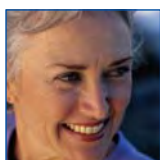
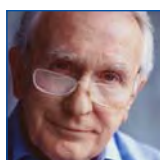


M A N A G I N G P A T I E N T S



T H R O U G H A G G R E S S I V E



C A N C E R T H E R A P I E S

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INTRODUCTION

This is the second independent study activity in a 3-part educational program (EDII) that contains the following learning modules:

- “Casemat” format of a clinical case study
- Slide presentation in the form of a slide workbook

For the purpose of achieving maximum learning as well as contact hours, both modules must be completed. This educational program, as an EDII, is not intended to be used as a group activity. Please refer to the slide workbook for CNE information.

OVERVIEW

Lung cancer is the leading cause of cancer death in the United States among both men and women.¹ The majority of the lung tumors diagnosed are non–small-cell lung cancers (NSCLCs), with only 15% to 25% treatable with surgery.² As many as 40% of patients present with locally-advanced and/or unresectable disease.³ Traditionally, radiotherapy (RT) was the treatment of choice for patients with inoperable NSCLC.² However, more recently, numerous clinical studies have demonstrated increased survival rates for patients treated with combined chemotherapeutic regimens.^{3,4} Aggressive cancer therapies such as combined-modality approaches for NSCLC have improved outcomes; however, patients are at increased risk for dose-limiting toxicities that can result in treatment delays and potentially negatively impact quality of life.

SEQUENTIAL VERSUS CONCURRENT RADIOCHEMOTHERAPY

The goal of combined-modality therapy is to increase survival by increasing locoregional tumor control with RT +/- chemotherapy and increasing distant control with chemotherapy.⁵ Several trials have evaluated the timing of combined-modality approaches on clinical outcomes. Sequential radiochemotherapy (RCT) with platinum-based chemotherapy followed by RT has demonstrated improved clinical outcomes when compared with RT alone, although patients still had poor long-term survival rates.^{6,7} Combined RCT has the theoretical advantage over sequential RCT for radiosensitizing tumor cells to improve locoregional control. Randomized clinical trials have been conducted to evaluate whether concurrent RCT is better than a sequential regimen. The Radiation Therapy Oncology Group (RTOG) (9410) has demonstrated that concurrent RCT with cisplatin-based chemotherapy led to an increased time to progression as well as to an increased rate of survival but with increased acute toxicity.⁸⁻¹⁰ Similar results were obtained with another randomized trial that also addressed the question of sequential versus concurrent RCT utilizing a different radiation and chemotherapy regimen with mitomycin, vindesine, and cisplatin. Concurrent RCT was found to increase response rates and median survival; however, it also resulted in higher myelosuppression when compared with the sequential RCT arm.¹¹ Other studies have evaluated different combinations of chemotherapy, such as paclitaxel and carboplatin in combination with RT.^{12,13}

TOXICITIES ASSOCIATED WITH COMBINED-MODALITY THERAPY

Toxicities are a concern with combined-modality therapy in the treatment of patients with NSCLC. These toxicities can negatively affect a patient's quality of life as well as cause interruptions or delays in the treatment plan, which may influence patient survival.¹⁴ Toxicities associated with the chemotherapy component of RCT are pulmonary toxicity (esophagitis, pneumonitis, decreased pulmonary function, and fibrosis), myelosuppression, nephrotoxicity, and alopecia.³ The incidence of acute esophagitis and late-onset pneumonitis by grade of toxicity in patients participating in RTOG trials with combined-modality treatment with cisplatin-based regimens is shown in Table 1. Grade ≥ 3 toxicities range from 20% for late-onset pneumonitis to 37% for acute esophagitis. Grade 3-4 toxicities for acute esophagitis and late-onset pneumonitis have been found to be increased with concurrent RCT compared with either RT alone or sequential RCT.^{4,10}

Table 1. Incidence of Acute Esophagitis and Late-Onset Pneumonitis by Grade of Toxicity in RTOG Trials⁴

	<i>Acute Esophagitis</i>	<i>Late-Onset Pneumonitis</i>
GRADE	NO. OF PATIENTS (%)	NO. OF PATIENTS (%)
0	36 (6)	199 (34)
1	102 (18)	139 (24)
2	227 (39)	134 (22)
3	201 (34)	92 (16)
4	19 (3)	12 (2)
5	0 (0)	9 (2)
Total	585 (100)	585 (100)

Cytoprotection During Treatment for NSCLC

To minimize acute and chronic toxicities associated with treatment for NSCLC, there has been considerable interest in finding cytoprotective agents that protect normal tissues without compromising antitumor activity. Cytoprotective strategies recently investigated in the literature include: amifostine, gene therapy with manganese superoxide dismutase gene, TGF-beta, glutamine, melatonin, and omega-3 fatty acids.¹⁵ Of the FDA-approved cytoprotectants for use with chemotherapy regimens—amifostine, mesna, and dexrazoxane—amifostine has been the most extensively studied with regard to protecting cells against chemotherapy- and radiation-induced toxicities.^{2,3,16-19}

Cytoprotection With Amifostine Selectively Protects Normal Tissue

Amifostine is a prodrug that is dephosphorylated by alkaline phosphatase in tissues to pharmacologically active free thiol metabolite. It selectively protects normal cells from cytotoxic activity and scavenges free radicals produced by radiation and chemotherapy. The ability of amifostine to differentially protect normal cells is attributed to the higher alkaline phosphatase activity, higher pH, and better vascularity of normal tissue relative to tumor tissue, which results in a more rapid generation of the active thiol metabolite as well as a higher rate constant for uptake into normal tissues.²⁰

Using Amifostine in Practice

Amifostine is FDA approved to reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer or NSCLC. Patients with NSCLC treated with amifostine did not experience a reduction in efficacy of chemotherapy. Amifostine is also approved to reduce the incidence of moderate-to-severe xerostomia in patients undergoing postoperative radiation treatment for head and neck cancer, where the radiation port includes a substantial portion of the parotid glands.²⁰

Clinical Studies With Amifostine in Patients Undergoing Treatments for NSCLC

Amifostine has been studied for use as a cytoprotective agent in several different treatment settings for patients with NSCLC including: during chemotherapy to reduce renal toxicity associated with cisplatin (its approved indication), as well as, during RT or RCT to reduce radiation-induced mucositis and pulmonary toxicity.

Clinical Studies

Several studies have investigated the cytoprotective properties of amifostine prior to radiation alone or in combination with chemotherapy. (Tables 2 and 3; Figures 1-7)

Table 2. Clinical Trials in Radiotherapy ± Amifostine

STUDIES	PATIENTS	AMIFOSTINE DOSING	TREATMENT REGIMEN
Antonadou et al, 2001 ²	N=146	73 pts amifostine 340 mg/m ² vs 73 control pts	RT 55-60 Gy
Koukourakis et al, 2000 ²⁰	N=140 60 thoracic 40 head and neck 40 pelvic	Amifostine 500 mg/2.5 mL SC prior to RT vs RT alone	RT

Figure 1. Grade ≥2 Esophagitis and Pneumonitis in NSCLC ± Amifostine²

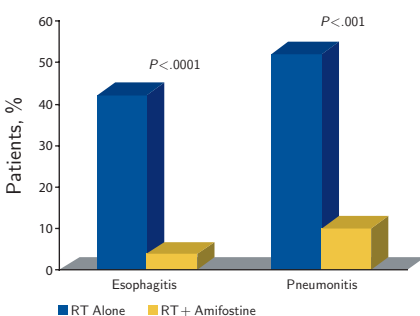


Figure 2. Mucosal Toxicity in Thoracic Cancer ± Amifostine²¹

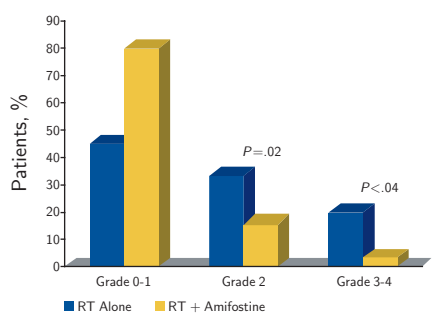


Table 3. Clinical Trials in Combined Modalities ± Amifostine

STUDIES	PATIENTS	AMIFOSTINE	REGIMEN
Werner-Wasik et al, 2002 ²²	N=24 Stage II/III NSCLC	12 pts Amifostine 500 mg IV 2x/wk	Paclitaxel 225 mg/m ² + carboplatin AUC 6 RT: 62.4 Gy + paclitaxel 60 mg/m ² q wk
Tannehill et al, 1997 ¹⁷	N=26 Unresectable stage IIIa/b NSCLC	Amifostine 740 or 910 mg/m ² , days 1, 29 Day 50, 200-340 mg/m ² 4-5 days/wk	Cisplatin 120 mg/m ² Vinblastine 5 mg/m ² RT total 60 Gy
Antonadou et al, 2003 ³	N=68 Stage IIIa/b NSCLC	36 pts amifostine 300 mg/m ² before RCT vs 32 control pts	36 pts paclitaxel 60 mg/m ² + RT 2 Gy 5d/wk or 32 pts carboplatin AUC 2 + RT
Komaki et al, 2004 ¹⁸	N=62 Stage II/III NSCLC	31 pts amifostine 500 mg IV x 2d vs 31 control pts	Cisplatin 50 mg/m ² Oral etoposide 50 mg bid RT 69.6 Gy at 1.2 Gy bid

Figure 3. Esophagitis Index (EI) During Radiochemotherapy ± Amifostine²²

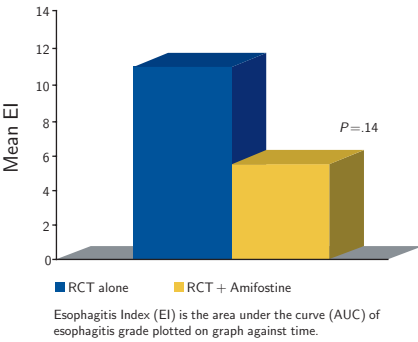


Figure 4. Acute Esophagitis Rates During Radiochemotherapy With Amifostine¹⁷

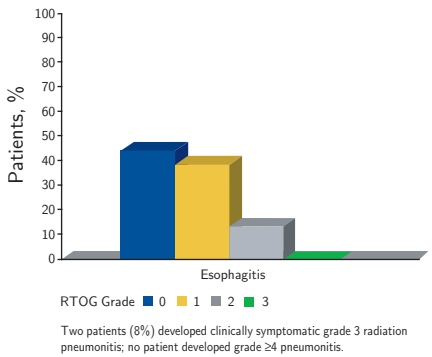


Figure 5. Incidence of Acute Toxicities (Grade ≥3) During Radiochemotherapy ± Amifostine³

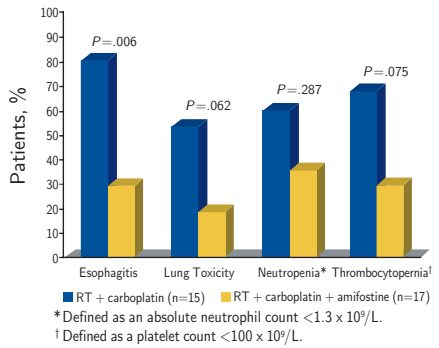
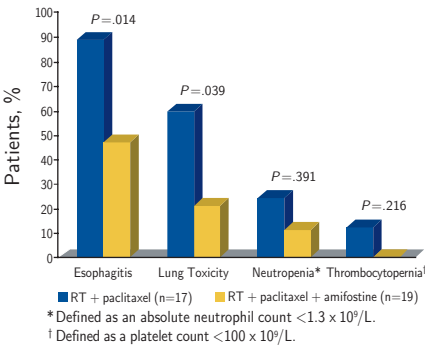
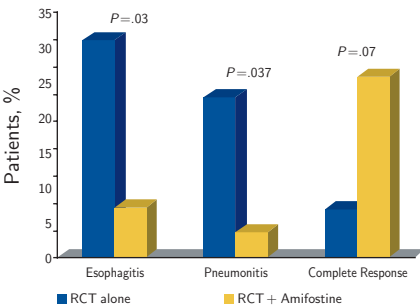


Figure 6. Concurrent Chemotherapy and Hyperfractionated Radiation Therapy for Inoperable NSCLC ± Amifostine²³



CLINICAL CASES

The following cases are intended to help you understand some of the patient-management considerations that must be addressed when amifostine is incorporated into NSCLC treatments.

Clinical Case #1

The patient is a 45-year-old man with NSCLC who has received amifostine for mucosal protection in the chemotherapy department and subsequently heads to the radiotherapy department for treatment. The nurse in the radiation department inquires about the duration of time that is necessary from administration of amifostine to the patient receiving RT.

Discussion Points

- Clinical experience with daily dosing suggests that dosing amifostine up to 60 minutes prior to radiation may provide protection.
- Studies continue to evaluate extending the dosing window beyond 30 minutes to ensure that the cytoprotective effects of amifostine may be maintained.
- Daily dosing of amifostine prior to each radiation treatment (5 times per week) is recommended.

The patient received amifostine with standard intravenous (IV) administration. What are the expected side effects and what measures decrease the side effects of IV amifostine administration?

IV Administration

The most common side effects that occur with standard IV amifostine administration are hypotension and nausea and/or vomiting.²⁴ In general, hypotension is transient and does not lead to discontinuation of treatment. Nausea and/or vomiting associated with amifostine are usually related to dose and duration of administration and are not cumulative with repeated dosing.²⁵

Administering amifostine by a bolus injection rather than a short infusion could prove less time intensive, easier, and more practical.²⁶ Recent research shows that shorter injection times may decrease the occurrence of some side effects associated with amifostine, thereby improving overall tolerance and patient compliance. In addition, there is no evidence that rapid infusion negatively impacts the effectiveness of amifostine or the antitumor efficacy of radiation or chemotherapy.²⁵⁻²⁷

Assessing Risk for Nausea and/or Vomiting: Standard IV Administration

Oral or intravenous 5-HT₃ receptor antagonists, alone or in combination with other antiemetics, have been used effectively in this setting, although other antiemetic regimens may be an option for some patients.

- Oral antiemetics should be given 90 to 120 minutes prior to amifostine administration.²⁵
- IV antiemetics should be given 60 minutes prior to amifostine administration.²⁵

Antiemetic regimens must be tailored to the patients' risk profiles, including their medical status, cancer therapy, and propensity to experience nausea and/or vomiting in other situations (Table 4).²⁵

Table 4. Patient Profile for Assessing Risk for Nausea and/or Vomiting²⁵

HIGH RISK	LOW RISK
Receiving highly emetogenic chemotherapy	Receiving radiation therapy alone or in combination with nonemetogenic chemotherapy
Experienced emesis with previous chemotherapy and/or amifostine	No emesis experienced with previous chemotherapy and/or amifostine
Not adequately hydrated	
Hypotensive	
Prone to nausea and/or vomiting in other situations (eg, during pregnancy; experienced motion sickness; with other medications)	

Hypotension

Amifostine should not be administered to patients who are dehydrated or hypotensive. Reclining patients during standard or rapid IV push administration is also recommended to help prevent hypotension. Patients should remain reclined for 15 minutes after amifostine is administered, and their blood pressure should be

monitored. Hypotension associated with amifostine is typically transient. If significant hypotension does occur, patients should be placed in the Trendelenburg position and given normal saline intravenously until it resolves.²⁰

Which patient hydration assessments should be performed daily prior to administering amifostine?

Adequate hydration prior to amifostine administration may also reduce the propensity for nausea and/or vomiting.

To evaluate for dehydration, patients should be assessed daily by checking for signs of:

- Poor skin turgor
- Dry oral mucosa
- Hypotension and tachycardia
- Decrease in weight
- Urine concentration
- Dizziness and lightheadedness

Patients should also be educated and encouraged to:

- Drink at least two 8-ounce glasses of water prior to treatment
- Drink 1 liter of water throughout the day
- Avoid caffeinated beverages and alcohol²⁵

If necessary, patients can be hydrated intravenously (250-500 mL of normal saline) 1 hour prior to amifostine administration.

Clinical Case #2

A 60-year-old man with stage IIIb NSCLC carcinoma has just completed his second week of combined-modality therapy and has had 10 subcutaneous (SC) injections of amifostine. When he arrives for his injection, you note a circular reddened area at the site of his last injection. He denies any itchiness at the site, and the area is not warm to the touch.

Questions for Consideration

- What steps would be prudent?
- How would you classify the rash? Is it a local injection site rash or a generalized rash?
- Do you withhold amifostine?
- What local measures could be utilized for symptomatic relief?

SC Administration*

SC dosing may be a practical alternative to the standard IV administration, especially for patients receiving daily fractionations who do not have a central or peripherally inserted venous catheter in place for chemotherapy.^{21,28}

SC dosing may:

- Minimize logistical issues present in the RT setting
- Eliminate the need for specialized personnel trained in IV administration
- Be less time intensive, easier, and more practical than other administration routes
- Decrease the occurrence of hypotension and nausea and/or vomiting

However, aggressive hydration and pretreatment with antiemetics are still recommended with SC administration of amifostine.²⁵ Refer to the package insert for approved dosing and administration of amifostine.²⁰

Cutaneous Reactions

Cutaneous reactions have been reported with the use of amifostine; patients should be monitored daily for cutaneous reactions prior to each amifostine administration.²⁹

During the evaluation, particular attention should be given to any rash on the lips, mucosa, palms, soles of feet, and trunk not due to another etiology, such as radiation-induced dermatitis. Amifostine should be immediately and permanently discontinued for any serious or severe cutaneous reaction including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, or exfoliative dermatitis, or for any cutaneous reaction associated with fever.¹⁶

Clinical Trials

In ongoing clinical trials evaluating SC administration, a 500-mg vial of amifostine is reconstituted with 2.9 mL normal saline. The final volume of approximately 3.2 mL is administered by 2 injections using a 25-g or 27-g needle at 2 sites (eg, upper left and upper right arm) while the patient is seated upright.³⁰ SC dosing has been associated with localized and generalized (systemic) cutaneous reactions, so

* Route of administration not approved by the FDA for amifostine. Refer to package insert for approved administration.

patients should receive a cutaneous evaluation prior to each amifostine administration. To help alleviate cutaneous reactions associated with amifostine, injection sites should be rotated.²⁹ Although SC administration may require less administration time for staff compared with IV administration, adequate time should still be scheduled to assess patients daily for signs of cutaneous reactions, hypotension, dehydration, and nausea and/or vomiting.²⁸

Strategies for Improving Tolerance and Managing Side Effects

The most common side effects associated with the standard IV administration as described in the Prescribing Information are nausea and/or vomiting and hypotension. Recent research has shown that the occurrence of nausea and/or vomiting should decrease when amifostine is administered by rapid IV push or SC administration. It is important to stress, however, that adequate hydration and premedication with antiemetics are still necessary with the SC route of administration of amifostine, to prevent side effects of nausea and vomiting.

Clinical Case #3

A 63-year-old man presented 3 months ago to urgent care with cough, mild dyspnea, and low-grade fever. He was initially treated with an antibiotic for 10 days. The patient returned to the clinic with increased dyspnea, cough, and weight loss. A physical exam revealed the following: a 5'11" person weighing 180 lbs with lung sounds distant in left lower lobe. His performance status was Karnofsky 90. A chest x-ray demonstrated a left lower lobe infiltrate and a mass approximately 2.5 cm. The patient was referred to a pulmonologist. Further diagnostic exams included obtaining sputum cultures and a CT (computerized tomography) guided biopsy, which revealed adenocarcinoma of the left lower lobe. Further staging included a mediastinoscopy and a PET (positron emission tomography) scan. The tumor was determined to be stage IIIb. The patient will receive combined-modality therapy for NSCLC.

Questions for Consideration

- What treatment-related toxicities would you anticipate from this regimen?
- Why would you recommend cytoprotection?

Discussion

The strategy to improve lung cancer treatment is to maintain the intensity of the radiation therapeutic dose so as to achieve maximum cell kill. This is feasible only if normal lung tissue can be protected. Esophagitis represents an acute dose-limiting side effect of radiation therapy to the lung. Pulmonary fibrosis represents a late effect of radiotherapy. Antonadou et al assessed the role of amifostine in patients with lung cancer prior to radiation therapy.² The control group of patients 14/73 (19%) experienced grade 2 esophagitis versus 4/73 (6%) patients receiving amifostine in week 3 of radiation. By week 4, 31/73 (42%) patients in the control group versus 3/73 (4%) in the amifostine group experienced grade 2 esophagitis ($P < .0001$).² Two months after radiation therapy was completed, 23/53 (43%) patients in the control group versus 4/44 (9%) patients in the amifostine group presented with clinical symptoms of grade ≥ 2 pneumonitis. At 3 months after radiation therapy, 24/46 (52%) patients in the control arm versus 4/32 (12%) patients in the amifostine arm presented with grade ≥ 2 pneumonitis.² This study concluded that both esophagitis and pneumonitis are decreased with the use of amifostine as a cytoprotector.

Several studies have shown that combined-modality treatments improve overall outcomes in patients with NSCLC. In NSCLC, however, combined-modality therapy may be limited by treatment-related toxicities. These toxicities may contribute to treatment delays and also may adversely affect a patient's quality of life because of esophagitis and pneumonitis.^{4,10,14} Several studies describe the use of cytoprotection with amifostine in patients with NSCLC to help reduce RCT-related side effects.

CONCLUSION

Oncology nurses play a key role in educating patients and their families on ways to minimize treatment-related side effects of RCT. Written and verbal instructions are necessary to ensure that the patient understands the importance of preventing treatment-associated side effects. Giving patients specific instructions for adequate hydration measures are helpful. Patients are advised to drink 2 to 3 glasses of water or sports drink prior to treatment and 1 liter of fluid throughout the day, and to avoid caffeinated beverages and alcohol.²⁰ Hydration prior to amifostine administration will decrease the propensity for nausea and vomiting. Although the occurrence of nausea and vomiting should decrease with rapid IV push or the use of SC amifostine, adequate self-hydration and premedication with antiemetics in the recommended

time frame are still necessary.²⁵

Oral or IV 5-HT₃ receptor antagonists have been used effectively in preventing nausea and vomiting prior to giving amifostine. The timing, however, is the most important factor in administering the antiemetic.²⁵ Oral antiemetics should be given 90 to 120 minutes prior to amifostine administration. IV antiemetics should be given 60 minutes prior to amifostine administration. Oncology nurses play a vital role in preventing side effects of amifostine. The oncology nurse provides the tools necessary to maintain patients through successful amifostine treatment. The use of cytoprotection significantly reduces the early side effects of RCT. Successfully avoiding treatment delays and decreasing esophagitis and pneumonitis increase the quality of life in the patient with NSCLC.

Upon completion of the CaseMat study program, the oncology nurse will be able to gain practice methods regarding amifostine dosing, administration, and side-effect management used to reduce the toxicity of concurrent chemotherapy and radiotherapy for patients with NSCLC. Through clinical case presentations and evidence-based practice methods, the oncology nurse can incorporate this vital information on the use of amifostine in patients with NSCLC and apply it to his/her practice.

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T H R O U G H A G G R E S S I V E



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For the purpose of achieving maximum learning as well as contact hours, both modules must be completed. This education program, as an EDII, is not intended to be used as a group activity.

OVERVIEW

Lung cancer is the leading cause of cancer death in the United States among both men and women.¹ The majority of the lung tumors diagnosed are non–small-cell lung cancers (NSCLCs), with only 15% to 25% treatable with surgery.² As many as 40% of patients present with locally-advanced and/or unresectable disease.³ Traditionally, radiotherapy (RT) was the treatment of choice for patients with inoperable NSCLC.² However, more recently, numerous clinical studies have demonstrated increased survival rates for patients treated with combined chemotherapeutic regimens.^{3,4} Aggressive cancer therapies such as combined-modality approaches for NSCLC have improved outcomes; however, patients are at increased risk for dose-limiting toxicities that can result in treatment delays and potentially negatively impact quality of life.

TARGET AUDIENCE

This CNE activity will be beneficial for nurse oncologists, as well as healthcare professionals involved in the diagnosis and treatment of patients with non–small-cell lung cancer.

LEARNING OBJECTIVES

After completing this CNE activity, participants should be able to:

- Identify the serious side effects related to the treatment of NSCLC
- Describe the utility of cytoprotective agents in the management of patients through aggressive therapies
- Demonstrate the role and proper use of amifostine in the treatment of patients with NSCLC
- Assess how the use of amifostine may affect patients, therapies, and/or treatment outcomes

CONTINUING NURSING EDUCATION

This offering is approved for 1.2 contact hours by Medical Education Group LLC. Medical Education Group LLC is an approved provider of continuing nursing education by the Pennsylvania State Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation. Accreditation refers to recognition of continuing nursing education activities and does not imply approval or endorsement of any commercial product.

1. American Cancer Society. *Cancer Facts and Figures 2004*. Atlanta, Ga: American Cancer Society; 2004.

2. Antonadou D, Coliarakis N, Synodinou M, et al, for the Clinical Radiation Oncology Hellenic Group. Randomized phase III trial of radiation treatment ± amifostine in patients with advanced-stage lung cancer. *Int J Radiat Oncol Biol Phys*. 2001;51:915-922.

3. Antonadou D, Throuvalas N, Petridis A, Bolanos N, Sagriotis A, Synodinou M. Effect of amifostine on toxicities associated with radiochemotherapy in patients with locally advanced non–small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2003;57:402-408.

4. Werner-Wasik M, Scott C, Curran WJ, Byhardt R. Correlation between acute esophagitis and late pneumonitis in patients (pts) with locally advanced non–small-cell lung cancer (LA-NSCLC) receiving concurrent thoracic radiotherapy (RT) and chemotherapy: a multivariate analysis of the Radiation Therapy Oncology Group (RTOG) database. *Proc Am Soc Clin Oncol*. 2002. Abstract 1192.

—ACKNOWLEDGMENT—

Medical Education Group LLC acknowledges an unrestricted educational grant from MedImmune Oncology, Inc. in support of this CNE activity.

—MEDIUM—

This multimodality approach was chosen as the instructional format to accommodate the learning preferences of a significant portion of the target audience.

—LEARNER PARTICIPATION—

Learners are advised to read and review the casemat case study and slide workbook and complete the Evaluation and Credit Form.

—ESTIMATED COMPLETION TIME—

The estimated time for completion of this educational activity should not exceed 1 hour.

—RELEASE AND EXPIRATION DATES—

This activity was approved for contact hours and released on January 1, 2006. Effective January 31, 2008, this activity will no longer be approved for contact hours but may still have value for the healthcare provider.

—DISCLOSURE DECLARATION—

It is the policy of Medical Education Group LLC to ensure balance, independence, objectivity, and scientific rigor in all continuing education activities.

—UNLABELED/INVESTIGATIONAL USE DECLARATION—

This educational activity does include discussion of an unlabeled or investigational use not approved for a commercial product.

—DISCLAIMER—

The faculty, Medical Education Group LLC, and MedImmune Oncology, Inc. do not recommend the use of any pharmaceutical, diagnostic test, or device outside of the labeled indications approved by the FDA. Please refer to the official prescribing information for each product for approved indications, contraindications, and warnings.

Any procedures, medications, devices, or other courses of diagnosis or treatment discussed or suggested in this CNE activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications or dangers of use. It is recommended that physicians review any applicable manufacturers' product information and compare any off-label discussions with other authorities.

—FEE—

There is no fee for this CNE activity. To obtain a credit certificate for this activity, participants must complete the Evaluation and Credit Form.

Slide 1



Managing Patients
Through Aggressive
Cancer Therapies

A Focus on
Non-Small-Cell Lung Cancer

The slide features a dark blue background with a yellow horizontal bar at the top. Below the bar are five vertical rectangular panels with a grid pattern. The main title is in large, bold, yellow font, and the subtitle is in white font below it.

Slide 2

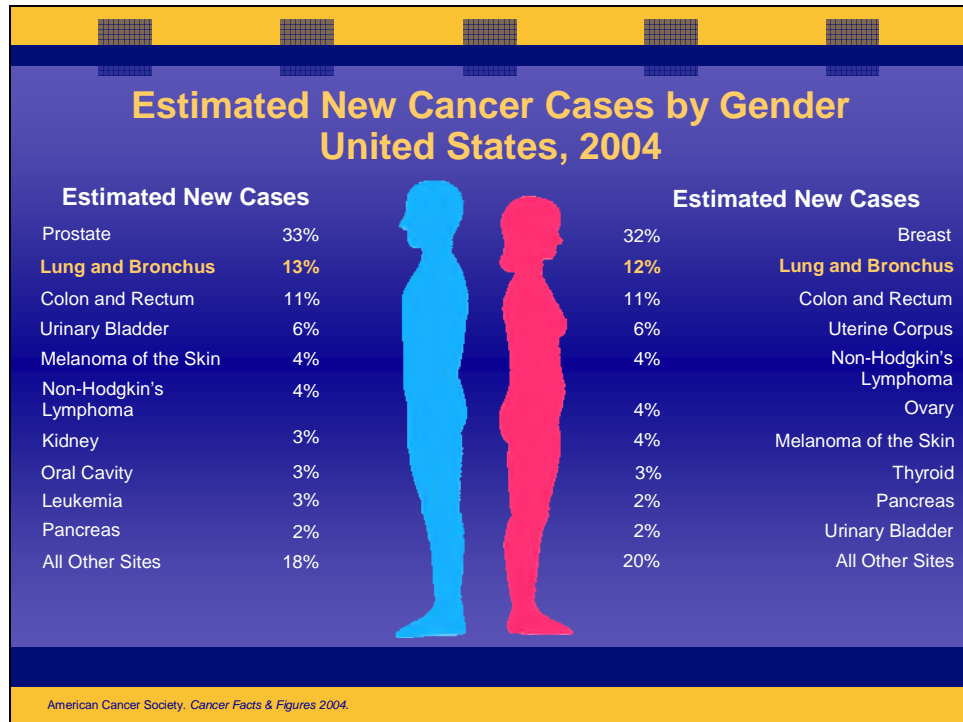


Learning Objectives

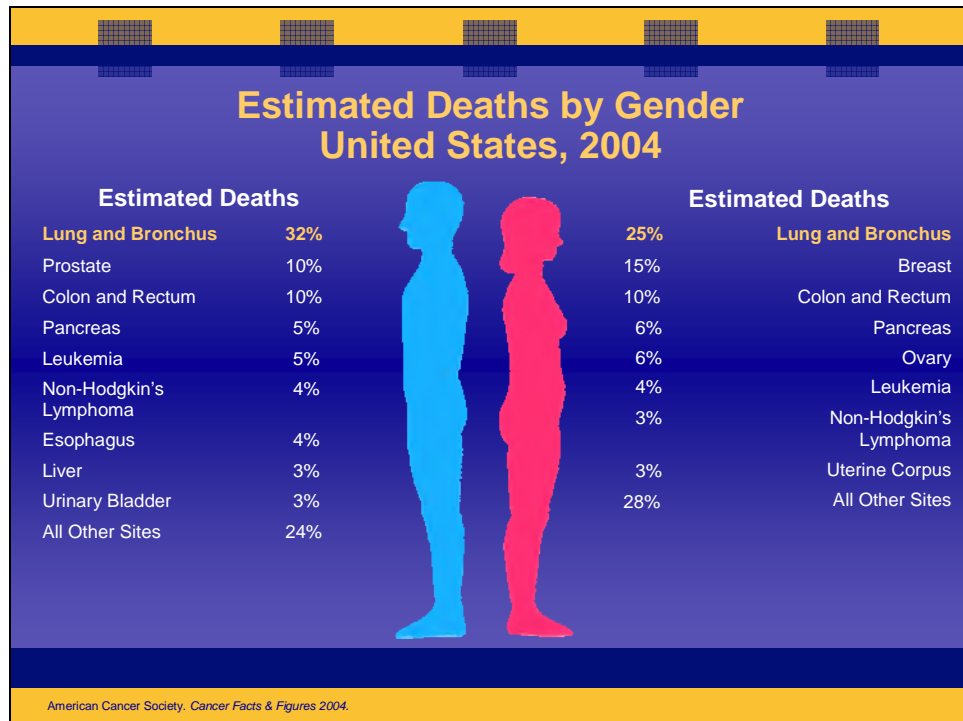
- ◆ Identify the serious side effects related to the treatment of NSCLC
- ◆ Describe the utility of cytoprotective agents in the management of patients through aggressive therapies
- ◆ Demonstrate the role and proper use of amifostine in the treatment of patients with NSCLC
- ◆ Assess how the use of amifostine may affect patients, therapies, and/or treatment outcomes

The slide features a dark blue background with a yellow horizontal bar at the top. Below the bar are five vertical rectangular panels with a grid pattern. The title is in large, bold, yellow font, and the list of objectives is in white font below it.

Slide 3



Slide 4



Slide 5

NSCLC Stage-Related Survival

Stage at Diagnosis (1995-2000)	5-Year Survival, %
All Stages	15.2
Local*	49.4
Regional	16.1
Distant	2.1

*Only 16% of lung cancers are diagnosed at this early stage.

American Cancer Society. Cancer Facts & Figures 2004. American Cancer Society. Detailed guide: lung cancer. How is lung cancer staged? Available at: http://www.cancer.org/docroot/CRI/content/CRI_2_4_3X_How_is_lung_cancer_staged_26.asp. Accessed September 13, 2004.

Slide 6

NSCLC Standard Therapies

Stage	Treatment
Ia T1, N0, M0	Surgery
Ib T2, N0, M0	Surgery + adjuvant CT
IIa T1, N1, M0	Surgery + adjuvant CT
IIb T2, N1, M0 T3, N0, M0	Surgery + adjuvant CT Surgery
IIIa T1-2, N2, M0 T3, N1, M0	Surgery vs S/CT/RT
IIIb Any T, N3, M0 T4, any N, M0	RT vs CT/RT vs S/CT/RT
IV Any T, any N, M1	Palliative or experimental

S = surgery; CT = chemotherapy; RT = radiation therapy.

American Cancer Society. Detailed guide: lung cancer. How is lung cancer staged? Available at: http://www.cancer.org/docroot/CRI/content/CRI_2_4_3X_How_is_lung_cancer_staged_26.asp. Accessed September 13, 2004; National Cancer Institute. Non-small-cell lung cancer: Treatment. Available at: <http://www.cancer.gov>.

Slide 7

Radiochemotherapy in Stage III NSCLC

- ◆ Goals
 - Local control (RT +/- CT)
 - Distant control (CT)
- ◆ Timing of modalities
 - Sequential platinum-based CT followed by RT improves survival compared with RT alone (CALGB, RTOG)
 - Concurrent radiochemotherapy may be superior to sequential therapy (SOLCSG, RTOG)

RT = radiation therapy; CT = chemotherapy; CALGB = Cancer and Leukemia Group B; RTOG = Radiation Therapy Oncology Group; SOLCSG = Southern Osaka Lung Cancer Study Group.

American Society of Clinical Oncology. *J Clin Oncol*. 1997;15:2996-3018; Dillman RO et al. *J Natl Cancer Inst*. 1996;88:1210-1215; Werner-Wasik M et al. *Am Soc Clin Oncol*. 2002. Abstract 1192; Furuse K et al. *Am Soc Clin Oncol*. 2000;19:484a. Abstract 1893; Mvasas B et al. *Am Soc Clin Oncol*. 2002;20:31a. Abstract 1247.

Slide 8

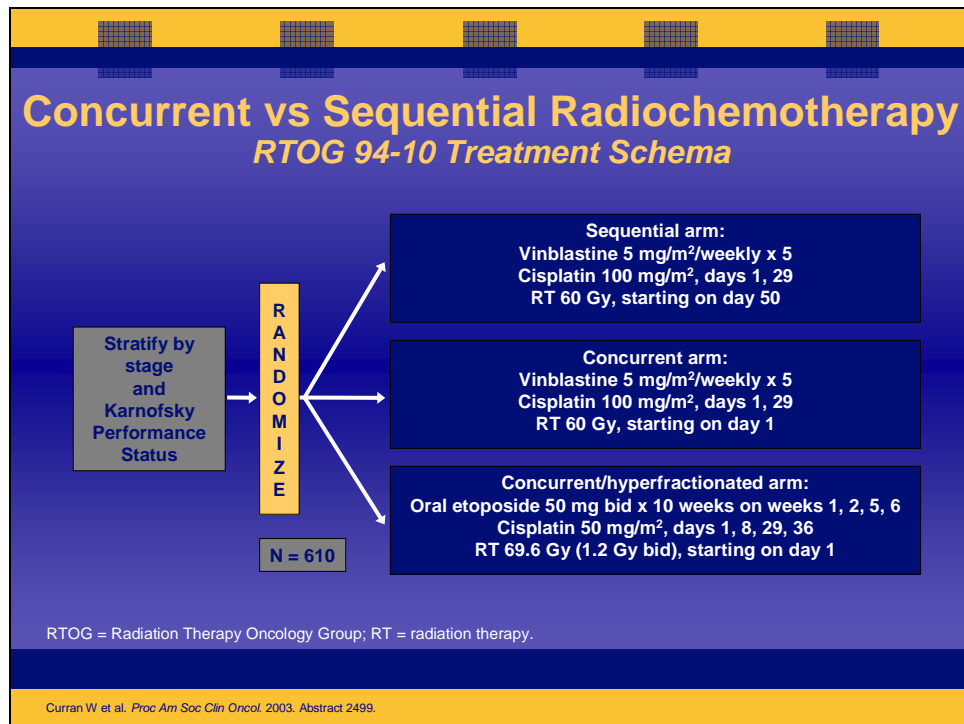
Sequential vs Concurrent Radiochemotherapy

- ◆ Sequential RCT
 - Initially delivers “systemic” chemotherapy doses
 - May compromise local control owing to delayed thoracic RT
- ◆ Concurrent RCT
 - “Radiosensitizing”
 - Significantly enhances toxicity of radiation
 - Better tumor control and improved survival (WOLCSG, RTOG 94-10, LAMP)

RCT = radiochemotherapy; RT = radiation therapy; WOLCSG = Western Osaka Lung Cancer Study Group; RTOG = Radiation Therapy Oncology Group; LAMP = Locally Advanced Multimodality Protocol.

Cox JD et al. *Int J Radiat Oncol Biol Phys*. 1993;27:493-498; Werner-Wasik M et al. *Proc Am Soc Clin Oncol*. 2002. Abstract 1192; Curran WJ et al. *Proc Am Soc Clin Oncol*. 2001. Abstract 1244; Furuse K et al. *Proc Am Soc Clin Oncol*. 2000;19:Abstract 1893.

Slide 9



Slide 10

Grade ≥ 3 Esophagitis With Concurrent Radiochemotherapy

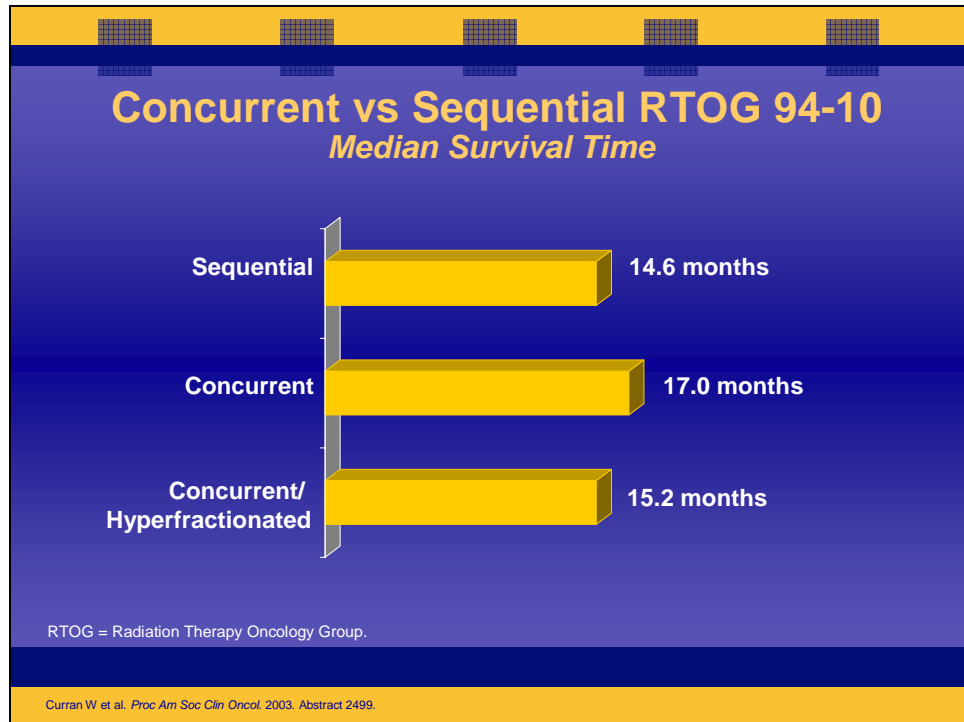
- ◆ LAMP (carboplatin/paclitaxel/63 Gy): 18%
- ◆ CALGB (cddP/Gem/63 Gy): 50%
- ◆ RTOG (cddP/Vbl or VP-16/63-69.6* Gy): 47%

LAMP = Locally Advanced Multimodality Protocol; CALGB = Cancer and Leukemia Group B; RTOG = Radiation Therapy Oncology Group.

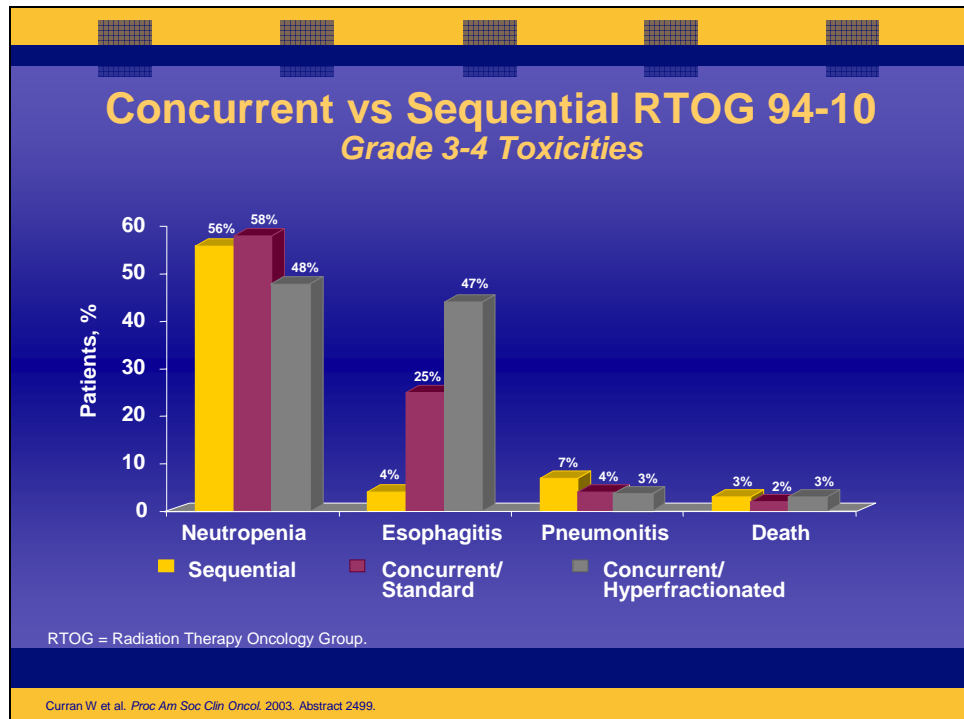
*Altered fractionation (bid) RT.

Curran WJ et al. *Proc Am Soc Clin Oncol*. 2001. Abstract 1244; Curran W et al. *Proc Am Soc Clin Oncol*. 2003. Abstract 2499; Dillman RO et al. *J Natl Cancer Inst*. 1996;88:1210-1215.

Slide 11



Slide 12



Slide 13

Lung and Esophageal Toxicity of Chemoradiation in NSCLC: RTOG Trials Study Descriptions

Trial #	N	RT Dose	Concurrent Chemotherapy
90-15	42	69.6 Gy bid	Cisplatin + vinblastine
91-06	79	69.6 Gy bid	Cisplatin + oral etoposide
92-04	168	1. 60 Gy 2. 69.6 Gy bid	Cisplatin + vinblastine Cisplatin + oral etoposide
94-10	398	1. 60 Gy 2. 69.6 Gy bid	Cisplatin + vinblastine Cisplatin + oral etoposide

RTOG = Radiation Therapy Oncology Group; NSCLC = non-small-cell lung cancer; RT = radiation therapy.

Werner-Wasik M. Proc Am Soc Clin Oncol. 2002. Abstract 1192.

Slide 14

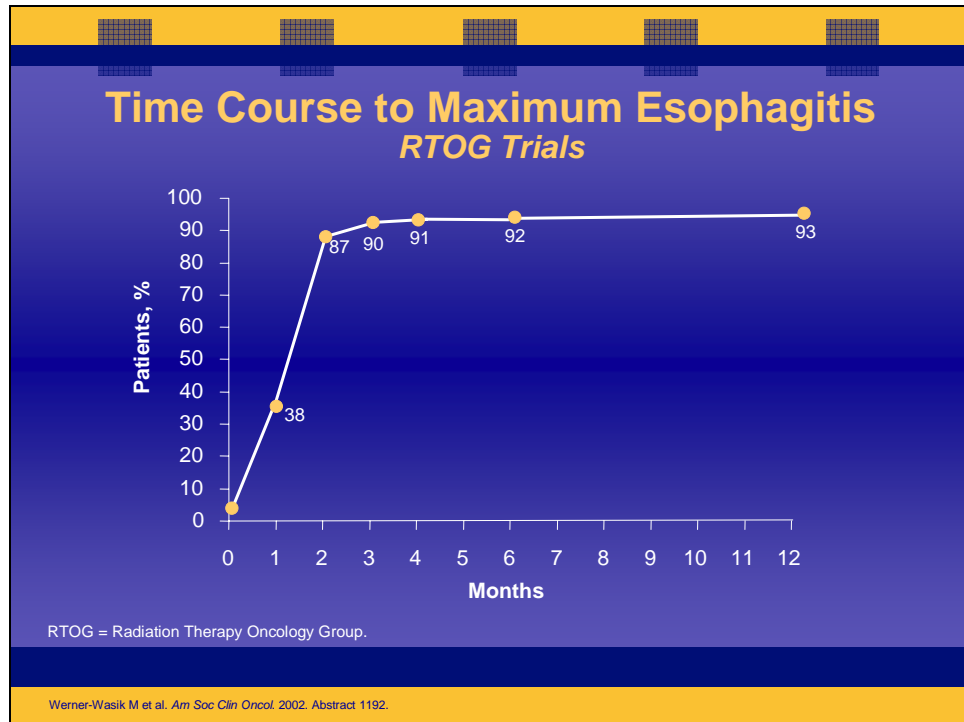
Incidence of Acute Esophagitis and Late-Onset Pneumonitis by Grade of Toxicity in RTOG Trials

Grade	Acute Esophagitis	Late-Onset Pneumonitis
	No. of Patients (%)	No. of Patients (%)
0	36 (6)	199 (34)
1	102 (18)	139 (24)
2	227 (39)	134 (22)
3	201 (34)	92 (16)
4	19 (3)	12 (2)
5	0 (0)	9 (2)
Total	585 (100)	585 (100)

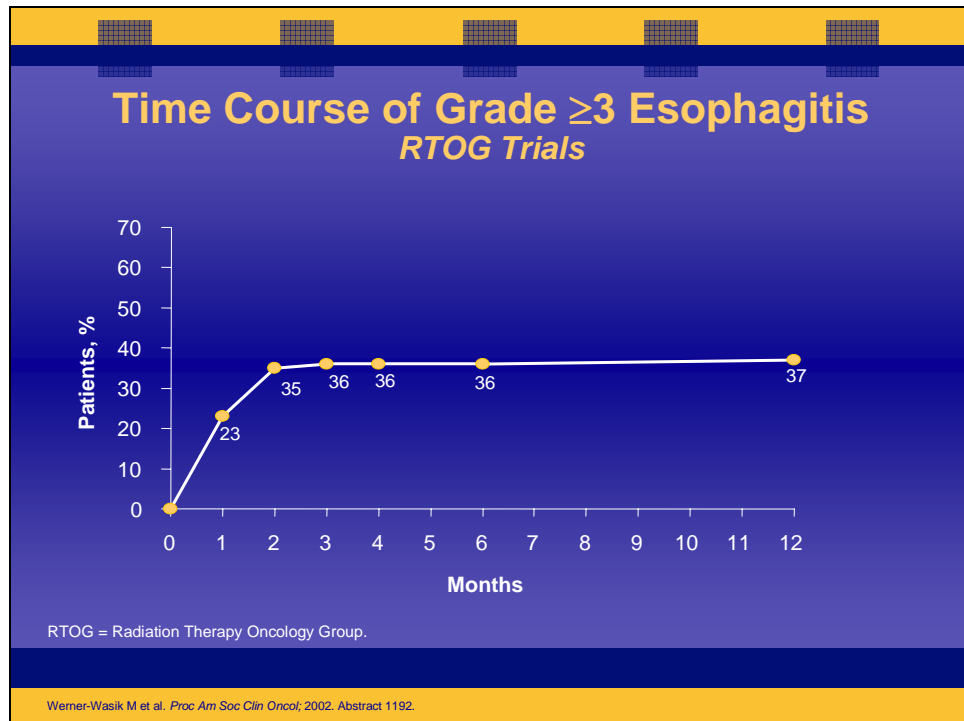
RTOG = Radiation Therapy Oncology Group.

Adapted from Werner-Wasik M. Proc Am Soc Clin Oncol. 2002. Abstract 1192.

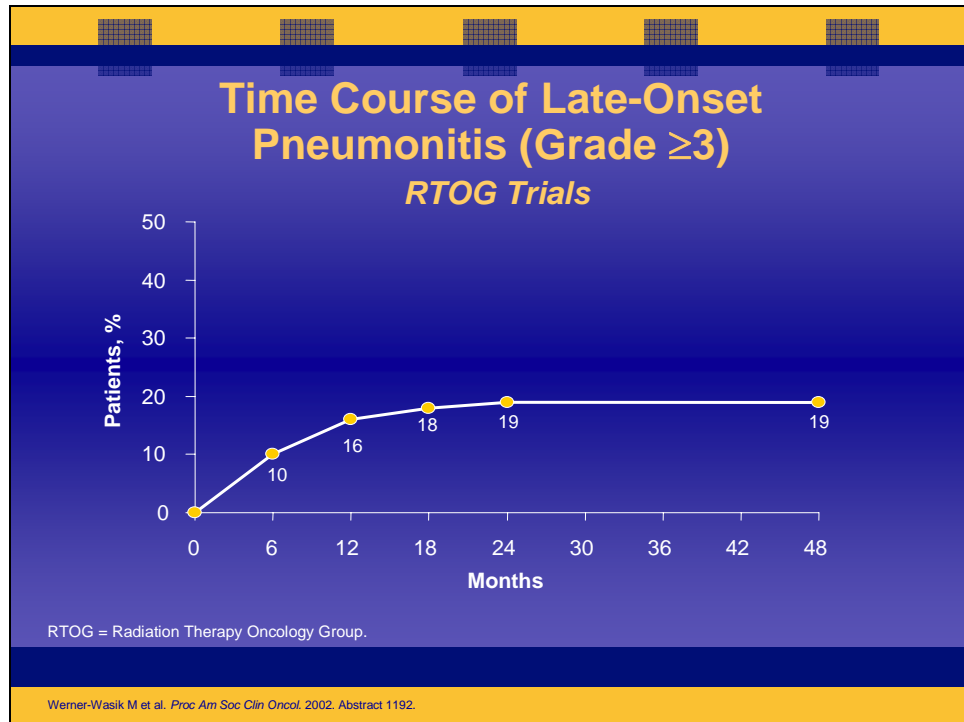
Slide 15



Slide 16



Slide 17



Slide 18

Incidence of Late-Onset Pneumonitis by Grade of Toxicity RTOG Trials

Grade	Patients, n	Patients, %
0	199	34
1	139	24
2	134	22
3	92	16
4	12	2
5	9	2
Total	585	100

RTOG = Radiation Therapy Oncology Group.

Werner-Wasik M et al. *Am Soc Clin Oncol*. 2002. Abstract 1192.

Slide 19

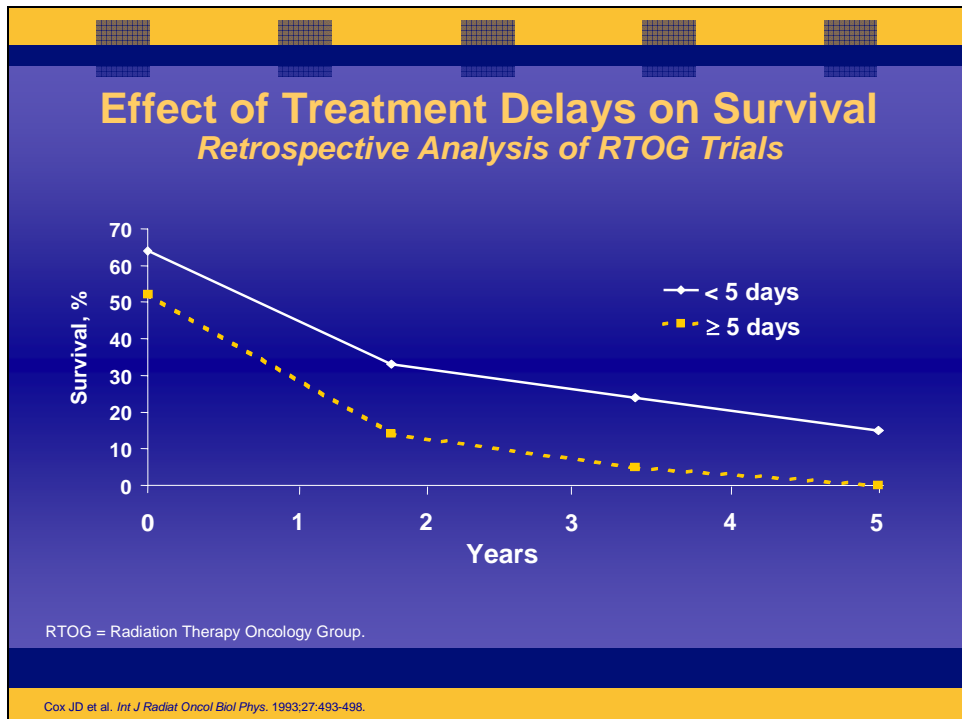
Effect of Treatment Delays on Survival *Retrospective Analysis of RTOG Trials*

- ◆ Analyzed survival following <5 vs ≥ 5 days of treatment delays
- ◆ 1244 patients with unresectable NSCLC
- ◆ Dose: 55-79.2 Gy

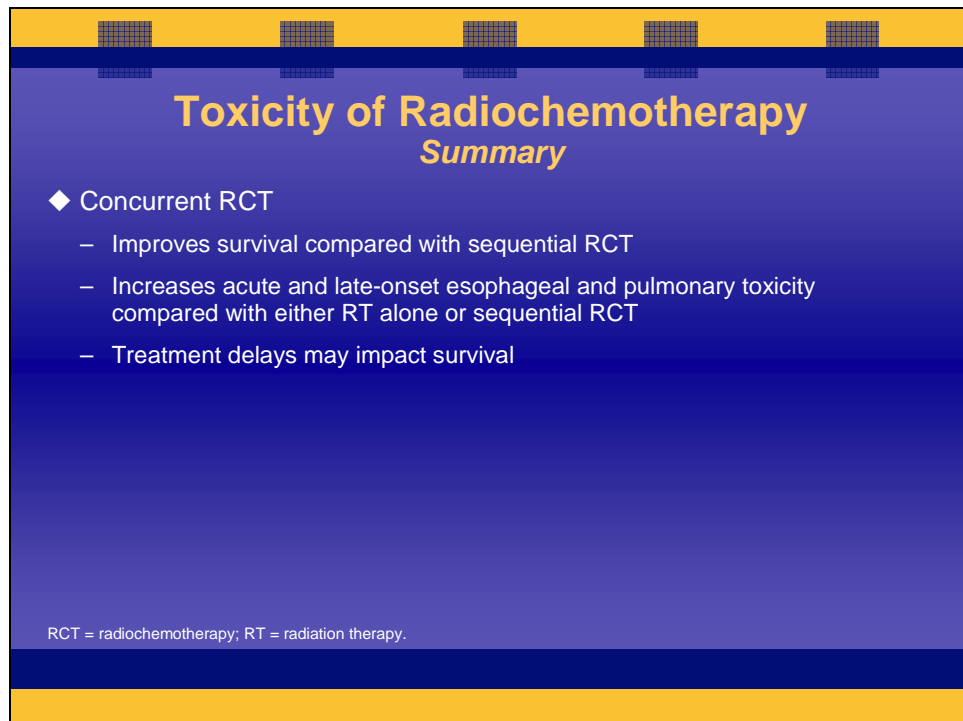
RTOG = Radiation Therapy Oncology Group.

Cox JD et al. *Int J Radiat Oncol Biol Phys.* 1993;27:493-498.

Slide 20



Slide 21



Toxicity of Radiochemotherapy
Summary

- ◆ Concurrent RCT
 - Improves survival compared with sequential RCT
 - Increases acute and late-onset esophageal and pulmonary toxicity compared with either RT alone or sequential RCT
 - Treatment delays may impact survival

RCT = radiochemotherapy; RT = radiation therapy.

Slide 22



Cytoprotective Strategies

Slide 23

Mucositis and Esophagitis Cytoprotective Strategies

- ◆ Amifostine
- ◆ Gene therapy: intratumoral injection of manganese SOD2-PL
- ◆ TGF- β
- ◆ Glutamine
- ◆ Interleukin-15
- ◆ Melatonin
- ◆ Omega-3 fatty acids
- ◆ KGF

SOD2-PL = superoxide dismutase-plasmid/liposome; TGF- β = transforming growth factor- β ;
KGF = keratinocyte growth factor.

Griggs JJ. *Leukemia Res.* 1998;1:27-33.

Slide 24

Amifostine

- ◆ Broad-spectrum cytoprotective agent that selectively protects normal tissue
- ◆ Mechanism of action
 - Decreased levels of membrane-bound AP in neoplastic tissue
 - Acidic pH down-regulates AP activity (normal cells: neutral pH)
 - Lower selective uptake by neoplastic tissues
 - Greater concentration in normal tissue vs neoplastic tissue
 - Protects DNA of normal cells from cytotoxic activity and from free radicals produced by RT and CT that alter structure and function of DNA

AP = alkaline phosphatase; DNA = deoxyribonucleic acid; RT = radiation therapy; CT = chemotherapy.

Capizzi RL. *Oncology*. 1999;13:47-59; Hensley ML et al. *J Clin Oncol*. 1999;17:3333-3355; Koukourakis MI. *Anti-Cancer Drugs*. 2002;13:181-209; Schuchter LM. *Oncology*. 1997;11:505-516; Yuhas JM. *Cancer Res*. 1980;40:1519-1524.

Slide 25

Amifostine as Cytoprotective Agent in NSCLC Treatment

- ◆ Chemotherapy setting
 - FDA approved to reduce cumulative renal toxicities associated with repeated administration of cisplatin
- ◆ Radiation setting
 - FDA approved to reduce incidence of moderate-to-severe xerostomia patients with head and neck cancer where radiation port includes substantial portion of parotid glands
 - ASCO clinical practice guidelines Level 1 evidence
 - Decreases incidence of acute and late xerostomia following fractionated radiation therapy in head and neck region
 - Investigated as a cytoprotectant
- ◆ Radiochemotherapy setting
 - Investigated as a cytoprotectant

Ethiyol [package insert], Gaithersburg, MD: MedImmune Oncology, Inc.; 2001; Henseley ML et al. *J Clin Oncol.* 1999;17:3333-3355.

Slide 26

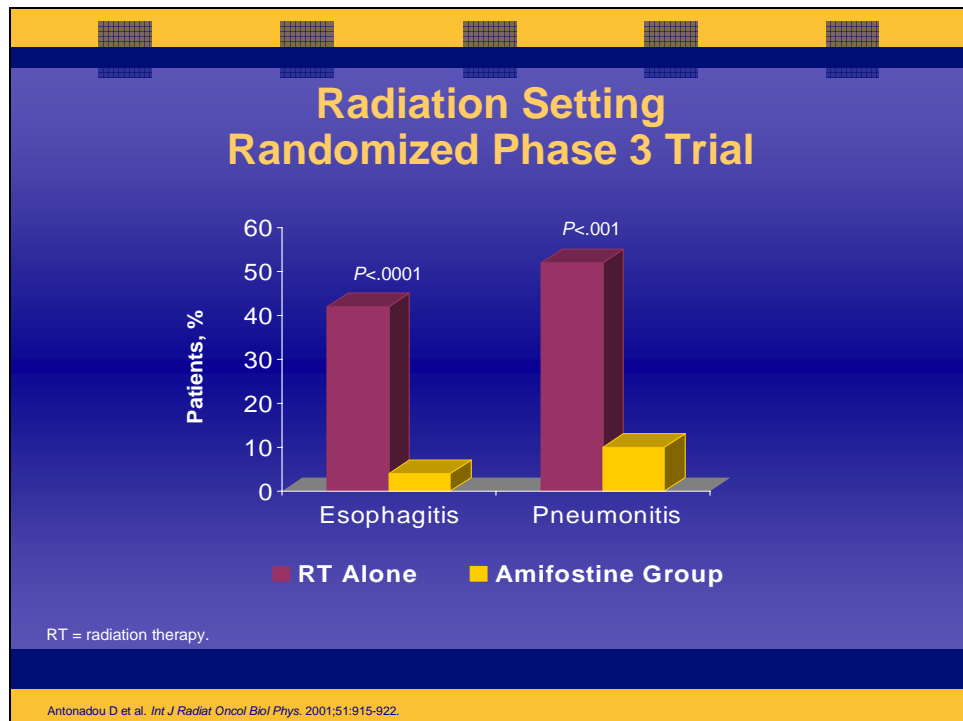
Amifostine Studies in Radiation Therapy Setting

Studies	Patients	Amifostine Dosing	Treatment Regimen
Randomized phase 3 Antonadou, 2001	N=146	73 pts amifostine 340 mg/m ² vs 73 control pts	RT 55-60 Gy
Randomized phase 2 Koukourakis, 2000	N=140 60 thoracic 40 head and neck 40 pelvic	Amifostine 500 mg/2.5 mL SC prior to RT vs RT alone	RT

SC = subcutaneous; RT = radiation therapy.

Antonadou D et al. *Int J Radiat Oncol Biol Phys.* 2001;51:915-922; Koukourakis MI et al. *J Clin Oncol.* 2000;18:2226-2233.

Slide 27



Slide 28

Radiation Setting Randomized Phase 2 Trial *Mucosal Toxicity*

Tumor Type	Grade 0-1, %	Grade 2, %	Grade 3-4, %
Head and Neck RT			
RT (n=20)	40	30	30
RT + A (n=19)	73	27	0
	Grade 0-1 vs 2 & 3-4, $P=.07$; Grade 0-1 vs 3-4, $P=.02$		
Thoracic RT			
RT (n=30)	46	34	20
RT + A (n=25)	80	16	4
	Grade 0-1 vs 2 & 3-4, $P=.02$; Grade 0-1 vs 3-4, $P=.08$		
Pelvic RT			
RT (n=20)	50	35	15
RT + A (n=16)	87	13	0
	Grade 0-1 vs 2 & 3-4, $P=.04$; Grade 0-1 vs 3-4, $P=.19$		

A = amifostine; RT = radiation therapy.

Koukourakis MI et al. *J Clin Oncol.* 2000;18:2226-2233.

Slide 29

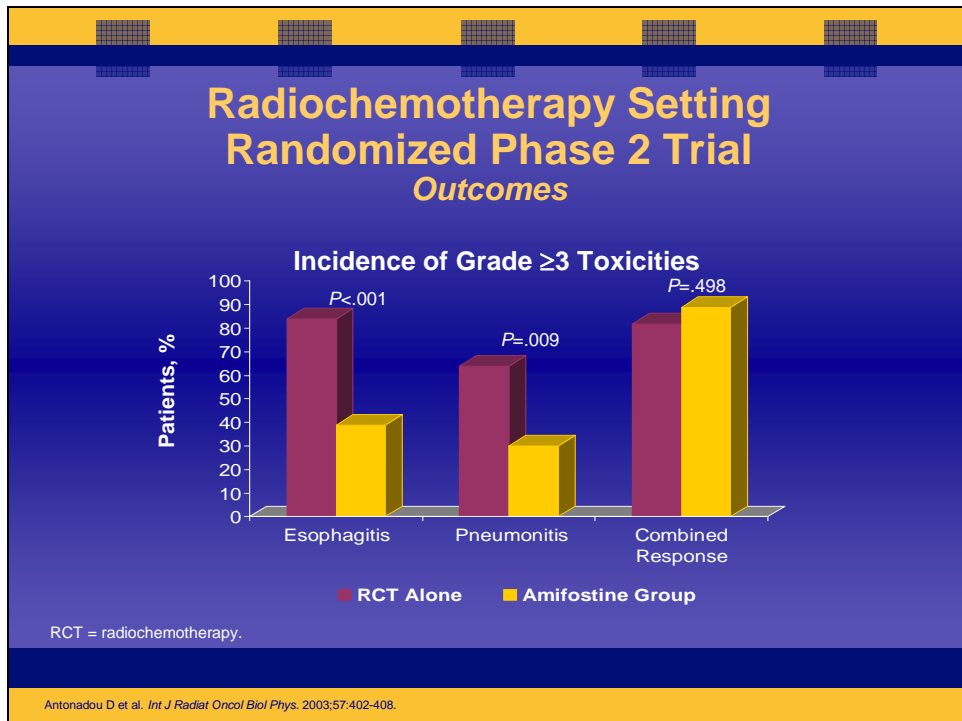
Amifostine Studies in Radiochemotherapy Setting

Studies	Patients	Amifostine	Regimen
Phase 2 Werner-Wasik, 2002	N=24 Stage II/III NSCLC	12 pts Amifostine 500 mg IV 2x/wk	Paclitaxel 225 mg/m ² + carboplatin AUC=6 RT: 62.4 Gy + paclitaxel 60 mg/m ² q wk
Phase 2 Tannehill, 1997	N=26 Unresectable stage IIa/b NSCLC	Amifostine 740 or 910 mg/m ² , days 1, 29 Day 50, 200-340 mg/m ² 4-5 days/wk	Cisplatin 120 mg/m ² Vinblastine 5 mg/m ² RT total 60 Gy
Phase 2 Antonadou, 2003	N=68 Stage IIIa/b NSCLC	36 pts amifostine 300 mg/m ² before RCT vs 32 control pts	36 pts paclitaxel 60 mg/m ² + RT 2 Gy 5d/wk or 32 pts carboplatin + RT
Phase 3 Komaki, 2004	N=62 Stage II/III NSCLC	31 pts amifostine 500 mg IV x 2d vs 31 control pts	Cisplatin 50 mg/m ² Oral etoposide (VP-16) 50 mg bid RT 69.6 Gy at 1.2 Gy bid

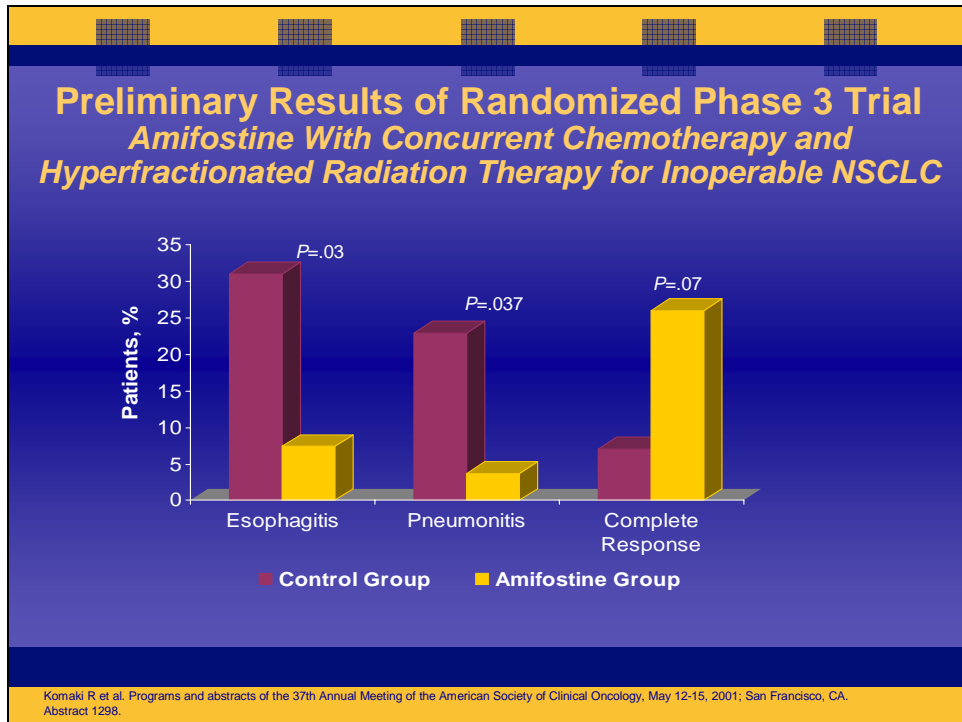
AUC = area under the curve; RCT = radiochemotherapy; RT = radiation therapy; IV = intravenous.

Werner-Wasik M et al. *Semin Radiat Oncol.* 2002;12(suppl 1):34-39; Tannehill SP et al. *J Clin Oncol.* 1997;15:2850-2857; Antonadou D et al. *Int J Radiat Oncol Biol Phys.* 2003;57:402-408; Komaki R et al. *Int J Radiat Oncol Biol Phys.* 2004;58:1369-1377.

Slide 30



Slide 31



Slide 32

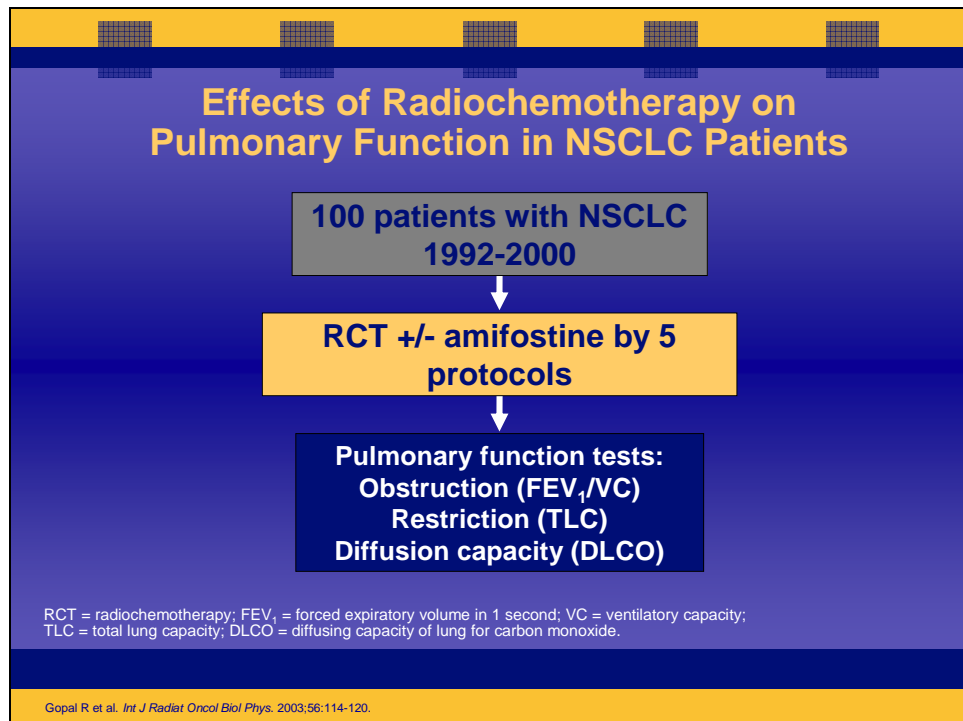
Results of Randomized Phase 3 Trial Amifostine With Concurrent Chemotherapy and Hyperfractionated Radiation Therapy for Inoperable NSCLC

	Control Group, %	Amifostine Group, %
Esophageal Toxicity*		
Grade 1	23	48
Grade 2	42	35
Grade 3	35	16
Pneumonitis*	16	0
Neutropenic fever*	39	16

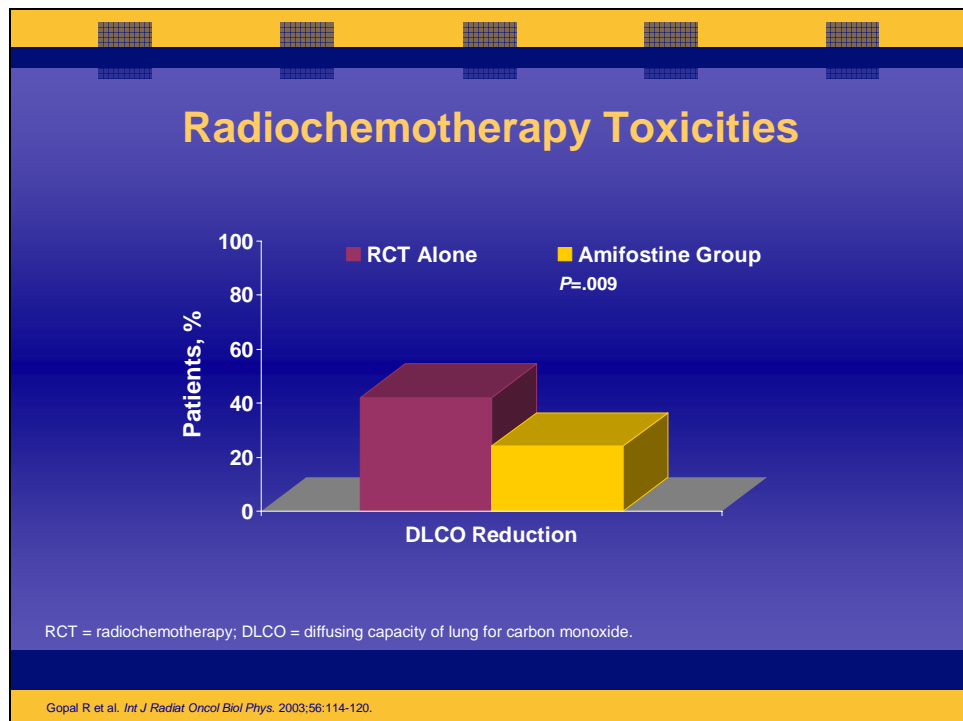
*P<.05.

Komaki R et al. *Int J Radiat Oncol Biol Phys.* 2004;58:1369-1377.

Slide 33



Slide 34



Slide 35

Effects of Radiotherapy on Quality of Life (ECOG 4593)

N=30
Nonresectable stage IIIa/IIIb NSCLC
RT = total dose 57.6 Gy

↓

**FACT-L questionnaire at
baseline, assessment 2
(last day of therapy)
and assessment 3
(4 weeks after therapy)**

ECOG = Eastern Cooperative Oncology Group; FACT-L = Functional Assessment of Cancer Therapy-Lung.

Auchter RM et al. *Int J Radiat Oncol Biol Phys.* 2001;50:1199-1206.

Slide 36

FACT-L Questionnaire

- ◆ The FACT-L includes specific subscales, including:
 - Physical well-being (7 items)
 - Social/family well-being (7 items)
 - Relationship with doctor (2 items)
 - Emotional well-being (5 items)
 - Functional well-being (7 items)
 - Lung cancer symptoms (7 items)
- ◆ TOI is a summation of the physical, functional, and lung cancer symptoms subscales (21 items), and the most clinically relevant aggregation of QOL dimensions

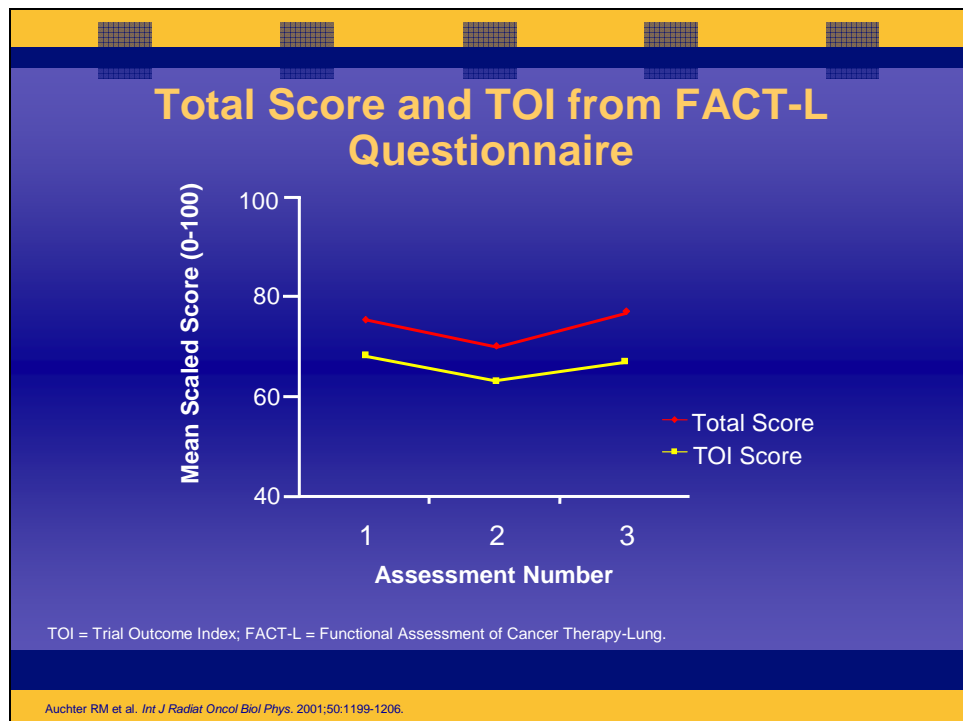
FACT-L = Functional Assessment of Cancer Therapy-Lung; TOI = Trial Outcome Index; QOL = quality of life.

Auchter RM et al. *Int J Radiat Oncol Biol Phys.* 2001;50:1199-1206.

Quality-of-Life Subscale Scores *Changes from Baseline*

- ◆ Decreases in physical well-being, functional well-being, and total scores at assessment 2 were significant compared to baseline ($P < .001$, $P = .01$, and $P = .02$, respectively)
- ◆ Changes in physical well-being, functional well-being, and total scores at assessment 3 were no longer significant compared to baseline ($P = .11$, $P = .48$, and $P = .99$, respectively)

Auchter RM et al. *Int J Radiat Oncol Biol Phys.* 2001;50:1199-1206.



Quality-of-Life Conclusions for Patients With NSCLC on Radiation Therapy (ECOG Study 4593)

- ◆ Significant declines in quality-of-life scores were observed for physical and functional scores when compared to baseline scores
- ◆ These scores returned to baseline levels 4 weeks after treatment
- ◆ Emotional well-being scores improved at all time points

ECOG = Eastern Cooperative Oncology Group.

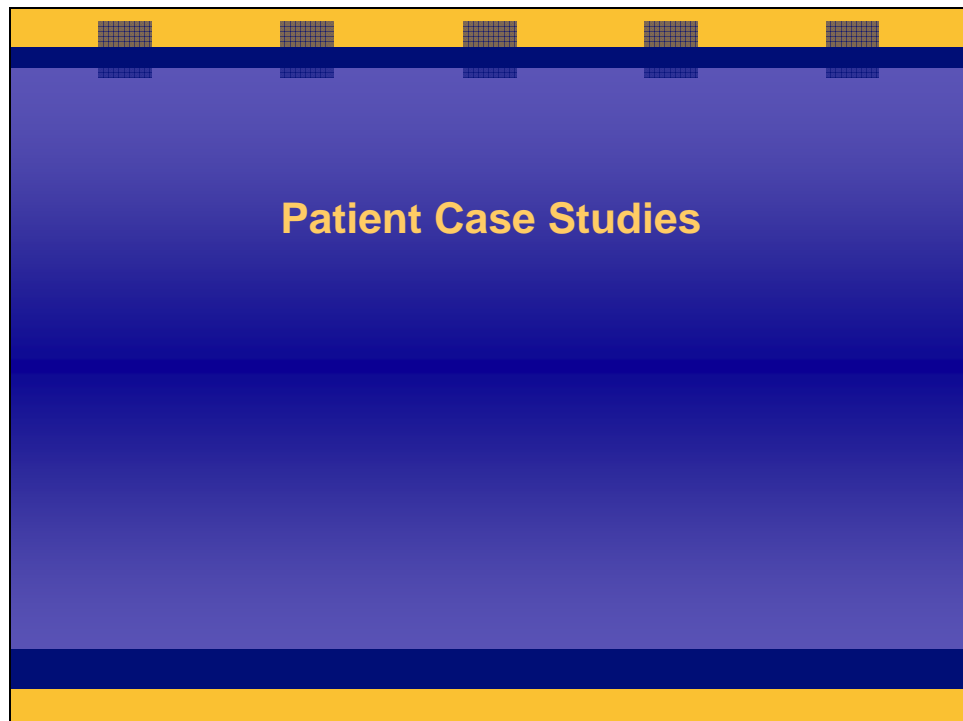
Auchter RM et al. *Int J Radiat Oncol Biol Phys.* 2001;50:1199-1206.

NSCLC and Amifostine Summary

- ◆ Amifostine has been shown to reduce the toxicity of single-modality therapy
- ◆ RCT is emerging as superior treatment for survival benefit
- ◆ RCT escalates toxicities that occur with single-modality therapy
- ◆ In this intensive therapy setting, amifostine has afforded the benefit of protection against symptomatic:
 - Mucositis
 - Esophagitis
 - Pneumonitis

RCT = radiochemotherapy.

Slide 41



Slide 42

A presentation slide with a blue gradient background and a yellow border. The title "Clinical Case Study #1" is centered in yellow text. Below the title are two bullet points in white text. At the bottom left, there is a small white text note: "RT = radiation therapy." At the top, there are five small grid icons on a yellow bar.

Clinical Case Study #1

- ◆ PS is a 45-year-old man with NSCLC who has received amifostine for mucosal protection in the chemotherapy department and subsequently heads to the radiotherapy department for treatment
- ◆ The nurse in the radiation department inquires about the duration of time that is necessary from administration of amifostine to the patient receiving RT

RT = radiation therapy.

Slide 43

Clinical Case Study #1 — Discussion

- ◆ Clinical experience with daily dosing suggests that dosing amifostine up to 60 minutes prior to radiation may provide protection
- ◆ Pharmacokinetic profile/preclinical data
- ◆ Studies continue to evaluate extending the dosing window beyond 30 minutes to ensure that the cytoprotective effects of amifostine may be maintained
- ◆ Daily dosing of amifostine prior to each radiation treatment (5 times per week) is recommended

Slide 44

Amifostine *Patient Management*

- ◆ Most common side effects with IV administration are nausea and/or vomiting and hypotension
 - Dose dependent (RT vs CT)
 - Hydration-status dependent
 - Infusion-length dependent
- ◆ Alternative dosing and administration strategies could:
 - Offer alternative logistics and improve cost-effectiveness
 - Enhance therapeutic index
 - Manage toxicities

IV = intravenous; RT = radiation therapy; CT = chemotherapy.

Boccia R. *Semin Oncol* 2002;29(suppl 19):9-13.

Slide 45

Amifostine

Rapid IV Push vs IV Infusion

- ◆ With rapid IV push (<1 min) vs 15-min IV infusion of amifostine (200 mg/m²), patients experienced less grade 1 hypotension and less grade 1-2 nausea/vomiting
- ◆ With rapid IV push of amifostine (500 mg), only 9% of patients experienced nausea/vomiting and/or hypotension

IV = intravenous.

Boccia RV. *Proc Am Soc Clin Oncol*. 2001;20:300b. Abstract 2953; Boccia R. *Semin Oncol*. 2002;29(suppl 19):9-13; Kemp GM et al. *Proc Am Soc Clin Oncol*. 2002;21. Abstract 2888.

Slide 46

Amifostine

Shortened Administration Time

- ◆ Shortened infusion (<3 min) prior to higher-dose monthly CT and rapid IV push (<1 min) prior to RT and weekly CT
 - May reduce side effects associated with amifostine and increase tolerability
 - Minimal nausea/vomiting
 - Minimal hypotension
 - Apparently maintain cytoprotectant properties

CT = chemotherapy; IV = intravenous; RT = radiation therapy.

Boccia RV. *Proc Am Soc Clin Oncol*. 2001;20:300b; Boccia R. *Semin Oncol*. 2002;29(suppl 19):9-13; Wagner W. *Anticancer Res*. 1999;19:2281-2283.

Slide 47

Amifostine *Risk of Nausea/Vomiting*

<u>High</u>	<u>Low</u>
<ul style="list-style-type: none">◆ Receiving highly emetogenic CT◆ Experienced emesis with previous CT and/or amifostine◆ Not adequately hydrated◆ Hypotensive◆ Prone to nausea/vomiting in other situations (eg, during pregnancy; experienced motion sickness; with other medications)	<ul style="list-style-type: none">◆ Receiving RT alone or in combination with nonemetogenic CT◆ No emesis experienced with previous CT and/or amifostine◆ Well hydrated

CT = chemotherapy; RT = radiation therapy.

Boccia R. *Semin Oncol*. 2002;29(suppl 19):9-13.

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Amifostine *Treatment of Nausea and Vomiting*

- ◆ Administer antiemetic medication in a timely manner prior to, in conjunction with, and following amifostine therapy
 - 90 to 120 minutes prior to amifostine administration
 - Phenothiazines are adequate for majority of patients
 - Oral or intravenous 5-HT₃ receptor antagonists alone or in combination with other antiemetics if simpler regimens ineffective

Boccia R. *Semin Oncol*. 2002;29(suppl 19):9-13.

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Amifostine

Minimizing the Risk of Hypotension

- ◆ Patients should be well hydrated prior to amifostine administration
 - Drink 1 liter of fluid throughout the day
 - Drink 2 cups of fluid 30 minutes prior to administration
- ◆ Patients should not be administered amifostine if dehydrated

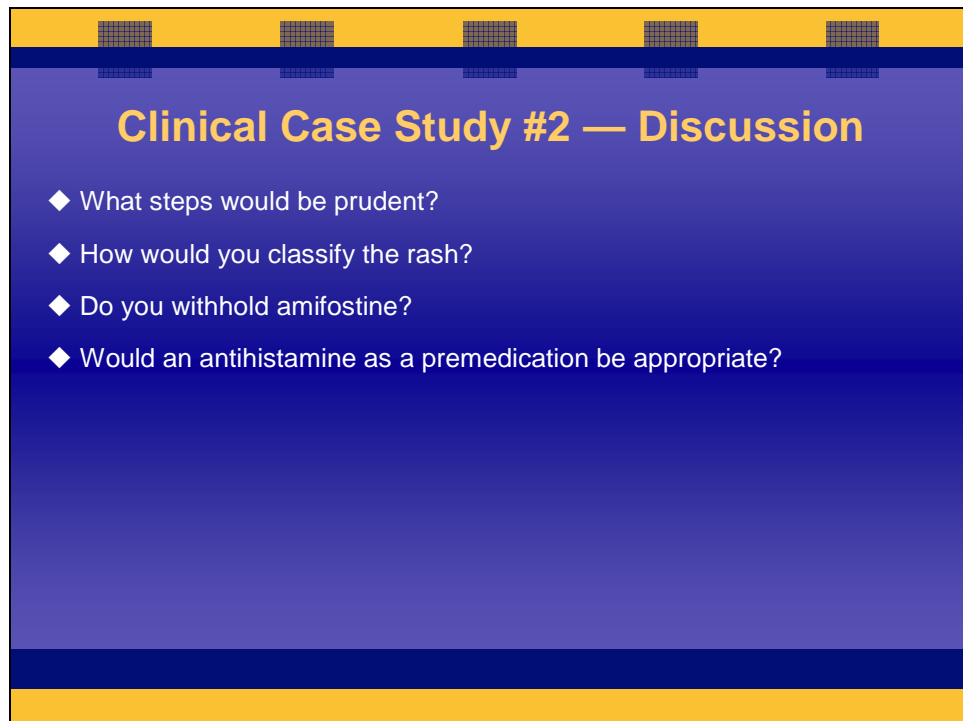
Werner-Wasik M et al. Clin Lung Cancer. 2001;2:284-289.

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Clinical Case Study #2

- ◆ MJ is a 60-year-old man with stage IIIb NSCLC carcinoma
- ◆ He has just completed his second week of combined-modality therapy and has had 10 subcutaneous injections of amifostine
- ◆ When he arrives for his injection, you note a circular reddened area at the site of his last injection
- ◆ He denies any itchiness at the site, and the area is not warm to the touch

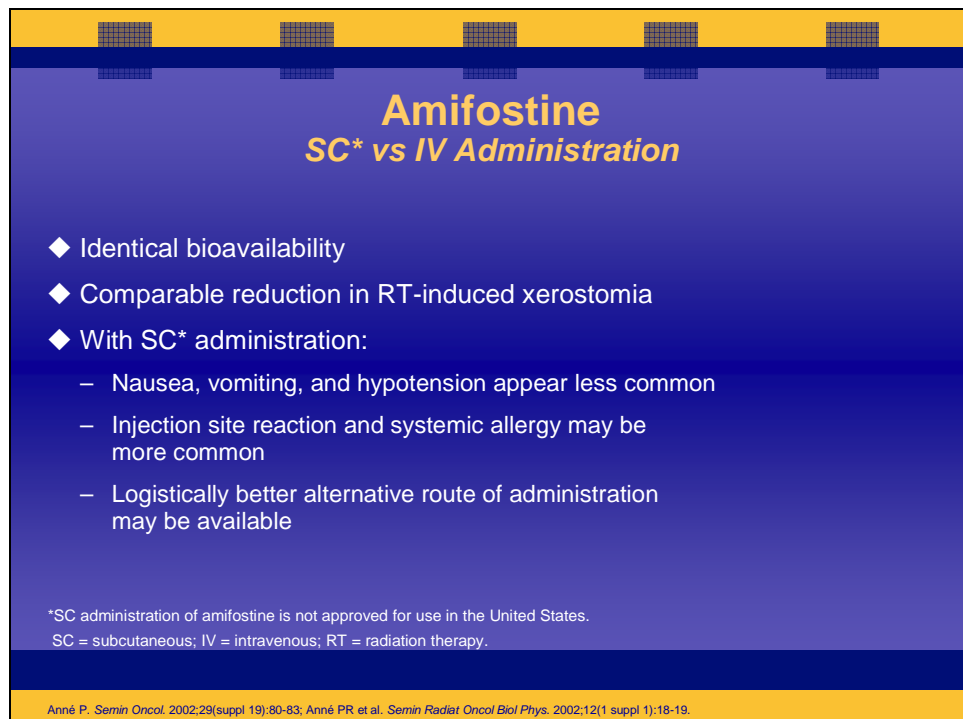
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Clinical Case Study #2 — Discussion

- ◆ What steps would be prudent?
- ◆ How would you classify the rash?
- ◆ Do you withhold amifostine?
- ◆ Would an antihistamine as a premedication be appropriate?

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Amifostine *SC* vs IV Administration*

- ◆ Identical bioavailability
- ◆ Comparable reduction in RT-induced xerostomia
- ◆ With SC* administration:
 - Nausea, vomiting, and hypotension appear less common
 - Injection site reaction and systemic allergy may be more common
 - Logistically better alternative route of administration may be available

*SC administration of amifostine is not approved for use in the United States.
SC = subcutaneous; IV = intravenous; RT = radiation therapy.

Anné P. *Semin Oncol.* 2002;29(suppl 19):80-83; Anné PR et al. *Semin Radiat Oncol Biol Phys.* 2002;12(1 suppl 1):18-19.

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Amifostine

Evaluation of Cutaneous Reactions

- ◆ Patients undergoing amifostine treatment should be evaluated thoroughly prior to administration of each dose
- ◆ Factors to consider
 - Distribution and severity of cutaneous reaction (ie, inside or outside injection site and/or radiation portals)
 - Presence of mucosal lesions inconsistent with therapy
 - Relationship of reaction to amifostine therapy
 - Other concomitant medications (eg, antibiotics, chemotherapy, other coadministered drugs)
 - Radiation itself
 - Possible infection
 - Fever

Hellman S. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer Principles of Oncology*. 5th ed. Philadelphia, PA: Lippincott-Raven; 1997.
Boccia R et al. *Int J Radiat Oncol Biol Phys*. 2004;60:302-309.

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Amifostine

Management of Cutaneous Reactions

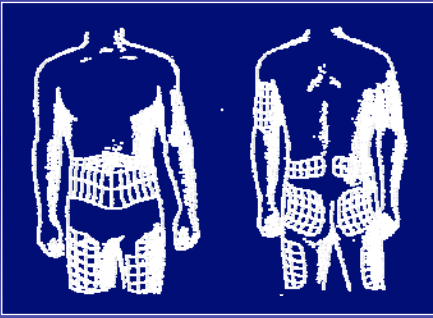
- ◆ Interrupt amifostine therapy; management dependent upon severity of reaction
 - Differentiate from radiation-induced dermatitis
 - May require dermatologic consultation (possible biopsy to classify reaction)
- ◆ Permanently discontinue amifostine if:
 - Cutaneous reactions are considered to be erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, or exfoliative dermatitis
 - Any cutaneous reaction is associated with fever or any constitutional symptoms are not known to be due to any other etiology

Boccia R et al. *Int J Radiat Oncol Biol Phys*. 2004;60:302-309.

Amifostine

Local Injection-Site Reactions

- ◆ Local injection-site reactions do not necessarily lead to general cutaneous reactions
- ◆ Treatment of symptoms and injection-site rotation may alleviate discomfort

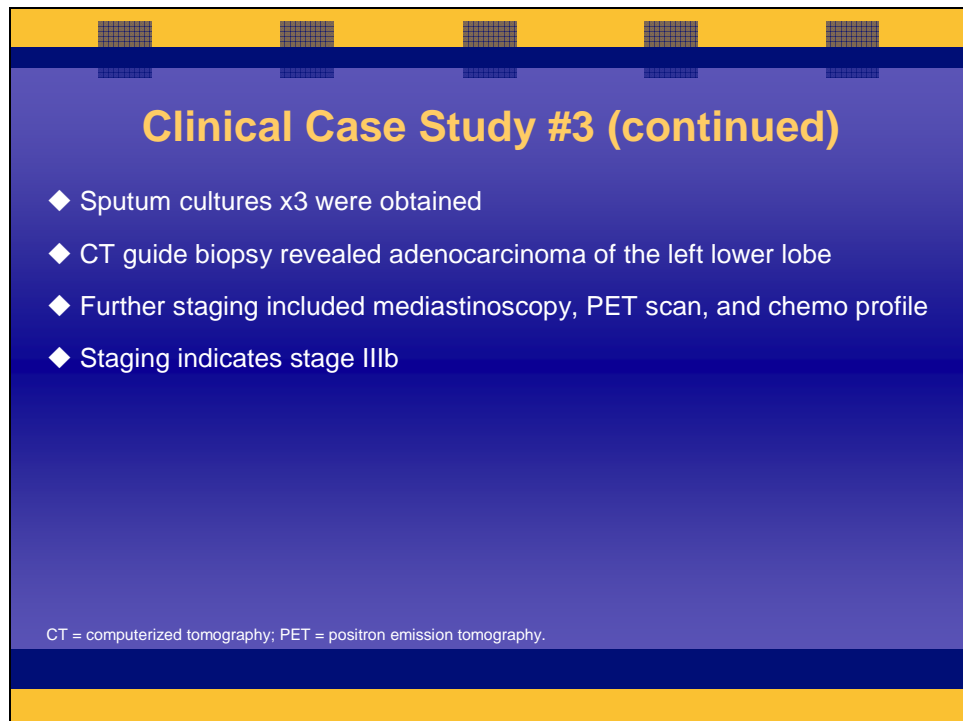


Boccia R et al. *Int J Radiat Oncol Biol Phys.* 2004;60:302-309. The figure on this slide is copyrighted 1997-1998 by Diabetes Scene and/or its suppliers. All rights reserved.

Clinical Case Study #3

- ◆ Patient profile: a 63-year-old man who presented 3 months ago to urgent care with cough, mild dyspnea, and low grade fever. He initially received an antibiotic for 10 days
- ◆ Patient returned to clinic with increased dyspnea, cough, and weight loss
- ◆ Physical exam: 180 lbs, 5'11", with lung sounds distant in left lower lobe
- ◆ Performance status: Karnofsky 90
- ◆ Chest x-ray demonstrated a left lower lobe infiltrate and a mass approximately 2.5 cm
- ◆ Patient was referred to a pulmonologist

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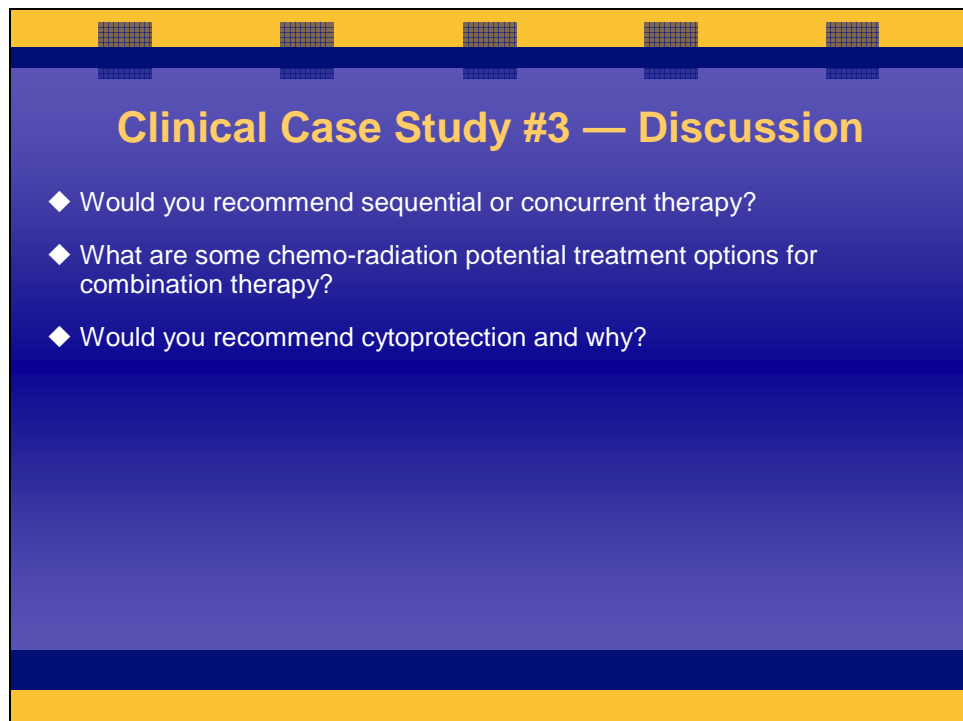


Clinical Case Study #3 (continued)

- ◆ Sputum cultures x3 were obtained
- ◆ CT guide biopsy revealed adenocarcinoma of the left lower lobe
- ◆ Further staging included mediastinoscopy, PET scan, and chemo profile
- ◆ Staging indicates stage IIIb

CT = computerized tomography; PET = positron emission tomography.

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Clinical Case Study #3 — Discussion

- ◆ Would you recommend sequential or concurrent therapy?
- ◆ What are some chemo-radiation potential treatment options for combination therapy?
- ◆ Would you recommend cytoprotection and why?

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Summary

- ◆ Esophagitis and pneumonitis represent acute dose-limiting side effects of radiation therapy and RCT to the lung
- ◆ Both esophagitis and pneumonitis are decreased with the use of cytoprotectants like amifostine
- ◆ Oncology nurses play a key role in educating patients and their families on ways to minimize treatment-related side effects of RCT, including:
 - Adequate hydration
 - Antiemetics
- ◆ The successful management of cutaneous reactions is critical, and injection sites should be rotated if possible

RCT = radiochemotherapy.

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Clinical Case Study: Extra

- ◆ Patient profile: MK is a 50-year-old man who presented with a 4-month history of shortness of breath, chest tightness, overall weakness, and an unintentional 20 lb weight loss over 4 months. He denied cough, respiratory infections, headaches, fevers, dysphasia, or other symptoms
- ◆ Medical history: Negative medical history except for:
 - + Cigarette smoker with a 30-pack-year smoking history
 - + Alcohol social drinker with no recreational drug use
 - Exposure history

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Clinical Case Study: Extra (continued)

- ◆ Results of MK's physical exam:
 - Weight, 173 lbs; height, 5'10"
 - Patient alert, no evidence of oral lesions
 - No palpable cervical or supraclavicular adenopathy or axillary lymph nodes
 - Absent breath sounds, right lower lobe and left lung clear to auscultate
 - Abdomen, soft nontender without hepatosplenomegaly or palpable mass
 - Heart rate normal and BP 150/74 mm Hg
 - No extremity weakness, gait stable
 - No medication use at this time

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Clinical Case Study: Extra (continued)

- ◆ Results of MK's diagnostic tests:
 - Abnormal chest x-ray prompted further workup; CT scan of the chest showed a 7 cm lesion in the right lower lobe and marginal enlargement of the pretracheal, precarinal, and anterior subcarinal lymph nodes
- ◆ Bronchoscopy established the diagnosis of poorly differentiated adenocarcinoma
 - Underwent a right pneumonectomy with central mediastinal lymph node sampling
 - The tumor was 7x6x6 cm and no vascular or lymphatic space invasion with negative margins
- ◆ Postsurgical diagnosis
 - Infiltrating poorly differentiated adenocarcinoma with local invasion of the bronchial and blood vessel wall
- ◆ 1 of 8 hilar lymph nodes positive for tumor
- ◆ Staging
 - T2N1M0 poorly differentiated adenocarcinoma of the right lower lobe

CT = computerized tomography.

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Clinical Case Study: Extra (continued)

- ◆ Treatment recommendations for MK
 - Adjuvant local regional radiotherapy in conjunction with systemic chemotherapy (cisplatin)
 - Radiotherapy daily at 180 cGy to the anterior and posterior right lung (dose of 4500 cGy) and 1080 cGy right lung off cord oblique and post right lung off cord oblique for a total dose of 5580 cGy
- ◆ Cytoprotection
 - Amifostine 500 mg SC daily 30 minutes prior to radiation therapy
 - Ondanestron 8 mg 90 minutes orally before daily amifostine SC with 2 to 3 glasses of fluid
- ◆ The patient completed therapy without requiring treatment breaks or hospitalization

SC = subcutaneous.

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Clinical Case Study: Extra — Discussion

- ◆ What treatment related toxicities would you anticipate from this regimen?
- ◆ How can amifostine help?
- ◆ Are there data suggesting amifostine's cytoprotective effects for use in this circumstance?
- ◆ For what types of toxicities has amifostine shown benefit in reducing?

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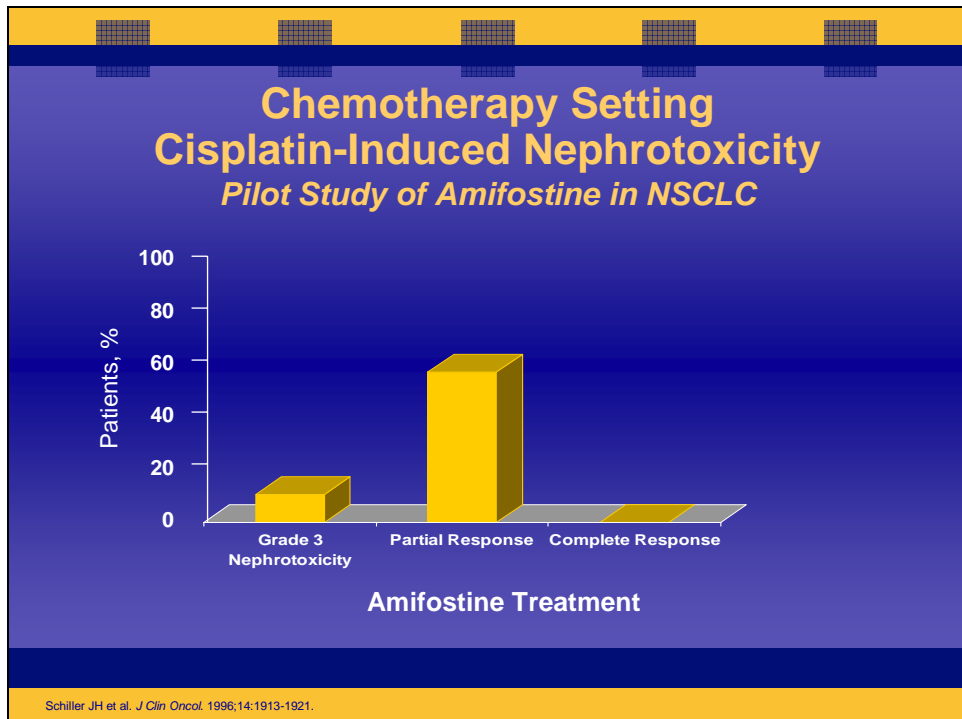
Amifostine Studies in Chemotherapy Setting

Study	Patients	Amifostine Dosing	Treatment Regimen
Pilot Schiller, 1996	N=25 Metastatic NSCLC	Amifostine 740-910 mg/m ² , day 1	Cisplatin 120 mg/m ² , day 1 Vinblastine 5 mg/m ² , days 1, 8, 15, 22
Phase 3 randomized Anderson, 1998	N=45 Advanced NSCLC	24 pts amifostine 740 mg/m ² x3 vs 21 pts G-CSF	45 pts carboplatin AUC=9

G-CSF = granulocyte colony-stimulating factor; AUC = area under the curve.

Schiller JH et al. *J Clin Oncol.* 1996;14:1913-1921.

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PLEASE ANSWER THE FOLLOWING QUESTIONS:

1. *Were the following learning objectives achieved?*

Please answer all questions using a scale of 1 to 5, where
1 = Strongly Disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly Agree.

a) Identify the serious side effects related to the treatment of NSCLC

1 2 3 4 5

Comment: _____

b) Describe the utility of cytoprotective agents in the management of patients through aggressive cancer therapies

1 2 3 4 5

Comment: _____

c) Demonstrate the role and proper use of amifostine in the treatment of patients with NSCLC

1 2 3 4 5

Comment: _____

d) Assess how the use of amifostine may affect patients, therapies, and/or treatment outcomes

1 2 3 4 5

Comment: _____

2. *Do you feel that the activity was balanced and free of bias toward the commercial supporter?*

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