Risk-Group Definition by Recursive Partitioning Analysis of Patients with Squamous Cell Head and Neck Carcinoma Treated with Surgery and Postoperative Radiotherapy

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BACKGROUND. The objective of this study was to define different prognostic groups with regard to locoregional control (LRC) derived from recursive partitioning analysis (RPA).

METHODS. Eight hundred one patients with squamous cell head and neck carcinoma underwent with primary surgery and received postoperative radiotherapy. For the definition of prognostic groups, the method of classification and regression trees was performed, including a large number of well known prognostic factors.

RESULTS. The final model was composed of six prognostic factors for LRC, resulting in seven terminal nodes. RPA Class I (intermediate risk) consisted of 381 patients who had no N3 lymph nodes, free surgical margins (> 5 mm), and no extranodal spread (ENS). RPA Class II (high risk) consisted of 189 patients who had 1 positive lymph node with ENS or had T1, T2, or T4 tumors with close or positive surgical margins. RPA Class III (very high risk) consisted of 231 patients who had a N3 neck, ≥ 2 positive lymph nodes with ENS, or a T3 tumor with close or positive surgical margins. The 5-year LRC rate was 88%, 73% and 58%, in RPA Class I, II, and III, respectively ($P < 0.0001$). The hazard ratio (HR) relative to RPA Class I was 2.3 (95% confidence interval [95%CI], 1.5–3.6) for RPA Class II and 4.2 (95%CI, 2.8–6.1) for RPA Class III.

CONCLUSIONS. The RPA classification scheme studied allowed for the clear definition of three prognostic groups with regard to LRC and OS. These groups may be useful in the design of future prospective, randomized studies investigating new treatment modalities. ***Cancer* 2005;104:1408–17.**

KEYWORDS: head and neck carcinoma, radiotherapy, prognostic factors, overall treatment time.

Squamous cell carcinoma of the head and neck (HNSCC) is a group of tumors that includes large numbers of relatively rare malignancies at different sites that, all together, account for almost 10% of all newly diagnosed carcinomas in The Netherlands. Many patients are treated with primary surgery with adjuvant radiotherapy if they have adverse prognostic factors, such as close or positive surgical margins[1–6] and extranodal spread.[3,5,7–9]

For the proper design of therapeutic trials investigating novel strategies, a thorough knowledge of differences in outcome of specific prognostic groups is essential. Moreover, the choice of adjuvant treatment (e.g., total dose, overall treatment time, chemoradiation) after primary surgery may depend on the risk on locoregional failure and

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the probability of distant metastases.[9–12] Classification and regression trees (CART), also known as recursive partitioning analysis (RPA), are techniques with which to construct subgroups that are as homogeneous as possible internally with regard to outcome and as separated as possible externally. Thus, the method leads directly to prognostic subgroups defined by the potential prognostic factor.[13–15]

Peters et al. were the first to use a classification system for patients with HNSCC who were treated with surgery and postoperative radiotherapy in a prospective, randomized study: In that study, patients were assigned randomly to different dose levels, depending on their risk level.[9] In that study, the risk group classification (low risk, intermediate risk, and high risk) was devised empirically, based on the best estimate of the relative importance of different clinical and pathologic factors in determining the risk of local and regional recurrence. Although it has been shown in a number of other studies that this classification system has value,[10,16] the question remains whether CART provides a more reliable estimate of the risk of locoregional recurrence. Therefore, the main objective of the current study was to identify different prognostic groups with regard to locoregional control (LRC) derived from RPA among patients with HNSCC who were treated with curative surgery and postoperative radiotherapy. In addition, the consequences of this classification system based on LRC regarding the incidence of distant metastases, disease-free survival (DFS), and overall survival (OS) were investigated.

MATERIALS AND METHODS

Patients Characteristics

The population in this retrospective study consisted of a consecutive series of 801 patients who underwent postoperative radiotherapy during the period from January 1985 to December 2000, for squamous cell carcinoma of the mucosal surfaces of the oral cavity (excluding the lip), oropharynx, hypopharynx, and larynx. Most patients (66.5%) were male. The median age was 59 years (range, 20–90 yrs). The pretreatment evaluation included a medical history, examination under general anesthesia with panendoscopy, and a chest radiograph in all patients. Ultrasound of the neck with or without fine-needle aspiration cytology, depending on site criteria, was performed in 257 patients (32%). Computed tomography scans of the involved head and neck region were performed in 298 patients (37%), and magnetic resonance images were obtained in 146 patients (18%). Additional diagnostic procedures for distant metastases, including computed tomography scans of the chest, liver ultrasound, bone scintigraphy, and/or (more recently) positron emission tomography scans were performed only if clinically indicated. Patients with distant metastases were excluded from the analysis. Tumor (T) classification and lymph node (N) classification were assigned according to the 1997 staging system of the International Union Against Cancer.[17] The pretreatment characteristics are listed in Table 1.

Surgery

All patients underwent surgery of their primary tumor. Minor surgery, which consisted of local excision of the primary site, was undergone by 157 patients (20%), mainly among patients with T1 and T2 tumors. In the remaining 644 patients (80%), surgery consisted of more extensive procedures, i.e., commando-resection, including partial or total glossectomy; partial or total pharyngectomy; marginal or segmental mandibulectomy; and/or total or partial laryngectomy. In 732 patients (91%), unilateral or bilateral neck dissection was undergone. In all patients, surgery was performed in the Vrije University Medical Center.

Radiotherapy

Radiotherapy was performed at the department of Radiation Oncology of the Vrije University Medical Center and was delivered using mega voltage (MV) equipment (6-MV linear accelerator). The clinical target volume of the initial field encompassed the primary site plus a 1–2 cm margin and the entire surgical bed. In patients with cervical lymph node metastases, the cervical lymph nodes on both sides of the neck also were included in the initial target volume. For the planning target volume (PTV), a margin of 0.5 cm was applied. Generally, the initial PTV was irradiated using two opposing lateral fields. The initial field was irradiated with a fraction dose of 2 gray (Gy) (5 times per week/once daily) to the central axis up to a total dose of 46–50 Gy. If the total dose was 50 Gy, then the spinal cord was shielded after 40 Gy, and the anterior part of the neck was irradiated with a dose per fraction of 2 Gy up to 50 Gy using photons, whereas the posterior triangle was irradiated using electrons (6–20 MeV) with a dose per fraction of 3 Gy up to a total dose of 49 Gy. The dose of the electrons was specified at the 100%-isodose level, and the energy of the electrons was determined such that the maximum dose to the spinal cord was $\leq$ 20% of the prescribed dose. In patients with negative surgical margins, the primary site with a 1-cm margin (i.e., 0.5 cm for the clinical target volume and 0.5 cm for the PTV) was boosted using a median dose per fraction of 2.5 Gy (range, 1.8–2.5 Gy; 5 times per week) up to a median total dose of 55 Gy (range, 20–70 Gy). In patients with positive surgical margins, the median total dose to the

TABLE 1
Pretreatment Characteristics and Univariate Analysis Regarding Locoregional Control

Variable	No. of patients (%)	LRC at 5 yrs (%)	Log-rank *P* value	Uncorrected OR	95%CI
Gender			0.491		
Male	533 (67)	76		1.00	
Female	268 (33)	76		0.89	0.63–1.24
Age			0.272		
0–59 yrs	382 (48)	78		1.00	
> 60 yrs	419 (52)	75		1.19	0.87–1.63
T classification			0.326		
T1	96 (12)	81		1.00	
T2	194 (24)	73		0.83	0.46–1.53
T3	259 (32)	75		1.30	0.85–1.98
T4	252 (32)	81		1.22	0.82–1.82
Lymph node status			0.0001		
N0	234 (29)	81		1.00	
N1	120 (15)	85		1.04	0.59–1.84
N2a	23 (3)	95		0.26	0.04–1.91
N2b	296 (37)	71		1.77	1.18–2.65
N2c	101 (13)	73		1.73	1.01–2.97
N3	27 (3)	55		4.19	2.13–8.26
Primary site			0.116		
Larynx	117 (3)	86		1.00	
Hypopharynx	55 (5)	71		1.79	1.02–3.15
Oropharynx	220 (20)	77		1.62	0.89–2.97
Oral cavity	409 (73)	74		2.36	1.11–5.02
Grade of differentiation			0.064		
Poorly differentiated	146 (51)	82		1.00	
Moderately differentiated	542 (28)	77		1.18	0.75–1.87
Well differentiated	114 (7)	69		1.73	1.00–3.00
Surgical margins at primary site			< 0.001		
Wide margins	519 (65)	82		1.00	
Close margins (1–5 mm)	110 (14)	65		2.13	1.40–3.22
Positive margins (< 1 mm)	170 (21)	66		1.93	1.34–2.79
Perineural invasion			0.026		
No	673 (84)	78		1.00	
Yes	128 (16)	69		1.56	1.06–2.31
Extracapsular lymph node extension			< 0.001		
No	391 (49)	83		1.00	
Yes	410 (51)	70		1.94	1.40–2.68
Angioinvasive growth			0.011		
No	646 (81)	79		1.00	
Yes	155 (19)	67		1.60	1.12–2.28
Lymphangioinvasion			0.046		
No	769 (96)	77		1.00	
Yes	32 (4)	62		1.91	1.01–3.63
Dysplasia in surgical margin			0.781		
No	705 (88)	76		1.00	
Yes	96 (12)	78		0.94	0.57–1.55

LRC: locoregional control; OR: odds ratio; 95%CI: 95% confidence interval.

primary site with a 1-cm margin was 63.5 Gy (range, 38.0–70.5 Gy). In patients with lymph node metastases who had extranodal spread, the median total dose to these regions was 62.5 Gy (range, 36.0–71.5 Gy). Until 1997, in most patients, the booster field was irradiated using a shrinking-field technique.

Statistics

LRC was defined as no tumor recurrence above the clavicles within the irradiated area. LRC, DFS, distant metastases-free interval (DMFI), and OS were calculated from the day of surgery. The minimal follow-up was 2 years. In the univariate analysis, LRC, DFS, and OS were estimated with the Kaplan–Meier method. To test the statistical significance of differences between curves, the log-rank test was used. A multivariate analysis using the Cox model also was performed to allow for the identification of independent prognostic factors for LRC.

The RPA method used for this analysis was derived from the CART method, which was developed for binomial data.[13] This method creates a decision tree to model prognostic factors and enables identify effect modifications between variables that are identified less easily by other regression models, such as the Cox proportional hazards model. A tree-based model is developed by recursively partitioning the data. The entire group of 801 patients was considered the primary node. In the RPA, the following factors were evaluated as prognostic indicators of LRC: gender (male vs. female), age (split at the median level, i.e., younger than 60 years vs. 60 years or older), T classification (ordinal: T1, T2, T3, and T4), N classification (ordinal: N0, N1, N2a, N2b, N2c, and N3), grade of differentiation (ordinal: well, moderately, and poorly differentiated), surgical margins (ordinal: free, > 5 mm; close, 1–5 mm; and positive, < 1 mm), extranodal spread (not present, present in 1 lymph node, and present in > 1 lymph node), tumor site (nominal: oral cavity, oropharynx, hypopharynx, and larynx), perineural invasion (yes vs. no), angioinvasion (yes vs. no), lymphangioinvasion (yes vs. no), and dysplasia in surgical margins (yes vs. no). To allow for the most optimal split, the log-rank statistics and corresponding *P* values were computed for all factors and for all allowable splits within the factor. For the nominal variable tumor site, comparisons were made between each site versus the rest. In each node, the group of patients was split into 2 groups based on the factor and the corresponding cut-off point with the minimal *P* value, provided that the minimal *P* value was ≤ 0.05 and that the minimum number of patients within the subgroups was ≥ 15. In addition, for each of the two resulting subgroups, the procedure was repeated. The

TABLE 2
Results of the Multivariate Analysis with Regard to Locoregional Control

Variable	Score	Regression coefficient	SE	*P* value	RR	95%C
Surgical margins	0 = free, 1 = close or positive	1.04	0.42	0.0134	2.8	1.2–6.4
Extranodal spread	0 = no, 1 = yes	0.89	0.27	0.0010	2.4	1.4–4.1
Lymph node status				0.0009		
N2b–N2c	Versus N0–N2a	0.54	0.21	0.0091	1.7	1.1–2.6
N3	Versus N0–N2a	1.26	0.35	0.0004	3.5	1.8–7.0
Grade of differentiation				0.0082		
Moderately differentiated	Versus well differentiated	−0.57	0.28	0.0408	0.6	0.3–1.0
Poorly differentiated	Versus well differentiated	−1.36	0.45	0.0025	0.3	0.1–0.6
Interaction terms[a]						
Extranodal spread surgical margins				0.0123		
Grade of differentiation: surgical margins				0.0473		

SE: standard error; RR: relative risk; 95%CI: 95% confidence interval.
[a] Note that only factors associated significantly with locoregional control are shown.

partition procedure was stopped if no allowable split existed, i.e., if the size of the subgroup was < 15 patients and/or if the minimum P value was > 0.05 (terminal nodes). In addition, Kaplan–Meier curves were estimated for the patients in each terminal node and were compared with the log-rank test. When the significance level of the comparison between 2 terminal nodes was > 0.05, the nodes were combined into the same RPA class. Finally, to investigate the importance of this classification system with regard to DMFI, DFS, and OS, Kaplan–Meier curves for the RPA classes were estimated and compared with the log-rank test.

RESULTS

Univariate Analysis

The median follow up was 46 months. LRC among all patients who were included in the study was 77% after 5 years. In total, 157 patients developed a locoregional recurrence (20%), and 138 of those recurrences occurred in the first 2 years after treatment (88%). In the univariate analysis, the following factors were associated significantly with LRC: N classification ($P = 0.0001$), surgical margins at the primary site ($P < 0.0001$), perineural invasion ($P = 0.026$), extranodal spread ($P < 0.0001$), angioinvasive growth ($P = 0.011$), and lymphangioinvasion ($P = 0.046$) (Table 1).

Cox Multivariate Regression Analysis

In the Cox regression analysis, the same variables were entered into the model. After backward elimination of the nonsignificant factors, there were four variables that were associated significantly with LRC, including extranodal spread, surgical margins, grade of differentiation, and N classification. Additional analysis revealed significant interaction terms between extranodal spread and surgical margins and between grade of differentiation and surgical margins (Table 2). In the subset of patients with free surgical margins, the 5-year LRC rate among patients without extranodal spread was 91%, compared with 74% among patients with extranodal spread ($P < 0.0001$), with a corresponding hazard ratio (HR) of 2.9 (95% confidence interval [95%CI], 1.8–4.8). In the group of patients with close or positive surgical margins, the 5-year LRC rate among patients without extranodal spread versus those with extranodal spread was 69% and 61% ($P = 0.07$), respectively, with a corresponding HR of 1.5 (95%CI, 0.9–2.4). Moreover, in the group of patients with free surgical margins, the 5-year LRC rate among patients with well, moderately, and poorly differentiated tumors was 73%, 82%, and 91%, respectively ($P = 0.023$), with a corresponding HR of 0.6 (95%CI, 0.4–1.1) for Grade 2 versus Grade 1 and an HR of 0.3 (95%CI, 0.1–0.7) for Grade 3 versus Grade 1. In the subset of patients with close or positive surgical margins, the 5-year LRC rates for those with Grade 1, 2, and 3 tumors were 60%, 67%, and 68%, respectively, with corresponding HRs of 0.8 (95%CI, 0.4–1.4) for Grade 2 and 1.0 (95%CI, 0.5–2.0) for Grade 3, a difference that was not statistically significant ($P = 0.60$).

RPA

The RPA was started with the entire group of 801 patients, who had a total of 157 events. A summary of this analysis is shown in Figure 1. The factor with the highest log-rank statistic (20.02; $P < 0.0001$) was surgical margin, which yielded a subgroup of 521 patients who had free surgical margins (5-year LRC rate, 82%) and a subgroup of 280 patients who had close or

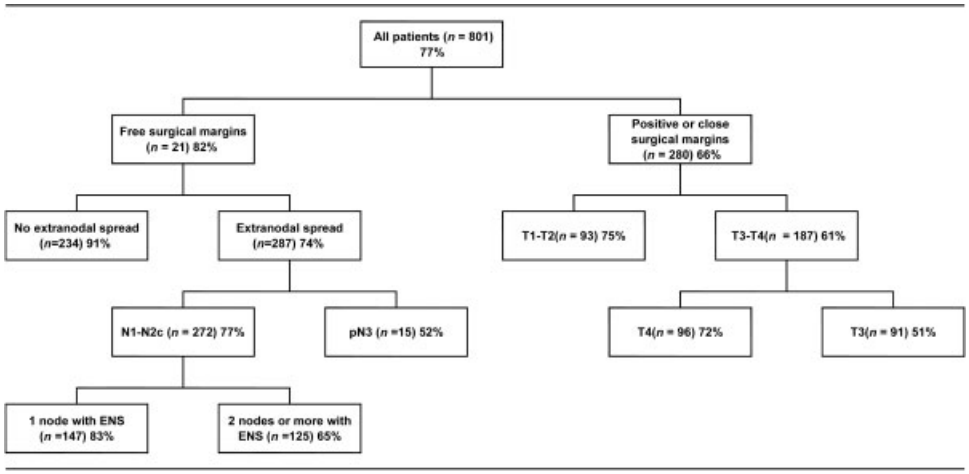

FIGURE 1. This classification and regression tree was obtained in 801 patients who had squamous cell head and neck carcinoma and who underwent surgery and postoperative radiotherapy. ENS: extranodal spread.

positive surgical margins (5-year LRC rate, 66%). The procedure was then repeated with the left node (free surgical margins) and the right node (close or positive surgical margins).

At this level, in the left node, extranodal spread appeared to be the strongest factor (log-rank statistic, 18.15; $P < 0.0001$). This yielded a subgroup of 234 patients without extranodal spread (5-year LRC rate, 91%) and a subgroup of 287 patients with extranodal spread (5-year LRC rate, 74%). In the subgroup without extranodal spread, no further splits were possible because of the *P* value criterion, and this node was regarded as a terminal node. The subgroup of patients with extranodal spread allowed further splits into a subgroup of 272 patients with N0–N2c neck disease (5-year LRC rate, 77%) and a subgroup of 15 patients with N3 neck disease (5-year survival rate, 52%; log rank statistic, 11.44; $P = 0.0007$). No further splits were possible in the N3 subgroup because of the minimal criterion. For the N0–N2c patients with extranodal spread, further splits were possible (log rank statistic, 9.69; $P = 0.0018$), yielding a subgroup of 147 patients with 1 metastatic lymph node with extranodal spread (5 year LRC rate, 83%) and a subgroup of 125 patients with $\geq$ 2 metastatic lymph nodes with extranodal spread (5-year LRC rate, 65%). No further splits were possible for these two subgroups because of the *P* value criterion.

In the right node with the subgroup of 280 patients who had close or positive surgical margins, the factor with the highest log-rank statistic was T classification (log rank statistic, 5.70; $P = 0.0169$), and this subgroup was split at the cut-off point of T2–T3, yielding a subgroup of 93 patients with T1–T2 tumors (5-year LRC rate, 75%) and a subgroup of 187 patients with T3–T4 tumors (5-year LRC rate, 65%). At this level, in the node with T3–T4 tumors, T classification again appeared to be the strongest factor (log-rank statistic, 6.15; $P = 0.0131$). This yielded a subgroup of 91 patients with T3 tumors (5-year LRC rate, 51%) and a subgroup of 96 patients with T4 tumors (5-year LRC rate, 72%). No further splits were possible in the subgroup of patients with T1–T2 tumors because of the *P* value criterion.

TABLE 3
Recursive Partitioning Analysis Classes

RPA class	Definition(s)
Class I (intermediate risk)	Free surgical margins and no extranodal spread
Class II (high risk)	T1, T2, and T4 tumors with close or positive surgical margins One lymph node metastasis with extranodal spread
Class III (very high risk)	T3 tumors with close or positive surgical margins Multiple lymph node metastases with extranodal spread N3 neck

RPA: recursive partitioning analysis.

The analysis resulted in 7 terminal nodes (Fig. 1). In addition, the terminal nodes were compared using the log-rank test, which eventually resulted in 3 RPA classes (Table 3). Class I (intermediate risk) consisted of 234 patients with free surgical margins and no extranodal spread. The 5-year LRC rate in this group was 92%. Class II (high risk) consisted of 336 patients with 1 lymph node metastasis with extranodal spread or with T1, T2, or T4 tumors with positive or close sur-

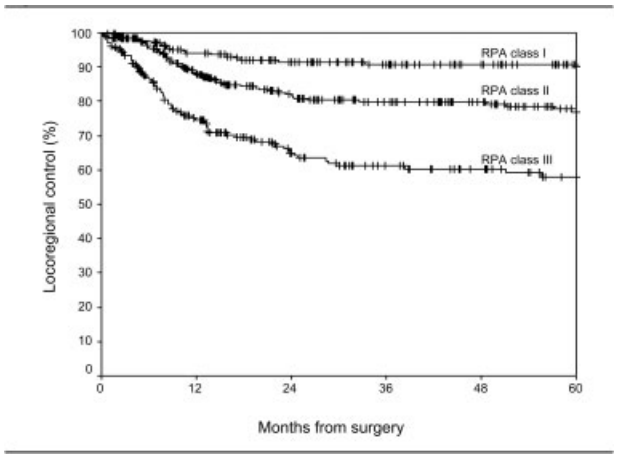

FIGURE 2. Locoregional control according to recursive partitioning analysis (RPA) class.

gical margins. The 5-year LRC rate in Class II was 78%. Finally, Class III (very high risk) consisted of 231 patients with ≥ 2 lymph node metastases with extranodal spread, N3 neck disease, or T3 tumors with positive or close surgical margins. The 5-year LRC rate for patients in Class III was 58% (Fig. 2).

Table 4 summarizes the results regarding the impact of the RPA classification on the other endpoints. For all endpoints, RPA class significantly predicted outcome.

TABLE 4
Recursive Partitioning Analysis Classes and Outcome

	RPA class			
Variable	Class I (intermediate risk)	Class II (high risk)	Class III (very high risk)	Log-rank *P* value (DF = 2)
Locoregional control				
5-yrs (%)	92	78	58	< 0.0001
HR	1.00	2.37	5.26	
95%CI	—	1.43–3.94	3.22–8.62	
Distant metastases-free interval				
5-yrs (%)	92	80	68	< 0.0001
HR	1.00	2.48	4.74	
95%CI	—	1.44–2.28	2.77–8.13	
Disease-free survival				
5-yrs (%)	65	47	32	< 0.0001
HR	1.00	1.54	2.48	
95%CI	—	1.20–1.97	1.93–3.20	
Disease-specific survival				
5-yrs (%)	88	69%	51%	< 0.0001
HR	1.00	2.51	4.79	
95%CI	—	1.64–3.84	3.14–7.29	
Overall survival				
5-yrs (%)	67	50%	36	< 0.0001
HR	1.00	1.49	2.35	
95%CI	—	1.56–1.91	1.81–3.04	

RPA: recursive partitioning analysis; DF: degrees of freedom; HR: hazard ratio; 95%CI: 95% confidence interval.

Additional Analyses

Because of the surprising finding that patients with T4 tumors fared significantly better than patients with T3 tumors in the group with close or positive surgical margins, additional analyses were performed with regard to the distribution of other variables within the group of patients with T3 and T4 tumors. This revealed a significant difference between T3 and T4 tumors with regard to primary tumor site, with significantly more oropharyngeal carcinomas in the T3 group (60% vs. 19%) and significantly more laryngeal carcinomas in the T4 group (26% vs. 4%). However, additional analysis of LRC stratified by tumor site yielded similar HRs for LRC for all sites, i.e., patients with T3 tumors fared worse than patients with T4 tumors in all sites.

DISCUSSION

The current study was undertaken to assess a classification system for postoperative radiotherapy among patients with HNSCC to distinguish subsets of patients with different prognoses regarding LRC. In the RPA, surgical margins, the number of lymph node metastases with extranodal spread, N classification, and T classification were prognostic factors that predicted outcome, resulting in three prognostic groups. The three RPA classes not only differed significantly regarding LRC but also provided important prognostic information with regard to DMFI, disease-specific survival, DFS, and OS. In the multivariate Cox regression analysis, almost all of the same factors were identified as important with the exception of grade of differentiation, which was an independent prognostic factor in the Cox model but was not important in the RPA. Moreover, in the Cox model, two significant interaction terms indicated that the association between grade of differentiation and extranodal spread depended on surgical margin status. In fact, regarding the interaction between surgical margin status and extranodal spread, similar results were found in the RPA.

In most prognostic factor studies, univariate analyses and/or multivariate analyses using the Cox proportional hazards model are applied to identify independent prognostic factors. However, in clinical practice, most patients present with a number of risk factors, resulting in a certain level of risk. Although it is possible to calculate a risk score based on the re-

gression coefficients for a given set of prognostic factors derived from the Cox proportional hazards model for each individual patient, interpretation of such a risk score remains difficult. Individuals with potentially disparate covariate patterns are combined and, hence, the resultant stratum is hard to interpret. Moreover, the cut-off values for defining risk groups in this fashion often are arbitrary. The major difference between RPA and multivariate regression analysis is that, with RPA, one branch can have different risk factors than a different branch; whereas, with multivariate regression analysis, the HRs apply for the entire population investigated and not for a certain subset. For this reason, RPA is suited better to data in which there are interactions; because, with interactions, a variable may be important only for a portion of the study group. This also was the case for the study group investigated in which two significant interaction terms were found. The presence of interaction terms makes distinction into prognostic groups based on the Cox proportional hazards model extremely difficult.

Another advantage of RPA is that the split points are chosen to result in the maximum separation between the resulting nodes. RPA allows prognostic variables to have impact in subsets of patients rather than globally characterizing main effects that operate across all patients. This was illustrated well by the results from the current study. In both univariate and multivariate analyses, the effect of T classification on LRC was not identified as significant. However, based on the RPA, T-classification was identified as important in the subset of patients who had close or positive surgical margins. This feature of unidentified interactions emphasizes the particular attractiveness of RPA. Finally, compared with multivariate regression analysis, RPA more closely reflects how physicians make decisions and often yield classification and prediction rules that are relatively easier to interpret for a wide variety of applications.

Various studies have documented the association between tumor characteristics and pathologic findings from the surgical specimen and the risk of locoregional recurrences. The most frequently mentioned risk factors for locoregional recurrence are the presence of extranodal spread,[3,5,8,9] close or positive surgical margins,[1–6] the size and extension of the primary tumor (T classification),[1,2] perineural growth,[7,19–21] and the size and number of positive cervical lymph nodes.[4,11] The prognostic significance of most of these factors was confirmed in the current study.

A surprising finding in the RPA analysis was the significant difference between T3 and T4 tumors, with better LRC in patients with T4 tumors. Additional analysis of the correlation between T classification and other variables revealed a significant difference regarding the location of the primary site, with more laryngeal tumors in the T4 category and more oropharyngeal tumors in the T3 category. However, additional analysis of the prognostic significance of T classification in this subset stratified by tumor site revealed better LRC for patients who had T4 tumors compared with patients who had T3 tumors in all sites, which means that this finding cannot be explained by differences in primary tumor sites. Furthermore, no differences were found with regard to the other pretreatment variables. It is possibly that the size of the primary tumor in patients with of close or positive surgical margins may be more important than the presence of tumor invasion in the surrounding tissues, a possibility that is supported by the gradual deterioration in LRC with increasing T classification from T1 to T3. However, the current data did not allow for a more accurate assessment of tumor size in the T4 category.

In the subset of patients with free surgical margins, the presence of extranodal spread was the most important prognostic factor. Extranodal spread has been identified as one of the most frequently reported and most consistent prognostic factors after primary surgery of the neck with or without postoperative radiotherapy for LRC in patients with HNSCC.[3,5,7–9,16,18,22–25] Moreover, numerous studies have shown that patients with lymph node metastases who have extranodal spread are more likely to develop distant metastases[7,25–27] and, thus, are more likely to have worse OS. In the current study, no distinction could be made between microscopic and macroscopic extranodal spread, because these features were not scored systematically. In a prospective study, de Carvalho[28] reported on the importance of the extent of extracapsular spread, classifying patients into those without any capsular invasion, those with invasion but without rupture, those with capsular invasion without extracapsular disease, those with microscopic breakthrough of the capsule, and those with macroscopic invasion through the capsule into the surrounding connective tissues. In that series, regional control was affected significantly by macroscopic transcapsular spread, whereas no adverse effect on the rates of recurrence or death was noted in patients who had only microscopic transcapsular spread. Conversely, Greenberg et al. found that, among patients with squamous cell carcinoma of the oral tongue, the extent of extracapsular spread outside the lymph node did not predict disease-specific survival or OS.[29] Similar results were reported by Coatesworth and MacLennan.[30]

In the fourth node, among the patients with extranodal spread and N1–N2c disease, LRC was signif-

icantly worse when multiple (≥ 2) lymph nodes showed extranodal spread compared with patients who had only 1 lymph node with extranodal spread. This finding is similar to what was reported by Greenberg et al., who found that the number of lymph node metastases bearing extranodal spread was highly predictive with regard to disease-specific survival, disease-free interval, and OS. In the subset of patients with close or positive surgical margins, the RPA analysis did not show a significant association between extranodal spread and LRC, a finding that was confirmed in the Cox model, in which surgical margin was a significant effect modulator for the effect of extranodal spread on LRC. Because we combined regional and local control into one endpoint (i.e., LRC), and because the survival of patients who developed locoregional recurrences was extremely poor, this lack of a significant association in this particular subset of patients may be explained at least in part by the presence of the phenomenon referred as to competing risks: i.e., Patients with local failure as a result of incomplete resection will not be capable of developing a regional recurrence from the cause of extranodal spread.

One of the limitations of the current study is that the results were based on a single-institution experience. Thus, the question arises whether the results of the current study can be extrapolated to other institutions and other studies. Furthermore, the results based on the histopathologic examination may be subject to differences in the quality of the assessments and techniques used and also to intraobserver and interobserver variability. From this point of view, the use of predefined checklists to assess and report histopathologic findings systematically should be supported actively.

For the design of future therapeutic trials and the decision about what should be considered standard treatment after primary surgery, the definition of different prognostic groups increasingly becomes important, in particular because new treatment modalities generally yield more acute and/or late toxicity.[10,12] The question arises about what should be the treatment of choice for patients in the different RPA classes. Recently, the European Organization for Research and Treatment of Cancer reported on a prospective, randomized study in which patients with ≥ 1 risk factors after primary surgery for HNSCC were assigned randomly to receive postoperative radiotherapy alone (66 Gy in 7 weeks) or the same postoperative radiotherapy with concomitant chemotherapy (3 × cisplatinum 100 mg/m^2).[11] The eligibility criteria for that study were relatively diverse, including patients with pathologic T3 (pT3)–pT4 tumors and any lymph node stage (except T3N0 of the larynx) with free surgical margins; patients with pT1–pT2 tumors and pN0–pN1 status who had unfavorable pathologic findings, including extranodal spread, positive surgical margins, perineural involvement, or vascular tumor embolism; and patients with oral cavity or oropharynx tumors who had involved lymph nodes at Level IV or IV. A significant improvement was found for progression-free survival, LRC, and OS in favor of the combined-treatment group. Those authors concluded that postoperative, concomitant chemoradiation was more efficacious than postoperative radiotherapy alone, but they also stated that the effect of the postoperative administration of concomitant chemoradiation is likely to be influenced by the criteria used to select patients. A similar trial was performed by the Radiation Therapy Oncology Group/Intergroup. In that study, only patients with multiple lymph node metastases, extranodal spread, and/or positive surgical margins were included. In that study, a significant improvement in LRC and DFS also was noted with combined-modality treatment, but no significant improvement was reported in OS. In both of those studies, no beneficial effect was noted with regard to the development of distant metastases. In another Phase III trial in 2001, patients who were at high risk according to the classic risk-group classification were assigned randomly to receive conventionally fractionated postoperative radiotherapy (63 Gy in 7 weeks) versus accelerated radiation (63 Gy in 5 weeks). In that study, LRC after 5 years improved from approximately 62% with conventional fractionation to 76% with accelerated fractionation; this also translated into higher OS rates, which improved from 30% to 48% after 5 years. However, these differences were not statistically significant possibly due to the relatively low number of patients included in that study. The 5-year LRC and OS rates among patients with intermediate risk in that study were approximately 93% and 68%, respectively, which were comparable to the Class I patients in the current study. In another relatively small, randomized study, shortening of the overall treatment time of postoperative radiotherapy by accelerated hyperfractionation provided a significant improvement in LRC without significantly improving OS only in patients with fast-growing tumors (see Awwad et al.[31]). It should be stressed that the results of shortening the overall treatment of radiation is likely to be influenced by the interval between surgery and the start of radiation treatment.[10,31]

In the current study, RPA class I consisted of patients with the most favorable prognosis, resulting in high rates of LRC and DMFI. Based on all of these findings, the most optimal approach probably is post-

operative radiotherapy alone. Until now, no convincing evidence has shown that, in this particular subset of patients, the addition of chemotherapy and/or accelerated radiotherapy will have a major impact on outcome, although retrospective data suggest that LRC worsens when conventionally fractionated, postoperative radiotherapy is delivered for > 6 weeks.[16]

Based on the 2 prospective, randomized studies on the addition of concomitant chemotherapy in the postoperative setting (Bernier et al.,[11] Cooper et al.[12]), patients in RPA Class II and III who are fit sufficiently to undergo chemotherapy probably are better off with combined-modality treatment. Based on the very poor outcomes of patients in RPA Class III, these patients are ideal candidates for further investigational adjuvant therapy. However, particularly for patients in RPA Class II and/or patients whose medical condition precludes the administration of chemotherapy, future trials also should focus on improving outcomes by using altered fractionation schedules.[10,31] Moreover, adjuvant treatment with biologic modifiers may be promising.

In conclusion, the RPA presented in this study defined three prognostic groups with regard to all relevant outcome determinants among patients with HNSCC who undergo primary surgery for whom adjuvant treatment with postoperative radiotherapy and/or chemotherapy is indicated. This classification may have important implications with regard to future trials and standard treatment; however, the value of this classification system needs to be validated further in independent study cohorts, preferably in a multicenter setting.

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