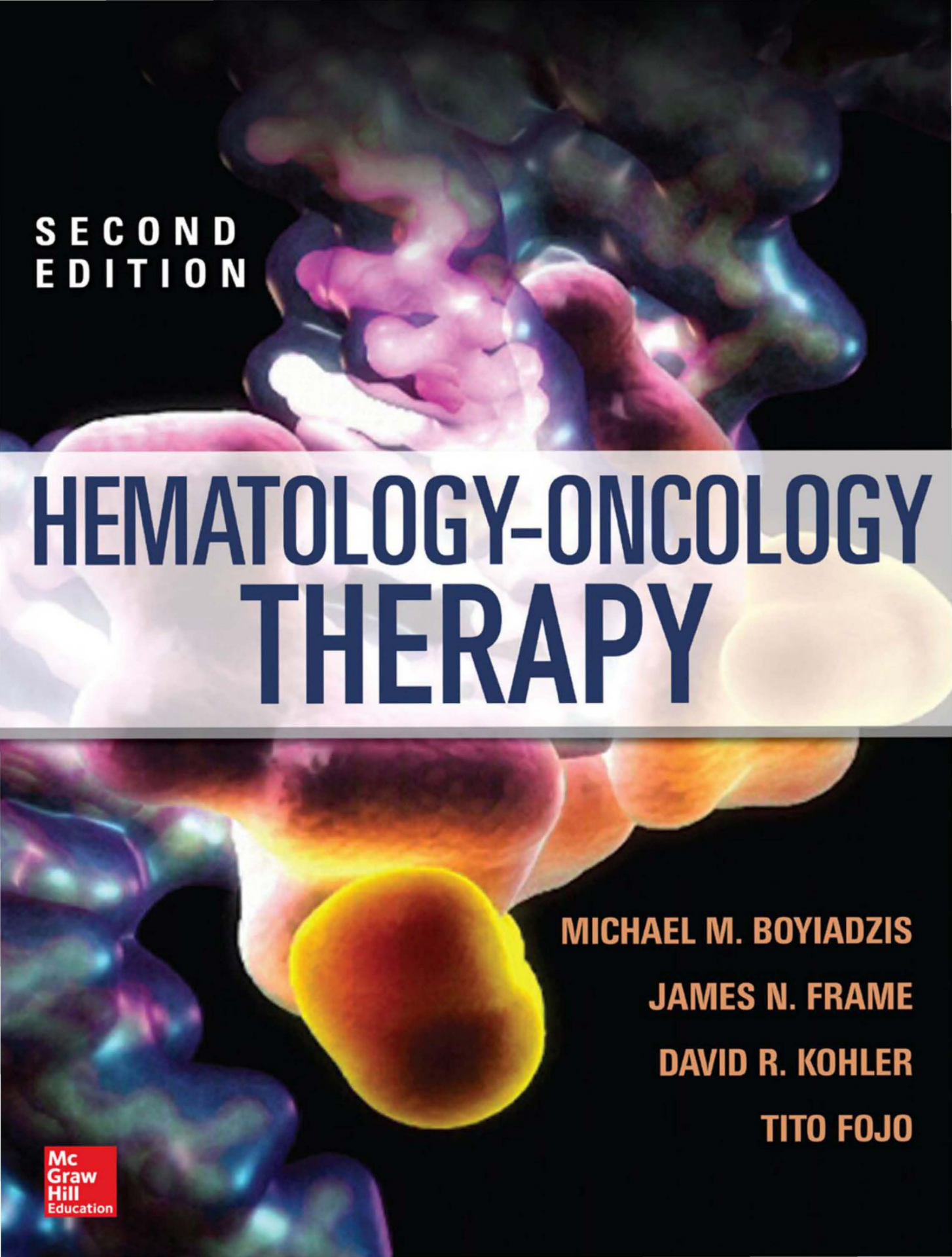
SECOND EDITION
HEMATOLOGY-ONCOLOGY THERAPY
MICHAEL M. BOYIADZIS
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DAVID R. KOHLER
TITO FOJO
Mc Graw Hill Education

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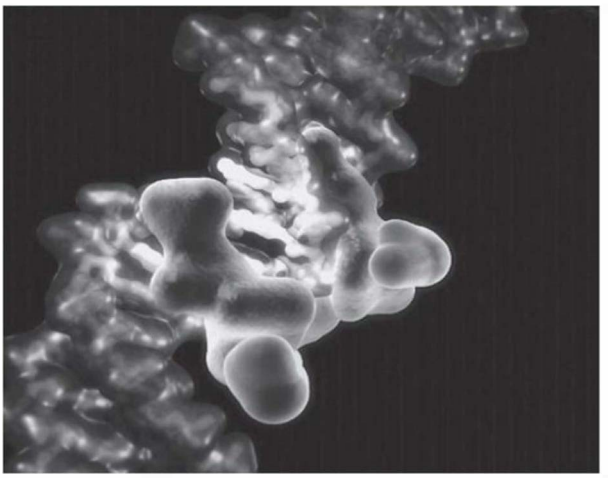

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To the patients our profession has the privilege to serve, and to our colleagues whose compassionate care and research efforts continue to extend the spectrum of hope.

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Contents

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Preface

The practical need for a readily accessible, up-to-date, comprehensive therapy resource, supported by referenced literature, was the original inspiration of the first edition of *Hematology-Oncology Therapy*. The book received considerable acclaim and filled a void in the medical literature as a practical guide and reference for practicing oncologists and hematologists. The rapid and numerous advances in the field of hematology-oncology are reflected in the updated information of this second edition. Over 500 treatment regimens are presented in a concise and uniform format that includes oncologic disorders, non-neoplastic hematologic disorders, and supportive care.

The three sections of *Hematology-Oncology Therapy* are:

I. Oncology
II. Supportive Care, Drug Preparation, Complications, and Screening
III. Selected Hematologic Diseases.

Section I provides detailed information about the administration, supportive care, toxicity, dose modification, monitoring, and efficacy of commonly used and recently approved chemotherapeutic regimens, drugs, and biological agents. Each chapter is focused on a specific cancer, and contains information about epidemiology, pathology, work-up, and staging, as well as survival data. In addition, each chapter has a new feature, Expert Opinion, in which experts in the field provide treatment recommendations and guidance on the use of the included regimens.

Section II consists of topics commonly encountered in clinical hematology-oncology practice. Section III provides an authoritative guide to therapy for principal diseases in consultative hematology.

Hematology-Oncology Therapy integrates extensive information that is critical to both office- and hospital-based clinical practice of hematology and oncology. This comprehensive approach makes the book invaluable to all practitioners involved in the care of patients with cancer or hematologic diseases and complements other excellent book references in hematology-oncology.

We wish to express our appreciation to the many contributors to this book, whose expert knowledge in their fields makes *Hematology-Oncology Therapy* a unique addition to the medical literature. They helped us compile the extensive and detailed therapy information contained in this book, which is a testament to the efforts of so many to improve the treatment of patients with oncologic and hematologic diseases. We also wish to thank our editors at McGraw-Hill for their continued support, patience, and faith in our vision and concept for this book. Their professional support has earned our praise and debt of gratitude. Finally, we would like to thank those with whom we work and those we love for their support during the writing and editing of the second edition.

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SECTION I. Oncology

(Continued on following page)

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(Continued on following page)

1. Adrenocortical Cancer

Peter F. Lebowitz, MD, PhD and Tito Fojo, MD, PhD

Epidemiology

Incidence: 0.5 to 2.0 cases per one million population
Deaths: 0.2% of cancer deaths
Median age: Bimodal median, at age 4 years and ages 40–50 years
Male to female ratio: 1:1.3

Cohn K et al. Surgery 1986;100:1170–1177
Wooten MD, King DK. Cancer 1993;72:3145–3155

Stage at Presentation
Stage I: 3%
Stage II: 29%
Stage III: 19%
Stage IV: 49%

Pathology

1. Unlike renal cell carcinoma, adrenocortical cancer stains positive for vimentin
2. >20 mitoses per HPF—median survival 14 months
   ≤20 mitoses per HPF—median survival 58 months
3. Tumor necrosis—poor prognosis
4. Vascular invasion—poor prognosis
5. Capsular invasion—poor prognosis

Weiss LM et al. Am J Surg Pathol 1989;13:202–206

Survival After Complete Resection

5-Year Actuarial Survival	
Stages I–II	54%
Stage III	24%
1-Year survival	
Stage IV	9%

Icard P et al. Surgery 1992;112:972–980; discussion 979–980
Icard P et al. World J Surg 1992;16:753–758

Work-up

1. CT scan of chest, abdomen, and pelvis to determine extent of disease
2. MRI of abdomen may help to identify and follow liver metastases
3. If IVC is compressed, consider IVC contrast study, ultrasound, or MRI to assess disease involvement before surgical exploration, although apparent extent of involvement should not deter exploration
4. Serum and 24-hour urinary cortisol; 24-hour urinary 17-ketosteroid
5. Additional studies can be performed to determine the functional status of the tumor including: serum estradiol, estrone, testosterone, dehydroepiandrosterone sulfate (S-DHAS), 17-OH-progesterone, and androstenedione

Staging

Stage I	<5-cm tumor confined to adrenal
Stage II	>5-cm tumor confined to adrenal
Stage III	Positive lymph nodes or local invasion with tumor outside adrenal in fat or adjacent organs
Stage IV	Distant metastasis

Macfarlane DA. Ann R Coll Surg Engl 1958;23:155–186
Sullivan M et al. J Urol 1978;120:660–665

Expert Opinion

1. *Primary therapy:* Primary therapy is complete surgical resection
2. *Surgery and Radio Frequency Ablation (RFA) as therapies for recurrences:* When possible, local recurrences should be addressed surgically. Some advocate surgical resection of metastatic disease, and although it may improve survival, firm evidence is lacking. Radio frequency ablation may be used as an alternative if the recurrence is deemed amenable to ablation and has an expendable margin. Just as incomplete resections should not be embarked on, neither should incomplete ablations be performed
3. *Management of excess hormone production:* Excess hormone production should not be ignored. Manage severe hypercortisolism aggressively. Because chemotherapy is usually ineffective, treatment of hormonal excess should not be delayed in expectation that chemotherapy will reduce the tumor burden and improve symptoms. Instead, use steroidogenesis inhibitors either singly or in combination. **Mitotane** is the cornerstone of any strategy and should be started as soon as a diagnosis has been made. Use mitotane at the highest tolerable dose. However, because a therapeutic mitotane level and steady state will not be reached for several months, other agents must be initiated concurrently. In patients with LFT results not more than 3 times normal range, begin therapy with **ketoconazole**, mindful of the potential for a pharmacokinetic interaction with other drugs. If LFTs are elevated, if an aggressive ketoconazole dose escalation is unsuccessful in controlling symptoms, or if toxicity develops, use **metyrapone***, either alone or in combination with ketoconazole. Cortisol levels must be monitored frequently to adjust steroidogenesis inhibitor drug doses and to avoid adrenal insufficiency, which occurs infrequently in patients with cortisol-producing tumors. Should adrenal insufficiency occur, hydrocortisone and mineralocorticoid replacement should be instituted as indicated below
   - *Mitotane:* Refer to section describing mitotane as a regimen for ACC
   - *Ketoconazole:* In patients with ACC and frank Cushing syndrome, treatment can start with 200 mg/dose given 3 or 4 times per day. The dose can then be increased by 400 mg/day every few days to a maximum single doses of 1200–1600 mg administered 3 or 4 doses per day (ie, total daily doses = 3600–6400 mg) while monitoring liver function. Because ketoconazole requires stomach acidity for absorption, proton pump inhibitors should be avoided, and achlorhydria should be suspected in elderly individuals who do not respond to therapy
   - *Metyrapone**: Metyrapone is begun at a low dose of 500–1000 mg (250–500 mg 2–4 times daily) and is escalated every few days to the maximum daily dose. The dose needed to inhibit cortisol production ranges from 500–6000 mg/day, although little is gained with total daily doses greater than 2000 mg
4. *Chemotherapy for unresectable, advanced, and recurrent disease:* Chemotherapy is recommended for patients with metastatic disease, although evidence of survival benefit is not and will never be available. EDP (etoposide + doxorubicin + cisplatin) plus mitotane or streptozocin plus mitotane should be used as first-line therapy. "Novel targeted therapies" that may seem attractive have not been proved and should not be substituted for these chemotherapies that have known activity in ACC
5. *Adjuvant mitotane:* A recent analysis of 177 patients with ACC compared the outcome in 47 patients treated with adjuvant mitotane therapy with 130 patients who received no additional therapy (Terzolo et al., 2007). Surprisingly, when used at "more tolerable" daily doses of 2000–3000 mg, the authors reported that mitotane demonstrated significant benefit in the adjuvant setting. However, the results of this retrospective nonrandomized study must be viewed cautiously. Because the advantage was confined to time to recurrence and not to overall survival, the value of adjuvant mitotane is diminished. Furthermore, the short follow-up period of patients treated with mitotane leaves the conclusions in doubt. The lack of convincing evidence and the difficulty of administering mitotane has often guided a recommendation that "adjuvant" mitotane therapy should be used only in cases where a tumor cannot be fully removed surgically or in patients with a high likelihood of recurrence; that is, large tumors with extensive necrosis, capsular, lymphatic, or venous invasion, a high mitotic or Ki67 labeling index, and small or questionable surgical margins. Until further data are available, this continues to be the most reasonable approach
6. *Long-term mitotane monotherapy:* Administer mitotane long-term only to patients who tolerate it well and experience a therapeutic response or those who are at high-risk for recurrence. The optimal duration of therapy is not known: a recommendation of "indefinite" is most conservative. *Prolonged therapy is often made possible by the fact that after months of therapy body stores are finally saturated, and the dose needed to maintain serum levels is then markedly reduced.* In this case the tolerability improves markedly. However, suboptimal therapy (judged by serum mitotane levels) that is limited by side effects should not be continued; in this setting there is little chance of benefit in the face of continued toxicity. Although suboptimal therapy cannot be accurately defined, blood levels of 10–14 mg/L are often cited as optimal based on two small studies, but lower levels are likely of some value; a clinical observation also noted in the recent retrospective analysis of adjuvant mitotane (Terzolo et al., 2007)

*At present, metyrapone is not available in pharmacies. To obtain metyrapone (Metopirone), a pharmacist or physician must call Novartis Pharmaceuticals Corporation at 1-800-988-7768

Ng L, Libertino JM. J Urol 2003;169:5–11
Terzolo M et al. N Engl J Med 2007;356:2372–2380
Vassilopoulou-Sellin R, Shultz PN. Cancer 2001;92:1113–1121
Veytsman I et al. J Clin Oncol 2009;27:4619–4629
Wajchenberg BL et al. Cancer 2000;88:711–736

REGIMEN

MITOTANE (*o,p'*-DDD)

Luton J-P et al. N Engl J Med 1990;322:1195–1201

Mitotane 2000–20,000 mg/day; administer orally as a single dose or in 2–4 divided doses

Glucocorticoid replacement is necessary in all patients:
Hydrocortisone 15–20 mg; administer orally every morning, *plus:*
Hydrocortisone 7.5–10 mg; administer orally every afternoon around 4 PM
Mineralocorticoid replacement is also recommended:
Fludrocortisone acetate 100–200 mcg/day; administer orally every morning, *or:*
Fludrocortisone acetate 100 mcg/day; administer orally every morning and every evening

Supportive Care
Antiemetic prophylaxis
Emetogenic potential: ***MINIMAL***
See Chapter 39 for antiemetic recommendations

Hematopoietic growth factor (CSF) prophylaxis
Primary prophylaxis is NOT indicated
See Chapter 43 for more information

Antimicrobial prophylaxis
Risk of fever and neutropenia is LOW
Antimicrobial primary prophylaxis to be considered:
- Antibacterial—not indicated
- Antifungal—not indicated
- Antiviral—not indicated unless patient previously had an episode of HSV

See Chapter 47 for more information

Mitotane is available in the United States for oral administration in tablets that contain 500 mg mitotane. Lysodren (mitotane tablets). Bristol-Myers Squibb Company, Princeton, NJ

Patient Population Studied

A study of 59 patients with adrenocortical carcinoma treated with mitotane at different times in relation to surgery

Efficacy (N = 37)

Overall response rate	22%
Stable disease >12 months	5%
Clinical benefit rate	27%

Complete responses have been reported in other studies but are rare

Toxicity

Adverse Event	% Patients	No. of Patients
Anorexia/nausea	93	28
Vomiting	82	
Diarrhea	68	
Skin rash	32	
Confusion/ sleepiness	100	18
Ataxia	39	
Depression	33	
Dysarthria	28	
Tremor	22	
Visual disturbance	17	
Leukopenia	17	

Van Slooten H et al. Eur J Cancer Clin Oncol 1984;20:47–53

Treatment Modifications

Adverse Event	Dose Modification
General Guidelines:	First step with most side effects, especially if they occur as mitotane dose is advanced: (1) stop mitotane; (2) wait up to 7 days for symptoms to resolve; (3) restart mitotane at lower dose (500–1000 mg/day less than previous dose) or at previously tolerated dose; (4) increase dose in 500-mg/day increments at 1-week intervals
Anorexia Nausea/vomiting	Administer mitotane in divided doses, and/or most of dose before bedtime. Crush tablets and dissolve in vehicle. Use antiemetics as needed. Reassess adrenal replacement
Diarrhea	Administer as divided doses. Use loperamide or diphenoxylate/ atropine
Altered mental status	Stop therapy. Follow general guidelines. Obtain imaging study only if symptoms persist after 1 week off therapy
Skin rash	If not severe, continue mitotane and treat rash with local measures and antipruritics

Therapy Monitoring

1. Check mitotane level at least every 4 weeks initially. Patients receiving long-term mitotane therapy can have monitoring reduced to every 2–3 months
2. Adrenal function can be monitored by measuring ACTH, but this alone is not reliable and should be interpreted together with clinical assessment
3. *Response assessment:* Initially every 6–8 weeks. Patients receiving long-term mitotane therapy can have monitoring reduced to every 3–6 months

Notes

1. Begin mitotane administration at a low dosage, usually no more than 2000 mg/day
2. Increase dose in increments of 500 mg to a maximum of 1000 mg/day, usually at intervals of not less than 1 week
3. Do not increase mitotane if a patient is experiencing side effects; follow General Guidelines in the Treatment Modifications section. Although mitotane is considered to have low to no emetogenic potential, it often produces low-grade nausea that is difficult to tolerate because it occurs every day. In some patients, chronic administration of antiemetics is required. See Chapter 39
4. The optimal dosage is not known; however, mitotane levels should be monitored with a goal of attaining a level of 14–20 mcg/mL. Levels greater than 20 mcg/mL are usually associated with intolerable side effects
5. A dosage of 4000–6000 mg/day usually results in a therapeutic level of mitotane in most patients after 6–10 weeks; however, some patients tolerate or require doses as high as 10,000–12,000 mg/day
6. Therapeutic levels can be achieved more quickly by administering higher doses and by increasing doses more aggressively, but this strategy usually fails because of side effects that result
7. With long-term administration of mitotane, the dosage required to maintain a therapeutic level may be substantially less, even as low as 500–1000 mg/day
8. Chronic administration results in adrenal insufficiency requiring steroid replacement therapy, as recommended in Regimen. Some physicians prefer to begin replacement therapy at the time mitotane therapy is started; others wait until there is evidence of incipient adrenal insufficiency, usually 6–8 weeks after the start of therapy. Replacement therapy is recommended with twice-daily hydrocortisone and with once- or twice-daily fludrocortisone replacement. Measuring ACTH levels to monitor the adequacy of replacement therapy is of limited value, because normal ACTH levels are difficult if not impossible to achieve. Patients should be instructed to obtain and wear identification that warns health care providers about possible adrenal insufficiency
9. Even without effecting a reduction in tumor size, mitotane may reduce circulating hormone levels, so that mitotane therapy can be continued solely to control the signs and symptoms of hormonal excess. Furthermore, if, after a period of mitotane administration, there is evidence of disease progression, discontinuing mitotane will result in a recurrence of the signs and symptoms of hormonal excess. The latter may appear gradually as mitotane is slowly cleared, but may eventually be worse than before mitotane therapy because of interval growth of the tumor. In these patients, consider continuing mitotane or begin an alternate drug to control hormonal excess

Haak HR et al. Br J Cancer 1994;69:947–951
Hoffman DL, Mattox VR. Med Clin North Am 1972;56:999–1012
Van Slooten H et al. Eur J Cancer Clin Oncol 1984;20:47–53

REGIMEN

CISPLATIN + MITOTANE

Bukowski RM et al. J Clin Oncol 1993;11:161–165

Hydration: ≥2000 mL 0.9% Sodium Chloride injection (0.9% NS), at ≥100 mL/hour before and after cisplatin administration. Also encourage increased oral fluid intake. Monitor and replace magnesium/electrolytes as needed

Cisplatin 75–100 mg/m²; administer intravenously in 50–250 mL of 0.9% NS over 30 minutes on day 1 every 3 weeks (total dosage per cycle = 75–100 mg/m²)
Mitotane* 4000 mg/day; administer orally, continually

Glucocorticoid replacement is necessary in all patients:
Hydrocortisone 15–20 mg; administer orally every morning, *plus*
Hydrocortisone 7.5–10 mg; administer orally every evening, continually
Mineralocorticoid replacement is also recommended
Fludrocortisone acetate 100–200 mcg/day; administer orally every morning, *or*
Fludrocortisone acetate 100 mcg/day; administer orally every morning and every evening, continually

Supportive Care
Antiemetic prophylaxis
Emetogenic potential on day 1: ***HIGH****. Potential for delayed symptoms*
Emetogenic potential on days with mitotane alone: ***MINIMAL***
See Chapter 39 for antiemetic recommendations

Hematopoietic growth factor (CSF) prophylaxis
Primary prophylaxis is NOT indicated
See Chapter 43 for more information

Antimicrobial prophylaxis
Risk of fever and neutropenia is LOW
Antimicrobial primary prophylaxis to be considered:
- Antibacterial—not indicated
- Antifungal—not indicated
- Antiviral—not indicated unless patient previously had an episode of HSV

See Chapter 47 for more information

*Mitotane therapy may be better tolerated if started at a dose of 2000 mg/day, increasing by 500–1000 mg/day at 1-week intervals. The total daily mitotane dosage can be taken in 2–4 divided doses or as a single daily dose, which often is best tolerated at bedtime

Mitotane is available in the United States for oral administration in tablets that contain 500 mg mitotane Lysodren (mitotane tablets). Bristol-Myers Squibb Company, Princeton, NJ

Treatment Modifications

Adverse Event	Dose Modification
CrCl 30–50 mL/min (0.5–0.83 mL/s)	Hold cisplatin until CrCl ≥50 mL/min (≥0.83 mL/s), then reduce dose to 75 mg/m² if previous dose was 100 mg/m² or 60 mg/m² if previous dose was 75 mg/m²
CrCl <30 mL/min (<0.5 mL/s)	Discontinue cisplatin
Unacceptable GI or neuromuscular side effects from mitotane	Reduce mitotane to 2000 mg/day
Unacceptable side effects from mitotane at 2000 mg/day	Reduce mitotane to 1000 mg/day
Unacceptable side effects from mitotane at 1000 mg/day	Discontinue mitotane

CrCl, creatinine clearance

Patient Population Studied

A trial of 42 patients with metastatic or residual adrenocortical carcinoma because complete resection was not possible. Prior therapy with mitotane was allowed

Efficacy (N = 37)

Complete response	2.7%
Partial response	27%
Median response duration	7.9 months
Median time to response	76 days

Toxicity (N = 36)

Adverse Event	% G1/2	% G3/4
Hematologic		
Anemia	8	8
Leukopenia	36	6
Thrombocytopenia	—	3
Nonhematologic		
Nausea/vomiting	75	22
Diarrhea	11	—
Mucositis	6	—
Increased bilirubin	6	—
Renal	17	8
Peripheral neuropathy	3	6
Myalgias	17	6

N = 36, but reported as percent of 37 eligible patients

Therapy Monitoring

1. CBC with leukocyte differential count, serum creatinine and electrolytes, serum magnesium, and LFTs on day 1
2. *Response assessment:* Repeat imaging studies every 2 cycles; 24-hour urine cortisol and 17-ketosteroids with each cycle, if abnormal at baseline
3. Mitotane level at least every 4 weeks initially. A level of 14–20 mcg/mL is desirable
4. Adrenal function can be monitored by measuring ACTH, but this alone is not reliable and should be interpreted together with clinical assessment

ADVANCED OR METASTATIC ADRENAL CANCER REGIMEN

ETOPOSIDE + DOXORUBICIN + CISPLATIN + MITOTANE (EDP-M)

Fassnacht M et al. N Engl J Med 2012;366:2189–2197

Mitotane 500–5000 mg/day; administer orally, continually

- If possible, mitotane is started a minimum of 1 week before cytotoxic treatment is initiated. The ultimate goal is to attain mitotane concentrations in blood of 14–20 mcg/mL over time, as tolerated, trying not to exceed these values as side effects worsen with higher values. Note that side effects may preclude this range from being attained
- Initiate treatment with doses of 1000–1500 mg per day at bedtime to minimize sedative effects during waking hours, and escalate doses as tolerated
- Large daily doses may be divided in ≥2 doses

Doxorubicin 40 mg/m^2; administer by intravenous injection over 3–5 minutes on day 1, every 4 weeks (total dosage/cycle = 40 mg/m^2)

Prehydration for cisplatin: ≥500 mL 0.9% sodium chloride injection (0.9% NS) per day; administer intravenously at ≥100 mL/hour for 2 consecutive days, starting before cisplatin on days 3 and 4

Cisplatin 40 mg/m^2 per day; administer intravenously in 50–500 mL of 0.9% NS over 30–60 minutes for 2 doses on 2 consecutive days, days 3 and 4, every 4 weeks (total dosage/cycle = 80 mg/m^2)

Posthydration for cisplatin: ≥500 mL 0.9% NS per day; administer intravenously at ≥100 mL/hour for 2 consecutive days, after cisplatin on days 3 and 4. Encourage increased oral fluid intake. Monitor and replace magnesium and electrolytes as needed

± *Mannitol diuresis:* May be given to patients who have received adequate hydration

Mannitol 12.5–25 g may be administered by intravenous injection before or during cisplatin administration, *or*

Mannitol 10–40 g; administer intravenously over 1–4 hours before or during cisplatin administration, or may be prepared as an admixture with cisplatin

Note: Diuresis with mannitol requires maintaining hydration with intravenously administered fluid during and for hours after mannitol administration

Etoposide 100 mg/m^2 per dose; administer intravenously diluted to a concentration within the range 0.2–0.4 mg/mL in 5% dextrose injection or 0.9% NS over at least 60 minutes for 3 consecutive days, on days 2, 3, and 4, every 4 weeks (total dosage/cycle = 300 mg/m^2)

Glucocorticoid replacement is necessary in all patients taking mitotane
Hydrocortisone 15–20 mg orally every morning, *plus*:
Hydrocortisone 7.5–10 mg orally every evening
Mineralocorticoid replacement is also recommended:
Fludrocortisone acetate 100–200 mcg/day orally every morning, *or*:
Fludrocortisone acetate 100 mcg/day orally every morning and every evening

Supportive Care
Antiemetic prophylaxis
Emetogenic potential on day 1: ***MODERATE***
Emetogenic potential on day 2: ***LOW***
Emetogenic potential on days 3 and 4: ***HIGH****. Potential for delayed symptoms*
See Chapter 39 for antiemetic recommendations

Hematopoietic growth factor (CSF) prophylaxis
Primary prophylaxis is NOT indicated
See Chapter 43 for more information

Antimicrobial prophylaxis
Risk of fever and neutropenia is LOW
Antimicrobial primary prophylaxis to be considered:
- Antibacterial—not indicated
- Antifungal—not indicated
- Antiviral—not indicated unless patient previously had an episode of HSV

See Chapter 47 for more information

Patient Population Studied

Patients with histologically confirmed adrenocortical carcinoma not amenable to radical surgical resection who had not received any previous treatment with cytotoxic drugs, except mitotane, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. One hundred fifty-one patients received etoposide + doxorubicin + cisplatin + mitotane

Age (y)	
Median	51.9
Range	19.0–76.2
Sex—Number (%)	
Male	60 (39.7)
Female	91 (60.3)
Tumor stage—Number (%)	
III	0
IV	151 (100.0)
Endocrine symptoms—Number (%)	
Cushing syndrome ± other symptoms	60 (39.7)
Conn syndrome only	2 (1.3)
Virilization only	6 (4.0)
Feminization only	3 (2.0)
No symptoms	70 (46.4)
Missing data	10 (6.6)
ECOG performance status score—Number (%)	
0	73 (48.3)
1	64 (42.4)
2	13 (8.6)
4	1 (0.7)
Time since primary diagnosis—Months	
Median	7.3
Range	0–183.7
Number of affected sites*	
Median	3
Range	1–7

*The following sites were calculated as separate sites of adrenocortical carcinoma: adrenal gland (including local recurrence), liver, lung, bone, peritoneum, retroperitoneum, pleura, mediastinum, central nervous system, soft tissue, spleen, and ovary

Treatment Modifications

Adverse Event	Dose Modification
Day 1 WBC <1000/mm³ *or* platelet count <100,000/mm³ *or* G >2 nonhematologic toxicity	Delay chemotherapy until WBC ≥1000/mm³ and platelet count ≥100,000/mm³, or nonhematologic toxicity G ≤1 for a maximum delay of 2 weeks
>2-week delay in reaching WBC >1000/mm³ *or* platelet count >100,000/mm³ *or* for resolution of non-hematologic toxicity to G ≤1	Discontinue therapy
G4 ANC or G ≥3 platelet counts	Reduce dosages of all drugs by 25% except mitotane
Creatinine clearance <50 to 60 mL/min	Hold cisplatin until creatinine clearance >50–60 mL/min

Efficacy

Efficacy in the Intention-to-Treat Population
Randomized Comparison versus Streptozocin + Mitotane*

Variable	EDP-M (N = 151)†	Sz-M (N = 153)†	P-Value
Type of response—no. (%)			
Complete response	2 (1.3)	1 (0.7)	
Disease-free by time of surgery‡	4 (2.6)	2 (1.3)	
Partial response	29 (19.2)	11 (7.2)	
Stable disease§	53 (35.1)	34 (22.2)	
Progressive disease	43 (28.5)	88 (57.5)	
Did not receive treatment	3 (2.0)	4 (2.6)	
Not evaluable for response	17 (11.3)	13 (8.5)	
Objective response¶			
Number of patients	35	14	
% (95% CI)	23.2 (16.7–30.7)	9.2 (5.1–14.9)	<0.001
Disease control**			
Number of patients	88	48	
% (95% CI)	58.3 (50.0–66.2)	31.4 (24.1–39.4)	<0.001
	EDP-M (N = 151)†	**Sz-M (N = 153)†**	**HR [95%CI]; P-Value**
Progression-free survival	5.0 months	2.1 months	0.55 [0.42–0.68]; <0.001
Overall survival††	14.8 months	12.0 months	0.79 [0.61–1.02]; 0.07

*Responses according to Response Evaluation Criteria in Solid Tumors (RECIST)
†EDP + M = etoposide + doxorubicin + cisplatin + mitotane; Sz + M = streptozocin + mitotane
‡Surgery performed >PR to study treatment; not included in PR category
§Stable disease was defined as no disease progression for at least ≥8 weeks and no objective response to treatment. Confirmatory scans were not required for this determination, according to the study protocol
¶Objective response = CR + PR
**Disease control + CR + PR + SD
††Patients classified according to first-line therapy, but they were allowed to receive the alternate therapy in second line

Toxicity

Event	Number of Patients (%)
Any serious adverse event	86 (58.1)
Adrenal insufficiency	5 (3.4)
Bone marrow toxicity	17 (11.5)
Cardiovascular or thromboembolic event	10 (6.8)
Fatigue or general health deterioration	8 (5.4)
Gastrointestinal disorder	6 (4.1)
Impaired liver function	0
Impaired renal function	1 (0.7)
Infection	10 (6.8)
Neurologic toxicity	5 (3.4)
Respiratory disorder	9 (6.1)
Other	15 (10.1)

Therapy Monitoring

1. CBC with leukocyte differential count, serum creatinine and electrolytes, serum magnesium, and LFTs on day 1 of each cycle
2. *Response assessment:* Repeat imaging studies every 2 cycles; 24-hour urine 17-ketosteroids and cortisol with each cycle if abnormal at baseline
3. Mitotane level at least every 4 weeks initially. A level of 14–20 mcg/mL is desirable but may not be attained
4. Adrenal function can be monitored by measuring ACTH, but this alone is not reliable and should be interpreted together with clinical assessment

REGIMEN

DOXORUBICIN

Decker RA et al. Surgery 1991;110:1006–1013

Doxorubicin 60 mg/m^2; administer by intravenous injection over 3–5 minutes on day 1, every 3 weeks to a maximum cumulative lifetime dosage of 500 mg/m^2 (total dosage per cycle = 60 mg/m^2)

Supportive Care

Antiemetic prophylaxis

Emetogenic potential: ***HIGH***

See Chapter 39 for antiemetic recommendations

Hematopoietic growth factor (CSF) prophylaxis

Primary prophylaxis may be indicated

See Chapter 43 for more information

Antimicrobial prophylaxis

Risk of fever and neutropenia is LOW

Antimicrobial primary prophylaxis to be considered:

- Antibacterial—not indicated
- Antifungal—not indicated
- Antiviral—not indicated unless patient previously had an episode of HSV

See Chapter 47 for more information

Patient Population Studied

A study of 31 patients with unresectable adrenocortical carcinoma with ECOG PS 0–3. Fifteen of the 31 patients had been treated with mitotane immediately before doxorubicin

Efficacy (N = 31)

	Response Rate	No. of Patients
Initial treatment with chemotherapy (doxorubicin); no prior mitotane	19%	16
Tumor did not respond, or progressed when treated with mitotane	0%	15

Toxicity (N = 31)

	% Mild/ Moderate	% Severe
Hematologic		
Any hematologic	48	19
Nonhematologic		
Nausea/vomiting	45	3
Diarrhea	19	3
Skin/mucosa	16	0
Neurologic	13	0
Hepatic	6	0

Bear HD et al. J Clin Oncol 2003;21:4165–4174

Therapy Monitoring

1. CBC with leukocyte differential count, serum creatinine, electrolytes, and LFTs on day 1
2. *Response assessment:* Repeat imaging studies every 2 cycles; 24-hour urine cortisol and 17-hydroxycorticosteroids with each cycle if abnormal at baseline

Treatment Modifications

Adverse Event	Dose Modification
Day 1 ANC <1500/mm^3, platelet count <75,000/mm^3	Delay chemotherapy until ANC >1500/mm^3 and platelet counts >75,000/mm^3 for a maximum delay of 2 weeks. Use filgrastim or pegfilgrastim in subsequent cycles if delay for low ANC
Febrile neutropenia	Filgrastim or pegfilgrastim in subsequent cycles
Febrile neutropenia on filgrastim or pegfilgrastim	Reduce doxorubicin dosage by 25%
G ≥3 Nonhematologic toxicity	Hold therapy until resolution to G1. Reduce doxorubicin dosage by 25% if recovery occurs in <2 weeks

Bear HD et al. J Clin Oncol 2003;21:4165–4174

Notes

The recommended limit for total cumulative lifetime doxorubicin dosage of 450–500 mg/m^2 may be exceeded, provided that adequate cardiac monitoring is conducted before every or every other chemotherapy cycle

ADVANCED OR METASTATIC ADRENAL CANCER REGIMEN

STREPTOZOCIN + MITOTANE (Sz-M)

Fassnacht M et al. N Engl J Med 2012;366:2189–2197

Mitotane 500–5000 mg/day; administer orally, continually

- If possible, mitotane is started a minimum of 1 week before cytotoxic treatment is initiated. The ultimate goal is to attain mitotane concentrations in blood of 14–20 mcg/mL over time, as tolerated, trying not to exceed these values as side effects worsen with higher values. Note that side effects may preclude this range from being attained
- Initiate treatment with doses of 1000–1500 mg/day at bedtime to minimize sedative effects during waking hours, and escalate doses as tolerated
- Large daily doses may be divided in ≥2 doses

Hydration for streptozocin (all cycles): 1000 mL 0.9% sodium chloride injection (0.9% NS) per day; administer intravenously with 500 mL given before streptozocin and 500 mL given after streptozocin

First cycle: **Streptozocin** 1000 mg/day; administer intravenously in 50–500 mL of 0.9% NS or 5% dextrose injection (D5W) over 30–60 minutes for 5 doses on 5 consecutive days, days 1–5, every 3 weeks (total dose/cycle = 5000 mg)

Second and subsequent cycles: **Streptozocin** 2000 mg; administer intravenously in 50–500 mL of 0.9% NS or D5W over 30–60 minutes on day 1, every 3 weeks (total dose/cycle = 2000 mg)

Glucocorticoid replacement is necessary in all patients taking mitotane
Hydrocortisone 15–20 mg orally every morning, *plus*:
Hydrocortisone 7.5–10 mg orally every evening
Mineralocorticoid replacement is also recommended:
Fludrocortisone acetate 100–200 mcg/day orally every morning, *or*:
Fludrocortisone acetate 100 mcg/day orally every morning and every evening

Supportive Care

Antiemetic prophylaxis

*Emetogenic potential is **HIGH** each day streptozocin is administered. Potential for delayed symptoms*
See Chapter 39 for antiemetic recommendations

Hematopoietic growth factor (CSF) prophylaxis

Primary prophylaxis is NOT indicated
See Chapter 43 for more information

Antimicrobial prophylaxis

Risk of fever and neutropenia is LOW

Antimicrobial primary prophylaxis to be considered:

- Antibacterial—not indicated
- Antifungal—not indicated
- Antiviral—not indicated unless patient previously had an episode of HSV

See Chapter 47 for more information

Treatment Modifications

Adverse Event	Dose Modification
Day 1 WBC <1000/mm³ *or* platelet count <100,000/mm³ *or* G >2 nonhematologic toxicity	Delay chemotherapy until WBC ≥1000/mm³ and platelet count ≥100,000/mm³, or nonhematologic toxicity G ≤1 for a maximum delay of 2 weeks
>2-week delay in reaching WBC, >1000/mm³ *or* platelet count >100,000/mm³, *or* for resolution of nonhematologic toxicity to G ≤1	Discontinue therapy
G4 ANC or G ≥3 platelet counts	Reduce streptozocin dose by 25%
Creatinine clearance <50–60 mL/min	Hold streptozocin until creatinine clearance >50–60 mL/min

Patient Population Studied

Patients with histologically confirmed adrenocortical carcinoma not amenable to radical surgical resection who had not received any previous treatment with cytotoxic drugs, except mitotane, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. One-hundred fifty-three patients received streptozocin + mitotane

Age (y)	
Median	50.0
Range	18.8–72.8
Sex—Number (%)	
Male	61 (39.9)
Female	92 (60.1)
Tumor stage—Number (%)	
III	1 (0.7)
IV	152 (99.3)
Endocrine symptoms—Number (%)	
Cushing syndrome ± other symptoms	64 (41.8)
Conn syndrome only	3 (2.0)
Virilization only	7 (4.6)
Feminization only	2 (1.3)
No symptoms	68 (44.4)
Missing data	9 (5.9)
ECOG performance status score—Number (%)	
0	72 (47.1)
1	60 (39.2)
2	21 (13.7)
4	0
Time since primary diagnosis—Months	
Median	4.5
Range	0–111.6
Number of affected sites*	
Median	3
Range	1–8

*The following sites were calculated as separate sites of adrenocortical carcinoma: adrenal gland (including local recurrence), liver, lung, bone, peritoneum, retroperitoneum, pleura, mediastinum, central nervous system, soft tissue, spleen, and ovary

Efficacy

Efficacy in the Intention-to-Treat Population
Randomized Comparison vs. Etoposide + Doxorubicin + Cisplatin + Mitotane*

Variable	EDP-M (N = 151)†	Sz-M (N = 153)†	P-Value
Type of response—no. (%)			
Complete response	2 (1.3)	1 (0.7)	
Disease-free by time of surgery‡	4 (2.6)	2 (1.3)	
Partial response	29 (19.2)	11 (7.2)	
Stable disease§	53 (35.1)	34 (22.2)	
Progressive disease	43 (28.5)	88 (57.5)	
Did not receive treatment	3 (2.0)	4 (2.6)	
Not evaluable for response	17 (11.3)	13 (8.5)	
Objective response¶			
Number of patients	35	14	
% (95% CI)	23.2 (16.7–30.7)	9.2 (5.1–14.9)	<0.001
Disease control**			
Number of patients	88	48	
% (95% CI)	58.3 (50.0–66.2)	31.4 (24.1–39.4)	<0.001
	EDP-M (N = 151)†	**Sz-M (N = 153)†**	**HR [95% CI]; P-Value**
Progression-free Survival	5.0 months	2.1 months	0.55 [0.42–0.68]; <0.001
Overall Survival*†	14.8 months	12.0 months	0.79 [0.61–1.02]; 0.07

*Responses according to Response Evaluation Criteria in Solid Tumors (RECIST)
†EDP + M = etoposide + doxorubicin + cisplatin + mitotane; Sz + M = streptozocin + mitotane
‡Surgery performed >PR to study treatment; not included in PR category
§Stable disease was defined as no disease progression for at least 8 weeks and no objective response to treatment. Confirmatory scans were not required for this determination, according to the study protocol
¶Objective response = CR + PR
**Disease control + CR + PR + SD
††Patients classified according to first-line therapy, but they were allowed to receive the alternate therapy in second line

Toxicity

Event	Number of Patients (%)
Any serious adverse event	62 (41.6)
Adrenal insufficiency	1 (0.7)
Bone marrow toxicity	3 (2.0)
Cardiovascular or thromboembolic event	0
Fatigue or general health deterioration	7 (4.7)
Gastrointestinal disorder	12 (8.1)
Impaired liver function	7 (4.7)
Impaired renal function	6 (4.0)
Infection	4 (2.7)
Neurologic toxicity	4 (2.7)
Respiratory disorder	5 (3.4)
Other	13 (8.7)

Therapy Monitoring

1. CBC with leukocyte differential count, serum creatinine, electrolytes, and LFTs on day 1; obtain creatinine clearance on day 1 if an elevation in serum creatinine is observed
2. Twenty-four–hour urine for protein on day 1
3. *Response assessment:* Repeat imaging studies every 2 cycles; 24-hour urine 17-ketosteroids and cortisol with each cycle if abnormal at baseline
4. Mitotane level at least every 4 weeks initially. A level of 14–20 mcg/mL is desirable, but may not be attained
5. Adrenal function can be monitored by measuring ACTH, but this alone is not reliable and should be interpreted together with clinical assessment

2. Anal Cancer

Irfan Jawed, MD and John Marshall, MD

Epidemiology

Incidence: 7,210 (male: 2,660; female: 4,550. Estimated new cases for 2014 in the United States)
1.5 per 100,000 male per year, 1.9 per 100,000 female
Deaths: Estimated 950 in 2014 (male: 370; female: 580)
Median age at diagnosis: 60 years
Male to female ratio: Slight female predominance

Stage at Presentation
Stages I/II: 50%
Stage III: 29–40%
Stage IV: 10–13%

Daling JR et al. J Natl Cancer Inst 2000;92:1500–1510
Fred Hutchinson Cancer Research Center, Changing Trends in Sexual Behavior May Explain Rising Incidence of Anal Cancer Among American Men and Women. Fred Hutchinson Cancer Research Center (fhcrc.org). 2004-07-06. Retrieved 2010-04
Frisch M et al. Gynecol Oncol 2009;114:395–398
Maggard MA et al. Dis Colon Rectum 2003;46:1517–1523; discussion 1523–1524; author reply 1524
Ryan DP et al. Int J Cancer 2010;127:675–684
Ryan DP et al. N Engl J Med 2000;342:792–800
Siegel R et al. CA Cancer J Clin 2014;64:9–29
Surveillance, Epidemiology and End Results (SEER) Program, available from http://seer.cancer.gov (accessed in 2013)
Uronis HE and Bendell JC. Oncologist 2007;12:524–534

Work-up

All stages

1. Sigmoidoscopy with biopsy
2. CT scan of abdomen and pelvis, or MRI
3. Chest x-ray or chest CT
4. Consider HIV testing
5. Consider PET-CT scan
6. Gynecologic exam for women, including screening for cervical cancer

Positive inguinal lymph node on imaging

1. Fine-needle aspiration or biopsy of node

Pathology

By convention, anal cancer should now refer only to *squamous cell cancers* arising in the anus. Earlier surgical series often did not make this distinction. *Adenocarcinomas* occurring in the anal canal should be treated according to the same principles applied to rectal adenocarcinoma. Similarly, melanomas and sarcomas should be treated according to the same principles applied to those tumor types at other sites

The distal anal canal is lined by squamous epithelium, and tumors arising in this portion are often keratinizing. Around the dentate line, the mucosa transitions from squamous mucosa to the nonsquamous rectal mucosa. Tumors arising in this transitional zone are often nonkeratinizing and previously were referred to as basaloid or cloacogenic

Clark MA et al. Lancet Oncol 2004;5:149–157
Ryan DP et al. N Engl J Med 2000;342:792–800

Five-Year Survival (After Chemoradiation)

Stages I/II: 80%
Stage III: 60%
Stage IV: 30.5%

Howlader N et al., eds. SEER Cancer Statistics Review, 1975–2008. Bethesda, MD: National Cancer Institute, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER website, 2011

Poor Prognostic Factors

1. Nodal involvement
2. Skin ulceration
3. Male gender
4. Tumor >5 cm

Bartelink F et al. J Clin Oncol 1997;15:2040–2049
Comments: Highlights of Gastrointestinal Cancer Research 1999;3:539–552
Gunderson LL et al. Proc Am Soc Clin Oncol 2011;29:257s [abstract 4005]
UKCCR (UK Co-ordinating Committee on Cancer Research). Lancet 1996;348:1049–1054

Staging

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* (Bowen disease, High-grade Squamous Intraepithelial Lesion (HSIL), Anal Intraepithelial Neoplasia II–III (AIN II–III)
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size invades adjacent organ(s), eg, vagina, urethra, bladder*

*Direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) is not classified as T4

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in perirectal lymph node(s)
N2	Metastasis in unilateral internal iliac and/or inguinal lymph node(s)
N3	Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes

Distant Metastasis (M)

M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis

Group	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
	T3	N0	M0
IIIA	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4	N0	M0
IIIB	T4	N1	M0
	Any T	N2	M0
	Any T	N3	M0
IV	Any T	Any N	M1

Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010

Expert Opinion

Locoregional disease ***(squamous cell cancers)***

Anal canal cancer

- Concurrent chemoradiation is the recommended primary treatment for patients with anal canal cancer that has not metastasized, with fluorouracil 1000 mg/m² per day by continuous intravenous infusion over 24 hours for 4 consecutive days on days 1–4, *plus* mitomycin 10 mg/m² by slow intravenous injection on day 1, every 28 days for 2 cycles (see Regimens below)
- Long-term update of U.S. GI intergroup RTOG 98-11 phase III trial for anal carcinoma: disease-free and overall survival with RT + fluorouracil + mitomycin versus RT + fluorouracil + cisplatin

Long-term Update of U.S. GI Intergroup RTOG 98-11

Gunderson LL et al. Proc Am Soc Clin Oncol 2011;29:257s [abstract 4005]

		DFS		OS		CFS		LRF		DM		CF	
	# Patients	TF	%, 5-Years	TF	%, 5-Years	TF	%, 5-Years	TF	%, 5-Years	TF	%, 5-Years	TF	%, 5-Years
RT + fluorouracil + mitomycin	325	117	67.7	80	78.2	101	71.8	67	20.0	45	13.1	38	11.9
RT + fluorouracil + cisplatin	324	156	57.6	108	70.5	126	64.9	86	26.5	60	17.8	55	17
p Value		0.0044		0.021		0.053		0.089		0.12		0.075	

CF, colostomy failure; CFS, colostomy-free survival; DFS, Disease-free survival; DM, distant metastases; LRF, locoregional failure; OS, overall survival; RT, radiation therapy; TF, total failures

- Locoregional failure rate is 10–30%. If locally persistent or progressive disease is present, consider abdominoperineal resection (APR). If positive lymph nodes are found, perform groin dissection with RT (if RT was not previously administered) or without RT

Anal margin cancer

- A well-differentiated anal margin lesion characterized as T1, N0, can be treated with margin negative excision alone with close follow-up
- For T2–T4 or any N, the recommended treatment is chemoradiation: fluorouracil 1000 mg/m² per day by continuous intravenous infusion over 24 hours for 4 consecutive days on days 1–4, *plus* mitomycin 10 mg/m² intravenously on day 1, every 28 days for 2 cycles (see Regimens below)

Metastatic anal cancer ***(squamous cell cancers)***

Metastatic disease should be treated with cisplatin-based chemotherapy or enrollment in a clinical trial

Faivre C et al. Bull Cancer 1999;86:861–865

(continued)

Expert Opinion (*continued*)

Fluorouracil 1000 mg/m^2 per day administer by continuous intravenous infusion over 24 hours for 5 consecutive days on days 1–5, every 4 weeks, *plus*
Cisplatin 100 mg/m^2 administer intravenously over 30–60 minutes on day 2, every 4 weeks

- The regimen of choice
- Should be repeated until there is evidence of disease progression or toxicity requires cessation of treatment

Note: If the above regimen fails, no other regimen has been shown to be effective

Supportive Care/Alternate Treatments

- Radiotherapy might be delivered with less toxicity by means of 3D conformal radiotherapy or IMRT followed by conventional radiotherapy as shown in RTOG 0529 trial (2-year outcomes of RTOG 0529: a phase II evaluation of dose-painted IMRT in combination with fluorouracil and mitomycin for the reduction of acute morbidity in carcinoma of the anal canal). However, IMRT is not recommended in obese patients with nonreproducible external skin contours or patients with a major component of tumor outside the anal canal

Two-Year Outcomes of RTOG 0529

Kachnic LA et al. J Clin Oncol 2011;29(Suppl 4) [abstract 368]

	0529 (N = 52)		9811 (N = 325)	
End Point	Events	2-Year % (95% CI)	Events	2-Year % (95% CI)
LRF	10	20 (9, 31)	67	19 (14, 23)
CF	4	8 (0.4, 15)	38	11 (8, 14)
OS	7	88 (75, 94)	80	91 (87, 94)
DFS	12	77 (62, 86)	117	76 (70, 80)
CFS	7	86 (73, 93)	101	83 (79, 87)

CF, colostomy failures; CFS, colostomy-free survival; DFS, disease-free survival; LRF, Locoregional failure; OS, overall survival

- Capecitabine has been assessed in a phase II trial as a replacement for fluorouracil, but, to date, there is insufficient evidence to recommend substitution (Glynne-Jones R et al. Int J Radiat Oncol Biol Phys 2008;72:119–126)
- Tolerance to treatment can be maximized with antibiotics, antifungals, antiemetics, analgesia, skin care, advice regarding nutrition, and psychological support

Prevention of Anal Cancer

The U.S. Food and Drug Administration in 2010 approved recombinant human papillomavirus quadrivalent vaccine (Gardasil) for use in females and males ages 9 through 26 years for indications, including the prevention of anal intraepithelial neoplasia and associated precancerous lesions caused by human papillomavirus (HPV) types 6, 11, 16, and 18

Management of HIV Positive Patients

HIV-positive patients are generally treated similarly to those without HIV infection, however dosage may need to be adjusted (or treat without mitomycin) specifically if CD4 count is <200 cells/mm^3 or patients with a history of HIV-related complications as outcomes appear to be comparable but treatment-related toxicity may be worse

Post-treatment surveillance

There are no prospective trials to guide the post-treatment surveillance strategy for patients treated for anal cancer

- For patients who have a complete remission at 8–12 weeks from initial chemoradiotherapy, guidelines from the NCCN suggest the following every three to six months for five years:
  - Digital rectal examination
  - Anoscopy
  - Inguinal node palpation
  - If initially T3-4 disease or inguinal node-positive, or for those with persistent disease at the initial post-treatment biopsy who regress on serial examinations, consider imaging of the chest/abdomen and pelvis annually for three years
- For patients who have persistent disease at 8–12 weeks on DRE, it is recommended to re-evaluate in four weeks, and, if regression is observed on serial exams, continue to observe and re-evaluate in 3 months. If progressive disease is documented, perform a biopsy and restage
- For patients who undergo APR for biopsy-proven progressive or recurrent disease, perform inguinal node palpation every three to six months for five years, and annual radiographic imaging of the chest/abdomen/pelvis for three years

Allal AS et al. Effectiveness of surgical salvage therapy for patients with locally uncontrolled anal carcinoma after sphincter-conserving treatment. Cancer 1999;86:405–409
Faivre C et al. 5-fluorouracile and cisplatin combination chemotherapy for metastatic squamous-cell anal cancer. Bull Cancer 1999;86:861–865
Glynne-Jones R et al. EXTRA—a multicenter phase II study of chemoradiation using a 5 day per week oral regimen of capecitabine and intravenous mitomycin C in anal cancer. Int J Radiat Oncol Biol Phys 2008;72:119–126
Gunderson LL et al. Long-term update of U.S. GI intergroup RTOG 98-11 phase III trial for anal carcinoma: disease-free and overall survival with RT + fluorouracil-mitomycin versus RT + fluorouracil-cisplatin [abstract 4005]. J Clin Oncol 2011;29:257s
Kachnic LA et al. Two-year outcomes of RTOG 0529: a phase II evaluation of dose-painted IMRT in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. J Clin Oncol 2011;29(Suppl 4) (2011 Gastrointestinal Cancers Symposium, American Society of Clinical Oncology; abstract 368)
Kreuter A et al. Anal carcinoma in human immunodeficiency virus-positive men: results of a prospective study from Germany. Br J Dermatol 2010;162:1269–1277
Schiller DE et al. Outcomes of salvage surgery for squamous cell carcinoma of the anal canal. Ann Surg Oncol 2007;14:2780–2789

REGIMEN

MITOMYCIN + FLUOROURACIL + RADIATION THERAPY (RTOG 8704/ECOG 1289 AND RTOG-0529)

Flam M et al. J Clin Oncol 1996;14:2527–2539
Kachnic LA et al. J Clin Oncol 2011;29(Suppl 4) (American Society of Clinical Oncology 2011 Gastrointestinal Cancers Symposium, abstract 368)

Mitomycin 10 mg/m² single dose (maximum dose = 20 mg); administer by intravenous injection over 3–5 minutes on day 1 every 4 weeks for 2 cycles (days 1 and 29 of radiation) (total dosage/cycle = 10 mg/m², but *not* greater than 20 mg)
Fluorouracil 1000 mg/m² per day (maximum daily dose = 2000 mg); administer by continuous intravenous infusion over 24 hours for 4 consecutive days, on days 1–4 every 4 weeks for 2 cycles (days 1–4 and 29–32 of radiation therapy) (total dosage/cycle = 4000 mg/m², but *not* greater than 8000 mg)
External beam radiation therapy 1.8 Gy/fraction; administer daily 5 days/week for 5 weeks (total dose to pelvis/complete course = 45 Gy in 5 weeks)
For patients with T3, T4, or N+ lesions or T2 lesions with residual disease after 45 Gy, current RTOG protocol recommends an additional 10–14 Gy to a reduced field

Alternate RT regimen: dose-painted (DP) IMRT
DP-IMRT prescribed as follows:
- T2N0: 42-Gy elective nodal and 50.4-Gy anal tumor planning target volumes (PTVs), 28 fractions
- T3-4N0-3: 45-Gy elective nodal, 50.4-Gy ≤3 cm, and 54-Gy >3 cm metastatic nodal and 54-Gy anal tumor PTVs, 30 fractions

Note: IMRT is not recommended in obese patients with nonreproducible external skin contours, or patients with a major component of tumor outside the anal canal

Supportive Care
Antiemetic prophylaxis
Emetogenic potential is ***LOW***
See Chapter 39 for antiemetic recommendations

Hematopoietic growth factor (CSF) prophylaxis
Primary prophylaxis is NOT indicated
See Chapter 43 for more information

Antimicrobial prophylaxis
Risk of fever and neutropenia is LOW
Antimicrobial primary prophylaxis to be considered:
- Antibacterial—not indicated
- Antifungal—not indicated
- Antiviral—not indicated, unless patient previously had an episode of HSV

See Chapter 47 for more information

Diarrhea management
***Latent or delayed onset diarrhea**:**
Loperamide 4 mg orally initially after the first loose or liquid stool, *then*
Loperamide 2 mg orally every 2 hours during waking hours, *plus*
Loperamide 4 mg orally every 4 hours during hours of sleep
- Continue for at least 12 hours after diarrhea resolves
- Recurrent diarrhea after a 12-hour diarrhea free interval is treated as a new episode
- Rehydrate orally with fluids and electrolytes during a diarrheal episode
- If a patient develops blood or mucus in stool, dehydration, or hemodynamic instability, or if diarrhea persists >48 hours despite loperamide, stop loperamide and hospitalize the patient for IV hydration

Alternatively, a trial of **Diphenoxylate hydrochloride** 2.5 mg **with Atropine sulfate** 0.025 mg (eg, Lomotil®)
- Initial adult dose is two tablets four times daily until control has been achieved, after which the dose may be reduced to meet individual requirements. Control may often be maintained with as little as two tablets daily

(continued)

Treatment Modifications

Adverse Event	Dose Modification
G3/4 Diarrhea or stomatitis	Reduce fluorouracil dosage 50% during second cycle
G3 Radiation dermatitis	
G4 Radiation dermatitis	Do not give second cycle of chemotherapy
ANC <500/mm³ or platelets <50,000/mm³	Reduce fluorouracil and mitomycin dosages 50%
G3/4 Hematologic or nonhematologic events	Suspend chemoradiation until recovers to G ≤2

Based on RTOG protocol 98-11

Toxicity (N = 146)

	% G4/5
Acute (≤90 days after starting treatment)	25
Hematologic	18
Nonhematologic (diarrhea, skin, mucositis)	7
Late (>90 days after starting treatment)	5
Any grade 4 adverse event	23
Toxic death rate*	2.8

*All treatment-related deaths occurred in a setting of neutropenia and sepsis
NCI Common Toxicity Criteria, version 2.0

Efficacy (N = 129–146)

Positive biopsy after induction	8%
5-Year locoregional failure	36%
5-Year colostomy rate	22%
5-Year colostomy-free survival	64%
5-Year disease-free survival	67%
5-Year overall survival	67%

Flam M et al. Classic Papers and Current Comments: Highlights of Gastrointestinal Cancer Research 1999;3:539–552

(continued)

- Clinical improvement of acute diarrhea is usually observed within 48 hours. If improvement of chronic diarrhea after treatment with a maximum daily dose of 8 tablets is not observed within 10 days, control is unlikely with further administration

Persistent diarrhea:

Octreotide 100–150 mcg subcutaneously 3 times daily. Maximum total daily dose is 1500 mcg

Antibiotic therapy during latent or delayed onset diarrhea:

A fluoroquinolone (eg, **Ciprofloxacin** 500 mg orally every 12 hours) if absolute neutrophil count $<500/mm^3$ with or without accompanying fever in association with diarrhea

- Antibiotics should also be administered if patient is hospitalized with prolonged diarrhea and should be continued until diarrhea resolves

*Rothenberg ML et al. J Clin Oncol 2001;19:3801–3807
Wadler S et al. J Clin Oncol 1998;16:3169–3178
Abigerges D et al. J Natl Cancer Inst 1994;86:446–449

Oral care

Prophylaxis and treatment for mucositis/stomatitis

General advice:

- Encourage patients to maintain intake of non-alcoholic fluids
- Evaluate patients for oral pain and provide analgesic medications
- Consider histamine (H_2-subtype) receptor antagonists (eg, ranitidine, famotidine), or a proton pump inhibitor for epigastric pain
- *Lactobacillus* sp.-containing probiotics may be beneficial in preventing diarrhea

Patients with intact oral mucosa:

- Clean the mouth, tongue, and gums by brushing after every meal and at bedtime with an ultra-soft toothbrush with fluoride toothpaste
- Floss teeth gently every day unless contraindicated. If gums bleed and hurt, avoid bleeding or sore areas, but floss other teeth
- Patients may use saline or commercial bland, non-alcoholic rinses
  - Do not use mouthwashes that contain alcohols

If mucositis or stomatitis is present:

- Keep the mouth moist utilizing water, ice chips, sugarless gum, sugar-free hard candies, or a saliva substitute
- Rinse mouth several times a day to remove debris
  - Use a solution of ¼ teaspoon (1.25 g) each of baking soda and table salt (sodium chloride) in one quart (~950 mL) of warm water. Follow with a plain water rinse
  - Do not use mouthwashes that contain alcohols
- Foam-tipped swabs (eg, Toothettes®) are useful in moisturizing oral mucosa, but ineffective for cleansing teeth and removing plaque
- Advise patients who develop mucositis to:
  - Choose foods that are easy to chew and swallow
  - Take small bites of food, chew slowly, and sip liquids with meals
  - Encourage soft, moist foods such as cooked cereals, mashed potatoes, and scrambled eggs
  - For trouble swallowing, soften food with gravies, sauces, broths, yogurt, or other bland liquids
  - Avoid sharp, crunchy foods; hot, spicy or highly acidic foods (eg, citrus fruits and juices); sugary foods; toothpicks; tobacco products; alcoholic drinks

Patient Population Studied

A study of 146 patients with localized (nonmetastatic) squamous cell cancer of the anal canal

Therapy Monitoring

1. *Every week:* CBC with differential
2. *Response assessment:* PE 6 weeks after completion of chemoradiotherapy. If there is regression of tumor on exam, then 12 weeks after completion of therapy repeat PE, perform sigmoidoscopy and obtain CT scan. If there is a residual mass or thickening, a biopsy should be performed. If there is residual disease at 12 weeks or if there is progression of disease on exam, consider salvage abdominoperineal resection

Notes

Severely immunocompromised patients or HIV-positive patients with low CD4 counts should be treated with caution. Consider omitting and/or reducing the dose of chemotherapy

REGIMEN

FLUOROURACIL + CISPLATIN + EXTERNAL BEAM RADIATION THERAPY

Doci R et al. J Clin Oncol 1996;14:3121–3125

Fluorouracil 750 mg/m² per day; administer by continuous intravenous infusion in 500–1000 mL 0.9% sodium chloride injection (0.9% NS) or 5% dextrose injection (D5W) over 24 hours for 4 consecutive days, on days 1–4, every 21 days for 2 cycles (total dosage/cycle = 3000 mg/m²)
(Days 1–4 and 21–24 of radiation therapy)
Hydration before cisplatin ≥1000 mL 0.9% NS; administer intravenously over a minimum of 2–4 hours
Cisplatin 100 mg/m²; administer intravenously in 50–250 mL 0.9% NS over 60 minutes, on day 1 every 21 days for 2 cycles (total dosage/cycle = 100 mg/m²)
(Days 1 and 21 of radiation therapy)
Hydration after cisplatin ≥1000 mL 0.9% NS; administer intravenously over a minimum of 2–4 hours. Encourage patients to supplement their usual oral hydration with extra non–alcohol-containing fluids for at least 24 hours after receiving cisplatin
External beam radiation therapy 1.8 Gy/fraction; administer daily 5 days/week up to 54–58 Gy

Supportive Care
Antiemetic prophylaxis
*Emetogenic potential on days with cisplatin, fluorouracil, and RT is **HIGH**. Potential for delayed symptoms*
*Emetogenic potential on days with fluorouracil and RT is **LOW***
See Chapter 39 for antiemetic recommendations

Hematopoietic growth factor (CSF) prophylaxis
Primary prophylaxis is NOT indicated
See Chapter 43 for more information

Antimicrobial prophylaxis
Risk of fever and neutropenia is LOW
Antimicrobial primary prophylaxis to be considered:
- Antibacterial—not indicated
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See Chapter 47 for more information

Diarrhea management
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- Continue for at least 12 hours after diarrhea resolves
- Recurrent diarrhea after a 12-hour diarrhea-free interval is treated as a new episode
- Rehydrate orally with fluids and electrolytes during a diarrheal episode
- If a patient develops blood or mucus in stool, dehydration, or hemodynamic instability, or if diarrhea persists >48 hours despite loperamide, stop loperamide and hospitalize the patient for IV hydration

Alternatively, a trial of **Diphenoxylate hydrochloride** 2.5 mg **with Atropine sulfate** 0.025 mg (eg, Lomotil®)
- Initial adult dose is two tablets four times daily until control has been achieved, after which the dose may be reduced to meet individual requirements. Control may often be maintained with as little as two tablets daily
- Clinical improvement of acute diarrhea is usually observed within 48 hours. If improvement of chronic diarrhea after treatment with a maximum daily dose of 8 tablets is not observed within 10 days, control is unlikely with further administration

(*continued*)

Patient Population Studied

A study of 35 patients with previously untreated basaloid (n = 5) or squamous cell carcinoma (n = 30) of the anus. In all patients, the cancer was located in the anal canal; in 28, the tumor extended to adjacent sites. Nine patients had nodal metastases; no patient had distant metastases

Efficacy (N = 35)

Complete response	94%
Partial response*	6%
Local recurrence	6%
At median follow-up of 37 months	
No evidence of disease	94%
Colostomy free	86%

Normal anal function preserved in 30 of 35 patients
*Two partial responses in 2 of 5 (40%) patients with T3 tumors

Toxicity* (N = 35)

	% G1	% G2	% G3
Hematologic (leukopenia)	40	31	—
Vomiting	40	33	10
Dermatitis, proctitis, diarrhea	8.5	88.5	3
Cardiac	—	3†	—

*Acute toxicities. Chronic toxicities not reported.
No grade 4 toxicities reported
†Transient at end of first cycle; resolved
WHO criteria

(continued)

Persistent diarrhea:

Octreotide 100–150 mcg subcutaneously 3 times daily. Maximum total daily dose is 1500 mcg

Antibiotic therapy during latent or delayed onset diarrhea:

A fluoroquinolone (eg, **Ciprofloxacin** 500 mg orally every 12 hours) if absolute neutrophil count <500/mm^3 with or without accompanying fever in association with diarrhea

- Antibiotics should also be administered if patient is hospitalized with prolonged diarrhea and should be continued until diarrhea resolves

*Rothenberg ML et al. J Clin Oncol 2001;19:3801–3807
Abigerges D et al. J Natl Cancer Inst 1994;86:446–449
Wadler S et al. J Clin Oncol 1998;16:3169–3178

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- *Lactobacillus* sp.-containing probiotics may be beneficial in preventing diarrhea

Patients with intact oral mucosa:

- Clean the mouth, tongue, and gums by brushing after every meal and at bedtime with an ultra-soft toothbrush with fluoride toothpaste
- Floss teeth gently every day unless contraindicated. If gums bleed and hurt, avoid bleeding or sore areas, but floss other teeth
- Patients may use saline or commercial bland, non-alcoholic rinses
  - Do not use mouthwashes that contain alcohols

If mucositis or stomatitis is present:

- Keep the mouth moist utilizing water, ice chips, sugarless gum, sugar-free hard candies, or a saliva substitute
- Rinse mouth several times a day to remove debris
  - Use a solution of ¼ teaspoon (1.25 g) each of baking soda and table salt (sodium chloride) in one quart (~950 mL) of warm water. Follow with a plain water rinse
  - Do not use mouthwashes that contain alcohols
- Foam-tipped swabs (eg, Toothettes®) are useful in moisturizing oral mucosa, but ineffective for cleansing teeth and removing plaque
- Advise patients who develop mucositis to:
  - Choose foods that are easy to chew and swallow
  - Take small bites of food, chew slowly, and sip liquids with meals
  - Encourage soft, moist foods such as cooked cereals, mashed potatoes, and scrambled eggs
  - For trouble swallowing, soften food with gravies, sauces, broths, yogurt, or other bland liquids
  - Avoid sharp, crunchy foods; hot, spicy or highly acidic foods (eg, citrus fruits and juices); sugary foods; toothpicks; tobacco products; alcoholic drinks

Note: The RTOG has amended the above regimen as follows:
Two cycles of chemotherapy are given before external beam radiation therapy commences; that is, radiation therapy begins coincident with the start of chemotherapy cycle 3
The chemotherapy regimen used has been modified as follows:
Fluorouracil 1000 mg/m^2 per day; administer by continuous intravenous infusion in 500–1000 mL 0.9% NS or D5W over 24 hours for 4 consecutive days on days 1–4, every 28 days for 4 cycles (total dosage/cycle = 4000 mg/m^2)
Cisplatin 75 mg/m^2; administer intravenously in 250 mL 0.9% NS over 60 minutes on day 1 every 28 days for 4 cycles on days 1, 29, 57, and 85 (total dosage/cycle = 75 mg/m^2)

Treatment Modifications

Adverse Event	Dose Modification
ANC <500/mm^3 or platelets <50,000/mm^3	Decrease fluorouracil and cisplatin dosages by 50%
G3/4 diarrhea or stomatitis	Decrease fluorouracil dosage by 50%
G3 radiation dermatitis	
G4 radiation dermatitis	Hold radiation until dermatitis resolves to G ≤2, and do not administer additional fluorouracil
Creatinine 1.5–2.0 mg/dL (133–177 µmol/L)	Decrease cisplatin dosage by 50%
Creatinine >2.0 mg/dL (>177 µmol/L)	Hold cisplatin

Recommended by RTOG 98-11

Therapy Monitoring

1. *Before each cycle:* CBC with differential, BUN, creatinine, magnesium, and electrolytes
2. *Response assessment:* PE 4–6 weeks after completion of chemoradiotherapy. Perform a biopsy only in the absence of a response to therapy. If there has been a response to therapy, reevaluate at 12 weeks with PE, sigmoidoscopy, and CT scan. If residual tumor is suspected, biopsy the affected area. If residual disease is documented at 12 weeks or if there is progression of disease on exam, consider salvage abdominoperineal resection

ADVANCED DISEASE REGIMEN

CISPLATIN + FLUOROURACIL BY CONTINUOUS INTRAVENOUS INFUSION

Faivre C et al. Bull Cancer 1999;86:861–865

Hydration before, during, and after cisplatin administration ± mannitol:

- *Pre-cisplatin hydration* with ≥1000 mL 0.9% sodium chloride injection (0.9% NS); administer intravenously with potassium and magnesium supplementation as needed based on pretreatment values
- *Mannitol diuresis:* May be given to patients who have received adequate hydration. A dose of **mannitol** 12.5–25 g may be administered by intravenous injection or a short infusion before or during cisplatin administration, or prepared as an admixture with cisplatin. Continued intravenous hydration is essential
- *Continued mannitol diuresis:* In an inpatient or day-hospital setting, one may administer additional mannitol in the form of an intravenous infusion: **mannitol** 10–40 g administer intravenously over 1–4 hours. This can be done either during or immediately after cisplatin, but requires maintenance of adequate intravenously administered fluids during and for hours after mannitol administration
- Post-cisplatin hydration with ≥1000 mL 0.9% NS; administer intravenously with potassium and magnesium supplementation as needed based on measured values. Encourage patients to supplement their usual oral hydration with extra non–alcohol-containing fluids for at least 24 hours after receiving cisplatin

Cisplatin 100 mg/m^2; administer intravenously in 100–500 mL 0.9% NS over 30–60 minutes on day 2, every 4 weeks (total dosage/cycle = 100 mg/m^2)
Fluorouracil 1000 mg/m^2 per day; administer by continuous intravenous infusion in 50–1000 mL 0.9% NS or 5% dextrose injection over 24 hours for 5 consecutive days, on days 1–5, every 4 weeks (total dosage/cycle = 5000 mg/m^2)

Notes:

- Ten patients received further local treatment
- Carboplatin used instead of cisplatin in the event of renal toxicity

Supportive Care

Antiemetic prophylaxis

*Emetogenic potential on days with cisplatin is **HIGH** Potential for delayed symptoms*
*Emetogenic potential on days with fluorouracil alone is **LOW***
See Chapter 39 for antiemetic recommendations

Hematopoietic growth factor (CSF) prophylaxis

Primary prophylaxis is NOT indicated
See Chapter 43 for more information

Antimicrobial prophylaxis

Risk of fever and neutropenia is LOW

Antimicrobial primary prophylaxis to be considered:

- Antibacterial—not indicated
- Antifungal—not indicated
- Antiviral—not indicated unless patient previously had an episode of HSV

See Chapter 47 for more information

Diarrhea management

Latent or delayed onset diarrhea*:

Loperamide 4 mg orally initially after the first loose or liquid stool, *then*
Loperamide 2 mg orally every 2 hours during waking hours, *plus*
Loperamide 4 mg orally every 4 hours during hours of sleep

- Continue for at least 12 hours after diarrhea resolves
- Recurrent diarrhea after a 12-hour diarrhea-free interval is treated as a new episode
- Rehydrate orally with fluids and electrolytes during a diarrheal episode
- If a patient develops blood or mucus in stool, dehydration, or hemodynamic instability, or if diarrhea persists >48 hours despite loperamide, stop loperamide and hospitalize the patient for IV hydration

(*continued*)

Treatment Modifications

Adverse Event	Dose Modification
G3/4 hematologic	Reduce fluorouracil and cisplatin dosages by 20%
Hand-foot syndrome (palmar-plantar erythrodysesthesia)	Interrupt fluorouracil therapy until symptoms resolve. Then, reduce fluorouracil dosage by 20%, or discontinue fluorouracil
Mucositis	Interrupt fluorouracil therapy until symptoms resolve. Then, reduce fluorouracil dosage by 20%
Diarrhea	
Reduction in creatinine clearance* to ≤60% of on study value	Delay therapy for 1 week. If creatinine clearance does not recover to pretreatment values, consider reducing cisplatin dose or replace cisplatin with carboplatin
Creatinine clearance* 40–60 mL/min (0.66–1 mL/s)	Consider reducing cisplatin dose, so that dose in milligrams equals the creatinine clearance* value expressed in mL/min†. Alternatively, replace cisplatin with carboplatin
Creatinine clearance* <40 mL/min (<0.66 mL/s)	Hold cisplatin
Clinically significant ototoxicity	Discontinue cisplatin
Clinically significant sensory loss	Discontinue cisplatin

*Creatinine clearance is used as a measure of glomerular filtration rate
†This also applies to patients with creatinine clearance of 40–60 mL/min before commencing treatment

Patient Population Studied

Study of 19 patients (3 males, 16 females), median age 58 years, WHO performance status: G0-1 in 68% and G2 in 32%. Metastasis were synchronous in 6 patients and metachronous in 13 patients. Metastatic sites included liver (10/19 patients), lymph nodes (11/19 patients: paraaortic 5, iliac 4, and inguinal 2) and pulmonary (3/11 patients). In 9 of 19 patients lymph node metastases were isolated; in 7 of 19 patients liver metastases were isolated