Lymph node ratio influence on risk of head and neck cancer locoregional recurrence after initial surgical resection: Implications for adjuvant therapy

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ABSTRACT: *Background.* The purpose of this study was to determine if lymph node ratio is associated with locoregional recurrence for patients with oral cavity or laryngeal cancer treated with initial surgical management.

Methods. The study included 350 patients with oral cavity (73%) or laryngeal cancer (27%) who underwent initial surgery. All analyses were multivariable, adjusting for primary site, pathologic prognostic factors, and adjuvant therapy.

Results. Lymph node ratio was significantly associated with locoregional recurrence, in which each 1% increase in lymph node ratio had an adjusted hazard ratio (HR) for locoregional recurrence of 1.02 (95% confidence interval [CI], 1.002–1.042; $p = .05$). Lymph node ratio was also associated with OS, in which each 1% increase in lymph node ratio had an adjusted HR for death of 1.028 (95% CI, 1.012–1.045; $p = .001$).

Conclusion. Adjusting for pathologic factors and adjuvant therapy, lymph node ratio was found to be an independent prognostic factor for locoregional recurrence and overall survival (OS). Patients with lymph node ratio $\geq$20% are at high risk of locoregional recurrence and death, and may be considered for adjuvant chemoradiation. © 2014 Wiley Periodicals, Inc. *Head Neck* **37:** 777–782, 2014

KEY WORDS: head and neck cancer, adjuvant radiotherapy, adjuvant chemoradiotherapy, otolaryngology, oral cavity cancer, larynx cancer

INTRODUCTION

Cancers of the head and neck comprise approximately 3% of all cancers in the United States, affecting an estimated 52,000 men and women in the United States in 2012.[1,2] Although organ preservation with definitive chemoradiation therapy (CRT) is a current standard approach for most oropharyngeal and intermediate stage laryngeal cancers, the primary initial therapy for oral cavity and bulky/nonfunctional laryngeal cancers is surgery followed by risk stratified adjuvant therapy.[3–6]

Locoregional recurrence of head and neck cancer is the principle source of mortality in this patient population. Significant improvements in locoregional control have been shown in large randomized trials to significantly improve overall survival (OS).[6–10] Intensive adjuvant therapy increases the morbidity of treatment. Pathologic factors currently used for risk stratification include advanced tumor (T) classification, advanced nodal (N) classification, perineural invasion (PNI), lymphovascular space invasion (LVSI), close/involved margins, and nodal extracapsular extension (ECE).[11] The indications for concurrent adjuvant CRT are positive margins and/or ECE.[6] However, the European Organization for Research and Treatment of Cancer (EORTC) trial defined positive margins as tumor within 5 mm of the mucosal margins,[4] whereas Radiation Therapy Oncology Group 95-01 considered positive margins to be tumors at the cut edge,[5] so even those indications are not clear cut. The risk of locoregional recurrence is a continuous spectrum in which different combinations of pathologic risk factors can convey a risk of locoregional recurrence high enough to justify intensified adjuvant therapy.[4,6]

In a variety of other disease sites, such as breast, colon, gastric, and vulvar cancer, the risk of locoregional recurrence has been associated with the extent of lymph node resection and the ratio of lymph nodes involved to the total number of lymph nodes examined (lymph node ratio).[12–15] However, the importance of lymph node ratio is not well established for patients with resected head and neck cancer.

The purpose of this study was to determine if lymph node ratio is an independent prognostic factor for locoregional recurrence when traditional pathologic risk factors and risk stratified adjuvant therapy are taken into account for patients with oral cavity carcinoma or locally advanced and/or nonfunctional laryngeal cancer treated

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with initial surgical resection and neck dissection. In contrast to patients with pharyngeal and intermediate stage laryngeal cancers in which definitive CRT is an option for organ preservation, this patient population represents those who are most likely to undergo initial surgery and have adjuvant therapy decisions made based on pathologic factors.

MATERIALS AND METHODS

Patients

The medical records of 432 patients with oral cavity carcinoma or locally advanced and/or nonfunctional laryngeal cancer treated with initial surgical resection and neck dissection between 2000 and 2011 were reviewed. All surgical specimens were reviewed by pathologists specializing in head and neck pathology. Exclusion criteria included previous neck dissection, previous radiation therapy (RT) or chemotherapy, N3 disease (because of the presence of uncountable matted lymph nodes), unresectable disease/macroscopic incomplete resection, synchronous malignancy, <10 cervical lymph nodes resected, and follow-up period <3 months. This left 350 patients eligible for inclusion. All patients were discussed in a multidisciplinary head and neck-specific tumor board to guide surgical and adjuvant therapy recommendations. Institutional review board approval was obtained for this study.

Interventions

The primary surgical resection technique was left to the discretion of the treating head and neck surgeon. Neck dissections were typically selective neck dissections with sparing of the sternocleidomastoid muscle and cranial nerve XI, if possible. Adjuvant RT was recommended for patients with intermediate risk factors, including T3/T4, N2/N3, PNI, LVSI, and/or close margins (<5 mm). Adjuvant CRT was recommended for patients with involved margins and/or nodal ECE. In cases of CRT, the choice of concurrent chemotherapy was left to the treating medical oncologist, but most commonly consisted of every 3 weeks of cisplatin, weekly cisplatin, or weekly carboplatin and taxol. Adjuvant therapy began 6 to 8 weeks after surgical resection. Follow-up with physical examination was every 3 months for the first 2 years, every 4 to 6 months for year 3, and then annually thereafter. Imaging with a positron emission tomography/CT occurred at 3 months after completion of therapy, with CT scans at 12 months, 18 months, and 24 months, followed by symptom-directed imaging after 24 months.

Statistical analysis

Descriptive statistics were compiled to characterize the patient population. Locoregional recurrence was defined as first local, regional, or combined locoregional relapse with or without synchronous distant metastases. Synchronous locoregional recurrence and distant metastases was defined as events occurring within 3 months of each other. All time to events were from the date of initial surgical resection. For the locoregional recurrence analysis, patients were censored at the time of last clinical follow-up, isolated distant metastases relapse, or second primary tumor, whichever came first. For the OS analysis, the event was death from any cause. Patients were censored at the time of last follow-up. The optimal cut point for the lymph node ratio variable for categorical analysis was determined using univariate Cox analysis. The continuous lymph node ratio variable for each patient was categorized based on units of 5% (ie, >0% to 5%, >5% to 10%, etc.). A univariate model of locoregional recurrence with categorized lymph node ratio as an indicator variable (reference level being >0% to 5%) was performed. The hazard ratio (HR) for each 5% increase in lymph node ratio relative to the reference value was determined and the cut point chosen was based on the value that demonstrated a significant break point in the calculated HRs. Cox adjusted cumulative incidence curves were generated to estimate actuarial rates of locoregional recurrence and death, adjusting for primary site, pathologic T classification, pathologic N classification, LVSI, PNI, margin status (negative, close [< 5 mm], or involved), nodal ECE, and adjuvant therapy (none, RT alone, or CRT). Cox proportional hazards modeling was used for multivariable analysis of potential prognostic factors for locoregional recurrence and OS. No variable selection algorithms were used in the multivariable analysis. Validated traditional pathologic risk factors, type of adjuvant therapy, and lymph node ratio were included to determine the independence and prognostic value of lymph node ratio. The same model was used for OS, except for the additional inclusion of age as a covariate. Lymph node ratio was defined as: [the total number of involved lymph nodes/the total number of resected lymph nodes] $\times 100$. All analyses were carried out using the SPSS version 20.0 statistical software package (IBM, Armonk, NY). All statistics were 2-sided, and a value of $p < .05$ was considered statistically significant.

RESULTS

Patient characteristics

The study population consisted of 350 patients with oral cavity carcinoma or locally advanced/nonfunctional laryngeal cancer treated with initial surgical resection and neck dissection. The median follow-up period for patients without locoregional recurrence was 26.6 months (range, 3.1–139 months). The median follow-up period for alive patients was 34.1 months (range, 3.1–152.7 months). The primary site was oral cavity in 72.6% and larynx in 27.4%. The median number of lymph nodes resected was 24 (range, 10–111). The median number of lymph nodes involved for patients who were pathologically node (pN) positive ($n = 161$) was 2 (range, 1–43). See Table 1 for additional patient and tumor characteristics.

Interventions

There were a total of 432 neck dissections in 350 patients, with 268 patients undergoing unilateral neck dissection and 82 undergoing bilateral. Neck levels dissected were I to III for 115 dissections (26.6%), I to IV for 152 (35.2%), I to V for 45 (10.4%), and II to IV for 120 (27.8%). One hundred thirty-two patients (37.7%) did not receive any adjuvant therapy, 154 (44%) received

TABLE 1. Patient and tumor characteristics.

Characteristic	No. of patients	%
Total	350	100
Age, y		
Median	60 (range, 24–94)	
Sex		
Male	216	61.7
Female	134	38.3
Primary site		
Larynx	96	27.4
Oral cavity	254	72.6
Primary subsite		
Transglottic	13	3.7
Supraglottic	45	12.9
Glottic	31	8.9
Subglottic	1	0.3
Retromolar trigone	32	9.1
Oral tongue	119	34
Alveolar ridge	31	8.9
Lip	1	0.3
Floor of mouth	51	14.6
Hard palate	2	0.6
Buccal mucosa	24	6.9
Pathologic T classification		
pT1	99	28.3
pT2	80	22.9
pT3	55	15.7
pT4	116	33.1
Pathologic N classification		
pN0	189	54
pN1	54	15.4
pN2	107	30.6
Nodal ECE		
Yes	62	17.7
LVSI		
Yes	91	26
PNI		
Yes	131	37.4
Margin status		
Negative	210	60
Close (<5 mm)	117	33.4
Involved	23	6.6
Adjuvant therapy		
None	132	37.7
RT alone	154	44
Chemoradiation	64	18.3
Lymph node resected		
Median	24 (range, 10–111)	
10–15	67	19.1
16–20	65	18.6
21–25	64	18.3
26–30	46	13.1
>30	108	30.9
Lymph node ratio (%)		
Median*	8 (range, 1–81)	
0	189	54
>0–5	41	11.7
>5–10	45	12.9
>10–15	21	6
>15–20	18	5.1
>20–25	14	4
>25–20	11	3.1
>30	11	3.1

Abbreviations: ECE, extracapsular extension; LVSI, lymphovascular space invasion; PNI, perineural invasion; RT, radiation therapy.
* Median lymph node ratio for patients with pathologically involved lymph node ($n = 161$).

TABLE 2. Cox multivariable analysis for locoregional recurrence with lymph node ratio.

Variable	HR	95% CI	*p* value
Primary (oral cavity vs larynx)	1.51	0.89–2.59	.13
Pathologic T3/T4 vs pT1/T2	1.61	0.99–2.6	.054
pN0	Reference		
pN1	1.96	1.05–3.66	.04
pN2	1.81	0.92–3.57	.09
LVSI	1.63	1.01–2.63	.04
PNI	1.82	1.18–2.8	.007
Negative margins	Reference		
Close margins (<5 mm)	1.07	0.69–1.67	.76
Involved margins	1.68	0.79–3.57	.18
Nodal ECE	1.04	0.56–1.92	.91
No adjuvant therapy	Reference		
Adjuvant RT alone	0.43	0.26–0.7	.001
Adjuvant CRT	0.48	0.25–0.92	.03
Lymph node ratio (%, continuous)	1.02	1.002–1.04	.05

Abbreviations: HR, hazard ratio; CI, confidence interval; LVSI, lymphovascular space invasion; pN0, pathologic node negative; PNI, perineural invasion; ECE, extracapsular extension; RT, radiation therapy; CRT, chemoradiation therapy.

adjuvant RT alone, whereas 64 (18.3%) received adjuvant CRT.

Patterns of failure

Cumulatively, 121 of 350 patients (34.6%) experienced disease relapse. First relapse was locoregional recurrence with or without synchronous distant metastases in 99 patients (28.3%) and distant metastases alone in 22 patients (6.3%). Twenty-three patients (6.6%) developed second primary tumors as a first event.

Lymph node ratio and locoregional recurrence

Of the 350 patients, 189 (54%) were pN-negative, 161 (46%) were pN positive, and all 350 (100%) had ≥10 lymph nodes removed. Among pN-positive patients ($n = 161$), the median lymph node ratio was 8% (range, 1% to 81%). The distribution of lymph node ratio in intervals of 5% can be seen in Table 1. After adjustment for primary site, pathologic T classification, pathologic N classification, LVSI, PNI, margin status, nodal ECE, and adjuvant therapy, lymph node ratio as a continuous variable was independently associated with risk of locoregional recurrence ($p = .05$). Each increase in lymph node ratio of 1% was associated with an adjusted HR for locoregional recurrence of 1.02 (95% confidence interval [CI], 1.002–1.042; $p = .05$). See Table 2 for details of the multivariable analysis. The optimal threshold for lymph node ratio that maximized differences in risk of locoregional recurrence was found to be 20% (Table 3). The adjusted HR for patients with lymph node ratio ≥20% versus <20% was 2.01 (95% CI, 1.23–3.87; $p = .04$). The Cox adjusted actuarial 2-year cumulative incidence of locoregional recurrence was 48% for ≥20% lymph node ratio versus 28% for <20% lymph node ratio (Figure 1). Of the 45 patients with lymph node ratio ≥20%, 4 received no adjuvant therapy, 30 received adjuvant RT, and 11 received adjuvant CRT.

TABLE 3. Cox univariable analysis for locoregional recurrence with lymph node ratio.

Lymph node ratio, %	HR	*p* value
0	0.49	.02
>0–5	Reference	–
>5–10	1.15	.64
>10–15	1.37	.42
>15–20	1.54	.11
>20–25	2.12	.03
>25–30	2.36	.01
>30	2.47	<.01

Abbreviation: HR, hazard ratio.

Lymph node ratio and overall survival

Of the 350 patients in this study, 163 (46.6%) had died by the time of analysis. Lymph node ratio as a continuous variable was significantly associated with risk of death, adjusting for traditional pathologic risk factors, type of adjuvant therapy, and age. Each increase in lymph node ratio of 1% was associated with an adjusted HR for death of 1.028 (95% CI, 1.012–1.045; $p = .001$). See Table 4 for details of the multivariable analysis. The prognostic significance of lymph node ratio for OS persisted when the lymph node ratio was examined as a categorical variable (≥20% vs <20%). The adjusted HR for patients with lymph node ratio ≥20% versus <20% was 2.38 (95% CI, 1.32–4.29; $p = .004$). The Cox adjusted actuarial 2-year OS was 51% for ≥20% lymph node ratio versus 75% for <20% lymph node ratio (Figure 2).

DISCUSSION

The goal of local adjuvant therapy after resection of head and neck cancer is to reduce the risk of locoregional recurrence, a major cause of morbidity and mortality in this patient population. Several randomized trials have demonstrated a benefit in OS driven by reductions in locoregional recurrence with more intensive locoregional therapy.[7–10] Even with significant improvements in RT delivery, the intensification of adjuvant RT with concurrent chemotherapy is associated with an increased risk of severe acute toxicity.[16] Patients at high risk of locoregional recurrence, those who would benefit from intensified adjuvant therapy, should be recommended adjuvant CRT. Traditional pathologic risk factors that define an intermediate risk of locoregional recurrence include advanced T classification, advanced N classification, PNI, LVSI, and close resection margins. High-risk patients are defined by involved surgical margins and/or nodal ECE,

TABLE 4. Cox multivariable analysis for death with lymph node ratio.

Variables	HR	95% CI	*p* value
Primary (oral cavity vs larynx)	1.3	0.87–1.95	.19
Pathologic T3/T4 vs pT1/T2	1.42	0.97–2.09	.07
pN0	Reference		
pN1	1.84	1.12–3.01	.02
pN2	1.67	0.99–2.81	.06
LVSI	1.65	1.1–2.47	.02
PNI	1.3	0.92–1.84	.13
Negative margins	Reference		
Close margins (<5 mm)	1.14	0.81–1.61	.46
Involved margins	1.76	0.97–3.19	.06
Nodal ECE	0.81	0.5–1.34	.42
No adjuvant therapy	Reference		
Adjuvant RT alone	0.73	0.5–1.08	.12
Adjuvant CRT	0.7	0.4–1.22	.21
Age (≥65 vs <65 y)	1.53	1.07–2.19	.02
Lymph node ratio (%, continuous)	1.028	1.01–1.045	.001

Abbreviations: HR, hazard ratio; CI, confidence interval; LVSI, lymphovascular space invasion; pN0, pathologic node negative; PNI, perineural invasion; ECE, extracapsular extension; RT, radiation therapy; CRT, chemoradiation therapy.

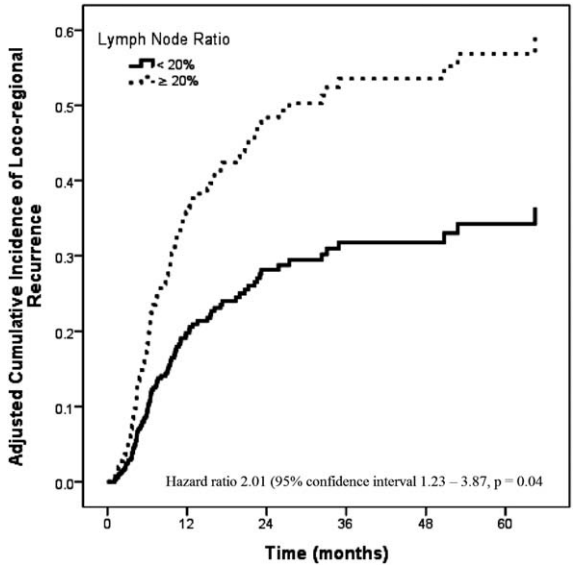

FIGURE 1. Adjusted cumulative incidence of locoregional recurrence by lymph node ratio ≥20% versus <20%.

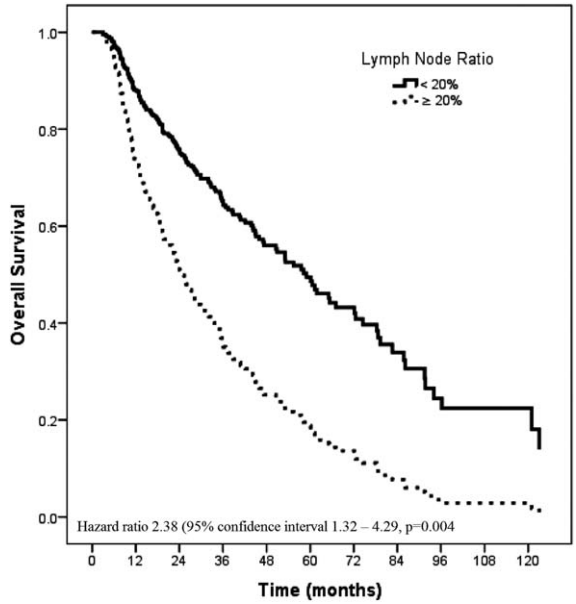

FIGURE 2. Adjusted overall survival by lymph node ratio ≥20% versus <20%.

as first demonstrated in a trial by Peters et al.[17] The combined analysis of the Radiation Therapy Oncology Group and EORTC adjuvant trials demonstrated an OS benefit for adjuvant CRT versus RT that was limited to patients with involved surgical margins and/or nodal ECE.[6] However, adjuvant CRT was associated with significantly improved OS in the intention to treat analysis of the EORTC study and there was evidence for improvement in the non-common risk factor cohort from the EORTC trial in the combined analysis as well.[4,6] These data indicate that the risk of locoregional recurrence in resected head and neck cancer is a spectrum, and patients at high risk of locoregional recurrence from either a combination of intermediate factors or from the classic high-risk factors might benefit from intensified adjuvant therapy.

This study has demonstrated that lymph node ratio is a significant prognostic factor for locoregional recurrence after initial resection of oral cavity carcinoma or locally advanced/nonfunctional laryngeal cancer, accounting for traditional pathologic risk factors and adjuvant therapy. Lymph node ratio has been demonstrated in several disease sites to have independent prognostic significance, including in breast, gastric, colon, and vulvar cancers.[12–15] In breast and vulvar cancers specifically, lymph node ratios $\geq$20% has been shown to be associated with increased rates of locoregional recurrence and is currently used to justify radiation coverage of the axilla in breast cancer or the groin and pelvis in vulvar cancer after initial resection. We did exclude patients with $<$10 lymph nodes resected from the lymph node ratio analysis for several reasons: (1) to avoid bias in the calculation of lymph node ratio because of a small lymph node resected denominator; (2) the known independent detrimental effect of limited nodal resection in head and neck cancer[18]; and (3) the correlation between the number of lymph nodes resected and the lymph node ratio variable.

Each 1% increase in lymph node ratio was associated with a 2% increased risk of locoregional recurrence (HR, 1.02; 95% CI, 1.002–1.042; $p = .05$). Consistent with published studies from other disease sites, we found that a threshold lymph node ratio value of 20% had the highest prognostic value.[13,15] The Cox adjusted actuarial 2-year cumulative incidence of locoregional recurrence was 48% for $\geq$20% lymph node ratio versus 28% for $<$20% lymph node ratio, with an adjusted HR of 2.01 (95% CI, 1.23–3.87; $p = .04$). The exact causal mechanism between lymph node ratio and locoregional recurrence is unknown, but higher lymph node ratio may be a surrogate marker of higher risk of residual subclinical disease left in the neck after neck dissection.

A similar finding was demonstrated in the analysis of lymph node ratio and OS. Each 1% increase in lymph node ratio was associated with a 3% increased risk of death (HR, 1.028; 95% CI, 1.012–1.045; $p = .001$). In addition, the magnitude of the HR for death for lymph node ratio $\geq$20% versus $<$20% (HR, 2.38; 95% CI, 1.32–4.29; $p = .004$) was similar to the HR for locoregional recurrence, adjusting for the same pathologic risk factors and adjuvant therapy. This indicates that the risk of locoregional recurrence is associated with the risk of death, and, therefore, reductions in locoregional recurrence could potentially improve OS. Patients with lymph node ratios $\geq$20%, even without involved margins and/or nodal ECE, are at high risk of locoregional recurrence, and may be considered for adjuvant CRT. In this series, the minority of these patients (20%) underwent adjuvant CRT. We were unable to explore the effect of adjuvant RT versus CRT in patients with lymph node ratios $\geq$20% because of small patient numbers.

Other studies have investigated lymph node ratio in head and neck cancer. Several studies have reported on the prognostic value of lymph node ratio specifically in oral cavity squamous cell carcinoma.[19–21] These demonstrated a continuous association between lymph node ratio and outcomes, and categorized the highest risk group as those with lymph node ratios ranging from $>$13% to $>$20%. Our series differs from these studies in that a large number of patients with laryngeal cancer were included in the current study. This allowed for a comparison between oral cavity and laryngeal primary sites, with no difference in outcome by primary site being evident. Also, we accounted for adjuvant therapy in addition to pathologic risk factors in our multivariable analysis. It is important to include adjuvant therapy in the multivariable models because adjuvant RT or CRT, given because of other pathologic factors, can affect the risk of locoregional recurrence and consequently the association between lymph node ratio and oncologic outcomes. Wang et al[22] published a population-based analysis using Surveillance, Epidemiology, and End Results (SEER) that demonstrated lymph node ratio as an independent prognostic factor for cause-specific survival in patients with hypopharyngeal cancer. They found the highest risk group to be those with lymph node ratio $>$30%. Similar findings were noted in a population-based SEER analysis of patients with oral cavity cancer, with the highest risk group being defined as those with lymph node ratio $>$12.5%.[21] However, the limitations of SEER apply to both studies, including a lack of detailed pathologic information, such as margin status and nodal ECE, treatment information, including chemotherapy use, and locoregional recurrence outcomes in their analyses. There is also a growing body of literature related to the variability of the quality of SEER data, specifically that of the recorded receipt of RT.[23,24]

CONCLUSION

Patients with resected oral cavity carcinoma or locally advanced/nonfunctional laryngeal cancer have a spectrum of locoregional recurrence risk based on pathologic risk factors than can be used to tailor adjuvant therapy. Traditional pathologic risk factors are used to identify patients at intermediate and high risk of locoregional recurrence so that adjuvant RT alone or CRT can be recommended, respectively. We have demonstrated that increasing lymph node ratio is significantly associated with higher risks of locoregional recurrence and death in patients with $\geq$10 lymph nodes resected, after adjusting for traditional pathologic risk factors and adjuvant therapy. Patients with lymph node ratios $\geq$20% had similar magnitudes of excess risk of locoregional recurrence and death, indicating that the risk of locoregional recurrence is associated with the risk of death, and reductions in locoregional recurrence could potentially improve OS. Patients with

lymph node ratios ≥20%, even without the traditional high-risk factors of involved margins and/or nodal ECE, are at high risk of locoregional recurrence and death, and may be considered for adjuvant CRT. Prospective studies are needed to confirm these findings.

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