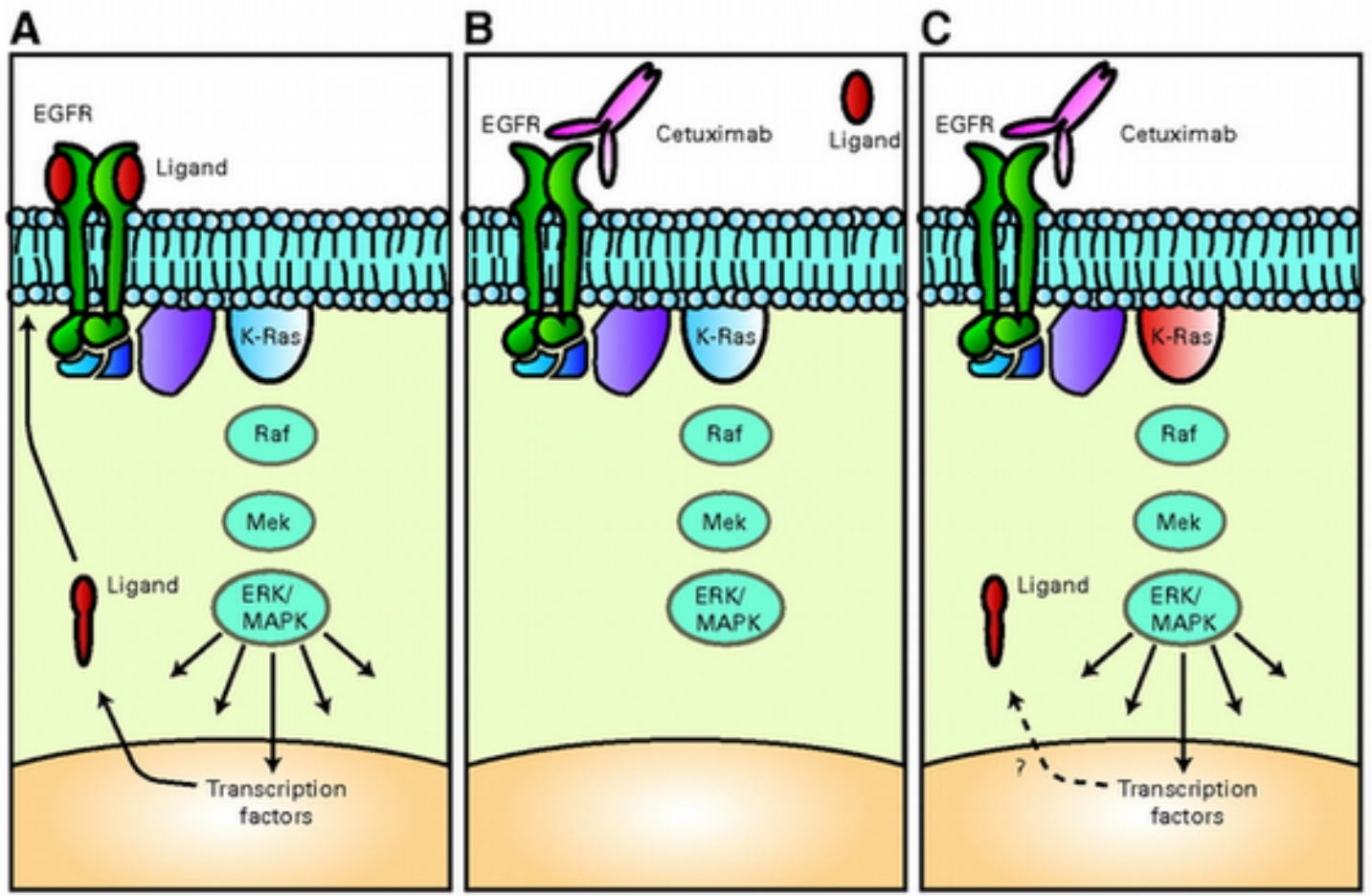
Progression-free survival (PFS)



Overall survival (OS)

Hurwitz i wsp. N Engl J Med 2004;350:2335-42.

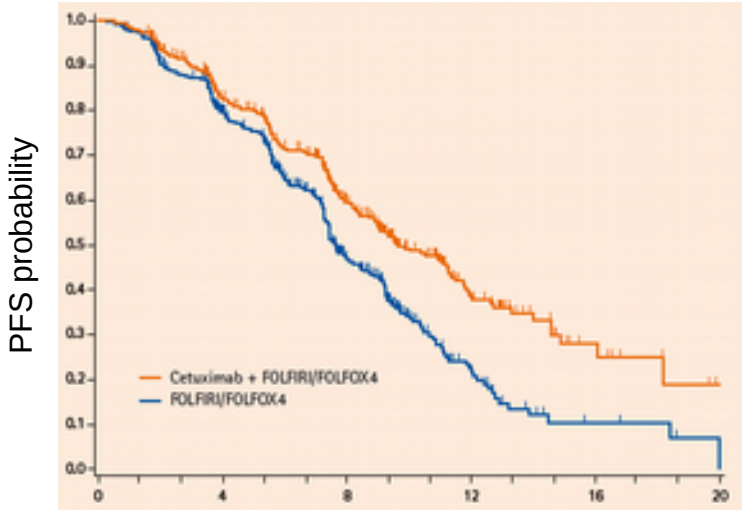
BLOCKING EGFR in advanced colorectal cancer - RAS mutation significance

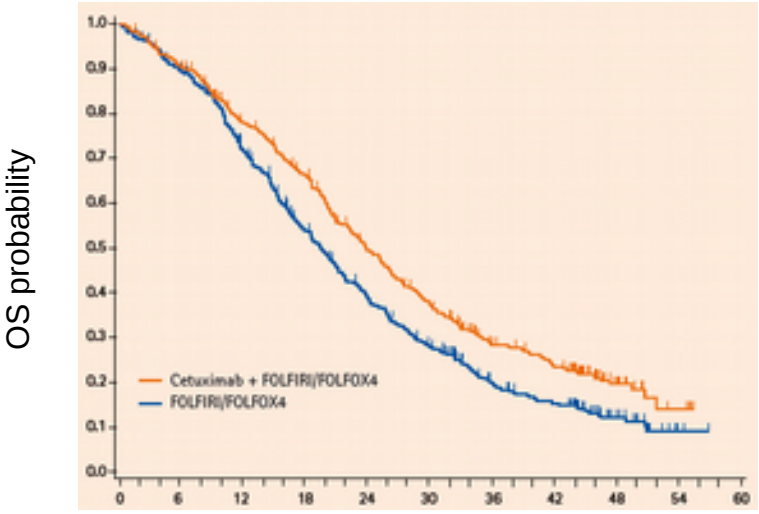


CETUXIMAB in advanced colorectal cencer :

CRYSTAL and OPUS trials

COMBINED ANALYSIS: increased survival in unmutated KRAS population





wtKRAS population	FOLFIRI/FOLFOX4	FOLFIRI/FOLFOX4 + cetuximab	p=
Median progression-free survival	7,6 months	9,6 months	<0,0001
Median overall survival	19,5 months	23,5 months	0,0062

Köhne i wsp. ASCO GI 2010, Abstract # 406

MONOCLONAL ANTIBODIES (MoAb)

CETUXIMAB and PANITUMUMAB

- ✓ appear to have comparable efficacy when used for salvage therapy in patients with chemotherapy-refractory mCRC
- ✓ both target the same antigen (the EGFR), and preclinical data suggest a similar mode of action

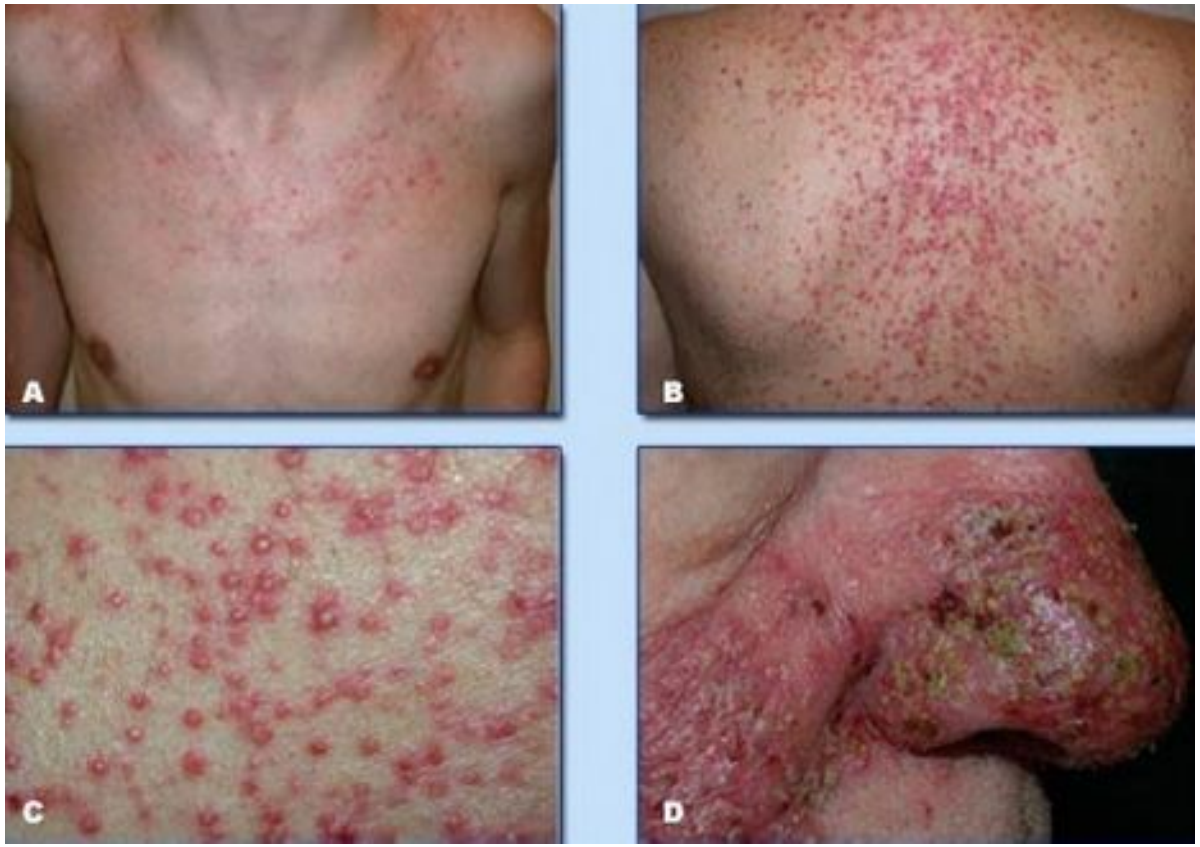
DIFFERENCE?

- ✓ cetuximab is a chimeric mouse/human MoAb
- ✓ panitumumab is a completely human MoAb - the incidence of hypersensitivity reactions with panitumumab is much lower, and this eliminates the need for routine premedication before therapy

MONOCLONAL ANTIBODIES (MoAb)

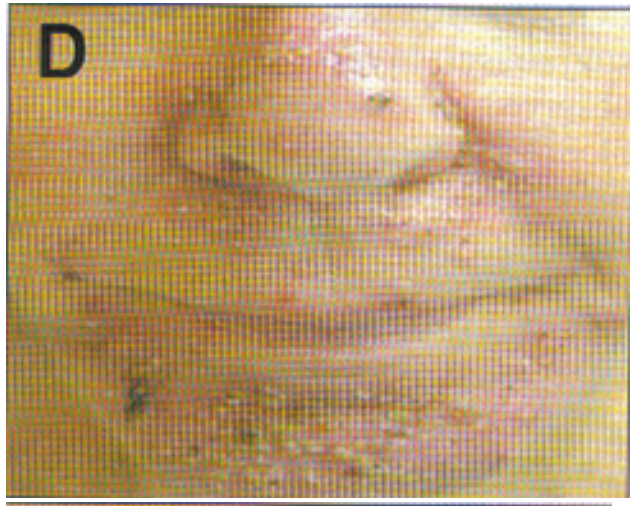
TOXICITY OF EGFR INHIBITORS: CETUXIMAB, PANITUMUMAB

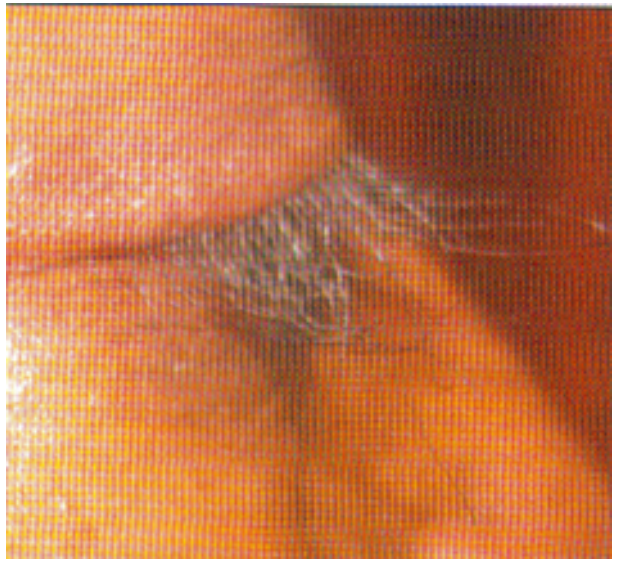
ACNE LIKE RASH

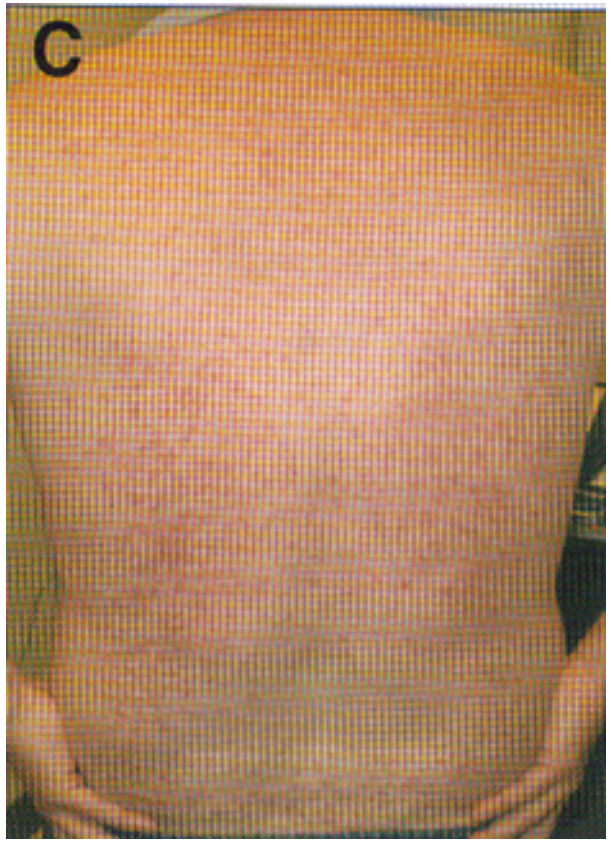


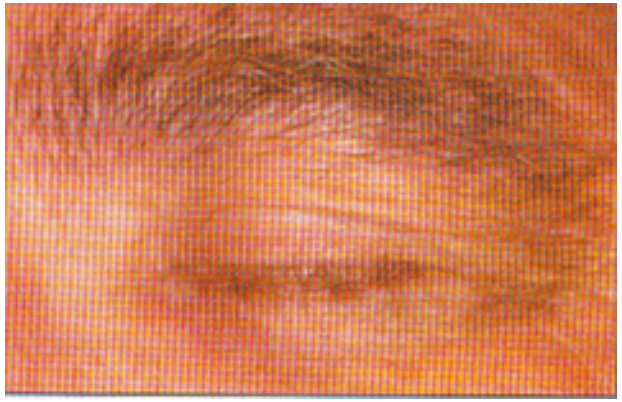
MONOCLONAL ANTIBODIES (MoAb)

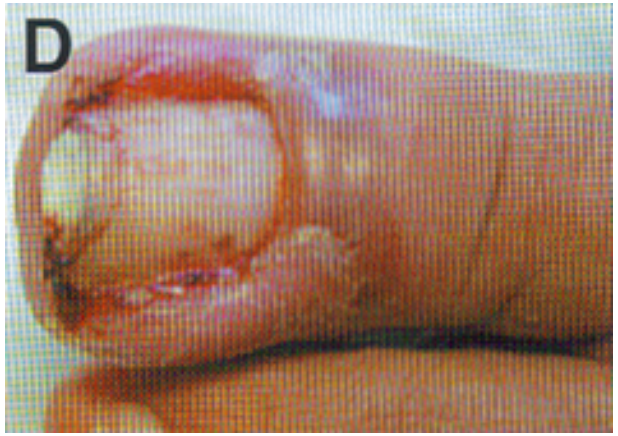
TOXICITY OF EGFR INHIBITORS: CETUXIMAB, PANITUMUMAB







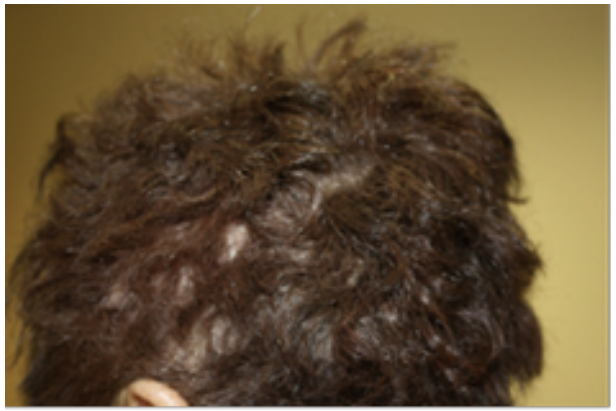




MONOCLONAL ANTIBODIES (MoAb)

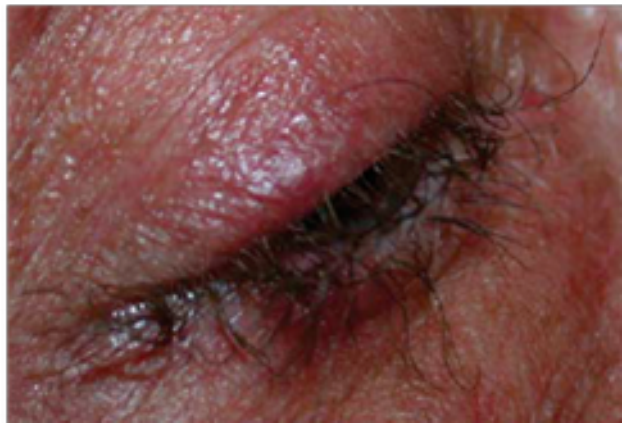
TOXICITY OF EGFR INHIBITORS: CETUXIMAB, PANITUMUMAB

HAIR CHANGES

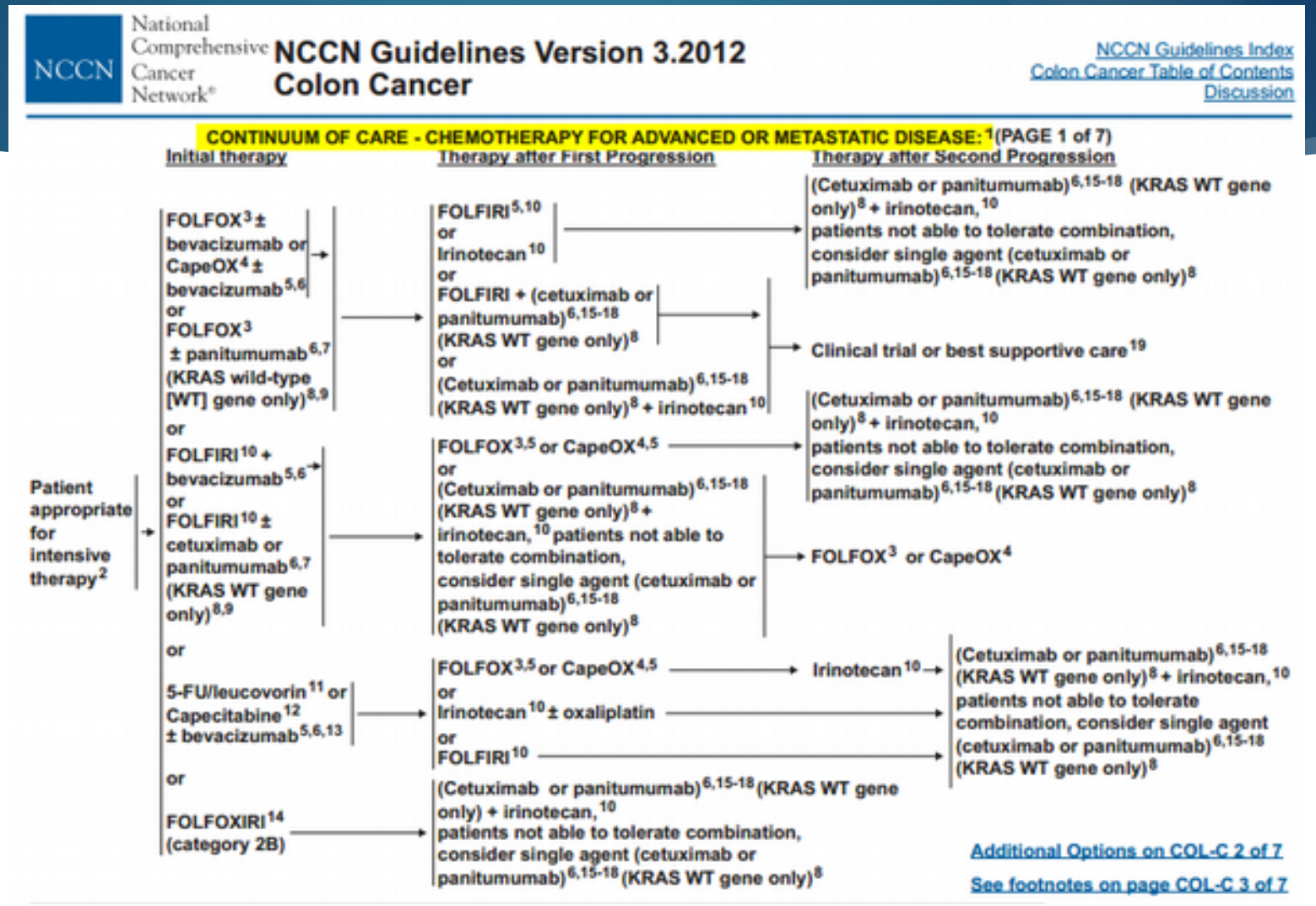


thin , curly hair

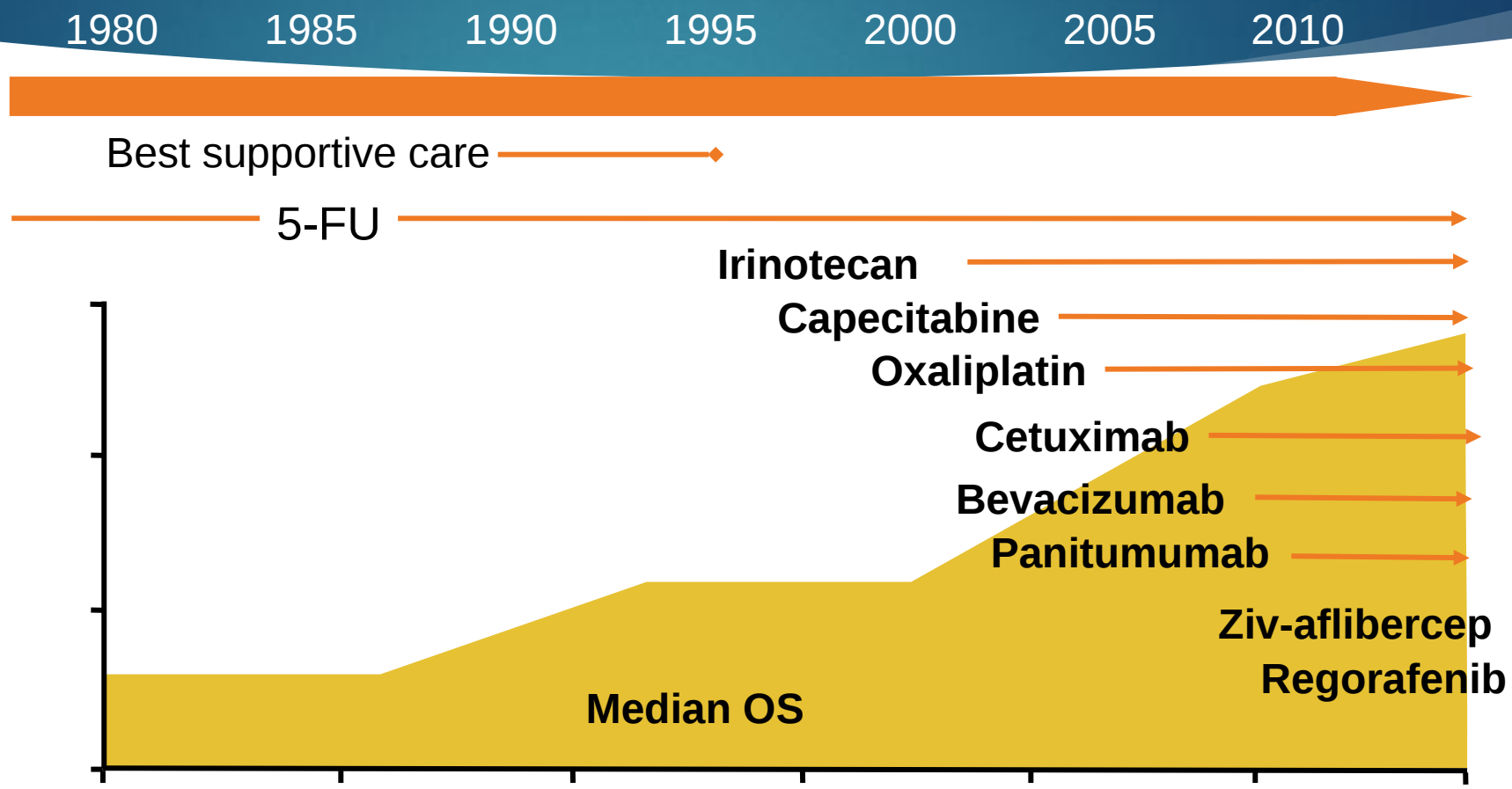
long eyelashes



mCRC TREATMENT



Stage IV CRC: 2014



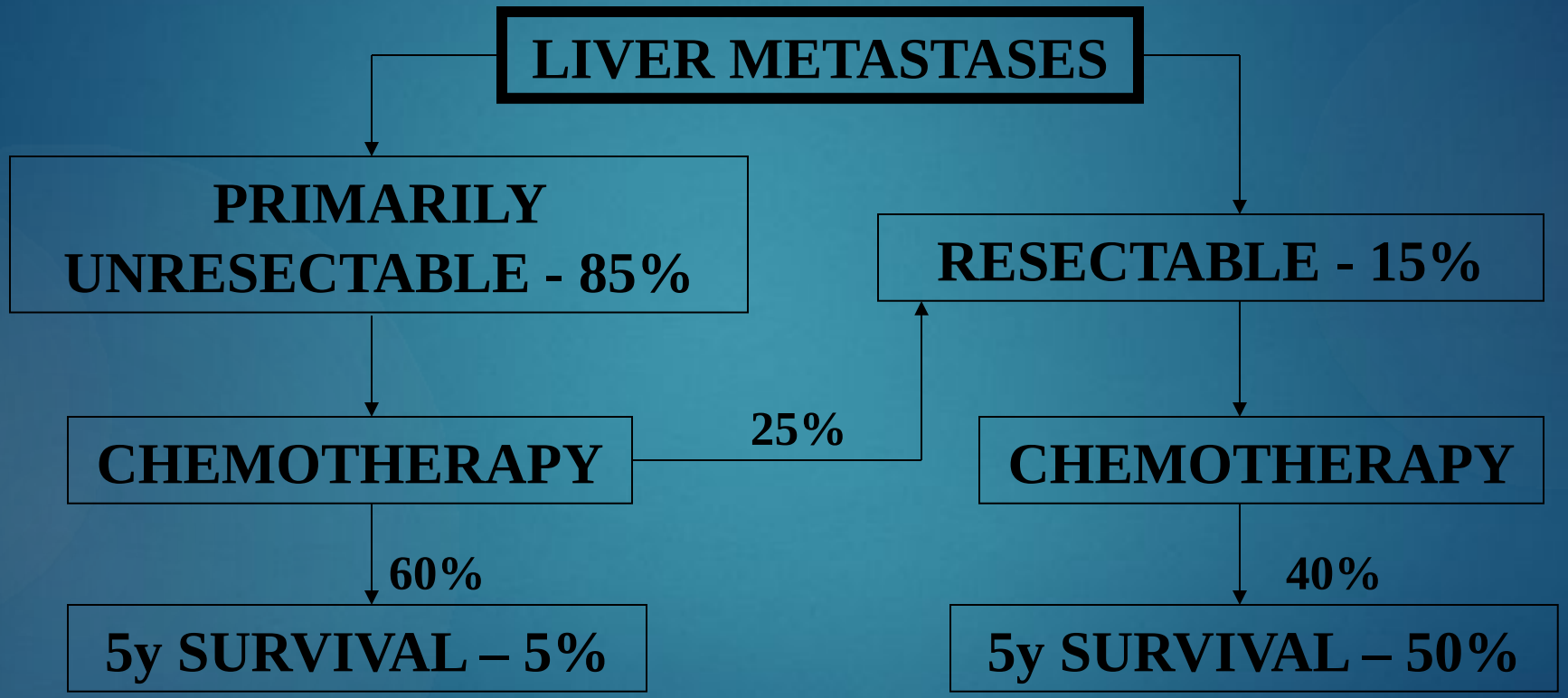
Curative treatment of metastatic colorectal cancer

CURATIVE TREATMENT OF metastatic CRC

- patients with isolated liver/lung metastases
- surgery of liver metastases (metastasectomy) + adjuvant CTH
- 5-year overall survival 24-58%
- patients who survive 10 years appear to be cured
- **modern criteria for resectability** have been expanded to include any patient in whom all disease can be resected with negative margins and who has adequate hepatic volume/reserve
- for patients with primarily unresectable metastases induction CTH (conversion CTH) downstages the metastases and allows for complete resection in 12-33% with 5-year survival of about 30-35%
- addition of cetuximab or bevacizumab to a chemotherapy backbone may increase the number of patients potentially eligible for resection

METASTATIC COLORECTAL CANCER

SURGICAL TREATMENT



MODERN CHEMOTHERAPY

Hereditary CRC syndromes

- Familial adenomatous polyposis
- Lynch syndrome

GENETIC SYNDROMES

- **Familial adenomatous polyposis (FAP)**

  - < than 1% of colorectal cancers

  - germline mutations in the adenomatosis polyposis coli (APC) gene which is located on chromosome 5

  - numerous colonic adenomas appear during childhood

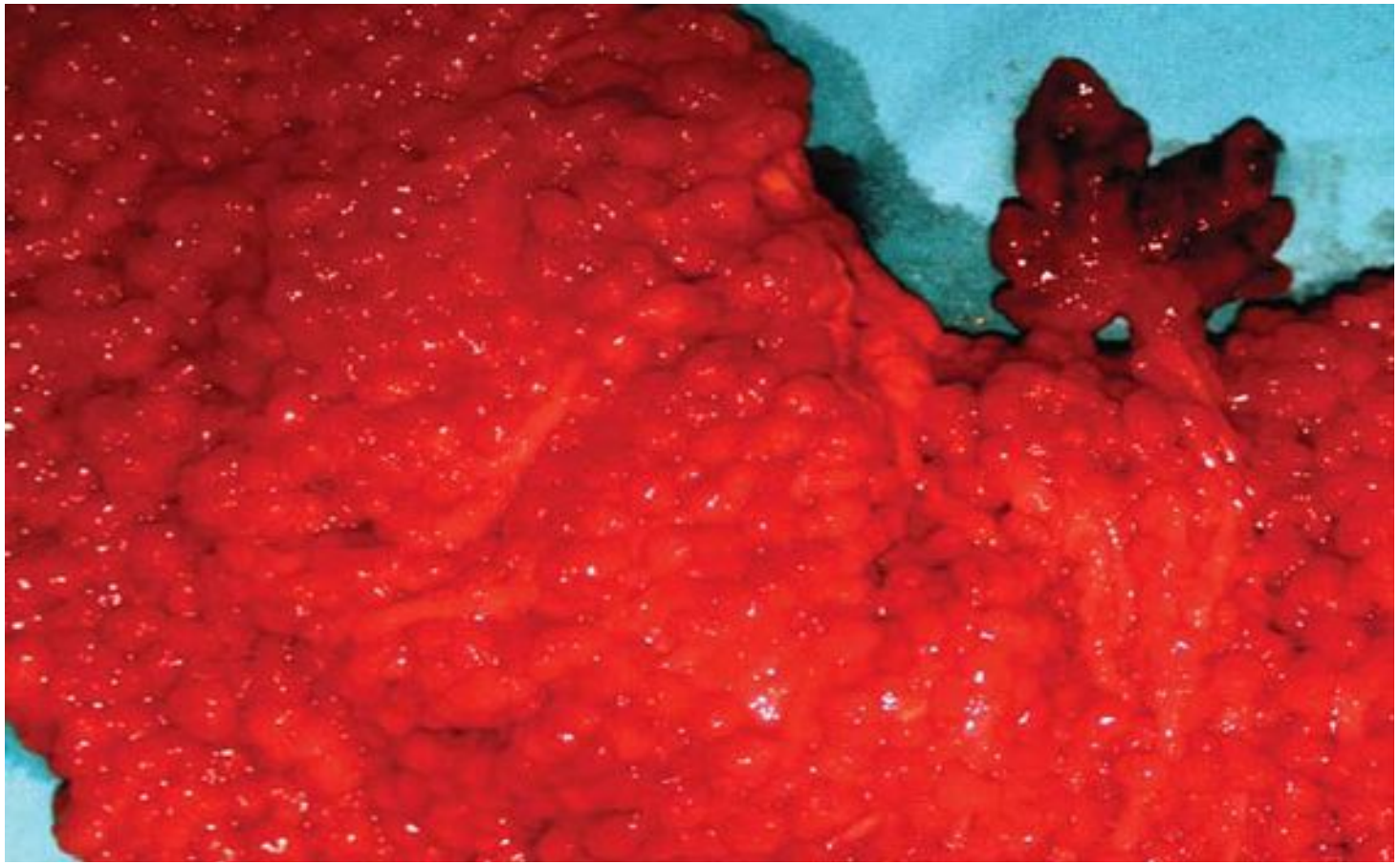
  - symptoms appear at an average age of approximately 16 years

  - colonic cancer occurs in 90% of untreated individuals by age 40

  - attenuated form of APC (AAPC) carries a similarly high risk of colon cancer but is characterized by fewer adenomas and an older average age of cancer diagnosis of 54 years

GENETIC SYNDROMES

Familial adenomatous polyposis (FAP)



FAP management

- FAP is the paradigm for preventive removal of the end-organ before tumor development in a cancer syndrome
- *APC* gene testing should be performed at 10 to 12 years of age, about the time that sigmoidoscopy would begin
- If *APC* gene mutation has been identified, and when adenomas are found, **prophylactic colectomy** is performed

GENETIC SYNDROMES

Hereditary nonpolyposis colorectal

cancer (HNPCC; Lynch syndrome)

- 1 to 5% of all colonic adenocarcinomas
- caused by mutations in one of the mismatch repair genes, hMLH1, hMSH2, hMSH6, or PMS2
- primarily characterized by early age of onset and predominant involvement of the right colon
- mean age at initial cancer diagnosis is 48 years, with some patients presenting in their 20s
- approximately 10 percent will have synchronous or metachronous cancers
- extracolonic cancers – mostly endometrial carcinoma; other sites: ovary, stomach, small bowel, hepatobiliary system, and renal pelvis or ureter

HNPCC management

- annual screening colonoscopy beginning at age 20 to 25 years
- Because of the high rate of synchronous and metachronous colon cancers in HNPCC kindreds, **subtotal colectomy** has been recommended at the first diagnosis of colon cancer in a member of an HNPCC family
- Prophylactic colectomy in HNPCC gene carriers remains a controversial recommendation
- Chemoprevention trials in HNPCC utilizing cyclooxygenase-2 inhibitors are underway
- Screening for cancer in other sites (endometrium, ovaries etc)

Thank you