Adjuvant Radiotherapy Improves Overall Survival for Patients With Lymph Node-Positive Head and Neck Squamous Cell Carcinoma

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BACKGROUND. Although adjuvant radiotherapy (RT) is often recommended for locally advanced squamous cell carcinoma of the head and neck (HNSCC), its effect on overall or cancer-specific survival has not been clearly demonstrated. In the current study, the frequency and effect of adjuvant RT on overall survival was investigated in patients with resected lymph node-positive head and neck cancer.

METHODS. Within the Surveillance, Epidemiology, and End Results (SEER) database, patients were selected with lymph node-positive HNSCC (American Joint Committee on Cancer and SEER stage 3/4) who were treated either with surgery alone or surgery and RT and were diagnosed between 1988 and 2001. A total of 8795 patients who met the inclusion criteria for analysis comprised the study population, with a median follow-up of 4.3 years for patients still alive at the time of last follow-up.

RESULTS. Adjuvant RT was utilized in 84% of patients. Adjuvant RT improved the 5-year overall survival (43.2% [95% confidence interval (95% CI), 41.9–44.4%] for surgery + RT vs 33.4% [95% CI, 30.7–36.0%] for surgery alone; $P < .001$) and cancer-specific survival (50.9% for surgery + RT vs 42.1% for surgery) on univariate analysis. On multivariate analysis, adjuvant RT (hazards ratio [HR] of 0.78; 95% CI, 0.71–0.86 [$P < .001$]) remained a significant predictor of improved survival. The significant benefit of radiation on overall survival was noted for lymph node-positive patients with both primary tumors localized to the involved organ (HR of 0.81; 95% CI, 0.71–0.94 [$P = .007$]) and more locally invasive primary tumors (HR of 0.77; 95% CI, 0.68–0.87 [$P < .001$]).

CONCLUSIONS. In what to the authors' knowledge is the largest reported analysis of adjuvant RT in patients with locally advanced HNSCC published to date, adjuvant RT resulted in an approximately 10% absolute increase in 5-year cancer-specific survival and overall survival for patients with lymph node-positive HNSCC compared with surgery alone. Despite combined surgery and adjuvant RT, outcomes in this high-risk population remain suboptimal, emphasizing the need for continued investigation of innovative treatment approaches. ***Cancer* 2008;112: 535–43.** © *2007 American Cancer Society.*

KEYWORDS: adjuvant radiotherapy, squamous cell carcinoma, head and neck, survival.

Although approximately 80% to 90% of patients with stage I or II head and neck cancer are cured with surgery or radiotherapy (RT) alone, outcomes for patients with locally advanced stage III to IVB head and neck cancer have been less promising.[1–3] Because the primary pattern of failure is locoregional, combined surgery and RT has been advocated to address disease above the clavicles in a comprehensive fashion.[4,5] Although this approach has been widely prac-

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ticed since Maccomb and Fletcher's landmark article in 1957,[6] whether surgery and RT improves survival compared with surgery alone has not been definitively proven. Although 2 small randomized trials suggested an improvement in locoregional control for combined surgery and RT compared with surgery alone, neither was adequately powered to demonstrate an overall survival advantage.[7,8]

A matched pair analysis performed at the Mayo Clinic demonstrated improved neck control, cause-specific survival, and overall survival for patients with stage III to IV head and neck cancer who were treated with combined surgery and RT compared with surgery alone.[9] Additional retrospective comparative series from the University of Texas M. D. Anderson Cancer Center, the University of Florida, and the Medical College of Virginia demonstrated significantly improved locoregional control with the addition of adjuvant RT to surgery.[5,10,11] RT may improve locoregional control via 3 mechanisms: improving local control at the primary tumor site, improving regional control of a dissected neck, or sterilizing occult disease in the undissected neck. Multiple randomized trials have now demonstrated that improved locoregional control translates into a survival advantage, even if there is no detectable impact on distant metastases.[12–14] Adjuvant RT is currently indicated for advanced lymph node disease (N2-3); extracapsular extension; close or positive surgical margins; bone, perineural, or lymphovascular invasion; and high likelihood of occult disease in an undissected neck.[2,15] It is unlikely that a large randomized trial will ever be mounted to definitively demonstrate the impact of adjuvant RT on survival for advanced head and neck cancer. Therefore, a retrospective review of high-quality, population-based data would provide significant insight into the impact of adjuvant RT on cancer-specific and overall survival.

MATERIALS AND METHODS

Data and Study Population

The Surveillance, Epidemiology, and End Results (SEER) database is a longitudinal database that collects information from 17 cancer registries covering 26% of the U.S. population.[16] The SEER database is composed of 17 population-based cancer registries from Connecticut, New Jersey, Atlanta, Kentucky, Louisiana, Rural Georgia, Detroit, Iowa, Hawaii, New Mexico, Seattle-Puget Sound, Utah, San Francisco-Oakland, San Jose-Monterey, Los Angeles, Greater California, and Alaska Native Tumor Registry.[17] Serial registry data are deidentified and submitted to the U.S. National Cancer Institute on a biannual basis and these data are publicly available for researchers.[17] Therefore, approval by an ethics committee is not necessary to perform the analyses.[18] The population covered by the SEER database is considered representative of the U.S. population and the case ascertainment rate is reportedly 97.5%.[18]

The histologic types selected for analysis are those coded as squamous cell carcinoma or variants of squamous cell carcinoma (papillary squamous cell carcinoma, verruccous carcinoma, squamous cell carcinoma, lymphoepithelial carcinoma, adenosquamous carcinoma, and basaloid squamous carcinoma) based on the International Classification of Diseases of Oncology codes (ICD-O-2).[19] We identified adult patients aged $\geq$21 years with pathologically confirmed squamous cell carcinoma of the head and neck (HNSCC) (coded as lip, oral cavity, oropharynx, hypopharynx, larynx, sinonasal and middle ear, salivary gland or other oral cavity, and pharynx) diagnosed between 1988 and 2001 who were treated with cancer-directed surgery (n = 42,076). We excluded patients with nasopharyngeal cancer because the primary locoregional treatment is RT rather than surgery. Patients with metastatic disease or tumors of an unknown stage (n = 5586), in situ carcinoma (n = 2183), no pathologic confirmation (n = 1), and unknown administration of RT (n = 842) were also excluded. Use of RT was abstracted by local tumor registries and reported to SEER. Patients were considered to have received RT if they received external beam RT, brachytherapy, or both. Patients who received only radioisotopes (n = 9) were not considered to have received adjuvant RT. To account for perioperative mortality, 516 patients were excluded who died within 4 months of diagnosis. A total of 24,153 eligible patients were lymph node negative. The remaining 8795 lymph node-positive patients were included for this analysis. The most recent follow-up available was November 2005 and the median follow-up available for living patients was 4.7 years.

Statistical Analysis

Categoric variables included patient age at diagnosis ($<$50 years, 50–69 years, or $\geq$70 years), sex, race, year of diagnosis, primary site, SEER 1977 stage (localized or invasive), lymph node stage (N1, N2a, N2b, N2c, N3, or supraclavicular lymph nodes), lymph node surgery, tumor size ($\leq$2 cm, 2.1–4 cm, and $\geq$4 cm), tumor grade, marital status, and use of RT. Marital status has recently been shown to be an important prognostic factor for head and neck cancer patients.[20] Due to the prognostic significance of primary tumor extent in head and neck cancer, we specifically analyzed the effect of RT on survival on

TABLE 1
SEER 1977 Summary Staging System[34]

Stage	Description
0	In situ: noninvasive; intraepithelial
1	Localized only: invasive tumor confined to primary site
2	Regional by direct extension only: invasive tumor extending to adjacent organs and/or subsites
3	Regional lymph node(s) involved only
4	Regional by both direct extension and regional lymph node(s)
7	Distant site(s)/lymph node(s) involved
9	Unknown

SEER indicates the Surveillance, Epidemiology, and End Results program.

localized primary tumors and more extensive primary tumors. Although the American Joint Committee on Cancer (AJCC) T classification was not available in the SEER database, SEER 1977 provided a measure of primary tumor extent (Table 1). SEER stage 3 is defined as lymph node-positive patients with a primary tumor localized to the involved site without extension to adjacent organs or subsites. By contrast, SEER stage 4 includes patients with positive lymph nodes and a primary tumor that extends to adjacent organs or subsites.

Patient age in years, tumor size, and year of diagnosis were analyzed as categoric variables on univariate analysis but as continuous variables on multivariate analysis. Information regarding surgical margin status, extent of lymph node surgery, extracapsular extension, perineural or lymphovascular invasion, use of adjuvant chemotherapy, performance status, recurrent or second head and neck primary tumor, and RT details (dose, fractionation, 3-dimensional conformal/intensity modulated RT, etc.) were not available within the SEER database and this information is not included for analysis. Overall survival was the primary endpoint and cancer-specific survival was the secondary endpoint. To determine the effect of adjuvant RT survival stratified by primary tumor invasiveness and extent, subset analyses were performed on patients with SEER stage 3 and 4 disease.

The Pearson chi-square test was utilized to assess unadjusted associations between adjuvant RT and categoric variables. Overall survival was calculated from the time of diagnosis to the time of death or last follow-up. Cancer-specific survival was calculated from the time of diagnosis to the time of death from any cancer or last follow-up. Nonparametric survival estimates were calculated by the Kaplan-Meier method (product-limit estimate). When applicable, the stratified log-rank test was utilized to compute survival estimates were within specified strata levels. Cancer-specific survival was calculated using SEER*Stat software (version 6.2.4). All other data were analyzed using Stata software (version 8.0; StataCorp, College Station, Tex) by importing data from the SEER (available at URL: www.seer.cancer.gov accessed on November 21, 2006) 1973–2003 Public Use Data (National Cancer Institute, April 2006 release based on the November 2005 submission) into Stata. Results were considered to be statistically significant when $P < .05$.

Cox proportional hazards regression modeling was limited to covariates that we found to be statistically significant on univariate analysis. Due to missing data, a multivariate analysis was developed for the 4572 patients with complete datasets. A multivariable Cox model was developed to calculate the adjusted hazards ratios (HRs) and 95% confidence intervals (95% CIs). Separate multivariate models were developed for 3 groups: all lymph node-positive patients, patients with localized tumors but positive lymph nodes (SEER stage 3), and patients with invasive tumors and positive lymph nodes (SEER stage 4). A formal examination of the proportional hazards assumption was performed graphically by plotting –log(log(S(t)) versus log(t) for each covariate. This confirmed that the covariates are independent with respect to time and their HRs are constant over the clinically relevant period of follow-up.

RESULTS

Among the 8795 patients with lymph node-positive HNSCC meeting eligibility criteria, 7379 (84%) received adjuvant RT. Nearly 96% of irradiated patients received external beam RT alone with 3% receiving external beam RT and brachytherapy, 0.3% receiving brachytherapy alone, and 0.7% receiving an unknown method of RT. Nearly 89% of irradiated patients received postoperative RT, whereas 7% received preoperative RT, 1% received both preoperative and postoperative RT, 0.2% received intraoperative RT with or without additional RT, and in 3% of patients the sequence of surgery and RT was unknown. The median patient age at diagnosis was 60 years (range, 21–100 years). A description of patient demographics and tumor characteristics and their relation to adjuvant RT use is shown in Table 2. Strong predictors of RT use were younger patient age, male sex, non-Black race, diagnosis after 1992, locally invasive tumor, nonoral cavity or salivary gland primary tumor, advanced lymph node disease, first primary tumor, and single or married marital status. By contrast, tumor size failed to predict for adjuvant RT use.

TABLE 2
Patient Characteristics and Prevalence of Adjuvant RT Use

Demographic	No of patients (n = 8795)	% Who received observation (n = 1416)	% Who received adjuvant RT (n = 7379)	*P*
Age, y				<.001
<50	1958	13.0	87.0	
50–69	4869	14.3	85.7	
≥70	1968	23.6	76.4	
Sex				<.001
Male	6588	14.8	85.2	
Female	2207	20.0	80.0	
Race				.016
White	7317	16.1	83.9	
Black	1061	18.3	81.7	
Asian/Pacific Islander/ Native American	408	11.0	89.0	
Other	3	33.3	66.7	
Unknown	6	16.7	83.3	
Year of diagnosis				.001
1988	412	23.1	76.9	
1989	379	19.8	80.2	
1990	389	18.3	81.8	
1991	358	14.3	85.8	
1992	552	20.1	79.9	
1993	559	15.0	85.0	
1994	565	12.6	87.4	
1995	509	14.9	85.1	
1996	577	15.6	84.4	
1997	607	15.8	84.2	
1998	645	15.7	84.3	
1999	644	15.7	84.3	
2000	1270	14.7	85.3	
2001	1329	15.6	84.4	
Tumor size, cm				.490
≤2	1856	17.0	83.0	
2.1–4	3350	16.3	83.7	
≥4	1340	15.8	84.2	
Unknown	2249	15.3	84.8	
Tumor extent				.004
Localized (SEER stage 3)	4345	17.2	82.8	
Invasive (SEER stage 4)	4450	15.0	85.0	
N classification (2002 AJCC)				<.001
N1	2736	21.4	78.7	
N2a	1454	16.2	83.8	
N2b	950	14.3	85.7	
N2c	377	16.2	83.8	
N3	268	9.0	91.0	
Other lymph nodes	980	11.2	88.8	
N+ NOS	2030	13.1	86.9	
Primary site				<.001
Lip	61	29.5	70.5	
Other oral cavity	2300	22.1	77.9	
Oropharynx	3412	11.6	88.4	
Hypopharynx	1067	13.1	86.9	
Larynx	1297	17.4	82.6	
Sinonasal and ear	63	14.3	85.7	
Salivary gland	288	26.7	73.3	
Other	307	14.0	86.0	
Grade	610	20.5	79.5	<.001
1 (well-differentiated)	3875	17.7	82.3	
2 (moderately differentiated)	3482	13.7	86.3	
3 (poorly differentiated)	123	18.7	81.3	
4 (undifferentiated)	705	15.2	84.8	
Unknown				.001
Marital status	1278	14.6	85.4	
Single	2281	18.4	81.6	
Widowed, divorced or separated	4931	15.2	84.8	
Married	305	20.3	79.7	
Unknown				

RT indicates radiation therapy; SEER, Surveillance, Epidemiology, and End Results program; AJCC, American Joint Committee on Cancer; NOS, not otherwise specified.

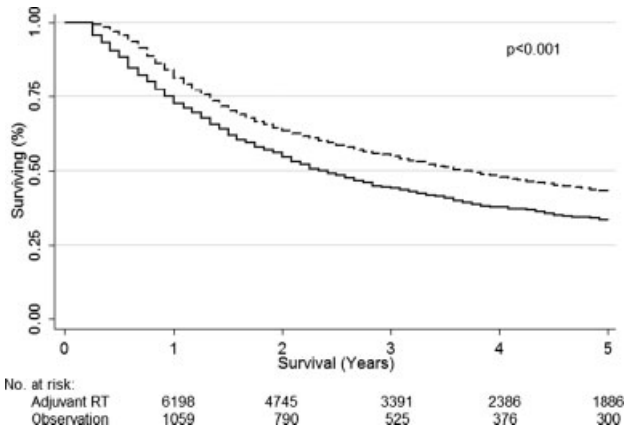

FIGURE 1. Plot of overall survival for all lymph node-positive patients stratified by use of adjuvant radiotherapy (RT). The solid line represents patients receiving surgery alone and the dashed line represents patients who received surgery and RT.

On univariate analysis for all lymph node-positive patients, adjuvant RT was associated with significantly improved overall survival. The 3-year overall survival rate with surgery and RT was 54.9% (95% CI, 53.8–56.1%) compared with 44.4% (95% CI, 41.7–47.0%) for surgery alone ($P < .001$). The 5-year overall survival with surgery and RT was 43.2% (95% CI, 41.9–44.4%) compared with 33.4% (95% CI, 30.7–36.0%) for surgery alone. (See Fig. 1 for Kaplan-Meier plots of overall survival stratified by RT use.) In the largest subset of patients treated by postoperative external beam RT, the 3-year and 5-year overall survival rates were 54.8% (95% CI, 53.5–56.0%) and 43.0% (95% CI, 41.6–

TABLE 3
Univariate Estimates for 3-Year and 5-Year Overall Survival

Demographic	3-Year overall survival	5-Year overall survival	*P*
RT			<.001
Adjuvant RT	54.9	43.2	
Observation	44.4	33.4	
Age, y			<.001
<50	63.7	55.6	
50–69	54.9	42.2	
≥70	38.6	26.5	
Sex			.071
Male	53.9	41.9	
Female	51.3	40.5	
Race			<.001
White	55.2	43.4	
Black	39.7	28.2	
Asian/Pacific Islander/ Native American	52.4	43.4	
Other	33.3		
Unknown	83.3	66.7	
Year of diagnosis			<.001
1988	43.5	31.6	
1989	49.5	35.7	
1990	47.3	34.5	
1991	49.0	34.7	
1992	47.6	37.5	
1993	49.6	37.2	
1994	54.9	43.2	
1995	50.6	40.8	
1996	52.5	42.6	
1997	52.8	42.4	
1998	55.6	44.7	
1999	54.6	45.0	
2000	57.4		
2001	60.4		
Tumor size, cm			<.001
≤2	62.5	50.3	
2.1–4	51.6	39.9	
≥4	40.1	29.5	
Unknown	55.9	44.2	
Tumor extent			<.001
Localized (SEER stage 3)	61.8	49.7	
Invasive (SEER stage 4)	44.9	33.8	
N classification (2002 AJCC)			<.001
N1	62.0	50.5	
N2a	53.3	40.8	
N2b	51.0	39.4	
N2c	46.2	33.3	
N3	38.0	30.4	
Other lymph nodes	48.3	35.8	
N+ NOS	48.0	36.8	
Primary site			<.0001
Lip	41.7	23.7	
Other oral cavity	40.0	30.5	
Oropharynx	68.2	57.5	
Hypopharynx	45.1	31.6	
Larynx	49.6	35.4	
Sinonasal and ear	28.5	18.8	
Salivary gland	46.3	33.5	
Other			
Grade			<.001
1 (well-differentiated)	49.2	38.7	
2 (moderately differentiated)	50.8	39.3	
3 (poorly differentiated)	56.1	44.8	
4 (undifferentiated)	58.9	50.0	
Unknown	54.7	38.9	
Marital status			<.001
Single	47.7	39.1	
Widowed, divorced, or separated	44.9	32.0	
Married	58.2	46.2	
Unknown	57.4	50.2	

RT indicates radiation therapy; SEER, Surveillance, Epidemiology, and End Results program; AJCC, American Joint Committee on Cancer; NOS, not otherwise specified.

44.3%), respectively. Other factors found to be predictive of improved survival were younger age, white or Asian race, diagnosis after 1993, small tumor size, poorly differentiated tumor, lower AJCC 2002 N classification, localized tumor, first primary tumor, and currently married status. Sex failed to significantly impact survival. The results of all univariate analyses of demographics and tumor characteristics and their correlation with overall survival are listed in Table 3. The 5-year cancer-specific survival was 50.9% (standard error [SE]: 0.6%) for surgery and RT versus 42.1% for surgery alone (SE: 1.3%).

To determine whether a measure of tumor invasiveness impacted the efficacy of adjuvant RT, subset analyses were performed for SEER 1977 stage 3 (primary tumor localized to involved site and lymph node positive) and SEER 1977 stage 4 (primary tumor that extends to adjacent organs or subsites and lymph node positive) disease. Additional subset analyses were considered but some patients had missing tumor size and AJCC 2002 N classification. The 5-year overall survival for patients with localized tumors treated with surgery and adjuvant RT was 51.6% (95% CI, 49.8–53.4%) versus 40.6% (95% CI, 36.7–44.5%) for surgery alone ($P < .001$) (see Figure 2 for Kaplan-Meier survival curves for this subset stratified by RT use.) The 5-year cancer-specific survival was 59.9% (SE: 0.9%) with surgery and RT compared with 51.0% (SE: 1.8%) for surgery alone. The 5-year overall survival for invasive tumors treated with combined surgery and RT was 35.3% (95% CI, 33.6–36.9%) versus 25.2% (95% CI, 21.8–28.8%) for surgery alone ($P < .001$). Kaplan-Meier plots for this subset of

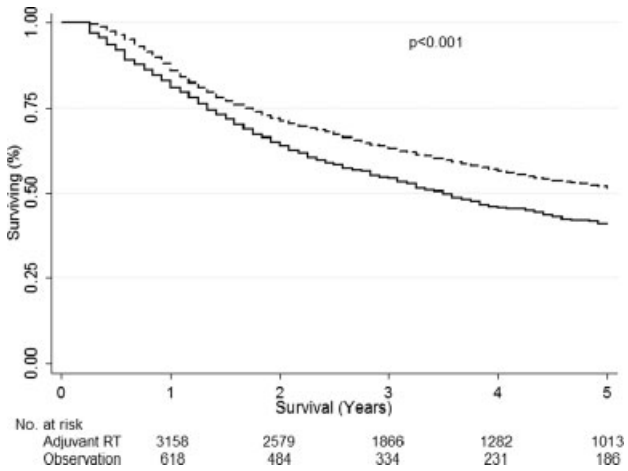

FIGURE 2. Plot of overall survival for patients with lymph node-positive disease and localized primary tumors (Surveillance, Epidemiology, and End Results [SEER] stage 3) stratified by use of adjuvant radiotherapy (RT). The solid line represents patients receiving surgery alone and the dashed line represents patients who received surgery and RT.

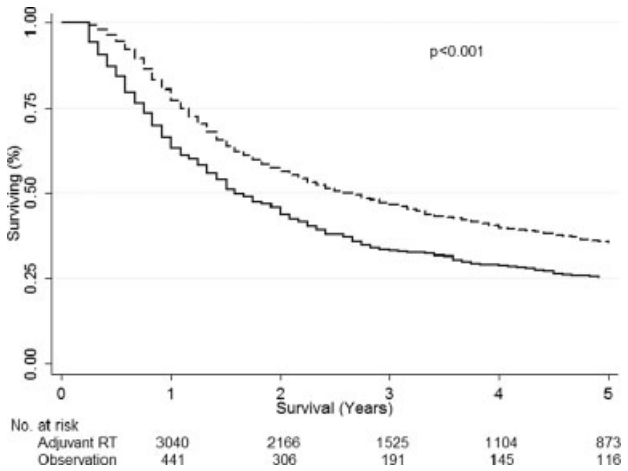

FIGURE 3. Plot of overall survival for patients with lymph node-positive disease and locally invasive primary tumors (Surveillance, Epidemiology, and End Results [SEER] stage 4) stratified by use of adjuvant radiotherapy (RT). The solid line represents patients receiving surgery alone and the dashed line represents patients who received surgery and RT.

patients stratified by RT use are presented in Figure 3. The 5-year cancer-specific survival was 42.3% (SE: 0.8%) for surgery and adjuvant RT and 32.6% (SE: 1.7%) for surgery without RT.

On multivariate analysis of all patients with a complete dataset, adjuvant RT (HR of 0.78; 95% CI, 0.71–0.86 [$P < .001$]), age, primary tumor site, lymph node staging, SEER tumor staging, tumor size, marital status, and race were all found to be significant predictors of overall survival. Year of diagnosis and tumor grade did not significantly improve survival. Separate multivariate analyses for patients with localized tumors and locally invasive tumors demonstrated that the use of adjuvant RT was associated with significantly improved survival in both subgroups. The magnitude of the risk reduction of death was greater for locally invasive tumors (HR of 0.77; 95% CI, 0.68–0.87 [$P < .001$]) than localized tumors (HR of 0.81; 95% CI, 0.71–0.94 [$P = .007$]), but both were found to be statistically significant. The subset analysis recapitulated the findings of the multivariate analysis for all lymph node-positive patients, with the exception that race failed to predict survival for localized tumors and patients with poorly differentiated tumors with locally invasive tumors had better survival. The results of all multivariate analyses are shown in Table 4.

DISCUSSION

The current study was performed to assess the effect of adjuvant RT on cancer-specific and overall survival for patients with locally advanced head and neck cancer. RT was found to significantly improve overall and cancer-specific survival for patients with lymph node-positive, stage III to IVB head and neck cancer. To our knowledge, as the largest reported population analysis of the use of adjuvant RT in patients with locally advanced head and neck cancer published to date, it is significant that our study reveals a clinically significant survival benefit for adjuvant RT in patients with stage III to IVB disease. This information confirms the results of smaller series that demonstrate that adjuvant RT increases cause-specific and overall survival for patients with lymph node-positive head and neck cancer.[2,9,11,21] These data support current guidelines that recommend adjuvant RT for the vast majority of lymph node-positive patients treated with primary surgery.[22]

Although to our knowledge the current study represents the largest published series focused on advanced head and neck cancer patients treated with primary surgery, this U.S. population-based study has a number of limitations that must be considered. The SEER data are collected retrospectively and confounding factors that may have influenced the treating physician's decision to recommend adjuvant RT such as surgical margin status, extracapsular extension, perineural invasion, lymphovascular invasion, and performance status were not available for analysis.[5] Although the presence or absence of lymph node positivity is well documented, N classification was available for 77% of patients, tumor size was documented for 74% of patients, and tumor grade was known for 92%. Whether lymph node surgery

TABLE 4
Predictors of Death From Any Cause in Multivariable Analysis

	All patients (N = 4573)			Localized (N = 2188)			Invasive (N = 2385)		
Demographic (Variable)	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
RT (yes)	.784	.038	<.001	.812	.059	.004	.769	.050	<.001
Age (continuous)	1.022	.002	<.001	1.025	.003	<.001	1.021	.002	<.001
Race (non-black)	.769	.043	<.001	.882	.088	.211	.730	.050	<.001
Site (OPX)	.575	.026	<.001	.481	.035	<.001	.649	.038	<.001
Grade (continuous)	.948	.028	.069	1.028	.046	.539	.896	.035	.005
Year of diagnosis (continuous)	.991	.005	.069	.989	.008	.149	.994	.006	.385
N classification (continuous)	1.126	.014	<.001	1.139	.0228	<.001	1.117	.018	<.001
T classification (invasive)	1.306	.052	<.001						
Tumor size (continuous)	1.007	.001	<.001	1.010	.002	<.001	1.007	.001	<.001
Marital status (continuous)	.885	.023	<.001	.881	.037	.002	.891	.030	.001

HR indicates hazards ratio; 95% CI, 95% confidence interval; RT, radiation therapy; OPX, oropharynx.

was performed was poorly characterized in the database. Specifics of RT quality including dose, field sizes, treatment time, and compliance with therapy are not available. AJCC T classification was not documented for this cohort of patients. SEER T classification for head and neck cancer specifies only in situ, localized, and locally extensive tumors, which does not necessarily correlate with the AJCC T classification. In addition, the database did not contain specific information regarding performance status. The limitations of this database complicate proper interpretation of the data and reduce the power of subset analyses designed to determine cohorts of patients more likely to benefit from adjuvant RT.

To enhance the statistical power of the study, patients with squamous cell carcinoma of all sites, excluding the nasopharynx, were grouped together rather than analyzed separately. Certain subsites appear to have different prognoses and this potentially confounds analysis of the data.[15] Conversely, clinical trials studying advanced head and neck cancer often are not site specific because the prognosis of patients with stage III to IVb head and neck cancer is generally considered poor.[12–14,23,24] Finally, the SEER database did not collect information concerning the use of chemotherapy in this patient population. The additional benefit of concurrent chemotherapy on a subset of patients receiving adjuvant RT was published in 2004.[12,24] Before these studies the use of adjuvant chemoradiation was not considered effective at improving locoregional control or overall survival and this variable is unlikely to be a significant confounding factor.[25,26]

Despite these significant limitations, the HRs for survival for adjuvant RT were found to be greater on multivariate analysis than on univariate variable analysis. These data are consistent with the notion that higher-risk patients within each SEER stage are referred for adjuvant RT and this treatment has a favorable impact on the natural history of advanced head and neck cancer. Conversely, only 16% of the 8795 patients failed to receive adjuvant RT. This raises the possibility that adjuvant RT was considered the standard of care for most patients with lymph node-positive disease and was not offered to less robust patients. We attempted to control for this by excluding patients that died within 4 months of surgery and by incorporating available demographic data into our multivariate analysis. Although adjuvant RT clearly reduced the incidence of death from cancer (absolute benefit of 9.7% at 5 years) and death from any cause (absolute benefit of 9.8% at 5 years), these data do not prove a causal relation. The SEER database does not collect cause of treatment failure, whether locoregional or distant. Taken together, these data support the notion that the benefit attributable to adjuvant RT was not due to imbalances in patient factors favoring the treated cohort.

Although adjuvant RT is associated with significantly improved survival, the outcomes for lymph node-positive patients remain suboptimal. Even with combined surgery and RT, the 5-year survival for patients with lymph node-positive head and neck cancer was only 43%. The vast majority of the deaths were due to cancer. These data are consistent with the surgery + RT arms from the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) trials, which reported 5-year overall survival rates of approximately 40%.[12,24] Taken together, it appears that surgery alone cures approximately one-third of patients with locally advanced but resectable disease.

Adjuvant RT confers an absolute survival benefit of approximately 10%. Particularly for patients with extracapsular extension or microscopic positive surgical margins, adding platinum-based chemotherapy to adjuvant RT further increases survival by 6% to 13%.[27] These data highlight the importance of investigating novel strategies such as increasing RT dose intensity, intensified chemoradiation protocols, and integrating new treatment modalities such as biologic therapy and intensity-modulated RT.[1,15,28–33] Conversely, the finding that marital status affects outcome on both univariate and multivariate analysis suggests that family support might enhance the patient's ability to complete surgery and RT in a timely fashion. These data suggest a potential role for social support services and patient counseling in nonmarried patients, which have become more important in patients receiving intensive combinations of surgery, RT, and chemotherapy. Finally, the data reported herein represent results in a contemporary cohort of patients with locally advanced head and neck cancer who were treated with surgery and adjuvant RT that can be used to compare the efficacy of alternative approaches.

In summary, analysis of the SEER database demonstrated that adjuvant RT offers a significant survival benefit for patients with lymph node-positive squamous cell carcinoma of the head and neck. Future studies are needed to determine whether there are subgroups of patients with lymph node-positive disease that do not benefit from adjuvant RT and whether adjuvant RT improves survival in a subset of patients with locally advanced but lymph node-negative disease.

REFERENCES

1. Forastiere A, Koch W, Trotti A, Sidransky D. Head and neck cancer. *N Engl J Med*. 2001;345:1890–1900.
2. Million RR, Cassisi NJ. Management of head and neck cancer: a multidisciplinary approach. 2nd ed. Philadelphia: Lippincott; 1994.
3. Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. *N Engl J Med*. 1993;328:184–194.
4. Fletcher GH. Textbook of radiotherapy. 3rd ed. Philadelphia: Lea & Febiger; 1980.
5. Marcus RB Jr, Million RR, Cassissi NJ. Postoperative irradiation for squamous cell carcinomas of the head and neck: analysis of time-dose factors related to control above the clavicles. *Int J Radiat Oncol Biol Phys*. 1979;5:1943–1949.
6. Maccomb WS, Fletcher GH. Planned combination of surgery and radiation in treatment of advanced primary head and neck cancers. *Am J Roentgenol Radium Ther Nucl Med*. 1957;77:397–414.
7. Kokal WA, Neifeld JP, Eisert D, et al. Postoperative radiation as adjuvant treatment for carcinoma of the oral cavity, larynx, and pharynx: preliminary report of a prospective randomized trial. *J Surg Oncol*. 1988;38:71–76.
8. Mishra RC, Singh DN, Mishra TK. Post-operative radiotherapy in carcinoma of buccal mucosa, a prospective randomized trial. *Eur J Surg Oncol*. 1996;22:502–504.
9. Lundahl RE, Foote RL, Bonner JA, et al. Combined neck dissection and postoperative radiation therapy in the management of the high-risk neck: a matched-pair analysis. *Int J Radiat Oncol Biol Phys*. 1998;40:529–534.
10. Barkley HT Jr, Fletcher GH, Jesse RH, Lindberg RD. Management of cervical lymph node metastases in squamous cell carcinoma of the tonsillar fossa, base of tongue, supraglottic larynx, and hypopharynx. *Am J Surg*. 1972;124:462–467.
11. Huang DT, Johnson CR, Schmidt-Ullrich R, Grimes M. Postoperative radiotherapy in head and neck carcinoma with extracapsular lymph node extension and/or positive resection margins: a comparative study. *Int J Radiat Oncol Biol Phys*. 1992;23:737–742.
12. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 2004;350:1945–1952.
13. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2006;354:567–578.
14. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet*. 2006;368:843–854.
15. Ang KK, Trotti A, Brown BW, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2001;51:571–578.
16. Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol*. 2006; 24:2998–3006.
17. Surveillance, Epidemiology, and End Results (SEER) Program Limited-Use Data (1973–2004), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch. Bethesda, MD. Released April 2006. Available at URL: http://seer.cancer.gov/publicdata/ Accessed on November 11, 2006.
18. Lee CM, Szabo A, Shrieve DC, Macdonald OK, Gaffney DK. Frequency and effect of adjuvant radiation therapy among women with stage I endometrial adenocarcinoma. *JAMA*. 2006;295:389–397.
19. Piercy C, Van Holten VCM. International classification of diseases for oncology. 2nd ed. Geneva: World Health Organization; 1990.
20. Konski AA, Pajak TF, Movsas B, et al. Disadvantage of men living alone participating in Radiation Therapy Oncology Group head and neck trials. *J Clin Oncol*. 2006;24:4177–4183.
21. El Badawi SA, Goepfert H, Fletcher GH, Herson J, Oswald MJ. Squamous cell carcinoma of the pyriform sinus. *Laryngoscope*. 1982;92:357–364.
22. NCCN. Clinical Practice Guidelines in Oncology: Head and Neck Cancers. (Version 1.2007). National Comprehensive Cancer Network. Jenkintown, PA. Available at URL: http://seer.cancer.gov/publicdata/ Accessed on November 29, 2007.
23. Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 1998;338:1798–1804.

24. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2004;350:1937–1944.
25. Jacobs C, Makuch R. Efficacy of adjuvant chemotherapy for patients with resectable head and neck cancer: a subset analysis of the Head and Neck Contracts Program. *J Clin Oncol*. 1990;8:838–847.
26. Laramore GE, Scott CB, al-Sarraf M, et al. Adjuvant chemotherapy for resectable squamous cell carcinomas of the head and neck: report on Intergroup Study 0034. *Int J Radiat Oncol Biol Phys*. 1992;23:705–713.
27. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). *Head Neck*. 2005;27:843–850.
28. Cohen EE, Haraf DJ, Stenson KM, et al. Integration of gefitinib (G), into a concurrent chemoradiation (CRT) regimen followed by G adjuvant therapy in patients with locally advanced head and neck cancer (HNC)—a Phase II trial. *Proc Am Soc Clin Oncol*. 2005;23(suppl 16S):5506a.
29. Peters LJ, Goepfert H, Ang KK, et al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. *Int J Radiat Oncol Biol Phys*. 1993;26:3–11.
30. Vokes EE, Stenson K, Rosen FR, et al. Weekly carboplatin and paclitaxel followed by concomitant paclitaxel, fluorouracil, and hydroxyurea chemoradiotherapy: curative and organ-preserving therapy for advanced head and neck cancer. *J Clin Oncol*. 2003;21:320–326.
31. Chao KS, Ozyigit G, Tran BN, Cengiz M, Dempsey JF, Low DA. Patterns of failure in patients receiving definitive and postoperative IMRT for head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2003;55:312–321.
32. Kao J, Garofalo MC, Milano MT, Chmura SJ, Citron JR, Haraf DJ. Reirradiation of recurrent and second primary head and neck malignancies: a comprehensive review. *Cancer Treat Rev*. 2003;29:21–30.
33. Milano MT, Vokes EE, Kao J, et al. Intensity-modulated radiation therapy in advanced head and neck patients treated with intensive chemoradiotherapy: preliminary experience and future directions. *Int J Oncol* 2006;28: 1141–1151.