

Postradiotherapy Neck Dissection for Lymph Node–Positive Head and Neck Cancer: The Use of Computed Tomography to Manage the Neck

Stanley L. Liauw, Anthony A. Mancuso, Robert J. Amdur, Christopher G. Morris, Douglas B. Villaret, John W. Werning, and William M. Mendenhall

From the Departments of Radiation Oncology, Radiology, and Otolaryngology, University of Florida College of Medicine, Gainesville, FL.

Submitted October 25, 2005; accepted January 13, 2006.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to William M. Mendenhall, MD, Department of Radiation Oncology, University of Florida Health Science Center, P.O. Box 100385, Gainesville, FL 32610-0385; e-mail: mendewil@shands.ufl.edu.

© 2006 by American Society of Clinical Oncology

0732-183X/06/2409-1421/\$20.00

DOI: 10.1200/JCO.2005.04.6052

ABSTRACT

Purpose

To determine how to use node response on computed tomography (CT) to indicate the need for neck dissection.

Patients and Methods

Five hundred fifty patients with lymph node–positive head and neck cancer were treated between 1990 and 2002 with radiotherapy (RT) at a median dose of 74.4 Gy; 24% of these patients (n = 133) were treated with chemotherapy. Three hundred forty-one patients (62%) underwent planned post-RT neck dissection. Physical examination and contrast-enhanced CT were performed 30 days after completion of RT. CT images were reviewed in 211 patients for lymph node size (largest axial dimension) and presence of a focal abnormality (lucency, enhancement, or calcification). By correlating post-RT CT to neck dissection pathology, criteria associated with a low likelihood of residual disease were identified. A subset of patients who fit these criteria of radiographic response who did not undergo post-RT neck dissection was observed for recurrence.

Results

Radiographic complete response (rCR) was defined as the absence of any large (> 1.5 cm) or focally abnormal lymph node. Correlation of response with neck dissection pathology indicated a negative predictive value of 77% for complete clinical response and 94% for rCR. In 32 patients (median follow-up time, 3.2 years) with rCR who did not undergo post-RT neck dissection, the 5-year ultimate neck control rate (100%) and cause-specific survival rate (72%) were not significantly different from the rates of patients with a negative post-RT neck dissection.

Conclusion

Patients with rCR 4 weeks after RT can be spared from a post-RT neck dissection regardless of initial node stage.

J Clin Oncol 24:1421-1427. © 2006 by American Society of Clinical Oncology

INTRODUCTION

Approximately 40,000 patients in the United States are diagnosed each year with head and neck cancer.¹ Many present with locally advanced disease that is amenable to organ-preserving radiation therapy (RT), in which neck dissection is often an important additional component of treatment.^{2,3} Traditionally, after definitive RT to the head and neck, patients with extensive neck disease are felt to be at higher risk for locoregional failure, and thus, neck dissection is recommended even after complete response to initial therapy.^{3,4} However, over the last decade, treatment for head and neck cancer has become increasingly successful, in part as a result of the incorporation of adjuvant chemotherapy and altered fractionation. Optimal management of the

neck after RT remains undefined; unfortunately, no data from randomized controlled trials adequately address this issue.

In the 1990s, institutions began to report acceptable neck control in patients treated with definitive RT who had a complete response in the neck by physical examination.⁵⁻⁸ Shortly thereafter, at the University of Florida, computed tomography (CT) was used to assess post-treatment response 4 weeks after RT. The first analysis of the data⁹ found that radiographic complete response (rCR; no lymph nodes > 1.5 cm and no focal lucency or extracapsular extension) was associated with a negative post-RT neck dissection specimen 97% of the time. Patients with an rCR have since been observed clinically, regardless of initial nodal staging. The primary purpose of this study is to update the correlation

between complete response and neck dissection pathology using re-defined CT criteria and to describe the outcome of patients who are spared neck dissection based on post-treatment response. A secondary goal is to report the outcome of lymph node-positive patients who undergo definitive RT with or without chemotherapy and to identify factors that may influence response to and success of treatment.

PATIENTS AND METHODS

The records of 1,001 consecutive patients with head and neck cancer who were treated with definitive RT at the University of Florida between January 1990 and November 2002 were retrospectively reviewed under institutional review board approval. This study included 550 patients who underwent RT with curative intent for lymph node-positive squamous cell carcinoma of the oropharynx, hypopharynx, larynx, or an unknown head and neck primary site and who had no prior neck dissection or history of RT. Patient characteristics are listed in Table 1. RT usually consisted of a parallel-opposed lateral technique, as defined by CT planning, using 6-MV photons or cobalt-60, with a

median dose of 74.4 Gy (range, 55.0 to 81.75 Gy) predominantly administered at 1.2 Gy/fraction (77%) twice daily to the primary field and upper neck. An off-cord reduction was made after 40 to 45 Gy, and 8 to 10 MeV electrons were used to supplement the dose to the tissues overlying the spinal cord. For oropharyngeal, hypopharyngeal, and laryngeal primary tumors, a second mucosal reduction was performed after 60 Gy. The low neck was treated with an anterior field prescribed to D_{max} (the depth at which the dose is maximum) and typically received 70 Gy at 2 Gy/fraction once daily if the patient was lymph node positive and 50 Gy if the patient was clinically negative. Doses to treat an unknown head and neck primary site tended to be lower (median dose, 59.5 Gy administered at 1.8 Gy/fraction once daily), and the low neck doses were typically 60 to 70 Gy at 2 Gy/fraction once daily to the involved neck. The median total treatment time for all patients was 46 days (range, 26 to 77 days). Chemotherapy was administered in 133 patients; it was administered neoadjuvantly (67%), concurrently (32%), or both (1%) and was usually cisplatin based (78%). Neoadjuvant chemotherapy usually consisted of fluorouracil 600 to 1,000 mg/m² over 4 to 5 days and cisplatin 80 to 100 mg/m² bolus, with a median of three cycles administered. When cisplatin was administered concurrently, it was administered as 6 mg/m² daily, 30 mg/m² weekly, or bolus 80 to 100 mg/m² for two to three cycles. Fifteen patients (10%) received intra-arterial cisplatin for four cycles, as outlined by an institutional protocol. Twenty-one patients (16%) received concurrent carboplatin and paclitaxel, which was most commonly administered in doses of 100 and 45 mg/m², respectively, for 5 to 7 weekly cycles.

Post-treatment response of the neck was assessed by physical examination and contrast-enhanced CT ($n = 211$) at a median of 29 days (range, -3 to 125 days) after completion of RT. Only four patients had CT scans within 2 weeks of the completion of RT, and the cause was related to patient-specific scheduling conflicts. Complete response by physical examination (clinical complete response [cCR]) was defined as resolution of all adenopathy and induration in the initially involved areas. Complete response by CT (rCR) was defined as absence of lymph nodes of more than 1.5 cm and lymph nodes with any focal lucency, focal enhancement, or focal calcification. Two hundred eleven sets of contrast-enhanced CT images between 1995 and 2002 were available for blinded rereview on soft copy (ie, digital film that could be manipulated on a workstation). CT images were rereviewed for patients known to have neck dissection data available for correlation or, in later years, if post-RT CT was used to manage the neck. Maximum and minimum lymph node diameter (greatest axial dimension of lymph nodes in levels I to V) and number of abnormal lymph nodes were recorded for each hemi-neck. Data was collected only for those hemi-necks initially involved with disease. Lymph node abnormalities were graded jointly by one neuroradiologist and one radiation oncologist on the following 5-point scale: 0, definitely normal; 1, probably normal; 2, indeterminate; 3, probably abnormal; and 4, definitely abnormal. The radiation oncologist was able to learn the system quickly and consistently report findings in agreement with the neuroradiologist for this study. At the time of CT scan before this study, images were initially interpreted by the neuroradiologist and later agreed on by the radiation oncologist at tumor board. Examples of post-treatment CTs are included in Figures 1 through 6.

Three hundred forty-one patients (62%) underwent post-RT planned neck dissection, which was usually a modified radical neck dissection including levels I to V, at a median of 47 days (range, 23 to 175 days) after completion of RT. Two hundred eighty-six patients had a unilateral neck dissection, and 55 patients had a bilateral neck dissection. Standard pathologic processing of the neck dissection specimen involved sectioning at 4- μ m slices before microscopic examination. After the first review of the data indicated high neck control rates without planned neck dissection, patients with a complete response on post-treatment CT did not routinely undergo neck dissection. Forty-eight patients did not receive planned post-RT neck dissection because of unresectable neck disease ($n = 19$), medical contraindications ($n = 11$), development of distant metastases ($n = 8$), refusal ($n = 5$), uncontrolled primary disease ($n = 3$), intercurrent death ($n = 1$), and unresectable neck disease with distant metastases ($n = 1$). For this study, the neck dissection specimen was correlated to post-RT CT characteristics for all patients for whom time between imaging and surgery was ≤ 60 days. This time interval

Table 1. Patient Characteristics

Characteristic	No. of Patients (N = 550)	%
Male	468	85
Primary site		
Oropharynx		
Tonsil	177	32
Base of tongue	147	27
Soft palate	14	3
Hypopharynx		
Piriform sinus	48	9
Posterior pharyngeal wall	33	6
Postcricoid area	3	1
Laryngeal		
Supraglottic	60	11
Glottic	9	2
Unknown head and neck primary	44	8
Multiple synchronous primaries	15	3
Tumor stage		
T0	44	8
T1	48	9
T2	198	36
T3	156	28
T4	104	19
Node stage		
N1	98	18
N2a	52	9
N2b	175	32
N2c	130	24
N3	95	17
Fixed at presentation*	94	23
Poorly differentiated*	204	37
Fractionation		
Conventional, once daily	104	19
Hyperfractionation	427	78
Concomitant boost	19	3
Chemotherapy	133	24
Concurrent	89	67
Neoadjuvant	42	32
Both neoadjuvant and concurrent	2	1

*Data not available for all patients.

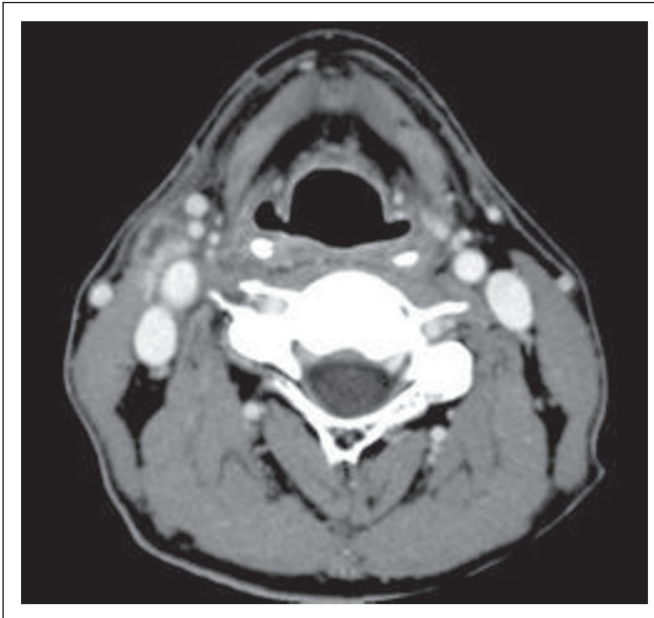


Fig 1. This 44-year-old patient received radiotherapy (76.2 Gy at 1.2 Gy/fraction bid) for T2N2b base of tongue cancer. Postradiotherapy computed tomography demonstrated a 1.4-cm lymph node with definite (grade 4) focal lucency and focal enhancement in the right neck at level II. Neck dissection was positive, and the patient was controlled with 7 years of follow-up.

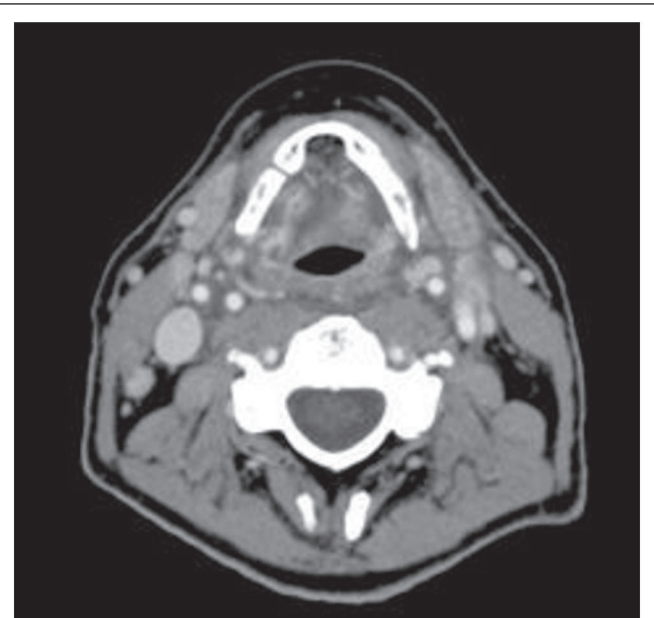


Fig 3. This 52-year-old patient received chemoradiotherapy (70 Gy at 2 Gy/fraction every day with fluorouracil/cisplatin) for T3N2b tonsil cancer. Post-radiotherapy computed tomography demonstrated a 1.7-cm lymph node with probable (grade 3) focal enhancement in the left neck at level II. Neck dissection was positive, with extracapsular extension. The patient was controlled with 4 years of follow-up.

was chosen because most neck dissections are performed no more than 60 days from post-treatment scan, and any greater interval could confound study results as a result of a change in burden of disease from time of CT scan (although no discrepancy was seen in the seven excluded patients in this study with a time interval > 60 days). Return follow-up appointments occurred on a 4- to 6-week basis for the first year and were gradually extended to yearly after 5 years. Patients unavailable for clinical follow-up were contacted by phone. Minimum potential follow-up was 2 years, whereas median observed

follow-up was 3.3 years (range, 0.1 to 14.7 years); 23 patients (4%) were lost to follow-up and censored at time of last follow-up at a median of 5.0 years (range, 0.5 to 9.4 years) after completion of RT. Follow-up on living patients ranged from 0.5 to 14.7 years (median, 5.2 years).

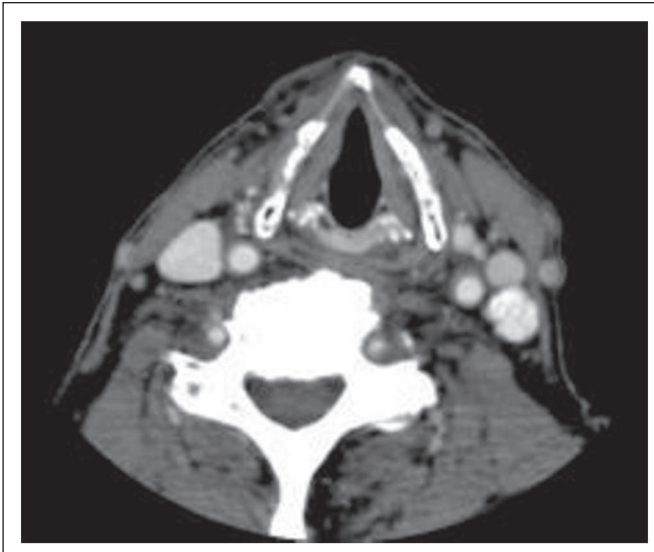


Fig 2. This 83-year-old patient received radiotherapy (76.8 Gy at 1.2 Gy/fraction bid) for T2N2b base of tongue cancer. Postradiotherapy computed tomography demonstrated a 1.1-cm lymph node with definite calcification in the left neck at level III. Neck dissection was positive, with extracapsular extension. The patient died of intercurrent disease with 4 months of follow-up.

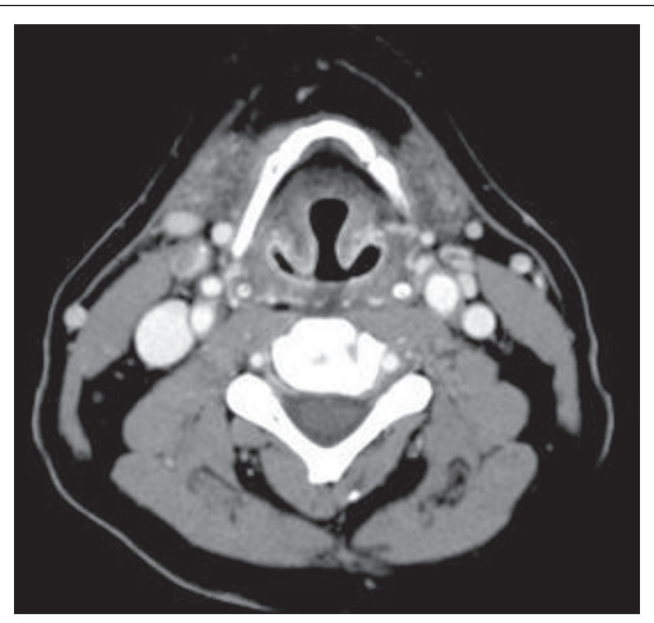


Fig 4. This 42-year-old patient received induction chemotherapy followed by radiotherapy (76.8 Gy at 1.2 Gy/fraction bid) for T3N2b tonsil cancer. Postradiotherapy computed tomography demonstrated a 1.1-cm node with definite calcification and probable focal lucency on the right and a fatty hilum on the left. Neck dissection was negative; the patient was controlled with 3 years of follow-up.

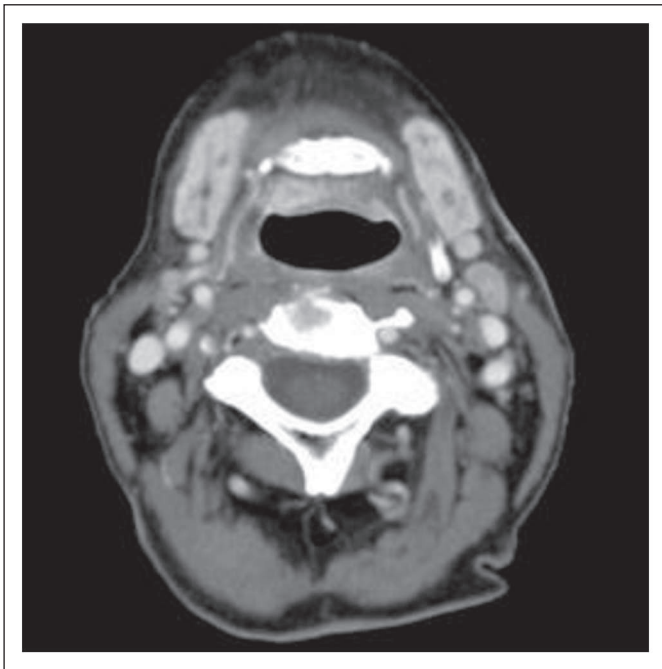


Fig 5. This 72-year-old patient received radiotherapy (74.8 Gy at 1.2 Gy/fraction bid) for T2N2b tonsil cancer. Postradiotherapy computed tomography demonstrated a 1.3-cm lymph node with questionable (grade 2) focal lucency in the left neck at level II. No neck dissection was performed. The patient was controlled and died of intercurrent disease with 3.5 years of follow-up.

All data were analyzed using SAS statistical software (SAS OnlineDoc, Version 8; SAS Institute Inc, Cary, NC). Estimates of freedom from selected time-dependent end points were calculated using the Kaplan-Meier product-limit method.¹⁰ The log-rank test statistic was used to detect

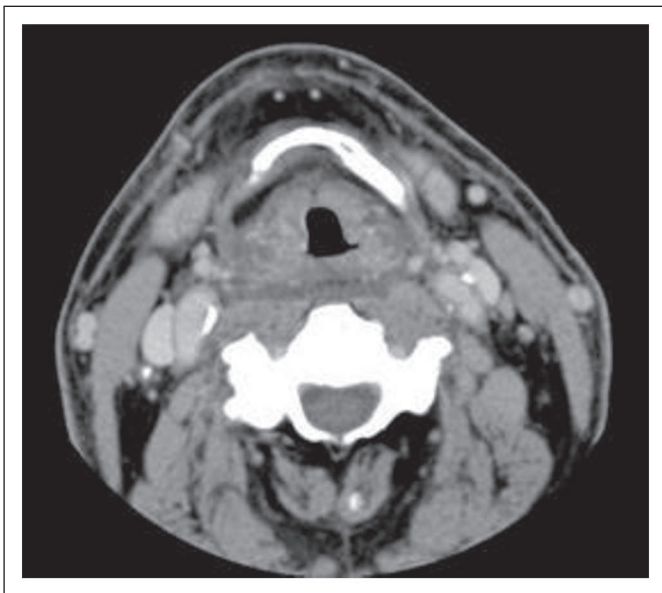


Fig 6. This 53-year-old patient received chemoradiotherapy (70 Gy at 2 Gy/fraction every day with fluorouracil/cisplatin) for T3N2b false vocal cord cancer. Postradiotherapy computed tomography demonstrated a residual 0.5-cm lymph node with definite calcification in the right neck and incidental calcifications in the carotid vessels. Neck dissection was positive. The patient was controlled with 4.5 years of follow-up.

statistically significant differences in freedom from these end points between strata of selected explanatory variables. Multiple regression of these end points on a select group of explanatory variables was accomplished with Cox proportional hazards regression.¹¹ Nominal logistic regression was used for the analysis of CT response.

RESULTS

Post-RT Neck Dissection

In 550 patients, there were 704 hemi-necks initially involved with disease. Three hundred ninety-six post-RT neck dissections were performed in 341 patients. Neck dissection pathology was available in 383 hemi-necks (325 patients) and was negative in 256 hemi-necks (67% of dissections). The specimen contained a single positive node in 19%, two to three positive nodes in 9%, and four or more positive nodes in 5% of dissections. Of 121 patients with residual disease in the neck, 59 patients (of 86 with available data, 69%) had extracapsular spread (62 hemi-neck specimens).

Correlation of Post-RT Physical Examination to Neck Dissection Pathology

Of 537 patients (684 hemi-necks) with physical examination data available at the completion of RT, 259 (435 heminecks, 64%) had a cCR. Correlation of cCR by physical examination to the neck dissection specimen (363 hemi-necks) demonstrated a sensitivity of 73%, specificity of 45%, positive predictive value of 41%, and negative predictive value of 77%. Thirty-three (23%) of 142 patients with a cCR by physical examination had residual disease in the neck dissection; 17 patients had one positive node, 11 patients had two to three positive nodes, and five patients had four or more positive nodes. cCR was associated with improved neck control at 5 years (94% for those who had cCR v 86% for those who did not have cCR; $P = .0018$).

Correlation of Post-Treatment CT to Neck Dissection Pathology

Of 211 patients (266 hemi-necks) with CT data available for rereview, 61 (73 hemi-necks, 28%) had an rCR based on the criteria of all lymph nodes ≤ 1.5 cm and no focally abnormal nodes. Correlation of complete response by CT to the neck dissection specimen (193 hemi-necks) demonstrated a sensitivity of 96%, specificity of 24%, positive predictive value of 35%, and negative predictive value of 94%. Two (6%) of 34 hemi-necks with an rCR had residual disease in the neck dissection; both of these patients had one positive residual node.

The negative predictive values of other post-RT CT criteria to predict for a negative neck dissection specimen are listed in Table 2. The presence of any lymph node with a focal abnormality or large size was associated with a positive predictive value as follows: focal lucency, 36%; focal enhancement, 46%; calcification, 31%; and size more than 1.5 cm, 32%.

Outcomes for Patients With Complete Response by CT (rCR)

Sixty-one patients met criteria for an rCR. Thirty patients (49%) were stage T3-4, 37 patients (61%) were stage N2, and four patients (7%) were stage N3. With a median follow-up of 3.2 years after RT (range, 0.3 to 6.3 years), the 32 patients who did not undergo neck dissection had the same ultimate neck control at 5 years as the 29 patients who did undergo neck dissection (100%). Outcomes for these

Table 2. Predictive Value of Postradiotherapy Computed Tomography Findings at 4 Weeks in the Hemi-Neck Correlated to Neck Dissection Pathology (n = 193 hemi-necks)

Finding	NPV		PPV	
	No./Total No.	%	No./Total No.	%
Any lymph node > 1.5 cm	85/118	72	24/75	32
Any focally abnormal lymph node*	49/57	86	49/136	36
Any lymph node with focal lucency	75/98	77	34/95	36
Any lymph node with enhancement	111/147	76	21/46	46
Any lymph node with calcification	102/144	71	15/49	31
Two or more focally abnormal lymph nodes*	90/113	80	34/80	43
Any lymph node > 1.5 cm and any focally abnormal lymph node	32/34	94	55/159	35

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

*Focally abnormal lymph node = grade 3 to 4 focal lucency, focal enhancement, or focal calcification.

patients in relation to other patients who did and did not undergo neck dissection are listed in Table 3. Patients with a complete response by post-treatment CT who were observed did not have a significantly inferior outcome compared with patients with a negative post-RT neck dissection (5-year neck control rate, 97% v 98%, respectively; $P = .4747$; and cause-specific survival rate, 72% v 85%, respectively; $P = .2225$). Only one of 32 patients who did not undergo neck dissection because of rCR experienced a neck failure, at 0.5 years from the end of RT. He was treated with RT alone for a T2N1 soft palate cancer. Ipsilateral neck failure was suspected clinically at his 4-month follow-up examination, and CT demonstrated multiple abnormal nodes. He underwent immediate salvage neck dissection, which showed five of 21 positive nodes in the specimen. Without any further adjuvant treatment, he has no evidence of disease 6 years after salvage neck dissection.

Univariate analysis indicated a higher likelihood of rCR for patients with N1 disease (67% rCR rate for N1 patients v 21% for > N1 patients; $P = .0009$). There were no significant differences in the rates of rCR with regard to chemotherapy ($P = .4148$), primary site ($P = .1282$), T stage ($P = .3923$), differentiation ($P = .5568$), initially

fixed lymphadenopathy ($P = .6848$), or fractionation ($P = .2071$). Multivariate analysis also indicated that only earlier nodal stage was associated with rCR (Table 4).

Neck and Survival Outcomes for All Patients

The 5-year outcome rates were as follows: neck control, 90%; local control, 84%; cause-specific survival, 69%; freedom from recurrence, 66%; and overall survival, 52%. At 5 years, patients who underwent neck dissection, compared with patients who did not, were more likely to have a better neck control rate (94% v 85%, respectively; $P = .0051$) and cause-specific survival rate (72% v 63%, respectively; $P = .0042$). However, after exclusion of patients who did not receive neck dissection as recommended because of unresectable neck disease, progression of disease, refusal, or comorbidity, these differences disappeared. Patients with negative neck specimens fared better than those with positive specimens, with 5-year neck control rates of 98% v 86%, respectively ($P < .0001$), and cause-specific survival rates of 85% v 56%, respectively ($P < .0001$). For patients with any residual disease in the neck dissection specimen, a shorter time to neck dissection (< a median of 47 days from the

Table 3. Five-Year Outcomes of Patients With or Without Post-RT Neck Dissection

Patient Group	No. of Patients	Local Control (%)	Neck Control (%)	Ultimate Neck Control (%)	FFDM (%)	DFS (%)	CSS (%)	OS (%)
No neck dissection								
All patients	209	76	84	85	79	57	63	45
Patients who could not undergo neck dissection as planned (eg, unresectable neck disease, medical contraindications)	48	80	49	49	55	27	18	11
Excluding patients who were ineligible for post-RT neck dissection	161	76	94	96	85	66	75	55
Patients with rCR 4 weeks after RT	32	79	97	100	87	69	72	66
Neck dissection								
All patients	341	88	93	94	83	71	72	56
Negative specimen	204	93	98	98	89	83	85	68
Positive specimen	121	80	84	86	73	54	56	42
Single positive node	68	84	90	92	83	66	67	51
Multiple positive nodes	53	74	75	77	57	37	41	30
Patients with rCR 4 weeks after RT	29	92	100	100	87	88	82	68

Abbreviations: RT, radiotherapy; FFDM, freedom from distant metastasis; DFS, disease-free survival; CSS, cause-specific survival; OS, overall survival; rCR, radiographic complete response.

Table 4. Multivariate Analyses for Radiographic Complete Response, Neck Control, and CSS

Variable	P for Specified End Point
Patients with CT data available, n = 211	
Radiographic complete response	
Node stage, N1 v N2-3	.0009
Fractionation	.0856
Site, oropharynx v other	.3079
Initially fixed adenopathy	.4746
Chemotherapy	.3376
Poorly differentiated histology	.7762
Tumor stage, T0-2 v T3-4	.9972
Neck control	
Tumor stage, T0-2 v T3-4	.1710
Node stage, N1 v N2-3	.7587
Neck dissection	.8156
Chemotherapy	.5676
Complete response by CT	.4736
CSS	
Tumor stage, T0-2 v T3-4	.6774
Node stage, N1 v N2-3	.4924
Neck dissection	.9243
Chemotherapy	.1530
Complete response by CT	.4797
Patients eligible for neck dissection, n = 502	
Neck control	
Tumor stage, T0-2 v T3-4	.6476
Node stage, N1 v N2-3	.0948
Neck dissection	.5547
Chemotherapy	.8349
CSS	
Tumor stage, T0-2 v T3-4	< .0001
Node stage, N1 v N2-3	.0037
Neck dissection	.3793
Chemotherapy	.7580

Abbreviations: CT, computed tomography; CSS, cause-specific survival.

end of RT) was associated with a more favorable 5-year neck control rate compared with patients with no residual disease (91% v 76%, respectively; $P = .0030$), but this did not translate into a significant benefit in cause-specific survival rate at 5 years (61% v 51%, respectively; $P = .2685$).

Multivariate analysis was performed to identify potential factors associated with neck control and cause-specific survival (Table 4). Complete response by rCR was not associated with improved neck control or cause-specific survival. None of the patient parameters that were analyzed were associated with improved neck control. However, tumor and node stage were significantly associated with cause-specific survival (Table 4).

DISCUSSION

The role of planned neck dissection after definitive RT is not well defined. The goal to achieve regional disease control at the outset is critically important, given that the reduction of regional failures may improve survival¹²⁻¹⁴ and that salvage neck dissection is noted by some to be rarely, if ever, successful.^{15,16} However, because the post-RT neck

dissection is often negative, some patients undergo surgery with its associated risks for little benefit. Physical examination is a relatively unreliable method to assess disease status of the post-RT neck; the negative predictive value of a cCR 4 to 6 weeks after therapy for negative neck dissection was 77%, which is similar to other reported series.^{12,17-21} However, whether residual disease in the post-RT neck specimen consistently represents viable disease that is at risk for progression is uncertain because not all residual disease seen on hematoxylin and eosin staining shows proliferative capacity by Ki-67 staining.²² The rate of post-RT pathologic failure does not seem to correlate well with the rate of clinical neck failure in patients observed without neck dissection, and timing between RT and neck dissection may play a factor in this discrepancy.

At present, clinical outcomes do not provide any consensus opinion. In the last decade, the concept of a planned neck dissection after RT has been challenged by several authors using aggressive definitive RT (ie, altered fractionation or concurrent chemotherapy) who report high rates of complete response and low rates of isolated neck recurrence without adjuvant neck dissection.^{5-8,18,19,23} Other recent reports continue to support planned neck dissection for patients with N2 or N3 disease^{12,13,17,19} even after complete clinical response because of inferior neck control and disease-free survival¹³ and/or overall survival¹² with observation.

Our data indicate that CT is a more reliable method than physical examination to assess post-RT response. The absence of lymph nodes larger than 1.5 cm and lack of any focal lymph node defect on post-RT CT 4 weeks after therapy had a negative predictive value of 94%. Similar results were reported previously,⁹ but in an attempt to reduce the subjectivity of interpretation, post-RT CT was graded based on the presence of focal abnormality and size and not on the presence of extracapsular spread.

Although patient numbers are still relatively small, patients who have an rCR have a high rate of neck control. Only one (3%) of 32 observed patients with rCR experienced treatment failure in the neck. Included in these 32 patients who were observed after rCR were 19 patients with N2-3 disease and three patients with fixed lymphadenopathy, indicating that all patients may be candidates for observation if complete response criteria by post-RT CT are met. Neck control and cause-specific survival were not different compared with patients who had a negative adjuvant neck dissection.

This updated study seems to be the only reported series in which CT is used to manage the post-RT neck. A few reports have attempted to identify the utility of positron emission tomography (PET) in this setting, but data are limited, and the timing and interpretation of post-RT PET are not standardized. Fluorodeoxyglucose-18 PET (FDG-PET) 1 month after RT is unreliable; seven of 35 patients who were observed after negative FDG-PET scan eventually experienced failure in the neck (negative predictive value, 72%),²⁴ whereas six of seven patients who underwent planned neck dissection had residual disease in the neck specimen (negative predictive value, 14%).²⁵ FDG-PET has been shown to have a higher negative predictive value for neck control at 3 to 5 months (negative predictive value, 97% to 100%),²⁶⁻²⁸ but assessment of the neck at this time frame may be too late for a planned post-RT neck dissection. The optimal timing of adjuvant neck dissection is between 4 and 8 weeks after RT,²⁹ to allow for resolution of acute inflammatory effects while minimizing the chance for metastatic development and preceding development of late fibrosis, which could complicate neck dissection. Our institutional

preference is to rely on post-RT CT 4 weeks after RT to manage the neck, particularly given these timing limitations.

Lymph nodes characterized by post-RT CT 4 weeks after RT are highly likely to be associated with negative neck dissection pathology if they are less than 1.5 cm in size and without focal abnormality. Pa-

tients meeting these criteria who do not undergo planned neck dissection after RT can have an ultimate neck control rate that approximates 100%. Patients who do not undergo neck dissection should undergo surveillance CT every 3 to 4 months for approximately 1 year after therapy to maximize the chance for salvage neck dissection.

REFERENCES

1. Ries LAG, Eisner MP, Kosary CL, et al: (eds): SEER Cancer Statistics Review, 1975-2002. Bethesda, MD, National Cancer Institute, 2005
2. Kutler DI, Patel SG, Shah JP: The role of neck dissection following definitive chemoradiation. *Oncology (Williston Park)* 18:993-998, 2004
3. Mendenhall WM, Villaret DB, Amdur RJ, et al: Planned neck dissection after definitive radiotherapy for squamous cell carcinoma of the head and neck. *Head Neck* 24:1012-1018, 2002
4. Mendenhall WM, Million RR, Cassisi NJ: Squamous cell carcinoma of the head and neck treated with radiation therapy: The role of neck dissection for clinically positive neck nodes. *Int J Radiat Oncol Biol Phys* 12:733-740, 1986
5. Peters LJ, Weber RS, Morrison WH, et al: Neck surgery in patients with primary oropharyngeal cancer treated by radiotherapy. *Head Neck* 18:552-559, 1996
6. Johnson CR, Silverman LN, Clay LB, et al: Radiotherapeutic management of bulky cervical lymphadenopathy in squamous cell carcinoma of the head and neck: Is postradiotherapy neck dissection necessary? *Radiat Oncol Investig* 6:52-57, 1998
7. Corry J, Rischin D, Smith JG, et al: Radiation with concurrent late chemotherapy intensification ('chemoboost') for locally advanced head and neck cancer. *Radiother Oncol* 54:123-127, 2000
8. Chan AW, Ancukiewicz M, Carballo N, et al: The role of postradiotherapy neck dissection in supraglottic carcinoma. *Int J Radiat Oncol Biol Phys* 50:367-375, 2001
9. Ojiri H, Mendenhall WM, Stringer SP, et al: Post-RT CT results as a predictive model for the necessity of planned post-RT neck dissection in patients with cervical metastatic disease from squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 52:420-428, 2002
10. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457-481, 1958
11. Cox DR: Regression models and life tables. *J R Stat Soc B* 34:187-220, 1972
12. Brizel DM, Prosnitz RG, Hunter S, et al: Necessity for adjuvant neck dissection is setting of concurrent chemoradiation for advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 58:1418-1423, 2004
13. Lavertu P, Adelstein DJ, Saxton JP, et al: Management of the neck in a randomized trial comparing concurrent chemotherapy and radiotherapy with radiotherapy alone in resectable stage III and IV squamous cell head and neck cancer. *Head Neck* 19:559-566, 1997
14. Ellis ER, Mendenhall WM, Rao PV, et al: Incision or excisional neck-node biopsy before definitive radiotherapy, alone or followed by neck dissection. *Head Neck* 13:177-183, 1991
15. Bernier J, Bataini JP: Regional outcome in oropharyngeal and pharyngolaryngeal cancer treated with high dose per fraction radiotherapy: Analysis of neck disease response in 1646 cases. *Radiother Oncol* 6:87-103, 1986
16. Mabanta SR, Mendenhall WM, Stringer SP, et al: Salvage treatment for neck recurrence after irradiation alone for head and neck squamous cell carcinoma with clinically positive neck nodes. *Head Neck* 21:591-594, 1999
17. McHam SA, Adelstein DJ, Rybicki LA, et al: Who merits a neck dissection after definitive chemoradiotherapy for N2-N3 squamous cell head and neck cancer? *Head Neck* 25:791-798, 2003
18. Grabenbauer GG, Rodel C, Ernst-Stecken A, et al: Neck dissection following radiochemotherapy of advanced head and neck cancer: For selected cases only? *Radiother Oncol* 66:57-63, 2003
19. Argiris A, Stenson KM, Brockstein BE, et al: Neck dissection in the combined-modality therapy of patients with locoregionally advanced head and neck cancer. *Head Neck* 26:447-455, 2004
20. Stenson KM, Haraf DJ, Pelzer H, et al: The role of cervical lymphadenectomy after aggressive concomitant chemoradiotherapy: The feasibility of selective neck dissection. *Arch Otolaryngol Head Neck Surg* 126:950-956, 2000
21. Wanebo H, Chougule P, Ready N, et al: Surgical resection is necessary to maximize tumor control in function-preserving, aggressive chemoradiation protocols for advanced squamous cancer of the head and neck (stage III and IV). *Ann Surg Oncol* 8:644-650, 2001
22. Strasser MD, Gleich LL, Miller MA, et al: Management implications of evaluating the N2 and N3 neck after organ preservation therapy. *Laryngoscope* 109:1776-1780, 1999
23. Garden AS, Glisson BS, Ang KK, et al: Phase I/II trial of radiation with chemotherapy "boost" for advanced squamous cell carcinomas of the head and neck: Toxicities and responses. *J Clin Oncol* 17:2390-2395, 1999
24. Greven KM, Williams DW III, McGuirt WF Sr, et al: Serial positron emission tomography scans following radiation therapy of patients with head and neck cancer. *Head Neck* 23:942-946, 2001
25. Rogers JW, Greven KM, McGuirt WF, et al: Can post-RT neck dissection be omitted for patients with head-and-neck cancer who have a negative PET scan after definitive radiation therapy? *Int J Radiat Oncol Biol Phys* 58:694-697, 2004
26. Yao M, Graham MM, Smith RB, et al: Value of FDG PET in assessment of treatment response and surveillance in head-and-neck cancer patients after intensity modulated radiation treatment: A preliminary report. *Int J Radiat Oncol Biol Phys* 60:1410-1418, 2004
27. Yao M, Buatti JM, Dornfeld KJ, et al: Can post-RT FDG PET accurately predict the pathologic status in neck dissection after radiation for locally advanced head and neck cancer? In regard to Rogers, et al (*Int J Radiat Oncol Biol Phys* 2004;58:694-697). *Int J Radiat Oncol Biol Phys* 61:306-307, 2005
28. Porceddu SV, Jarmolowski E, Hicks RJ, et al: Utility of positron emission tomography for the detection of disease in residual neck nodes after (chemo)radiotherapy in head and neck cancer. *Head Neck* 27:175-181, 2005
29. Million RA, Cassisi NJ: Management of Head and Neck Cancer: A Multidisciplinary Approach (ed 2). Philadelphia, PA, J.B. Lippincott Company, 1994

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Author Contributions

Conception and design: Stanley L. Liauw, Anthony A. Mancuso, Robert J. Amdur, William M. Mendenhall

Administrative support: William M. Mendenhall

Provision of study materials or patients: William M. Mendenhall

Collection and assembly of data: Stanley L. Liauw, Anthony A. Mancuso

Data analysis and interpretation: Stanley L. Liauw, Anthony A. Mancuso, Robert J. Amdur, Christopher G. Morris, Douglas B. Villaret, John W. Werning, William M. Mendenhall

Manuscript writing: Stanley L. Liauw

Final approval of manuscript: Stanley L. Liauw, Anthony A. Mancuso, Robert J. Amdur, Christopher G. Morris, John W. Werning, William M. Mendenhall

Other: Anthony A. Mancuso, Robert J. Amdur, Douglas B. Villaret, John W. Werning, William M. Mendenhall

JOURNAL OF CLINICAL ONCOLOGY

Official Journal of the American Society of Clinical Oncology

Vol 24, No 9

C O N T E N T S

March 20, 2006

Editorials

Tales From a Targeted Therapy

Richard M. Elledge ([see article on page 1332](#)) 1323

The Ongoing Search for the Sources of the Breast Cancer Survival Disparity

James J. Dignam ([see article on page 1342](#)) 1326

Angiogenesis Inhibitors and Hypertension: An Emerging Issue

Domenic A. Sica ([see article on page 1363](#)) 1329

Original Reports

BREAST CANCER

Tamoxifen After Adjuvant Chemotherapy for Premenopausal Women With Lymph Node–Positive Breast Cancer: International Breast Cancer Study Group Trial 13-93

International Breast Cancer Study Group ([see editorial on page 1323](#)) 1332

Meta-Analysis of Survival in African American and White American Patients With Breast Cancer: Ethnicity Compared With Socioeconomic Status

Lisa A. Newman, Kent A. Griffith, Ismail Jatoi, Michael S. Simon, Joseph P. Crowe, and Graham A. Colditz ([see editorial on page 1326](#)) 1342

Contentment With Quality of Life Among Breast Cancer Survivors With and Without Contralateral Prophylactic Mastectomy

Ann M. Geiger, Carmen N. West, Larissa Nekhlyudov, Lisa J. Herrinton, In-Liu A. Liu, Andrea Altschuler, Sharon J. Rolnick, Emily L. Harris, Sarah M. Greene, Joann G. Elmore, Karen M. Emmons, and Suzanne W. Fletcher 1350

Missed Opportunities: Racial Disparities in Adjuvant Breast Cancer Treatment

Nina A. Bickell, Jason J. Wang, Soji Oluwole, Deborah Schrag, Henry Godfrey, Karen Hiotis, Jane Mendez, and Amber A. Guth 1357

TREATMENT-RELATED COMPLICATIONS

Mechanisms of Hypertension Associated With BAY 43-9006

Maria Luisa Veronese, Ari Mosenkis, Keith T. Flaherty, Maryann Gallagher, James P. Stevenson, Raymond R. Townsend, and Peter J. O'Dwyer ([see editorial on page 1329](#)) 1363

(continued on following page)

Journal of Clinical Oncology (ISSN 0732-183X) is published 36 times a year, three times monthly, by American Society of Clinical Oncology, 1900 Duke St, Suite 200, Alexandria, VA 22314. Periodicals postage is paid at Alexandria, VA, and at additional mailing offices. Publication Mail Agreement Number 863289.

Editorial correspondence should be addressed to Daniel G. Haller, MD, *Journal of Clinical Oncology*, 330 John Carlyle St, Suite 300, Alexandria, VA 22314. Telephone: (703) 797-1900; Fax: (703) 684-8720. E-mail: jco@asco.org. Internet: www.jco.org.

POSTMASTER: ASCO members send change of address to American Society of Clinical Oncology, 1900 Duke St, Suite 200, Alexandria, VA 22314. Nonmembers send change of address to *Journal of Clinical Oncology* Customer Service, 330 John Carlyle St, Suite 300, Alexandria, VA 22314.

2006 annual subscription rates, effective September 1, 2005: United States and possessions: individual, \$435; single issue, \$35. International: individual, \$605; single issue, \$45. Institutions: Tier 1: \$615 US, \$870 Int'l; Tier 2: \$715 US, \$970 Int'l; Tier 3: \$1,035 US, \$1,290 Int'l; Tier 4: \$1,140 US, \$1,395 Int'l; Tier 5: contact JCO for a quote. See <http://www.jco.org/subscriptions/tieredpricing.shtml> for descriptions of each tier. Student and resident: United States and possessions: \$215; all other countries, \$300. To receive student/resident rate, orders must be accompanied by name of affiliated institution, date of term, and the *signature* of program/residency coordinator on institution letterhead. Orders will be billed at individual rate until proof of status is received. Current prices are in effect for back volumes and back issues. Back issues sold in conjunction with a subscription rate are on a prorated basis. Subscriptions are accepted on a 12-month basis. Prices are subject to change without notice. Single issues, both current and back, exist in limited quantities and are offered for sale subject to availability. JCO Legacy Archive (electronic back issues from January 1983 through December 1998) is also available; please inquire.

HEMATOLOGIC MALIGNANCIES

Antibiotic Treatment Is Not Effective in Patients Infected With *Helicobacter pylori* Suffering From Extragastic MALT Lymphoma

Birgit Grünberger, Stefan Wöhrer, Berthold Streubel, Michael Formanek, Ventzislav Petkov, Andreas Puespoek, Michael Haefner, Michael Hejna, Ulrich Jaeger, Andreas Chott, and Markus Raderer 1370

■ Prognostic Factors in Primary Cutaneous B-Cell Lymphoma: The Italian Study Group for Cutaneous Lymphomas

Pier Luigi Zinzani, Pietro Quaglino, Nicola Pimpinelli, Emilio Berti, Gianandrea Baliva, Serena Rupoli, Maurizio Martelli, Mauro Alaiabac, Giovanni Borroni, Sergio Chimenti, Renato Alterini, Lapo Alinari, Maria Teresa Fierro, Nazario Cappello, Alessandro Pileri, Davide Soligo, Marco Paulli, Stefano Pileri, Marco Santucci, and Maria Grazia Bernengo 1376

AIDS-RELATED CANCER

① Elevated Incidence of Lung Cancer Among HIV-Infected Individuals

Eric A. Engels, Malcolm V. Brock, Jinbo Chen, Craig M. Hooker, Maura Gillison, and Richard D. Moore 1383

① Randomized Phase II Trial of Matrix Metalloproteinase Inhibitor COL-3 in AIDS-Related Kaposi's Sarcoma: An AIDS Malignancy Consortium Study

Bruce J. Dezube, Susan E. Krown, Jeannette Y. Lee, Kenneth S. Bauer, and David M. Aboulafia 1389

GASTROINTESTINAL CANCER

■ ① Hepatic Arterial Infusion Versus Systemic Therapy for Hepatic Metastases From Colorectal Cancer: A Randomized Trial of Efficacy, Quality of Life, and Molecular Markers (CALGB 9481)

Nancy E. Kemeny, Donna Niedzwiecki, Donna R. Hollis, Heinz-Josef Lenz, Robert S. Warren, Michelle J. Naughton, Jane C. Weeks, Elin R. Sigurdson, James E. Herndon II, Chunfeng Zhang, and Robert J. Mayer 1395

SUPPORTIVE CARE AND QUALITY OF LIFE

Incidence, Risk Factors, and Outcomes of Catheter-Related Thrombosis in Adult Patients With Cancer

Agnes Y.Y. Lee, Mark N. Levine, Gregory Butler, Carolyn Webb, Lorrie Costantini, Chushu Gu, and Jim A. Julian 1404

■ ① Phase III Comparison of Depomedroxyprogesterone Acetate to Venlafaxine for Managing Hot Flashes: North Central Cancer Treatment Group Trial N99C7

Charles L. Loprinzi, Ralph Levitt, Debra Barton, Jeff A. Sloan, Shaker R. Dakhil, Daniel A. Nikcevich, James D. Bearden III, James A. Mailliard, Loren K. Tschetter, Tom R. Fitch, and John W. Kugler 1409

HEAD AND NECK CANCER

Phase II Study of Donepezil in Irradiated Brain Tumor Patients: Effect on Cognitive Function, Mood, and Quality of Life

Edward G. Shaw, Robin Rosdhal, Ralph B. D'Agostino Jr, James Lovato, Michelle J. Naughton, Michael E. Robbins, and Stephen R. Rapp 1415

Postradiotherapy Neck Dissection for Lymph Node–Positive Head and Neck Cancer: The Use of Computed Tomography to Manage the Neck

Stanley L. Liauw, Anthony A. Mancuso, Robert J. Amdur, Christopher G. Morris, Douglas B. Villaret, John W. Werning, and William M. Mendenhall 1421

LUNG CANCER

① Phase III Study of Gemcitabine and Cisplatin With or Without Aprinocarsen, a Protein Kinase C-Alpha Antisense Oligonucleotide, in Patients With Advanced-Stage Non–Small-Cell Lung Cancer

Luis Paz-Ares, Jean-Yves Douillard, Piotr Koralewski, Christian Manegold, Egbert F. Smit, José Miguel Reyes, Gee-Chen Chang, William J. John, Patrick M. Peterson, Coleman K. Obasaju, Michael Lahn, and David R. Gandara 1428

(continued on following page)

THORACIC ONCOLOGY

■ Short-Term Treatment-Related Symptoms and Quality of Life: Results From an International Randomized Phase III Study of Cisplatin With or Without Raltitrexed in Patients With Malignant Pleural Mesothelioma: An EORTC Lung-Cancer Group and National Cancer Institute, Canada, Intergroup Study

Andrew Bottomley, Rabab Gaafa, Christian Manegold, Sjaak Burgers, Corneel Coens, Catherine Legrand, Mark Vincent, Giuseppe Giaccone, and Jan Van Meerbeeck 1435

Phase II Study of Pemetrexed Plus Carboplatin in Malignant Pleural Mesothelioma

Giovanni L. Ceresoli, Paolo A. Zucali, Adolfo G. Favaretto, Francesco Grossi, Paolo Bidoli, Guido Del Conte, Anna Ceribelli, Alessandra Bearz, Emanuela Morengi, Raffaele Cavina, Maurizio Marangolo, Hector J. Soto Parra, and Armando Santoro 1443

MOLECULAR ONCOLOGY

① Differential CD146 Expression on Circulating Versus Tissue Endothelial Cells in Rectal Cancer Patients: Implications for Circulating Endothelial and Progenitor Cells As Biomarkers for Antiangiogenic Therapy

Dan G. Duda, Kenneth S. Cohen, Emmanuelle di Tomaso, Patrick Au, Rachael J. Klein, David T. Scadden, Christopher G. Willett, and Rakesh K. Jain 1449

GYNECOLOGIC CANCER

Pretreatment CA-125 and Risk of Relapse in Advanced Ovarian Cancer

Maurie Markman, P.Y. Liu, Mace L. Rothenberg, Bradley J. Monk, Mark Brady, and David S. Alberts 1454

Review Article

① Cancer Symptom Assessment Instruments: A Systematic Review

Jordanka Kirkova, Mellar P. Davis, Declan Walsh, Eoin Tiernan, Norma O'Leary, Susan B. LeGrand, Ruth L. Lagman, and K. Mitchell Russell 1459

Diagnosis in Oncology

Case 1. Unusual Complications of a Hickman Catheter

Anne M. Horgan, Clodagh Kenny, Austin Duffy, and Seamus O'Reilly 1474

Case 2. Osteonecrosis of the Jaws Associated With Bisphosphonate Therapy

Michele D. Mignogna, Lucio Lo Russo, Stefano Fedele, Roberto Ciccarelli, and Lorenzo Lo Muzio 1475

Case 3. Upper Limb Lymphangiosarcoma Following Breast Cancer Therapy

Alberto Ocaña, Carlota Delgado, Cesar A. Rodríguez, Lorena Bellido, Noelia Izquierdo, Rebeca Martín, and Juan J. Cruz 1477

Case 4. Pulmonary Stent Migration and Ingestion in a Lung Cancer Patient

Jason W. Brown, Neil A. Christie, Carol Evans, and Merrill J. Egorin 1478

Correspondence

Stroke As a Late Treatment Effect of Hodgkin's Disease

Lucille Désirée Dorresteijn, Fiona Anne Stewart, and Willem Boogerd 1480

In Reply

Daniel C. Bowers and Kevin C. Oeffinger 1480

Progesterone Receptor and Human Epidermal Growth Factor Receptor 2 Status: An Independent Influence on the Efficacy of Endocrine Therapy in Breast Cancer?

Riccardo Ponzzone, Furio Maggiorotto, Claudio Robba, Luca Fuso, and Piero Sismondi 1481

In Reply

Mitch Dowsett, Jack Cuzick, Chris Wale, Tony Howell, Joan Houghton, Michael Baum, and Aman Buzdar 1482

● Medullary Renal Cell Carcinoma and Response to Therapy With Bortezomib

Ellen A. Ronnen, G. Varuni Kondagunta, and Robert J. Motzer e14

(continued on following page)

e Portal Hypertension and Liver Surgery Following Selective Internal Radiation Therapy With ⁹⁰Yttrium Microspheres

Richard S. Stubbs e15

Erratum 1484

Also in This Issue

Announcements

Information for Contributors

Current Abstracts

Calendar of Oncology Events



Online supplementary information available at **www.jco.org**



Article was published online ahead of print at **www.jco.org**



Additional correspondence available online at **www.jco.org**

www.jco.org

www.asco.org