Colon Cancer Treatment

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Division of Medical Oncology
The Ohio State University Wexner Medical Center

Colon cancer

• Incidence
• Risk Factors
• Screening
• Hereditary Syndromes
• Signs and Symptoms
• Diagnostic work-up
• Staging
• Treatment
Colon cancer

Adenocarcinomas that occur anywhere along the large bowel (ascending, transverse, and descending) into the rectum.

Wikimedia Commons
2012 Estimated US Cancer Cases

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
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</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>28%</td>
<td></td>
<td>Breast</td>
<td>29%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>14%</td>
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<td>Lung &amp; bronchus</td>
<td>14%</td>
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<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
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<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td></td>
<td>Uterine corpus</td>
<td>6%</td>
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<tr>
<td>Melanoma of skin</td>
<td>5%</td>
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<td>Thyroid</td>
<td>5%</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
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<td></td>
<td>Melanoma of skin</td>
<td>4%</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td></td>
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<td>4%</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>3%</td>
<td></td>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td></td>
<td>Ovary</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3%</td>
<td></td>
<td>Pancreas</td>
<td>3%</td>
</tr>
<tr>
<td>All Other Sites</td>
<td>18%</td>
<td></td>
<td>All Other Sites</td>
<td>20%</td>
</tr>
</tbody>
</table>

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.

2012 American Cancer Society, Inc

2012 Estimated US Cancer Deaths

<table>
<thead>
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<th></th>
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<td></td>
<td>Pancreas</td>
<td>7%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>5%</td>
<td></td>
<td>Ovary</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td></td>
<td>Leukemia</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td></td>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
</tr>
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<td>Urinary bladder</td>
<td>3%</td>
<td></td>
<td>Uterine corpus</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
<td></td>
<td>Liver &amp; intrahepatic bile duct</td>
<td>2%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td></td>
<td>Brain/other nervous system</td>
<td>2%</td>
</tr>
<tr>
<td>All other sites</td>
<td>25%</td>
<td></td>
<td>All other sites</td>
<td>24%</td>
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</table>

2012 American Cancer Society, Inc
Colorectal Stage Distribution at Diagnosis (%)

- Localized: 39%
- Regional: 19%
- Distant: 5%
- Unknown: 37%

19% patients have Stage IV disease on diagnosis
5 year-survival of Stage IV disease is 12%


Risk Factors

- Personal or family history of colorectal cancer or adenomatous polyps before age 50
- Inflammatory bowel disease
  - Ulcerative colitis > Crohn's disease
- History of abdominal radiation
- Acromegaly (increased adenomas)
- Familial syndromes
- High fat and low fiber diets
- Obesity
Protective factors

- NSAIDs
- Exercise
- High fiber, low fat diet
- Folic acid supplementation
- Vitamin D and calcium

Screening recommendations:

- 90% colon cancer cases occur after age 50
- Starting at age 50:
  - Fecal occult blood test (annually)
  - Flexible sigmoidoscopy (every 5 years)
  - Colonoscopy (every 10 years)
  - Air contrast barium enema (every 5 years)
- If patients are diagnosed with colon cancer, their 1st degree relatives should start having screening colonoscopies 10 years junior to their age at diagnosis or at age 50, whichever occurs earlier.
Screening decreases mortality

Screening with flexible sigmoidoscopy, repeat at 3 or 5 years

Usual care

154,900 people (55-74 years)

• 21% reduction in incidence of colorectal cancer in the intervention group
• 26% reduction in deaths from colorectal cancer in the intervention group
• 50% reduction in mortality from distal colorectal cancer

Schoen et al. NEJM 2012;366:2345-2357.

Hereditary Syndromes
FAP

- Familial adenomatous polyposis (FAP)
- Germline mutation in the adenomatous polyposis coli (APC) gene
- 1% of all colon cancer
- Autosomal dominant
- Patients have hundreds to thousands of colonic polyps, which place them at high risk for mutation into tumors at a young age (45 years)
- Extracolonic tumors: CNS tumors, small bowel cancer, thyroid cancer, pancreatic cancer, gastric cancer, pediatric hepatoblastoma

Wikimedia Commons
**FAP- Personal history**

- **Treatment**: proctocolectomy or colectomy
- **Surveillance**:
  - Endoscopic evaluation of remaining bowel
  - Upper endoscopy
  - Annual thyroid exam

**FAP- Family history**

- APC gene mutation in family member

  - **Detected**
    - Flexible sigmoidoscopy annually starting age 10-15 years
  - **Not detected**
    - Average risk screening
### HNPCC

- Hereditary Non-Polyposis Colorectal Cancer (HNPCC) or Lynch syndrome
- Germline mutation in genes involved in mismatch repair enzymes
  - Important in surveillance and repair of errors that occur during DNA synthesis
    - MLH1, MSH2, MSH6, PMS2
- 2-3% of all colon cancer
- Autosomal dominant
- Patients present at young age

### Amsterdam criteria for HNPCC

- > 3 family members with colorectal cancer (> 2 first degree relatives)
- > 2 successive family generations affected
- Colorectal cancer before age 50 in at least 1 family member
- FAP excluded
**HNPCC**

- Extracolonic tumors: breast, pancreas, gastric, gynecologic, and genitourinary cancers
- **Screening recommendations:**
  - Colonoscopy, age 20-25
  - EGD and duodenoscopy, age 30-35
  - Urinalysis, age 25-30
- Consider prophylactic hysterectomy and bilateral salpingo-oophrectomy

---

### CAPP2 study

<table>
<thead>
<tr>
<th>937 carriers of Lynch syndrome</th>
<th>Aspirin 600mg</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Resistant starch 30g</td>
<td>Resististant starch 30g</td>
</tr>
<tr>
<td></td>
<td>Aspirin 600mg</td>
<td>Placebo</td>
</tr>
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<td></td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

Aspirin intervention, follow-up at 55.7 months:
- **HR 0.63**
  - (95% CI 0.35-1.13, p=0.12)

2 year intervention with aspirin:
- **HR 0.41**
  - (95% CI 0.91-0.86, p=0.02)

Primary outcome: Development of colon cancer

## Peutz-Jegher syndrome

- Germline mutation of serine threonine kinase (STK11)
- Autosomal dominant
- **Diagnosis**: (2 of the following)
  - Freckling at the mouth, lips, fingers, and genitals
  - More than 2 hamartomatous polyps of small intestine
  - Family history
- Extracolonic tumors: breast, ovarian, testicular, pancreas, small intestine, stomach

<table>
<thead>
<tr>
<th>Peutz-Jeghers syndrome</th>
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<tbody>
<tr>
<td><strong>Surveillance:</strong></td>
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<tr>
<td>- Mammogram, age 25</td>
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<tr>
<td>- Upper endoscopy and colonoscopy, late teens</td>
</tr>
<tr>
<td>- Pancreas imaging?, age 25-30</td>
</tr>
<tr>
<td>- Small bowel imaging, age 8-10</td>
</tr>
<tr>
<td>- Testicular exam, age 10</td>
</tr>
<tr>
<td>- Pelvic exam and Pap smear, age 18-20</td>
</tr>
</tbody>
</table>

| Signs and symptoms |
### Signs and Symptoms

- Weight loss
- Fatigue
- Anemia
  - Microcytic, due to iron deficiency
- Abdominal pain
- Melena
- Rectal bleeding
- Change in bowel movements
  - Constipation or diarrhea

### Diagnostic work-up

- CBC + differential
- Comprehensive metabolic panel
- Serum CEA
- Colonoscopy with biopsy
- CT chest/abdomen/pelvis
- PET/CT scan
Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor</th>
<th>Node</th>
<th>Metastasis</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T3-4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>Any T</td>
<td>N1-2</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Staging Affects Survival

<table>
<thead>
<tr>
<th>Category</th>
<th>SEER</th>
<th>SE</th>
<th>SEER</th>
<th>SEER</th>
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<tbody>
<tr>
<td>TN</td>
<td>Relative survival, 5-year (%)</td>
<td>SE</td>
<td>TNM stage, 6th ed</td>
<td>TNM stage, 7th ed</td>
</tr>
<tr>
<td>T1N0</td>
<td>97.4</td>
<td>0.6</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>T2N0</td>
<td>96.8</td>
<td>0.6</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>T3N0</td>
<td>87.5</td>
<td>0.4</td>
<td>IIA</td>
<td>IIA</td>
</tr>
<tr>
<td>T4aN0</td>
<td>79.6</td>
<td>1.0</td>
<td>IIIB</td>
<td>IIIB</td>
</tr>
<tr>
<td>T4bN0</td>
<td>58.4</td>
<td>1.3</td>
<td>IIB</td>
<td>IIC</td>
</tr>
<tr>
<td>T1-2N1a</td>
<td>90.7</td>
<td>1.5</td>
<td>IIIA</td>
<td>IIIA</td>
</tr>
<tr>
<td>T1-2N1b</td>
<td>83.0</td>
<td>2.0</td>
<td>IIIA</td>
<td>IIIA</td>
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<tr>
<td>T1-2N2a</td>
<td>79.0</td>
<td>3.6</td>
<td>IIIC</td>
<td>IIIA/IIIIB</td>
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<tr>
<td>T3N1a</td>
<td>74.2</td>
<td>0.8</td>
<td>IIIB</td>
<td>IIIB</td>
</tr>
<tr>
<td>T4aN1a</td>
<td>67.6</td>
<td>2.0</td>
<td>IIIB</td>
<td>IIIB</td>
</tr>
</tbody>
</table>

AJCC 7th edition
## Treatment

- Surgery
- Chemotherapy
- Radiofrequency ablation
- Radiation therapy

## Resectable disease

- Stage I
- Stage II
  - High risk: Tumor perforation, lymphovascular invasion, perineural invasion, high-grade histology, <12 lymph nodes sampled
- Stage III (lymph node involvement)
Resectable disease

- Adjuvant chemotherapy
  - Goal: Eradicate micrometastases, reduce the risk of recurrence of cancer and improve survival

- 5-Fluorouracil (5FU)
- Capecitabine (Xeloda)
- Oxaliplatin

MOSAIC trial

2,246 patients with Stage II/III colon cancer, after surgical resection

<table>
<thead>
<tr>
<th>Stage</th>
<th>Intervention</th>
<th>Probability of surviving at 6 years</th>
</tr>
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<tbody>
<tr>
<td>III</td>
<td>5FU</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td>5FU + oxaliplatin</td>
<td>73% (20% reduction in risk of death)</td>
</tr>
<tr>
<td>II</td>
<td>5FU</td>
<td>87%</td>
</tr>
<tr>
<td></td>
<td>5FU + oxaliplatin</td>
<td>87%</td>
</tr>
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</table>

Andre et al. J Clin Oncol 2009;27:3109-3116,
Goals in Patients with Advanced Disease

- Resection if possible
- Conversion therapy if initial resection not possible
- Extension of length of life
- Maintenance of quality of life

### Metastatic disease

- Palliative chemotherapy
  - 5FU or capecitabine
  - Oxaliplatin
  - Irinotecan

- Metastectomy
- Radiation therapy
- Radiofrequency ablation

- Biologic agents
  - VEGF pathway - bevacizumab, aflibercept
  - EGFR pathway - cetuximab, panitumumab
  - Regorafenib

### EORTC 40983 – Peri-operative FOLFOX in Resectable Liver Metastasis

- Randomized
- FOLFOX4 → Surgery → FOLFOX4
  - 6 cycles (3 months)

- Surgery
- 6 cycles (3 months)

- n=364 patients (09/00-07/04)

Progression-Free Survival in Eligible Patients

- Surg only
- Periop. CT

100
90
80
70
60
50
40
30
20
10
0

- +8.1% at 3 years

MOSAIC: Oxaliplatin difference in 3-yr DFS for stage III: +7.2%


Complications of Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>With chemotherapy</th>
<th>Without chemotherapy</th>
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<tbody>
<tr>
<td>Post-operative</td>
<td>25.2 %</td>
<td>16 %</td>
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<tr>
<td>complications</td>
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<tr>
<td>Post-op deaths</td>
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<td>2 pt</td>
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</tbody>
</table>

HR = 0.77; CI: 0.60-1.00, p=0.041
Treatment-Associated Liver Toxicity

- 5-FU: steatosis
- Irinotecan: steatohepatitis
- Oxaliplatin: sinusoidal/vascular injury
- Bevacizumab
  - Potential wound healing complications
  - Wait 6-8 wks before surgical resection
- Cetuximab: no known acute/chronic effects
- Incidence of postoperative complications increases with prolonged use

Figure 1. Signaling pathways that are targeted in colon cancer.
## Survival for patients with metastatic colorectal cancer (mCRC)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median survival</th>
</tr>
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<tbody>
<tr>
<td>No treatment</td>
<td>6 months</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>10-12 months</td>
</tr>
<tr>
<td>FOLFOX or FOLFIRI</td>
<td>14-16 months</td>
</tr>
<tr>
<td>Chemotherapy and bevacizumab</td>
<td>20-24 months</td>
</tr>
</tbody>
</table>

## Anti-VEGF therapy

- **Agents:** Bevacizumab or aflibercept
- **Administered:** intravenously
- **Side effects:**
  - Hypertension
  - Proteinuria
  - Poor wound healing
  - Bowel perforation
  - Arterial thromboembolic events
Bevacizumab + IFL

Patients with untreated mCRC
n= 813

IFL (irinotecan + bolus 5FU)
n= 411
15.6 months OS 6.2 months PFS

20.3 months OS 10.2 months PFS

IFL + bevacizumab
n= 402


Anti-EGFR therapy

- Agents: Cetuximab or panitumumab
- Administered: intravenously
- Side effects:
  - Hypomagnesemia and hypocalcemia
  - Acneiform rash
    - Tx: Minocycline, hydrocortisone cream, sunblock
  - Hypersensitivity reaction
  - Pulmonary fibrosis
Cetuximab n= 111 patients

10.8% ORR 1.5 mo TTP

No Impact on Overall Survival

22.9% ORR 4.1 mo TTP

Cetuximab and Irinotecan n= 218 patients

Patients with mCRC refractory to irinotecan n= 329


KRAS results available for 92% patients

Progression-free survival by treatment within KRAS groups.

Progression-free survival by randomized treatment in (A) mutant and (B) wild-type KRAS groups.

Amado R G et al. JCO 2008;26:1626-1634
Regorafenib

- Administered: orally
- Side effects:
  - Hand-foot syndrome
  - Hypertension
  - Diarrhea
  - Hepatotoxicity

In summary, colon cancer...

- 3rd most common cancer
- Screening starts at age 50
- Familial syndromes:
  - FAP, HNPCC, Peutz-Jegher syndrome
- Diagnostic work-up and staging
- Adjuvant chemotherapy to prevent cancer recurrence
- New targeted therapies for metastatic disease
Colon Cancer

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Department of Surgical Oncology
The Ohio State University Wexner Medical Center

Outline

- Surgical Treatments
- Surgical Dogma
- Surgical Advances
Surgical Treatments

- Primary Tumors
  - Surgical resection remains mainstay of curative therapy
  - Resection
    - Minimally invasive (Laparoscopic, Robotic)
- Metastatic Disease
  - Surgical resection
  - Local therapies
    - Ablation (RFA/Microwave)
  - Regional therapies
    - SIRT (selective internal radiation therapy – Y-90)
    - Isolated hepatic perfusion (IHP)
    - Hepatic artery infusion pump (HAIP)
    - Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

Minimally Invasive Surgery

- Technological advances allowed less invasive approaches more feasible
- Requires technical expertise and resources
- Initially questioned quality of oncologic resection and outcomes
### Minimally Invasive Surgery (MIS) Considerations

- **Tumor Related**
  - Location (Right/Sigmoid easier)
  - Size/Invasion
  - Localization
- **Patient Related**
  - Body habitus
  - Previous surgery
  - Comorbidities

### MIS: Conversion to Open

- Occurs in 10-25 % cases
  - Body habitus
  - Prior surgery
  - Inflammation
  - Tumor size
  - Anatomic
- Not surgical failure
- Early conversion preserves outcomes
Benefits of Minimally Invasive Surgery (MIS)

Benefits of New Techniques

Risk/Effects Of Anesthesia, Trauma, Etc.

Operative Time

MIS: Data and Literature

- What are the benefits?
  - Return of bowel function (1-2 days earlier)
  - Decreased pain (less narcotics)
  - Length of stay (1 day less)
  - Earlier return to work/activities
  - Expectation bias may play a role
MIS: Outcomes

- Cost
  - Increased OR/time costs
  - ?Balance by shorter hospital stay
- Oncology
  - Are cancer outcomes preserved with MIS?

COST (Clinical Outcomes of Surgical Therapy)

- 872 patients with colon adenocarcinoma
- Recurrence
  - 16% Laparoscopic
  - 18% Open
- Survival
  - 86% Laparoscopic
  - 85% Open
- Hospital Stay
  - 5 days Laparoscopic
  - 6 days Open

**COST Trial**  
*(Clinical Outcomes of Surgical Therapy) Trial*

- 5 year data
- Disease-free 5 year survival
  - 68.4% Open
  - 69.2% Laparoscopic
- Overall survival
  - 74.6% Open
  - 76.4% Laparoscopic
- Recurrence
  - 21.8% Open
  - 19.4% Laparoscopic
- Replicated in other large trials (CLASICC - UK, COLOR - European)

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**MIS: Cosmesis**
Robotic Surgery Benefits

- Same patient benefits as MIS
- Technical
  - Allows HD 3-D visualization
  - Facilitates fine, precise movement within confined spaces (pelvis, ENT)
- 39 pts Rectal adenocarcinoma
  - Oncologic principles feasible
    - (-) Margins, LN harvest adequate, TME
  - Safe (12.8% morbidity, 0 Mortality)
  - OR time increased (285 min.)
  - Length of stay (median 4 days)

MIS: Robotic Surgery
MIS: Robotic Surgery

MIS: Robotic Surgery
### Colon Cancer Metastases

- Liver most common site
  - Approximate 50% incidence
  - Often only site
- Surgical resection remains mainstay of curative therapy
  - <20% amenable to resection
- Adjuncts to surgical resection
  - Ablation therapy (RFA, Microwave)
  - Minimally invasive approaches

### Colon Cancer therapies

- Chemotherapy (marked advances)
- Surgery (Primary tumor, metastatic disease, isolated hepatic perfusion)
- Locoregional therapy
  - SIRT (Selective internal radiation therapy; y-90)
  - HAIP (Hepatic artery infusion pump)
- Ablation therapy
- HIPEC
## Chemotherapy advancement

<table>
<thead>
<tr>
<th>1996</th>
<th>2013</th>
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<tbody>
<tr>
<td>• 5FU / Leucovorin</td>
<td>• Avastin (bevacizumab)</td>
</tr>
<tr>
<td>• Prolonged patient survival</td>
<td>• Aflibercept (Eylea)</td>
</tr>
<tr>
<td>• Induce disease/tumor shrinkage</td>
<td>• Erbitux (cetuximab)</td>
</tr>
<tr>
<td>• May allow resection in previously unresectable patients (response &gt; 50%)</td>
<td>• Vectibix (panitumumab)</td>
</tr>
<tr>
<td>• Chemotherapy toxicities</td>
<td>• Eloxatin (oxaliplatin)</td>
</tr>
<tr>
<td></td>
<td>• Camptosar (irinotecan)</td>
</tr>
<tr>
<td></td>
<td>• 5FU</td>
</tr>
<tr>
<td></td>
<td>• Xeloda (capecitabine)</td>
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<td></td>
<td>• Tarceva (erlotonib)</td>
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<td>• FUDR</td>
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<tr>
<td></td>
<td>• Leucovorin</td>
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<td></td>
<td>• Levamisole</td>
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<td></td>
<td>• Mitomycin-C</td>
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“Unresectability”

- Relative (eye of the beholder)
  - Expertise, Resources, Attitude
- Surgery Risk
  - Anatomic
  - Techniques
  - Mortality (20% in ’80’s →<5%)
- Better Chemotherapy and imaging → Better patient selection

Surgical Dogma

- ‘Unresectable’
  - Bilobar disease
  - >4 lesions
  - Extrahepatic/Metachronous disease
  - Lesions > 5cm
- SSO/SSAT/AHPBA Consensus
  - Dogma no longer valid; Important factors to consider for resection
    - Margin (-) resection
    - Complete resection/treatment of all intrahepatic/extrahepatic disease
    - Functional liver remnant with inflow/outflow/biliary drainage of >2 contiguous sectors(segments)
### Locoregional therapies

- Ablation
- SIRT
- Isolate Hepatic Perfusion (IHP)
- Hepatic artery infusion pump (HAIP)
- Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

#### Indications
- Unresectable disease
- Medically unfit for hepatectomy
- Poor biology (widespread extrahepatic disease, distant metastases, etc.)

### Ablation therapy

- Employs energy (radiofrequency or microwave) to cause tumor necrosis
  - RF uses high frequency AC current
  - Microwave uses electromagnetic waves at microwave energy for tissue heating
- Limited damage to surrounding liver
- Open, laparoscopic, percutaneous approaches
  - Efficacy: Open>Laparoscopic>Percutaneous
  - Inferior to resection in survival and recurrence
- Limited by tumor size (3 cm), anatomy, and heat sink
- Adjunct to major resection
Laparoscopic MWA

Laparoscopic MWA
Laparoscopic MWA

SIRT (yttrium-90 microspheres)

- Radiolabelled particles
  - TheraSpheres – MDS Nordion (HCC)
  - SIRSpheres – SIRTex (CRC)
- High dose radiation to tumor with low dose radiation to liver
- β particle emission with 2-3mm penetration
- Delivered into hepatic artery
## SIRT procedure

- Pre-treatment
  - Hepatic angiogram, MAA (shunt study)
  - Embolization of gastroduodenal artery and other vessels as needed
  - LFTs
- Treatment
  - Hepatic artery catheterization and microsphere implantation
- Post-treatment
  - Gamma scan to confirm sphere location

## SIRT Post-gamma scan

![SIRT Post-gamma scan images]
Isolated Hepatic Perfusion (IHP)

- Goal to provide durable control of isolated diffuse liver metastases of select tumor types
- Hepatic artery major blood supply to liver tumors
- Allows intense treatment to cancer-burdened liver without systemic toxicity
  - Hepatic circulation isolated on a circuit to continuously perfuse chemotherapy under mild hypothermic conditions
- Major operation with associated morbidity

IHP Technique

- Liver vasculature isolated
- Hepatic temperature probes placed
- 1 hour of hyperthermic (40°C.) perfusion with high dose chemotherapy administration
- Liver flushed of chemotherapy after perfusion
- Vascular catheters removed and vessels repaired

IHP: Treatment Response

- In 114 pts, 59% response rate seen
- Median progression free survival 7 months
- May be useful in conjunction with adjuvant chemotherapy in very select patients

| TABLE 4. Treatment Results With IHP for 120 Patients With CRC Liver Metastases Treated With IHP |
|-----------------------------------------------|--------|--------|--------|--------|
| Treatment                             | n*     | CR     | PR     | %      | Hepatic PFS (m) |
|-----------------------------------------------|--------|--------|--------|--------|
| Overall                                     | 114    | 2      | 67     | 59     | 7.0            |
| IHP (no HAI)                                | 58     | 0      | 33     | 57     | 5.8            |
| IHP (HAI)                                   | 46     | 2      | 30     | 65     | 13.0*          |
| IHP (TNF alone)                             | 10     | 0      | 4      |        | 3.0            |

*Evaluable for response.

*P < 0.001 vs. IHP (no HAI) and IHP (TNF alone).

### Peritoneal Metastases (PM)

- PM late manifestation of advanced cancer of various tumor types
- Poor prognosis and outcomes (avg 6 mos. survival)
- Significant treatment challenge
- Limited options

### Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Peritoneal Metastases

- Historical therapy: Chemotherapy, radiation, and palliative surgery
- Aggressive surgical approach: Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC)
- Utilized in very select patients with different tumor types (incl. colon, appendix)
Cytoreductive Surgery (CRS)/HIPEC

• 2 Major components to surgery
  • Cytoreductive surgery (CRS)
    • Address gross (visible) peritoneal tumor burden
    • Goal is to eliminate all gross disease (<2.5mm)
  • HIPEC
    • Address microscopic peritoneal disease after CRS
    • Regional perfusion utilizing hyperthermia and high dose chemotherapy

CRS

• Major Surgery
• Eliminate all gross tumor
  • May require peritonectomies
  • Multi-visceral (organ) resection sometimes necessary
• Completeness of cytoreduction important to outcome
• Increased morbidity and mortality
### CRS: Completeness of cytoreduction

- Major determinant of survival
- Glehen et al. – Multi-institutional study of 506 pts receiving CRS/HIPEC
  - Overall median survival 19.2 mos
  - Complete CRS/HIPEC median survival 32.4 mos
  - Incomplete survival 8.4 months
  - $P<0.0001$

Glehen et al. JCO 2004

### CRS: Predictive factors for success

- Peritoneal Surface Malignancy Group determined 8 predictive factors
  - ECOG $\leq 2$
  - No evidence of extra-abdominal disease
  - $\leq 3$ small, resectable liver metastases
  - No biliary obstruction
  - No ureteral obstruction
  - No bowel obstruction $> 1$ site
  - SB involvement
  - Small disease within lesser omentum

<table>
<thead>
<tr>
<th>HIPEC</th>
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| • Hyperthermia  
  • More toxic to cancer cells  
  • Potentiates cytotoxic effects of chemotherapy  
  • Direct effect on tumor tissue to soften the tissue and decrease interstitial pressure to improve chemotherapy penetration  
  • High dose chemotherapy administration with decreased systemic toxicity  
  • Continuous circulation of heated chemotherapy throughout the abdominal/peritoneal cavity |

![Image of HIPEC procedure]
CRS/HIPEC Complications

- Potential significant complications
- Surgical morbidity 22.9%
- Mortality 4%

<table>
<thead>
<tr>
<th>Type of Complication</th>
<th>No.</th>
<th>%</th>
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<tbody>
<tr>
<td>Digestive fistula</td>
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<tr>
<td>Hematologic toxicity</td>
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<td>2.4</td>
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<td>Systemic sepsis</td>
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<td>2</td>
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<td>Postoperative bleeding</td>
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<td>1.8</td>
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<tr>
<td>Intra-abdominal abscess</td>
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<td>1.8</td>
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<tr>
<td>Respiratory distress</td>
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<td>1.6</td>
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<tr>
<td>Pneumonia</td>
<td>8</td>
<td>1.6</td>
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<tr>
<td>Urinary fistula</td>
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<td>1</td>
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<tr>
<td>Line sepsis</td>
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<tr>
<td>Bowel obstruction</td>
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<tr>
<td>Pulmonary embolism</td>
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<tr>
<td>Peritonitis</td>
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<tr>
<td>Mortality</td>
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<td>4</td>
</tr>
</tbody>
</table>

Glehen et al. JCO 2004

HIPEC vs. Chemotherapy

- Verwaal et al. showed survival advantage for patients with colorectal PC
  - Median survival 22.3 months (CRS/HIPEC/Chemo-5-FU/Leucovorin)
  - Median survival 12.6 months for chemotherapy with or without palliative surgery
  - P=0.032
  - Selection bias?

Verwaal et al. JCO 2003
**HIPEC vs. Chemotherapy**

- **Elias et al. Case control study of 96 patients**
- **CRS/HIPEC (Oxaliplatin) vs. Modern chemotx (Oxaliplatin/Irinotecan)**
- **Median Survival**
  - CRS/HIPEC 62.7 mos.
  - Chemotherapy 23.9 mos.
  - P<0.05

**CRS/HIPEC Summary**

- **May be an effective therapy in well selected patients with colorectal cancer and GI tumors**
- **Complete cytoreduction paramount**
- **Major morbidity/mortality associated with aggressive surgical approach**
- **Multidisciplinary approach necessary in decision making**