


Colorectal Cancer
EXPANDING TREATMENT OPTIONS

*A continuing education seminar
for nurses and pharmacists*

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**Understanding Fundamental
Concepts in Colorectal Cancer
Disease Prevention, Diagnosis,
and Treatment**

Generalist Module

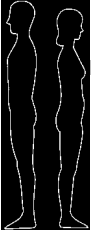
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Session Overview

- Review current knowledge of colon cancer, including risk factors, screening guidelines, pathophysiology, and staging
- Describe nationally accepted standards of practice and care for management of patients with colon cancer
- Differentiate among treatment options for colon cancer in both adjuvant and metastatic settings
- Through case study analysis, illustrate selected aspects of nursing management of patients undergoing active therapy for colon cancer, including treatment decision making, assessment, and symptom management interventions

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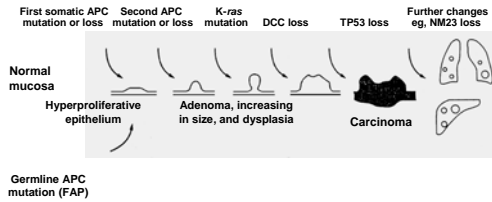
Cancer Incidence and Mortality: 2006 ACS Projections

	Cases	Deaths		Cases	Deaths	
Prostate	234,460	27,350		Breast	212,920	40,970
Lung & bronchus	92,700	90,330		Lung & bronchus	81,770	72,130
Colon & rectum	72,800	27,870		Colon & rectum	75,810	27,300
Urinary bladder	44,690	8,990		Uterine corpus	41,200	7,350
Lymphomas	34,870	10,770		Lymphomas	31,800	9,560
Melanoma	34,260	5,020		Melanoma	27,930	2,890
Kidney & renal pelvis	24,650	8,130		Ovary	20,180	15,310
Leukemia	20,000	12,470		Pancreas	16,580	16,210
Pancreas	17,150	16,090		Urinary bladder	16,730	4,070
All sites	720,280	291,270		All sites	679,510	273,560

Data from the ACS. Cancer facts and figures 2006.

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CRC Development: Adenoma-to-Carcinoma Sequence



Adapted from Bishop and Hall. *Eur J Cancer*. 1994;30A:1946-1956, with permission.

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Nonmodifiable Risk Factors

Personal History

- Age > 50 years
- Ethnicity
- Inflammatory bowel disease
- History of colonic polyps
- Inherited genetic abnormality

Family History

Relative Risk

1 first-degree relative with CRC	2.3
≥ 1 first-degree relatives < 45 y	3.9
≥ 2 first-degree relatives with CRC	4.3
≥ 1 first-degree relatives with colorectal adenoma	2.0

Johns and Houlston. *Am J Gastroenterol*. 2001;96:2992-3003.
Lindblom. *Curr Opin Oncol*. 2001;13:63-69.
NCI. Genetics of colorectal cancer (PDQ).

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Modifiable Risk Factors

Factors	Relative Risk	Strength of Evidence
Obesity (BMI > 27 vs < 21)	1.5	Definite
Eating red meat (≥ 7 servings/wk vs 1 serving/mo)	1.5	Probable
Smoking (≥ 25 cigarettes/d vs none)	1.5	Possible
Alcohol (> 1 drink/d vs none)	1.4	Probable

Colditz et al. *Cancer Causes Control*. 2000;11:477-488.
ACS. Colorectal cancer facts and figures: special edition 2005.

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National Screening Guidelines: Average Risk ≥ 50 Years

Test/Procedure	Frequency
FOBT or FIT*	Annually starting age 50
FSIG (60-cm or longer scope)	Every 5 y starting age 50
FOBT or FIT plus FSIG: preferred to either alone	Annual FOBT or FIT and FSIG every 5 y starting age 50
Colonoscopy	Every 10 y, starting age 50 and as follow-up if other screening tests are abnormal
DCBE	Every 5 y, starting age 50

*FIT added by ACS in 2002 and included in the American Academy of Family Physicians Practice Guidelines, 2005.
ACS. Guidelines for the early detection of cancer 2005.

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Presenting Signs and Symptoms Related to Tumor Location





- Transverse colon tumors
 - Occult blood in stool
 - Constipation, abdominal fullness
 - Cramping abdominal pain
- Ascending colon tumors
 - Dull, abdominal pain
 - Palpable mass in right lower quadrant of abdomen
 - Melena
 - Anemia, malaise, indigestion, weight loss
- Descending colon tumors
 - Change in bowel habits
 - Cramps, flatulence
 - ↓ Stool caliber
 - Bright red blood in stool
 - Incomplete stool evacuation
- Sigmoid colon and rectal tumors
 - Bleeding
 - Tenesmus



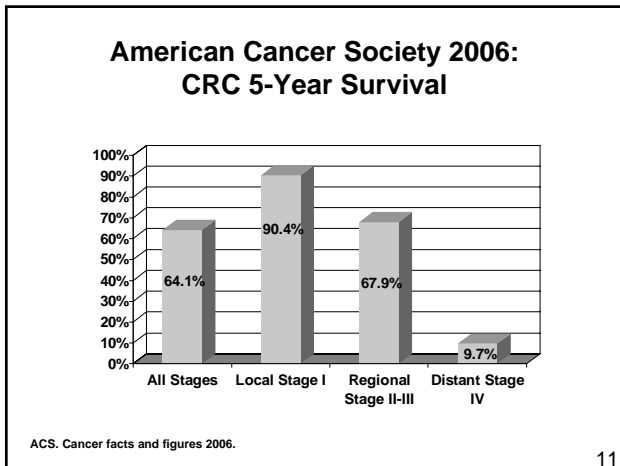
Sargent and Murphy. *Nursing*. 2003;33:36-41.

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CRC Management Overview by Stage

<p>Stage I (T1 or 2 N0 M0)</p>  <p>Routine surveillance only</p>	<p>Stage III</p> <table border="0"> <tr> <td style="text-align: center;">A T1-2 N1 M0</td> <td style="text-align: center;">B T3-4 N1 M0</td> <td style="text-align: center;">C Any T N2 M0</td> </tr> </table>  <p>Adjuvant therapy: options include FOLFOX, FLOX, 5-FU/LV, capecitabine</p>	A T1-2 N1 M0	B T3-4 N1 M0	C Any T N2 M0
A T1-2 N1 M0	B T3-4 N1 M0	C Any T N2 M0		
<p>Stage IIA or B (T3 or T4 N0 M0)</p>  <p>Consider adjuvant therapy, depending on risk factors or Clinical trial or Observation</p>	<p>Stage IV (any T/N + M1)</p>  <p>Manage sequentially with chemotherapy or BSC, depending on patient ability to tolerate aggressive therapy</p>			

FLOX = bolus 5-FU and oxaliplatin; FOLFOX = infusional 5-FU, LV, and oxaliplatin. NCCN. Clinical practice guidelines in oncology: colon cancer, v.2.2006.



Drug Treatments for CRC: Antineoplastic and Targeted Agents

- 5-FU
- Irinotecan
- Oxaliplatin
- Capecitabine
- Bevacizumab
- Cetuximab

Side Effect Profiles

5-FU	Diarrhea, mucositis, myelosuppression, nausea and vomiting, HFS
Irinotecan	Diarrhea, mucositis, myelosuppression, nausea and vomiting
Oxaliplatin	Myelosuppression, nausea and vomiting, acute and cumulative neuropathies, some reports of extravasation injury
Capecitabine	Diarrhea, myelosuppression, nausea and vomiting, abdominal pain, HFS, hyperbilirubinemia
Bevacizumab	Hypertension, proteinuria, wound dehiscence, arterial thrombosis, hemorrhage
Cetuximab	Skin rash, hypersensitivity reaction, electrolyte imbalance

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Treatment Decision Making: More Difficult Issues for Consideration



- **Patient issues**
 - Preferences
 - Physical status
 - Comorbidities
 - Past regimens
- **Regimen issues**
 - Response rates
 - Survival time
 - Toxicity profile
- **Quality of life issues**
 - Cost and reimbursement
 - Complexity (ie, need for venous access)
 - Access and convenience
 - Lifestyle issues

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Management of Advanced CRC: A Changing Picture

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Trends in Metastatic CRC Survival With Treatment Advances

Reference	Treatment Status	Median Survival
Scheithauer et al, 1993	Before any active chemotherapy (BSC)	→ 6 mo
Cochrane library	Fluoropyrimidine only	→ 10–12 mo
Saltz et al, 2000 de Gramont et al, 2000	Fluoropyrimidine and 1 other active cytotoxic chemotherapeutic agent (irinotecan or oxaliplatin)	→ 14–16 mo
Goldberg et al, 2004	Fluoropyrimidine, irinotecan, and oxaliplatin (in combination or as sequential therapy)	→ > 20 mo
Hurwitz et al, 2004	Cytotoxic chemotherapy and targeted therapy	→ > 20 mo

From Meyerhardt and Mayer. *N Engl J Med.* 2005;352:476-487, with permission.

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FDA Approvals of Chemotherapy for Metastatic CRC

- 1960s 5-FU used for CRC
 - 1980s 5-FU/LV used to prolong survival
 - 1996 Irinotecan receives accelerated approval for second-line therapy (full approval received in 1998)
 - 2000 Irinotecan + bolus or infusional 5-FU/LV for first-line therapy
 - 2001 Capecitabine for first-line therapy
 - 2002 Oxaliplatin + infusional 5-FU/LV for second-line therapy
 - 2004 Oxaliplatin + infusional 5-FU/LV for first-line therapy
- ↓
- Cetuximab + irinotecan or cetuximab alone if irinotecan not tolerated for second-line therapy
 - Bevacizumab + IV 5-FU–based chemotherapy for first-line therapy

US FDA. Listing of approved oncology drugs with approved indications. Available at: <http://www.fda.gov/cder/cancer/druglistframe.htm>.

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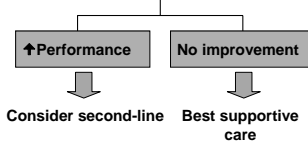
NCCN Treatment Guideline Summary: Chemotherapy Options for Metastatic Colon Cancer*

Can Tolerate Intensive Therapy

- **First-line therapies**
 - FOLFOX or FOLFIRI or IFL or 5-FU/LV or CAPOX + bevacizumab
- **Second-line therapies**
 - Irinotecan ± cetuximab
 - FOLFOX
 - FOLFIRI
- **Third-line therapies**
 - Irinotecan ± cetuximab
 - FOLFOX

Cannot Tolerate Intensive Therapy

- **First-line therapies**
 - Capecitabine
 - Bolus 5-FU + LV ± bevacizumab
 - Infusional 5-FU ± LV ± bevacizumab
 - Protracted 5-FU ± LV



*For detailed and specific information about NCCN treatment recommendations for colon cancer, review the NCCN clinical practice guidelines for colon cancer, v.2.2006. CAPOX = capecitabine and oxaliplatin; FOLFIRI = irinotecan plus modulated infusional 5-FU/LV; IFL = irinotecan plus bolus 5-FU/ LV.

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**First-Line Therapies for Metastatic CRC:
2006 Update**


- Approaches examined
 - Addition of targeted therapies
 - Application of oral fluoropyrimidine
- Specific clinical trials
 - Cetuximab + FOLFOX or FOLFIRI
 - Bevacizumab + standard chemotherapy
 - XELOX (capecitabine + oxaliplatin)
 - Oxaliplatin + fluoropyrimidines (all routes) ± bevacizumab

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**Adjuvant Therapy for CRC:
New Hope for Cure**

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**Adjuvant Therapy for CRC:
A Chronology of Developments**

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- 1990 5-FU/levamisole better than surgery alone
 - 1994 5-FU/LV better than surgery alone
 - 1998 5-FU/LV better than 5-FU/levamisole
 - Treatment duration ↓ to 6 months
 - Levamisole eliminated; low-dose LV sufficient
 - Monthly treatments equivalent to weekly
 - 2002 Semimonthly 5-FU/LV = monthly bolus 5-FU/LV
 - 2004 5-FU/LV + oxaliplatin = survival advantage in stage III
Bolus 5-FU/LV + irinotecan = no survival advantage in stage III
 - 2005 Capecitabine receives adjuvant indication from FDA
 - 20?? Tailored therapies by molecular/pathologic characteristics

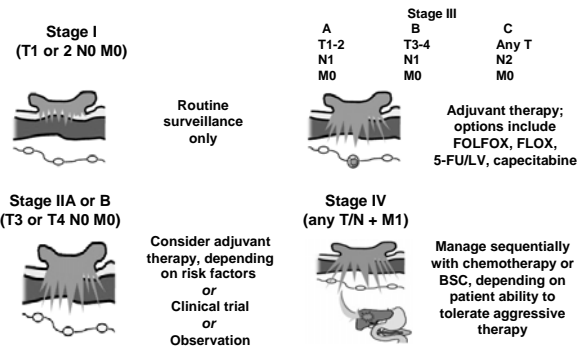
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Key Clinical Trials Supporting National Standards for Adjuvant Therapy

Study	Treatment Schema	Results
MOSAIC (N = 2,246)	Arm A: 5-FU/LV + oxaliplatin Arm B: 5-FU/LV	FOLFOX improved DFS and OS with ↑ AEs
X-ACT (N = 1,969)	Arm A: capecitabine Arm B: bolus 5-FU/LV	Capecitabine slightly superior to 5-FU/LV with ↓ AEs except for HFS and ↓ bilirubin
NSABP C-07 (N = 2,492)	Arm A: 5-FU/LV Arm B: FLOX	Adding oxaliplatin improves 3-year DFS in stage II/III patients with ↑ grade 3/4 diarrhea and neurotoxicity
CALGB C89803	Arm A: 5-FU/LV (Roswell) Arm B: bolus IFL	IFL of no benefit in stage III CRC with ↑ AEs
PETACC-3 (N = 3,278)	Arm A: FOLFIRI Arm B: LV5FU2	Primary end point of DFS did not differ for stage III disease between study arms; secondary pooled analysis showed Irinotecan ↑ efficacy of LV5FU2 population of stage II/III patients

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CRC Management Overview by Stage



FLOX = 5-FU and oxaliplatin; FOLFOX = 5-FU, LV, and oxaliplatin.
NCCN. Clinical practice guidelines in oncology: colon cancer, v.2.2006.

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NCCN Treatment Guidelines Summary: Adjuvant Therapy Options for Colon Cancer*

- For patients with T3, N0, M0 (without high risk) consider
 - 5-FU/LV or FOLFOX or FLOX or capecitabine
 - Clinical trial or observation*
- For patients with T3 (high-risk) or T4, N0, M0
 - 5-FU/LV or FOLFOX or FLOX or capecitabine
 - Clinical trial
 - Observation
- For patients with T1-4, N1-2, M0
 - 5-FU/LV or FOLFOX or capecitabine
- For patients with resectable liver or lung metastases – Stage IV
 - BV plus either FOLFOX, FOLFIRI, IFL, 5-FU/LV, or CAPOX
 - HAI ± 5-FU/LV or infusional 5-FU†
 - Observation if patient received neoadjuvant therapy

*For detailed and specific information about NCCN treatment recommendations for colon cancer, review the NCCN clinical practice guidelines for colon cancer, v.2.2006.
†For liver metastasis only.

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High-Risk Factors for Recurrent CRC

- Grade 3/4 histology
- Lymphatic or vascular invasion
- Presents with bowel obstruction
- < 12 lymph nodes examined
- Stage IIB (T4 N0 M0)
- Stage IIA with localized perforation or close, indeterminate, or positive margins

Benson et al. *J Clin Oncol*. 2004;22:3408-3419.
NCCN. Clinical practice guidelines in oncology: colon cancer, v.2.2006.

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Optimizing Patient Outcomes: A Case-Based Dialogue



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Case Presentation: M.M. Treatment Decision Making



- 68-year-old anxious man with 6-lb weight loss, pencil-thin stools, rectal bleeding for 1 year
- Consults GI specialist at urging of friend whose father was just diagnosed with advanced CRC
- Undergoes colonoscopy (positive for malignancy) and surgical resection for CRC
- Diagnosed with stage IIIC (T4 N2 M0) colon cancer
- Referred to medical oncologist for adjuvant chemotherapy

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Case Presentation: Pathology and Staging

- M.M.'s pathology report :
 - Tumor: 3-cm mass in the sigmoid colon that extends through muscle, with peritoneal invasion
 - Nodes: 5 of 12 positive lymph nodes
 - Metastasis: no evidence of distant spread of disease



Stage of disease?
T4 N2 M0 (stage IIIC)

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Case Presentation: Patient History

- **Family history:** negative for CRC and other malignancies
- **Social history:** widower living alone in a rural setting
- 4 children alive and well; all living within a 50-mile radius
- Retired elementary school teacher living on pension and Medicare
- Enjoys visits with grandson
- **Comorbidities:** physically active man with mild hypertension controlled with calcium channel blocker



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Case Presentation: Treatment Decision-Making Considerations

Question: What therapeutic options would you expect the medical oncologist to recommend and why?

- **What approach?**
 - Surveillance versus adjuvant chemotherapy?
- **Which regimen?**
 - 5-FU/LV or FOLFOX or FLOX or capecitabine?
 - Clinical trial or observation?
- **What influencing factors?**
 - Regimen efficacy, side effect profile?
 - Cost and convenience?

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Interventions to Enhance Informed Consent Communications

- Assessment parameters
 - Desired level of information and main concerns
 - Personal goals related to cancer treatment
 - Level of understanding and misperceptions
 - Members of support network
- Interventions
 - Arrange meeting with patient, designated caregiver, and health care team network members
 - Assist in creating question list for treatment discussion with health care providers
 - Provide verbal summary of treatment options presented by health care team
 - Offer print material or taped discussion as reinforcement
 - Offer Internet tools (eg, ACS Nexprofiler, Adjuvant.com, NCCN guidelines for patients) for patients with computer skills
 - Listen carefully; do not put words in your patient's mouth
 - Home management education

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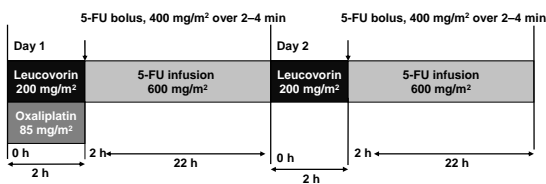
Case Presentation: Treatment Selection

- M.M. elects to undergo FOLFOX4 as adjuvant therapy after talking with a friend who had just completed therapy
- His children arrange to provide transportation and accompany him on treatment visits
- He is extremely nervous but wishes to proceed



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FOLFOX4



André et al. *N Engl J Med.* 2004;350:2343-2351.

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**NCI Common Terminology Criteria:
Diarrhea**

Severity Grade	1	2	3	4	5
Diarrhea without colostomy	Increase of < 4 stools/d over baseline	Increase of 4-6 stools/d over baseline; IV fluids indicated for < 24 h; not interfering with ADL	Increase of ≥ 7 stools/d over baseline; incontinence; IV fluids indicated for ≥ 24 h; hospitalization; interferes with ADL	Life-threatening consequences (eg, hemodynamic collapse)	Death
Diarrhea with colostomy	Mild increase in ostomy output compared with baseline	Moderate increase in ostomy output compared with baseline, but not interfering with ADL	Severe increase in ostomy output compared with baseline, hospitalization; interferes with ADL	Life-threatening consequences (eg, hemodynamic collapse)	Death

NCI CTCAE v3.0.

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Side Effect Management: Diarrhea

Acute-onset diarrhea

- Cholinergic mechanism
- Symptoms: rhinitis, salivation, miosis, lacrimation, abdominal cramping
- Treatment: symptomatic with atropine 0.25-1 mg

Delayed-onset diarrhea

- Changes in intestinal mucosa produce an imbalance between secretion and absorption of water and electrolytes
- Treatment is based on character of diarrhea (ie, uncomplicated vs complicated presentation)

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**Recommended Guidelines for
Chemotherapy-Induced Diarrhea**

- Uncomplicated cases
 - Loperamide 4 mg orally at the first episode, then 2 mg every 2-4 hours until improvement
 - If diarrhea persists for more than 24 hours, administer antibiotic therapy
- Complicated cases: aggressive management
 - Hospitalization/IV fluids/octreotide/antibiotics
 - Restart chemotherapy at reduced doses

Benson et al. *J Clin Oncol*. 2004;22:2918-2926.
Saltz. *J Support Oncol*. 2003;1:35-46.

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Case Presentation: Diarrhea

Case Review

- M.M. reports experiencing watery stools, 6–7 episodes per day with stomach cramps; it awakens him during the night
- He hasn't been able to get out to accomplish his errands
- He forgot what the nurse told him before he started his therapy and took some paregoric that was in the medicine cabinet for quite a while, but it didn't help him

Question: Based on your assessment findings, what instructions will you give M.M. for managing his diarrhea?

- **What severity grade?**
 - Grade 1/2 (mild-moderate) vs grade 3/4 (severe)
 - Uncomplicated vs complicated
- **What instructions?**
 - Antidiarrheals? Diet and fluids? Other?

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Side Effect Management: Mucositis

Scales for the Assessment of Mucositis

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
WHO	Painless ulcers, erythema, or mild soreness	Painful erythema, edema, or ulcers, but can eat solids	Painful erythema, edema, or ulcers and cannot eat solids	Mucositis to the extent that alimentation is not possible	
CTCAE v3.0 (clinical exam)	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
CTCAE v3.0 (functional/symptomatic)	Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function	Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL	Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death

Van Gerpen. *Oncol Support Care Q*. 2005;3(2):4-10.

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Side Effect Management: Neurotoxicity

Acute Onset

- Early: 1st 2 h–2 d
- 65% of patients
- Precipitated by cold exposure
 - Dysesthesias and paresthesias
 - Buccal and pharyngolaryngeal areas
 - Tightness in back of throat
 - Distal extremities
 - Muscle cramping
 - Jaw spasm
- Resolves within 14 d; may occur with subsequent cycles

Cumulative

- Later: after 6–10 cycles with cumulative dose \geq 540 mg/m²
- 57% of patients
- Similar to cisplatin effects
 - Hand or foot numbness, tingling
 - Interferes with ADL—using button and zippers
 - Difficulty walking from impaired proprioception
 - Tandem gait and Romberg's positive
- Usually resolves in 6–12 mo

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NCI Common Terminology Criteria: Neuropathy—Sensory

Grade	Symptoms
1	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function
2	Sensory alteration or paresthesia (including tingling) interfering with function but not interfering with ability to perform ADL
3	Sensory alteration or paresthesia (including tingling) interfering with ability to perform ADL
4	Disabling
5	Death

NCI CTCAE v3.0.

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Side Effect Management: Acute Sensory Neuropathy

Patient Teaching Points

- Present potential
- Describe possible symptoms
- Discuss management approaches
- Present prevention strategies involving avoidance of cold exposure

Interventions

- Assessment
 - Check vital signs to distinguish PLD from HSR
 - Use grading scale to describe
 - Monitor for possible aspiration
- Actions
 - *Prevention:* consider calcium gluconate and magnesium sulfate infusion pre- and post-chemotherapy
 - *Management:* keep patient calm and offer warm blanket; manage with appropriate supportive care

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Side Effect Management: Patient Education for Cold Dysesthesias

- Avoid cold weather, when possible
- Wear mittens, socks, shoes, hat, scarf
- Avoid breathing deeply in cold air or when opening freezer or refrigerator
- Wear gloves when reaching into freezer or refrigerator
- Avoid cold beverages, ice chips, and frozen foods
- Enter preheated car
- Avoid excessive air conditioning



Wilkes. Clin J Oncol Nurs. 2002;6:131-137.

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Side Effect Management: Cumulative Sensory Neuropathy

Patient Teaching Points

- Present potential
- Describe possible functional impairment
- Explain that symptoms
 - Usually regress between cycles but tend to last longer with subsequent doses
 - Usually resolve within 4–6 months
- Discuss safety measures
 - Avoid heat exposure
 - Use caution with dangerous activities (driving, using machinery, etc)

Interventions

- Assessment
 - Baseline neuroassessment
 - Neuroassessment after each cycle using grading scale
- Actions
 - Teach measures to prevent injury and manage symptoms
 - Increase infusion time from 2 to 6 hours as prescribed
 - Reduce or delay dose, or discontinue treatment based on grade of toxicity as prescribed

Wilkes. *Clin J Oncol Nurs*. 2002;6:131-137.
Wilkes. *Clin J Oncol Nurs*. 2005;9:31-44.

Side Effect Management: Patient Education for Cumulative Sensory Neuropathy

Prevention Strategies

- Assess home water temperature; use tepid water
- Use protective gloves when washing dishes
- Use pot holders when cooking
- Clothing: wear cotton socks, gloves in cold temperatures
- Lighting: ensure well-lit rooms without glare
- Environment: clear walkways; use nonskid showers and tub mats

Management Strategies

- Nonpharmacologic interventions
 - Exercise
 - Hydrotherapy
 - Massage, magnets, acupuncture
 - Meditation and relaxation
 - Electrotherapy: transeletrical nerve stimulation
 - Dietary supplements and diet
 - Home remedies
- Pharmacologic interventions
 - Topical/opioid analgesics

Cumulative Sensory Neuropathy: Innovative Prophylactic Strategies

- Neuroprotectant - xaliproden
- OPTIMOX study: "stop and go" strategy
 - Stop
 - After predefined cumulative oxaliplatin dose (ie, 6 cycles) or
 - When sensory neurotoxicity of certain grade develops
 - Go
 - At predefined reinitiation points (ie, 12 cycles of maintenance therapy)
 - When sensory neuropathy has regressed or
 - Before tumor progresses to baseline measure

André et al. *Proc Am Soc Clin Oncol*. 2003;22:253. Abstract 1016.
de Gramont et al. *J Clin Oncol*. 2004;22(suppl):251s. Abstract 3525.
Cassidy et al. *J Clin Oncol*. 2006;24(suppl, pt 1):147s. Abstract 3507.



Cumulative Sensory Neuropathy: Innovative Prophylactic Strategies

- **OPTIMOX1** – strategy of 5-FU/LV maintenance as active and better tolerated than FOLFOX4 until disease progression
- **OPTIMOX2** – no maintenance resulted in no survival advantage, however, chemotherapy-free interval may improve quality of life
- **Xaliproden** – oral nonpeptide neurotrophic agent to minimize neuritic damage
 - Significant reduction in risk of grade 3/4 sensory neuropathy without affecting FOLFOX4 efficacy

André et al. *Proc Am Soc Clin Oncol*. 2003;22:253. Abstract 1016.
de Gramont et al. *J Clin Oncol*. 2004;22(suppl):251s. Abstract 3525.
Cassidy et al. *J Clin Oncol*. 2006;24(suppl, pt 1):147s. Abstract 3507.

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Case Presentation: Neurotoxic Effects

Case Review:

- After the 4th cycle of FOLFOX4, the nurse notes that M.M. is having trouble walking; examination reveals loss of deep tendon reflexes
- On further assessment, M.M. reports glove-and-stocking paresthesias of his upper extremities that interfere with his ability to button his shirt
- He also tells the nurse that he cannot hold the paintbrush to help his grandson with his model planes

Question: What patient care plan will you initiate for M.M.'s neurotoxic effects?

- **What type and grade of neurotoxic effect?**
 - Distinguish between acute and cumulative effects
- **What pharmacologic interventions?**
 - Agents versus administration techniques
- **What patient education instructions?**

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Side Effect Management: HSRs

- Etiology of HSR unclear; no single biologic pathway identified
- Present as 4 different types; type I is most commonly associated with chemotherapy
- Onset usually acute (hypersensitivity), but delayed onset possible (idiosyncratic)
- Manifestations unpredictable with variable severity
- Premedication and desensitization are 2 management approaches, but results are primarily case reports

Gobel. *Oncol Nurs Forum*. 2005;32:1027-1035.
Bonosky and Miller. *Clin J Oncol Nurs*. 2005;9:325-331.

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NCI Common Terminology Criteria: HSRs

Adverse Event	Short Name	1	2	3	4	5
Allergic reaction/hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever 38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death

*Urticaria with manifestations of allergic or hypersensitivity reaction is graded as allergic reaction/hypersensitivity (including drug fever).
NCI CTCAE v3.0.

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Side Effect Management: HSRs

Grade 1/2 (Mild-Moderate)

- Symptoms
 - Hives
 - Rash
 - Fever
 - Itch
 - Anxiety
- Actions
 - Medicate: acetaminophen, diphenhydramine
 - Monitor vital signs q 15 min
 - Resume IV as prescribed

Grade 3/4 (Severe)

- Symptoms
 - May present with a variety of symptoms
 - Anxiety, dizziness, shortness of breath, bronchospasm, nausea and vomiting
- Actions
 - Stop drug infusion
 - Bolus NSS to maintain blood pressure
 - Administer O₂ therapy
 - Medicate: diphenhydramine, corticosteroids, epinephrine, bronchodilators
 - Cardiovascular support
 - Do not rechallenge!

Bonosky and Miller. *Clin J Oncol Nurs*. 2005;9:325-331.
Gobel. *Oncol Nurs Forum*. 2005;32:1027-1035.

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Case Presentation: HSRs

- During M.M.'s initial infusion of oxaliplatin, he suddenly becomes anxious after drinking a glass of water and tells the nurse that he is having trouble breathing and feels that his throat is "closing up"
- On rapid assessment, hypotension and tachycardia along with wheezing are noted. M.M. also has generalized erythema and is diaphoretic

Question: What are the most important actions to take in this situation?

- **What effect?**
 - Distinguish between PLD and HSR
- **What action?**
 - Stop infusion vs warm drinks
- **What plan for future therapy?**
 - Premedication

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Side Effect Management: Extravasation

Prevention

- Use central line or infusion port if available
- Monitor continuously if administering via peripheral line

Intervention

- At first patient complaint of pain or other findings, **stop the infusion**
- Follow institutional guidelines for extravasation management
- Report and document findings



Brown et al, eds. *ONS Chemotherapy and Biotherapy Guidelines and Recommendations for Practice*. Oncology Nursing Society; 2001.

Case Presentation: Capecitabine-Related HFS/PPE



- 77-year-old woman diagnosed with stage IIIB colon cancer
- Adjuvant therapy with single-agent capecitabine initiated
- History and physical examination
 - No family history of CRC, but she wants her children to have appropriate screening
 - Visual and hearing acuity poor
- Social history
 - Married, 3 children with their own families living in the area
 - Homemaker and caretaker for 2 of her 3 grandchildren

Side Effect Management: HFS/PPE

- Also known as palmar-plantar erythrodysesthesia (PPE)
- Occurs in 56% of patients receiving capecitabine and 34% of patients undergoing protracted 5-FU infusions
- Thought to be caused by crushing injury to deep capillaries
- Observed most commonly on soles and palms but may occur at any body site exposed to pressure
- Risk is heightened by heat exposure and repetitive pressure to the site
- Can progress from neurosensory effects only to moist desquamation and severe pain

Wilkes. *Clin J Oncol Nurs*. 2002;6:131-137.
Viale. *Clin J Oncol Nurs*. 2005;9:541-552.

Toxicity Grading Scale: HFS/PPE



Grade 1—numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema and/or discomfort of hands or feet not disrupting normal activities



Grade 2—painful erythema and swelling of hands or feet and/or discomfort affecting ADL



Grade 3—moist desquamation, ulceration, blistering or severe pain of hands or feet or severe discomfort preventing work or performance of ADL

Slides courtesy of Cheryl Moore, RN, Cancer Center of Boston. Blum et al. *J Clin Oncol.* 1999;17:485-493.

Side Effect Management: Capecitabine-Related HFS/PPE

Patient Teaching Points

- Notify MD or RN immediately if palms/soles become red or tender
- *Take medications as prescribed; do not make up missed doses*
- Reduce friction and heat exposure (short tepid bathing/showers)
- Reduce pressure on hands and feet
- Avoid extreme weather changes
- Use cool temperatures to relieve tenderness
- Gently apply emollients (eg, Bag Balm)
- Teach caregiver to assess for redness and color changes in skin

Intervention

- Assessment
 - Conduct baseline and follow-up using grading scale
 - Provide graphic scale to patient
- Action
 - Decrease dose and/or cycle frequency (eg, 21- to 28-day cycle)
 - Grade 2 or 3—interrupt therapy until event resolves or reduces to grade 1
 - Consider pyridoxine (vitamin B₆) and topical medications

Case Presentation: HFS/PPE

- During a follow-up telephone call after her 2nd cycle of capecitabine, M.T. reports that she has dry cracking skin on her hands and is experiencing so much foot discomfort that she had to buy larger shoes; she is wearing slippers at home. She describes the discomfort as “pins and needles”
- On further investigation you determine that she is taking extra doses of capecitabine to fill in when she forgets to take her evening or morning dose

Question: What is your diagnosis and immediate action plan?

- **What grade?**
 - Mild vs severe
- **Priority intervention?**
 - Treat symptoms vs stop drug
- **Long-term plan?**
 - Compliance strategies

NCI Common Toxicity and Common Terminology Criteria: Skin and Nail Effects

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Dry skin	Asymptomatic	Symptomatic; not interfering with ADL	Interfering with ADL	—	—
Nail changes	Discoloration; ridging (koilonychia); pitting	Partial or complete loss of nail(s); pain in nail bed(s)	Interfering with ADL	—	—
Pruritus/itching	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
Rash/desquamation	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering < 50% BSA	Severe. Generalized erythroderma or macular, papular, or vesicular eruption; desquamation covering < 50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
Rash; acne/acneiform	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death

Modified NCI CTCAE v3.0.
Perez-Soler et al. *Oncologist*. 2005;10:345-356.

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Side Effect Management: Skin and Nail Effects

- Papulopustular eruptions, dry skin, paronychia inflammation

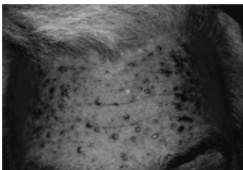


Photo on left courtesy of Howard Hochster, MD, New York University.
Photos on right from Dick and Crawford. *Community Oncol*. 2005;2:492-496, with permission.

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Side Effect Management: Bevacizumab

- Effects may include
 - Proteinuria—risk of nephrotic syndrome
 - HTN
 - Monitor patient
 - Use standard HTN medications
 - Bleeding
 - Often manifested as mild epistaxis
 - Antiangiogenic effect may delay wound healing
 - Interval of 28 days after major surgery before initiating therapy; document surgery date
 - GI perforation rare
 - Arterial thrombosis
 - Overall incidence 4.4%; permanently stop bevacizumab in patients who suffer a severe arterial thromboembolic event

Avastin (bevacizumab) prescribing information.

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CRC Treatment Summary

- Major improvements in the management of metastatic CRC are expanding options for patients
 - Infusional 5-FU superior to IV bolus administration
 - Multiple regimens now available for first-, second-, and third-line therapy
 - Integration of promising new biologic agents (ie, bevacizumab, cetuximab) are significantly improving patient outcomes
 - Paradigm is shifting from individual therapies to a continuum of sequentially introduced therapies
- Clinical trials confirm benefit of adjuvant therapies as standard of care for stage III patients; emerging data support treatment in stage II patients

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CRC Patient Care Summary

- Comprehensive patient assessment and education are vital to optimal treatment outcomes
- Prevention and effective management of treatment-related side effects will increase patient tolerance and encourage continued therapy
- New and more complex treatment regimens will require increasingly knowledgeable and skilled practitioners

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On the Horizon

- **Screening and prevention**
 - Fecal DNA screening
 - Virtual colonoscopy with PET scanning to diagnose and stage
 - Chemopreventive agents?
- **Adjuvant therapy**
 - Clinical trials evaluating risk benefit in stage II patients
- **Molecular profiling**
 - Pharmacogenomics
 - Proteomics
- **Molecularly targeted therapy**
 - Tyrosine kinase inhibitors
 - Gefitinib
 - Erlotinib
 - EGFR inhibitor
 - Panitumumab
 - Antiangiogenesis agents
 - Endostatin
 - VEGF inhibitors
 - Vatalanib
 - Insulin-like growth factors (IGF-1) and IGR binding protein-3 (IGFBP-3)
- **Vaccines**
- **Outcomes prediction**



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**Late-Breaking Update:
Bevacizumab Toxicity—Reversible Posterior
Leukoencephalopathy Syndrome**

- Incidence < 0.1%
- Occurs 16 hours to 1 year following drug administration
- Diagnosis made by MRI

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**Late-Breaking Update:
Bevacizumab Toxicity—Reversible Posterior
Leukoencephalopathy Syndrome (cont)**

- Symptoms
 - Headache
 - Lethargy
 - Confusion
 - Blindness and other visual symptoms
 - Neurologic symptoms

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**Late-Breaking Update:
Bevacizumab Toxicity—Reversible Posterior
Leukoencephalopathy Syndrome (cont)**

- Treatment includes
 - Discontinuation of drug—do *not* rechallenge patient
 - Aggressive antihypertensive management, which has resulted in decreased symptoms

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**Late-Breaking Update:
Bevacizumab Toxicity—
Nasal Septum Perforation**

- Incidence: 9 cases among 63,000 patients receiving this agent

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**Late-Breaking Update:
Panitumumab**

- EGFR-targeted monoclonal antibody
- Approved September 27, 2006, for patients who have failed irinotecan, oxaliplatin, and fluoropyrimidine therapies
- Pivotal trial was a comparison of panitumumab vs best supportive care
- Outcome data
 - Partial response in 19 of the 432 study patients
 - Overall response 8%
 - Patients receiving best supportive care alone allowed to crossover to receive panitumumab; median time to crossover 8.4 weeks

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**Late-Breaking Update:
Panitumumab Side Effects**

- Skin rash
- Paronychia
- Nausea
- Vomiting
- Diarrhea
- Hypomagnesemia occurred 6 weeks or longer after therapy
- Hypersensitivity reactions 3% all grades; < 1% grade 3/4

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End of Presentation

Please click on "close window" below to
return to the main program

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