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ORIGINAL ARTICLE

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Prognostic value of computed tomography scan detection of cartilage invasion in advanced laryngeal cancer treated with primary total laryngectomy

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Abstract

Background: We sought to determine whether detection of cartilage invasion (CI) by computed tomography predicts oncologic outcomes after primary total laryngectomy.

Methods: Retrospective cohort study comparing oncologic outcomes between radiologic versus pathologic diagnosis.

Results: Assessment of clear CI versus gestalt CI resulted in 84% versus 48% specificity, 90.9% versus 80.3% positive predictive value (PPV), 60.6% versus 80.3% sensitivity, 44.7% versus 48% negative predictive value (NPV), respectively. Disease-free survival (DFS) was similar between cT4a and cT3/cT2 patients ($p = 0.87$). DFS trended towards superiority among pT3/pT2 versus pT4a patients ($p = 0.18$). DFS was similar among patients with CI on radiologist gestalt versus no CI ($p = 0.94$). Histologically confirmed CI was associated with a hazard ratio (HR) of 1.46 ($p = 0.27$), gestalt CI 1.13 ($p = 0.70$), and clear CI 1.61 ($p = 0.10$) for DFS.

Conclusion: Gestalt determination of CI results in high sensitivity but low specificity, while clear determination of CI results in moderate sensitivity and high specificity.

KEYWORDS

cartilage invasion, computed tomography, head and neck cancer, laryngeal cancer, total laryngectomy

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1 | INTRODUCTION

Cartilage invasion is central to the staging and treatment of advanced laryngeal cancer. Under the American Joint Committee on Cancer (AJCC) seventh edition staging, tumor invasion through the outer cortex of the thyroid cartilage is considered T4a disease while T3 disease includes tumors with inner cortex invasion. The most recent American Society of Clinical Oncology guidelines support the use of primary total laryngectomy in patients with T4a disease.[1] However, treatment selection for advanced laryngeal cancer is a highly nuanced decision that takes into account many factors. For a group of carefully selected patients with T3 or T4a disease, organ preservation strategies including radiation with or without chemotherapy may not compromise overall survival. This is aided by the fact that up to a third of patients receive salvage laryngectomy for oncologic and functional purposes after organ preservation therapy.[2] Conversely, in patients with extensive T3 or T4a disease or poor laryngeal function, primary total laryngectomy can provide superior survival rates.[1] Typically, patients with tumors that exhibit cartilage invasion are considered poor candidates for organ preservation and receive primary total laryngectomy.[1,3] While partial laryngectomy may also be an option for some cT3/T2 tumors, these patients are not included in this study.

Because of the importance of cartilage invasion in determining primary treatment, diagnostic tests that can accurately detect cartilage invasion are needed. Typically, computed tomography (CT) scans are used as opposed to magnetic resonance imaging (MRI).[4] A systematic review of four studies found that the positive predictive value (PPV) of CT scans in detecting thyroid cartilage invasion varies widely from 44% to 80% while the negative predictive value (NPV) ranges from 85% to 100%.[4,5] Other modalities, such as dual energy CT and MRI, are more sensitive and specific than CT. However, these are not commonly used in staging of laryngeal cancer. More recently, a systematic review of eight studies determined that the sensitivity of CT in detecting cartilage invasion was 66% and specificity was 90%.[6] Given that CT scans may not always accurately detect the presence of cartilage invasion, an important question is whether determination of cartilage invasion by CT scan can be a predictive and/or prognostic factor for treatment outcomes.

Several small studies have reported that pretreatment CT exhibiting cartilage invasion predicts worse oncologic outcomes in response to radiation therapy.[7–10] Studies also show that patients with cartilage invasion may experience superior outcomes when treated with surgery as opposed to organ preservation.[11] However, whether determination of cartilage invasion by CT affects oncologic outcomes in patients receiving primary total laryngectomy remains unclear. In this study, we sought to determine the sensitivity, specificity, PPV, and NPV of CT imaging in predicting cartilage invasion for patients with advanced laryngeal cancer receiving primary total laryngectomy. Furthermore, we sought to determine whether the radiologic cartilage invasion was associated with oncologic outcomes in this patient population.

2 | MATERIALS AND METHODS

This was a retrospective cohort study. Patient data was extracted from the electronic medical record and placed in an institutional review board approved head and neck cancer registry. From this registry, we identified all patients receiving primary total laryngectomy for treatment of laryngeal cancer. All patients who had imaging available in the Picture Archiving and Communication System were included in the study. Patients were excluded if they did not have imaging available, received care for their primary cancer outside of the Cleveland Clinic system, or had less than 1 month of follow up.

Data extracted from the electronic medical record included: demographics (age, sex, ethnicity, smoking status, alcohol status), disease characteristics (clinical and pathologic staging), and outcomes (death, recurrence). Two independent neuroradiologists were asked to review the CT scans. Each scan was reviewed by one neuroradiologist according to the following yes or no categories: thyroid cartilage clear invasion; tumor abutting noncalcified thyroid cartilage; tumor abutting calcified thyroid cartilage with sclerosis; thyroid cartilage invasion radiologist gestalt assessment; cricoid cartilage clear invasion; tumor abutting cricoid cartilage with sclerosis; cricoid cartilage invasion radiologist gestalt assessment; arytenoid cartilage clear invasion; tumor abutting arytenoid cartilage with sclerosis; arytenoid cartilage invasion radiologist gestalt assessment. Results from the different subsites were combined to create categories for clear cartilage invasion, tumor abutting sclerosing cartilage, and radiologist gestalt assessment of cartilage invasion. AJCC seventh edition staging was used throughout this study.

A gestalt assessment is defined as a judgment call made by a radiologist when it is not obviously apparent whether cartilage invasion is present. For the purposes of this study, the radiologist chose one discrete variable (e.g., yes or no cartilage invasion) that they felt best characterized the patient's case, even in the setting of uncertainty.

Descriptive data are displayed as counts with percentages or means with standard deviations (SD). A

TABLE 1 Clinical and demographic characteristics of patients included in the study

	Number of patients	% of patients
Age (mean and SD)	63.65	9.68
Ethnicity		
Asian	1	1.10%
African American	22	24.20%
White	67	1.10%
Unknown	1	73.60%
Sex: Male	71	78%
Smoking history		
Use at time of diagnosis or until treatment	57	62.60%
Never smoker	3	3.30%
Former smoker	31	34.10%
Heavy alcohol use	36	39.60%
Clinical T		
cT2	3	3.30%
cT3	31	34.07%
cT4	57	62.64%
Clinical N		
cN0	34	37.36%
cN1	11	12.09%
cN2	42	46.15%
cN3	4	4.40%
Pathologic T		
pT2	1	1.10%
pT3	23	25.27%
pT4	67	73.63%
Pathologic N		
pN0	32	35.16%
pN1	7	7.69%
pN2	45	49.45%
pN3	7	7.69%

Note: Data are presented as counts with percentages or means with standard deviations (SD).

pathological diagnosis of cartilage invasion was used as the gold standard for calculating sensitivity, specificity, PPV, and NPV of CT scan for detecting cartilage invasion. Survival analysis was performed with Kaplan Meier analysis. Multivariable Cox proportional hazards models were used to model the hazards ratios for disease free survival. All models were adjusted for age and sex and data are presented as hazards ratios with 95% confidence intervals (CoI). Chi-square test was used to compare counts between groups. All analyses were performed using R statistical software (version 3.6.1, R Foundation for Statistical Computing).

3 | RESULTS

A total of 91 patients met inclusion criteria and were included in the study. The mean age at diagnosis was 63.7 (SD 9.7) and median follow up time was 23 months (range 2.5–118.6). Only three patients (3.3%) were never smokers and 36 (39.6%) patients had a history of heavy alcohol use (>7 drinks/week for women, >14 drinks/week for men). Clinically, 57 (62.6%) of tumors received T4a (cT4a) classification while 31 (34.1%) were cT3 and 3 (3.3%) were cT2. Pathologically, 67 tumors (73.6%) were T4a (pT4a), 23 were pT3 (25.3%), and one was pT2 (1.1%) (Table 1). Because of the low number of cT2/pT2 patients, these patients were combined with cT3/pT3 patients for further analysis. 22 (24.2%) tumors were glottic, 9 (9.9%) subglottic, 44 (48.4%) supraglottic, and 16 (17.6%) were unspecified.

Table 2 shows the classification of tumor cartilage invasion status by radiographic imaging compared to the classification by pathology. On pathological diagnosis, 66 of 91 (72.5%) of tumors exhibited cartilage invasion. Because PPV and NPV are associated with pretest probability, PPV and NPV need to be analyzed in the context of a population with high pretest probability for cartilage invasion. When a radiologist was asked whether there was clear invasion of the thyroid, cricoid, or arytenoid cartilage, the result was a high specificity (84%) and PPV (90.9%) but a relatively lower sensitivity (60.6%) and NPV (44.7%) for histologic cartilage invasion. However, when a radiologist was asked whether their gestalt judgment indicated cartilage invasion, sensitivity was increased to 80.3% while specificity dropped to 48%.

Tumor invasion of cartilage is preceded by inflammatory changes that induce new bone formation and osteolysis.[12] Therefore, sclerosis is thought to be a possible early radiological sign of histological cartilage invasion.[13,14] Radiologist assessment of whether there was any tumor abutting sclerosing cartilage resulted in a sensitivity of 78.8% and specificity of 32% for histological cartilage invasion. When combining this assessment of sclerosis with the radiologist gestalt for cartilage invasion, the sensitivity increases to 93.9% but specificity drops to 20%, likely representing a method that results in radiologic overdiagnosis of histological cartilage invasion.

To compare whether the radiologist assessment of cartilage invasion was associated with patients' oncologic outcomes, we assessed overall survival (OS) and disease-free survival (DFS) stratified by cartilage invasion status. OS was similar between cT4a and cT3/cT2 patients,

TABLE 2 Sensitivity and specificity tables for cartilage invasion [Color table can be viewed at wileyonlinelibrary.com]

Radiologist: gestalt of any cartilage invasion

	Pathology	No	Yes	Total	Sensitivity	0.80303	Positive likelihood ratio: 1.54
Radiologist	No	12	13	25	Specificity	0.48	
	Yes	13	53	66	PPV	0.80303	
	Total	25	66	91	NPV	0.48	

Radiologist: clear invasion of any cartilage

	Pathology	No	Yes	Total	Sensitivity	0.60606	Positive likelihood ratio: 2.64
Radiologist	No	21	26	47	Specificity	0.84	
	Yes	4	40	44	PPV	0.90909	
	Total	25	66	91	NPV	0.44681	

Radiologist: tumor abutting any sclerosing cartilage

	Pathology	No	Yes	Total	Sensitivity	0.78788	Positive likelihood ratio: 1.16
Radiologist	No	8	14	22	Specificity	0.32	
	Yes	17	52	69	PPV	0.75362	
	Total	25	66	91	NPV	0.36364	

Radiologist: invasion and/or sclerosis of cartilage

	Pathology	No	Yes	Total	Sensitivity	0.93939	Positive likelihood ratio: 1.17
Radiologist	No	5	4	9	Specificity	0.2	
	Yes	20	62	82	PPV	0.7561	
	Total	25	66	91	NPV	0.55556	

Note: Radiologists were asked to assess for three different outcomes: clear cartilage invasion, gestalt for cartilage invasion (e.g., when cartilage invasion was not clear the radiologist gave a gestalt answer), and whether the tumor abut against sclerosing cartilage. The final category is a combination category where the outcome is "yes" if the radiologist either deemed there to be cartilage invasion by gestalt or tumor abutting sclerosing cartilage. Data are presented as counts and colored so that a green color indicates a higher count while yellow indicates lower count. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are provided and colored so that green indicates a higher value while yellow indicates a lower value.

between pT4a and pT3/pT2 patients, between radiologist gestalt cartilage invasion (CI) and non-CI patients, and between radiologist assessment of clear CI and non-CI patients (Figure 1). DFS was similar among cT4a and cT3/cT2 patients. DFS trended towards being superior among pT3/pT2 patients as compared to pT4a patients, even though this difference was not statically significant (Figure 2A). One-year DFS in pT3/pT2 patients was 80% versus 64.9% in pT4 patients ($p = 0.17$ by chi squared test). Five-year DFS was 49.9% in pT3/pT2 patients versus 35.9% in pT4a patients ($p = 0.18$ by chi squared test). This same trend was not seen in radiologist gestalt CI versus non-CI patients (Figure 2C). One-year DFS was 72% among gestalt non-CI patients and 67.9% among CI patients ($p = 0.72$ by chi squared test). Five-year DFS was 41.4% among non-CI patients and 40.5% among CI patients ($p = 0.94$ by chi squared test). When comparing the radiologist assessment of clear CI versus non-CI, a slight trend towards better survival in non-CI patients was observed (Figure 2D). Therefore, cartilage invasion as determined through gestalt radiographic imaging may not be a strong predictive factor for disease free survival.

To further test this hypothesis, we performed a multivariable Cox proportional hazards analysis to assess the hazard for DFS with regards to pathological T classification or radiologist gestalt cartilage invasion. When adjusted for age, sex, and pN classification, no associations were statistically significant. However, pathology confirmed cartilage invasion trended towards an increased hazard for DFS whereas radiologist gestalt cartilage invasion did not seem to increase the hazard for DFS (Table 3).

4 | DISCUSSION

Treatment of advanced laryngeal cancer is largely dependent on cancer staging.[1] Therefore, the determination of cartilage invasion may affect outcomes. We show that, in line with previous studies, CT assessment of cartilage invasion per radiologist gestalt is associated with a sensitivity and specificity of 80.3% and 48%, respectively, for determination of histological cartilage invasion. To our knowledge, this study is the first to correlate radiologic

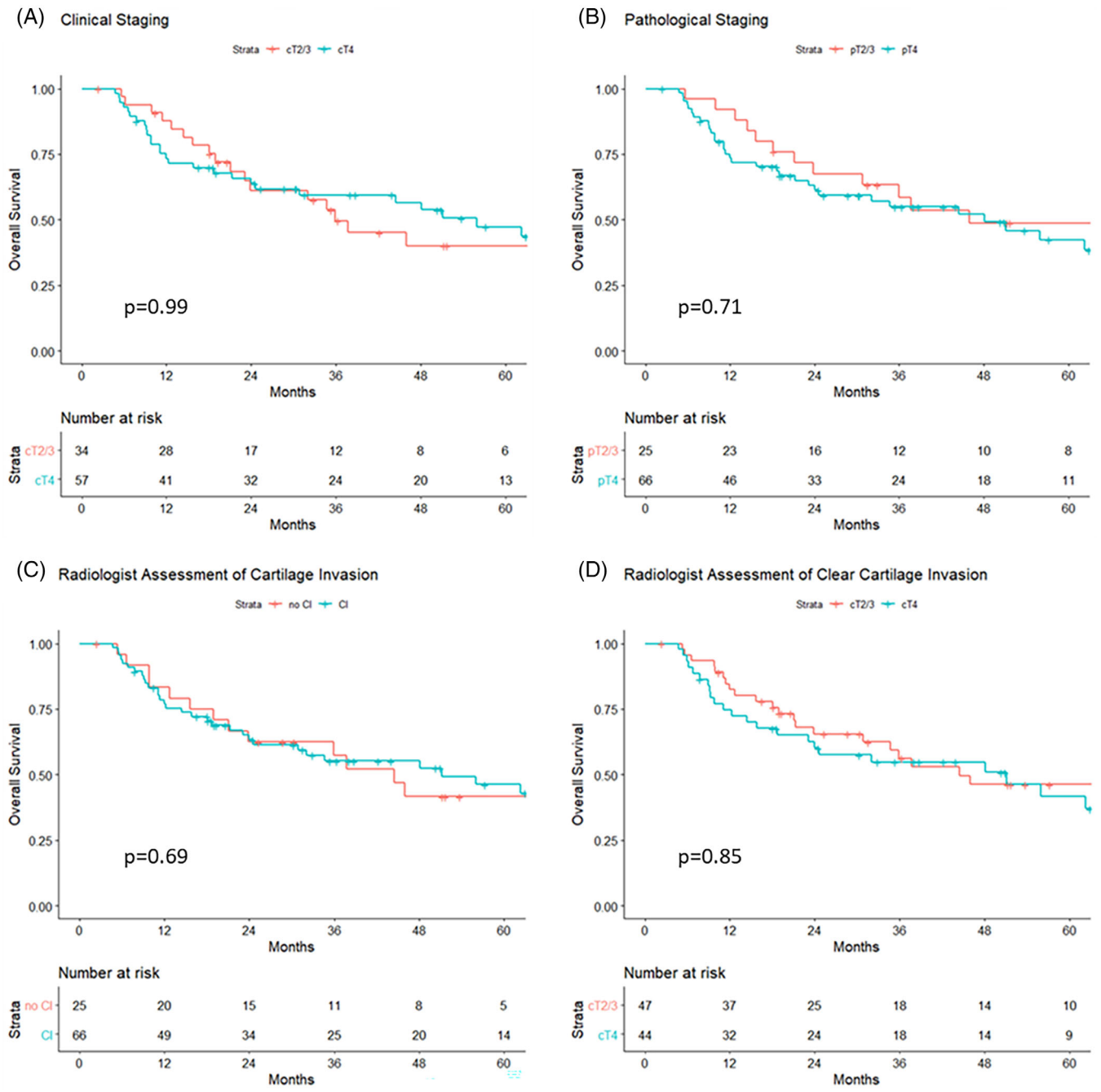

FIGURE 1 Kaplan–Meier survival curves for overall survival stratified by T stage. T stage was determined (A) clinically or (B) pathologically. In (C) the groups are separated by whether the radiologist deemed there to be cartilage invasion by gestalt. In (D) the groups are separated by whether the radiologist deemed there to be clear cartilage invasion [Color figure can be viewed at wileyonlinelibrary.com]

cartilage invasion with oncological outcomes in patients receiving primary total laryngectomy for advanced laryngeal cancer. While patients with histologic diagnosis of cartilage invasion trended towards worse DFS, patients with a radiologic diagnosis of cartilage invasion did not trend towards worse DFS. These findings may provide preliminary evidence that better diagnostic tools, such as dual energy CT or MRI, should be obtained in these patients when there is any concern for cartilage invasion by conventional CT.

It is often challenging to differentiate cartilage invasion from inflammation on CT. The clearest sign of cartilage invasion is extralaryngeal tumor spread, while sclerosis, lysis, and erosion of cartilage are less specific and more difficult to pinpoint.[15,16] A systematic review and meta-analysis of eight studies found a pooled

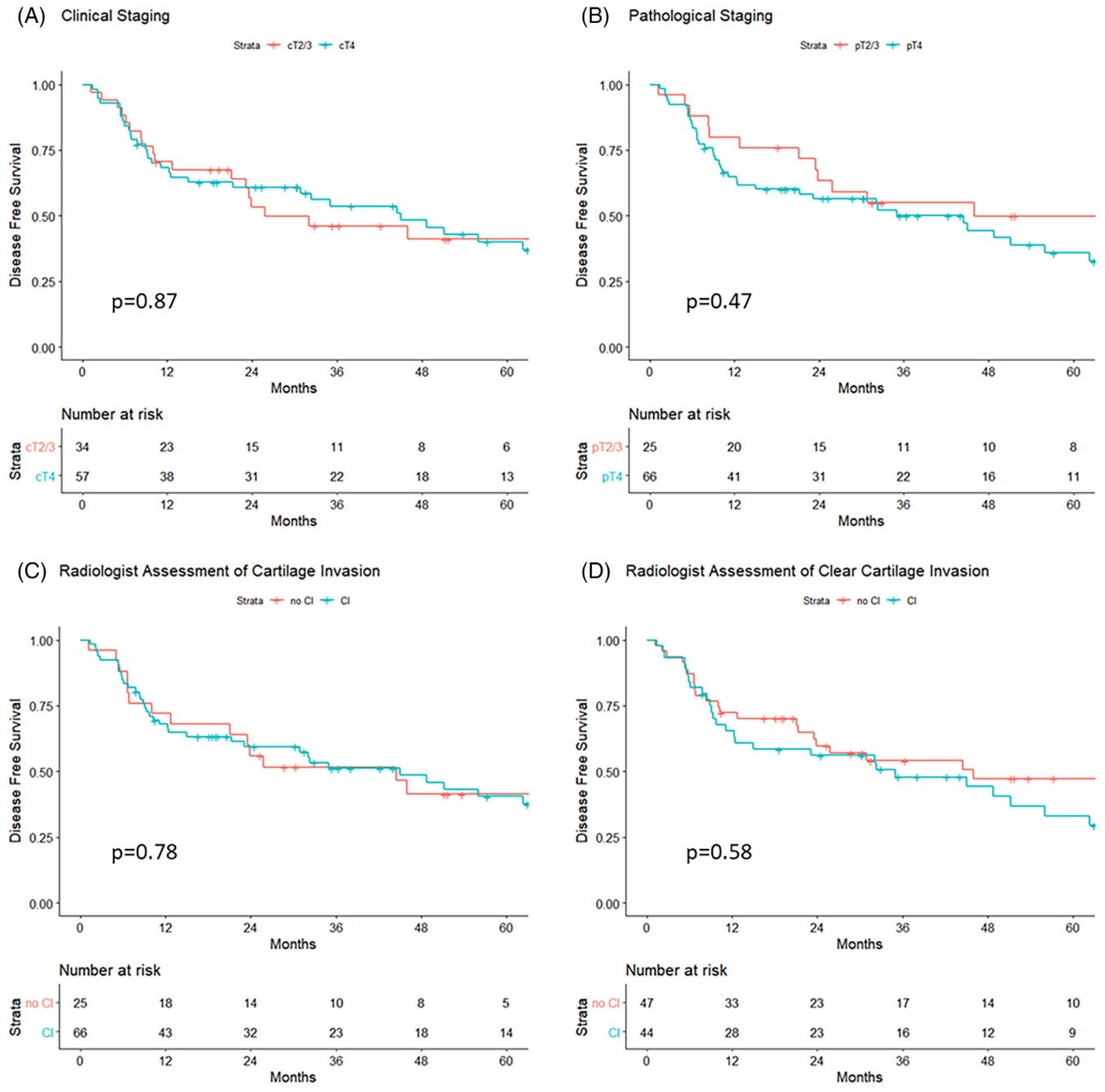

FIGURE 2 Kaplan–Meier survival curves for disease free survival stratified by T stage. T stage was determined (A) clinically or (B) pathologically. In (C) the groups are separated by whether the radiologist deemed there to be cartilage invasion by gestalt. In (D) the groups are separated by whether the radiologist deemed there to be clear cartilage invasion [Color figure can be viewed at wileyonlinelibrary.com]

sensitivity of 66% (95% CoI 49%–80%) and a pooled specificity of 90% (82%–94%).[6] These numbers are very similar to the sensitivity and specificity we found when the radiologist was asked to determine whether there was clear cartilage invasion. However, when the diagnosis was not clear and the radiologist was asked to give a gestalt determination, the specificity dropped significantly while the sensitivity increased.

The determination of cartilage invasion by radiologist gestalt was not associated with a trend in OS or DFS in our cohort whereas a pathological diagnosis of pT4a cancer was associated with a trend towards worse DFS. This may be due to a low specificity of 48%, indicating that over half of patients with histological cartilage invasion were classified as having no cartilage invasion after CT. The determination of clear cartilage invasion did

	Hazard ratio	2.5% CoI	97.5% CoI
Pathology confirmed cartilage invasion[a]	1.46	0.75	2.83
Radiologist gestalt cartilage invasion[a]	1.13	0.61	2.07
Radiologist clear cartilage invasion[a]	1.61	0.90	2.90

TABLE 3 Adjusted multivariable Cox proportional hazards analysis for disease free survival

Abbreviation: CoI: confidence interval.
Note: Two separate models were analyzed using either pathology confirmed cartilage invasion or radiologist gestalt cartilage invasion.
[a]Models were adjusted for age, sex, and pN classification.

trend slightly towards worse DFS in our cohort, possible because of an increased specificity of 84%, indicating that almost everyone in this group was diagnosed with histological cartilage invasion. These finding were echoed by our multivariable Cox proportional hazards analysis, which showed no increased hazard for DFS in patients with gestalt radiologic determination of cartilage invasion and a slight increased hazard for DFS in patients with either clear cartilage invasion or histological cartilage. These results may indicate that radiologist assessment of clear cartilage invasion may be a better prognostic factor than gestalt cartilage invasion on CT.

There are several limitations to our study. First, the population of patients who received total laryngectomy is likely to contain a high proportion of patients with true cartilage invasion. Since the pretest probability affects the PPV and NPV, the true values may be skewed for a more general population. Second, our sample size was sufficiently low that we were not able to detect a statistically significant difference in OS or DFS in pT4a versus pT3/pT2 patients. It is possible that we missed trends or differences that we could have seen with larger sample sizes. Lastly, each patient's CT was analyzed by a single radiologist who was not aware of the pathological data for the purposes of this study. It is possible that different radiologists would have analyzed the images differently, lending subjectivity to our results. Additionally, it is possible that the same radiologist performed the initial clinical read and the experimental read. In this case, it is possible that the radiologist may have recalled the ultimate pathology, leading to potential bias.

5 | CONCLUSIONS

Our study is the first to our knowledge to study the relationship between radiologic cartilage invasion and oncologic outcome in patients receiving primary total laryngectomy for advanced laryngeal cancer. We show that the sensitivity and specificity of CT scans for histologic cartilage invasion are 80.3% and 48%, respectively when utilizing the radiologist gestalt, but 60.6% and 84% when the radiologist identifies clear cartilage invasion. Cartilage invasion by radiologist gestalt did not appear to be associated with an increased hazard for DFS while a radiologist determination clear cartilage invasion trended towards an increased hazard for DFS. Additional studies with larger samples are warranted to further explore this relationship.

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CONFLICT OF INTEREST
No conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

APPROVAL AND CONSENT
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