Original paper

Computed tomography in the assessment of cartilage invasion in locally advanced laryngeal cancer

Zastosowanie tomografii komputerowej w ocenie nacieku chrząstek w raku krtani

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Słowa kluczowe: naciek chrząstek, tomografia komputerowa, ocena histopatologiczna, rak krtani, laryngektomia całkowita.

Abstract

Introduction: In laryngeal cancer, accurate assessment of the laryngeal cartilage is essential to ensure correct staging, prognosis, and treatment. This is especially important given organ preservation in cases with cartilage involvement.
Aim of the research: To assess the sensitivity, specificity, and positive and negative predictive values (positive predictive value (PPV), negative predictive value (NPV)) of computed tomography (CT) in detecting cartilage involvement. A second aim was to determine whether the time from the CT scan to surgery influences CT reliability.
Material and methods: We retrospectively reviewed data from 233 patients who underwent total laryngectomy from 2007 to 2018 at our institution. We compared the CT findings to the histopathological results to determine the CT reliability in terms of identifying the presence of cartilage invasion and in staging.
Results: In the full cohort, CT performance was as follows: sensitivity, 68.8%; specificity, 60.3%; PPV, 65.6%; and NPV, 63.8%. In the subgroup of patients (n = 68) who underwent surgery 14 days or fewer after the CT scan, the corresponding values were as follows: sensitivity, 82.1%; specificity, 57.5%; PPV, 57.5%; and NPV, 82.1%. CT staging was accurate in 53.2% of cases; postoperative histopathologic evaluation led to upstaging in 73 (31.3%) cases and downstaging in 34 (14.6%).
Conclusions: The novel findings of this study show that CT imaging is most accurate when performed no more than 14 days prior to surgery, suggesting that surgery should be performed ≤ 14 days after imaging to maintain the best accuracy of CT. Given the limited reliability of CT in detecting cartilage invasion, complementary imaging techniques such as magnetic resonance imaging and/or ultrasound should be performed in ambiguous cases.

Streszczenie

Wprowadzenie: Odpowiednia ocena nacieku chrząstek krtani jest kluczowa w diagnostyce raka krtani w celu określenia stopnia zaawansowania, prognozy oraz odpowiedniego leczenia. Jest to bardzo istotne przy strategiach zachowania narządu w przypadku obecności nacieku szkieletu chrzęstnego.
Cel pracy: Określenie czułości, swoistości oraz pozytywnej (PPV) i negatywnej wartości predykcyjnej (NPV) tomografii komputerowej (TK) w diagnozowaniu nacieku chrząstek krtani, a także wpływu czasu pomiędzy badaniem a operacją na jego wiarygodność.
Materiał i metody: Retrospektywnej analizie poddano 233 pacjentów, u których wykonano laryngektomię całkowitą w latach 2007–2018 w Klinice. Porównano opisy TK z wynikami oceny histopatologicznej preparatów pooperacyjnych w zakresie nacieku chrząstek krtani.
Wyniki: W całej populacji wiarygodność diagnostyczna TK wyniosła: czułość – 68,8%, swoistość – 60,3%, PPV – 65,6%, NPV – 63,8%. U pacjentów (n = 68), którzy zostali zoperowani w czasie 14 dni po wykonaniu TK, wartości prezentowały się następująco: czułość – 82,1%, swoistość – 57,5%, PPV – 57,5%, NPV – 82,1%. Stopień zaawansowania nowotworu na podstawie TK okazał się wiarygodny w 53,2%, a ocena histopatologiczna spowodowała wzrost stopnia zaawansowania w 73 (31,3%) przypadkach oraz obniżenie stopnia zaawansowania w 34 (14,6%) przypadkach.
Wnioski: Nowym odkryciem badania jest stwierdzenie, że TK jest bardziej wiarygodna, gdy operacja zostanie wykonana nie później niż 14 dni po obrazowaniu. Konieczne jest więc operowanie pacjentów w tym okresie czasowym w celu zachowania jak największej dokładności TK. W związku z ograniczoną wiarygodnością TK w niejednoznacznych przypadkach powinno zostać wykonane dodatkowe obrazowanie, takie jak rezonans magnetyczny lub ultrasonografia.

Introduction

Reliable imaging is essential to select the optimal multidisciplinary treatment approach in patients with cancer. Patients with laryngeal cancer who present with cartilage involvement have limited treatment options, and organ preservation may not be possible [1–3]. Patients with T1 or T2 laryngeal cancer generally undergo either surgical resection or radiotherapy, depending on the patient's preferences and/or anatomical limitations [2, 3]. In cases with cartilage erosion (stage T3), radical treatment with larynx preservation is possible, but chemoradiotherapy (CRT) is associated with high recurrence rates and the risk of cartilage necrosis [4]. Despite organ preservation strategies being designed with salvage surgery in mind for treatment failures, in these cases, total laryngectomy with adjuvant radiotherapy may be also the primary radical treatment option. In cases with an invasion through the thyroid cartilage (stage 4), total laryngectomy with adjuvant radiotherapy is the treatment of choice [2, 3]. However, some authors suggest that laryngeal preservation could be considered in cases with cartilage involvement [5, 6], and other authors suggest that thyroid cartilage invasion may not influence overall or local survival [7].

Accurate evaluation of the status of the laryngeal cartilage is essential for staging, prognosis, and treatment planning. However, accurate determination of the presence of cartilage invasion is a well-known pitfall in laryngeal cancer staging [1, 8]. Endoscopic examination plays an essential role in evaluating vocal cords, aryepiglottic folds, and the anterior commissure. However, endoscopy alone is insufficient to assess the true extent of the tumour, which is why radiological imaging is essential [2]. Computed tomography (CT) and magnetic resonance imaging (MRI) are the main tools to complement the laryngeal cancer diagnostic process [4, 9].

MRI has a sensitivity of 88%, specificity of 81%, and negative predictive value (NPV) of 96% in detecting laryngeal cartilage invasion. MRI has several important advantages over CT: it does not require iodine contrast agents, does not use ionizing radiation, and tooth amalgams do not affect image quality (no artifacts) [4, 9]. On the other hand, MRI has a lower specificity than CT due to its limited capacity to differentiate cancerous tissues from adjacent inflamed tissues. As a result, MRI potentially overestimates the extent of cartilage invasion. Another drawback of MRI is that artifacts caused by coughing, swallowing, and breathing during imaging can reduce image quality [4, 9].

CT has a higher specificity than MRI [9] and is particularly efficient in detecting tumours invading the cartilage, except for subtle inner cortex erosion [4]. Other advantages of CT versus MRI include lower costs, a more rapid procedure (which reduces the risk of artifacts), and widespread availability, which is especially important in resource-limited regions. In a recent meta-analysis, CT had a pooled sensitivity of 66% and specificity of 90% [9].

There are several studies that compared CT imaging to histopathological evaluation in laryngeal cancer staging. However, most of those studies had small sample sizes, thus limiting the strength of the findings [7, 10–23].

Aim of the research

In this context, the aim of the present study was to retrospectively assess the reliability of CT for the detection of laryngeal cartilage invasion in a large cohort. Other aims were to determine the impact of the time interval from CT to surgery on the performance of CT imaging and to assess the accuracy of CT laryngeal cancer staging.

Material and methods

We retrospectively reviewed data from 302 patients (261 (86.5%) men and 41 (13.5%) women), who underwent total laryngectomy from 2007 to 2018 at our institution. We conducted this study according to the declaration of Helsinki. The study did not require ethical approval because it was based on historical data of patients.

Inclusion criteria were as follows: contrast-enhanced CT with complete radiologist report available prior to surgery; total laryngectomy as primary treatment or salvage surgery; and complete histopathologic evaluation of resected tissues. Sixty-nine patients were excluded due to lack of precise data in the hospital database, 56 patients lacked detailed CT evaluation, and 13 patients lacked detailed histopathologic evaluation. The mean (± standard deviation (SD)) time interval from CT evaluation to total laryngectomy was 30 ±28 days (range: 0–228). Staging was determined according to the 8th edition of the Union for International Cancer Control (UICC) TNM classification.

Statistical analysis

We calculated the sensitivity, specificity, NPV, positive predictive value (PPV), and the accuracy of CT staging compared to the final histopathological findings. The χ^2 test was used to compare accuracy of staging based on CT and accuracy of cartilage invasion between primary and recurrent cancers. All analyses were performed with Microsoft Excel 2007 and the Statistica 12.0 (2012) statistical software package for Windows.

Results

A total of 233 patients were included in this study. Of these, 205 (88%) were men and 28 (12%) were women. The mean (SD) patient age was 61.1 ±9.5 years (range: 23–92). Of these 233 patients, 68 (29%) underwent surgery within 14 days of the CT scan. The CT

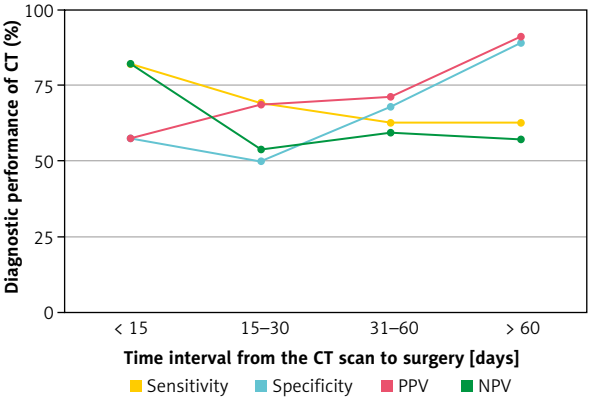

Figure 1. Performance of CT depending on the time interval from the CT scan to surgery

had a sensitivity of 68.9%, specificity of 60.4%, PPV of 65.6%, and NPV of 63.8%. Cartilage invasion was correctly assessed in 151 (64.8%) cases. The time interval from the CT scan to surgery had a major impact on the diagnostic power of the CT, with a significant decrease in sensitivity and NPV and an increase in specificity and PPV as a function of the time interval from CT to surgery (Table 1, Figure 1). In the subgroup of patients who underwent surgery ≤ 14 days after CT, the sensitivity was 82.1%, specificity 57.5%, PPV 57.5%, and NPV 82.1%. Radiological T staging was accurate in 52% of cases. CT failed to identify the presence of laryngeal cancer in 12 (5.2%) cases of clinically and histopathologically confirmed cancers, of which 9 were recurrences and 3 were primary tumours.

Final histopathological examination revealed invasion of the thyroid cartilage in 49.8% of resected larynges, cricoid cartilage in 3%, epiglottic cartilage in 1.3%, and arytenoid cartilage in 0.4%. Table 2 shows the performance of CT by type of cartilage. The results of histopathologic staging are summarized in Table 3.

Table 1. Performance of CT depending on the time interval from the CT scan to surgery

CT-to-surgery time	< 15 days	15–30 days	31–60 days	> 60 days
Sensitivity	82.1	69.2	62.8	62.5
Specificity	57.5	50	67.8	88.8
PPV	57.5	68.5	71	90.9
NPV	82.1	53.8	59.4	57.1

The final histopathological findings modified the clinical staging in 107 (45.9%) cases, leading to downstaging in 34 (14.6%) cases and upstaging in 73 (31.3%) cases (Table 4). However, the change in overall stage, T stage, and N stage were not significantly correlated with the CT-to-surgery time interval. There were no significant differences in accuracy of CT and the number of upstaged and downstaged tumours in patients operated within 14 days after imaging compared with patients operated later. Based on the false positive rate for cartilage invasion, we estimate that 44 (18.9%) cases could have been offered organ preservation strategy treatment, except for 3 patients who had a recurrent tumour following full-dose radiochemotherapy.

Total laryngectomy was performed in 186 (79.8%) patients as a primary treatment and in 47 (20.2%) patients as salvage surgery after primary radiotherapy or CRT (n = 30), after primary surgery with larynx preservation (n = 8), and after multiple previous treatment attempts (n = 9). In our study, there were 23 patients

Table 2. Performance of CT in detecting cartilage invasion in laryngeal cancer

Cartilage	*n*	TP	FP	TN	FN	Se	Sp	PPV	NPV	Acc
Thyroid	116	71	32	85	45	61.2	72.6	68.9	65.4	66.9
Cricoid	7	6	41	185	1	85.7	81.9	12.8	99.5	82
Arytenoid	1	1	31	201	0	100	86.6	3.1	100	86.7

n – number of invaded cartilages, TP – true positive, FP – false positive, Se – sensitivity, Sp – specificity, TN – true negative, FN – false negative, PPV – positive predictive value, NPV – negative predictive value, Acc – accuracy.

Table 3. Staging based on histopathological evaluation

T stage	*n*	%	Overall stage	*n*	%
1	6	2.6	1	6	2.6
2	17	7.3	2	11	4.7
3	107	45.9	3	95	40.8
4a	102	43.8	4a	112	48.0
4b	1	0.4	4b	9	3.9

T stage – tumour stage.

Table 4. Overall staging accuracy of CT in stage 3 and 4 of laryngeal cancer

CT stage 3	74	
Accurate evaluation	HP stage 3	
	35	
Underestimation by CT	HP stage 4	
	27	
Overestimation by CT	HP stage 1	HP stage 2
	2	10
CT stage 4	101	
Accurate evaluation	HP stage 4	
	83	
Overestimation by CT	HP stage 2	HP stage 3
	1	17

CT – computed tomography, HP – histopathological evaluation.

Table 5. Localization of the tumours

Localization	*N*	%
Epiglottis	18	7.7
Aryepiglottic fold	35	15.0
Piriformis recess	3	1.3
Vocal fold	71	30.5
Vestibular fold	17	7.3
Vallecula epiglottica	2	0.9
Subglottic area	7	3.0
Vast tumour (unknown primary site)	68	29.2
Not clear	12	5.2

with T1 or T2 tumours treated with total laryngectomy. Six patients with pT1 tumour had recurrent tumour, whereas, from 17 patients with pT2 tumour, 10 patients had recurrent tumour and in 7 patients treatment with CO_2 laser was not possible (6 of them refused the treatment with radiotherapy and one had undergone radiotherapy earlier due to oropharyngeal cancer).

Recurrent cancers had a significantly higher rate of incorrect CT staging $\chi^2(1, n = 233) = 6.0884$, $p = 0.0136$ than primary cancers (62% and 44% of incorrect CT staging, respectively), but those groups did not differ in terms of accurate assessment of cartilage invasion $\chi^2(1, n = 233) = 0.9233$, $p = 0.3366$ (63% accuracy in primary cancers and 60% in recurrent cancers). Most of the tumours were located in the glottic region (Table 5).

Discussion

This retrospective study was performed to evaluate the reliability of CT in the detection of laryngeal cartilage invasion on a large sample of patients treated at our institution. In the full cohort, CT imaging yielded a sensitivity, specificity, PPV, and NPV of 68.8%, 60.3%, 65.6%, and 63.8%, respectively. However, in the subgroup of patients who underwent surgery ≤ 14 days after the CT scan, the corresponding values were 82.1%, 57.5%, 57.5%, and 82.1%. In the overall cohort, CT staging was accurate in 53.2% of cases. On histopathologic evaluation, 73 (31.3%) patients were upstaged and 34 (14.6%) were downstaged. Although the change of overall histopathological stage had no correlation with the CT-to-surgery time interval, the diagnostic power of CT was higher when surgery was performed within 14 days, because of higher sensitivity and NPV. These findings show that CT is most reliable when performed no more than 14 days prior to surgery.

We also reviewed the literature to identify relevant studies published after 2010. We searched the PubMed database for the following terms: (laryngeal OR larynx) AND cartilage AND (invasion OR infiltration OR erosion) AND (computed tomography OR CT), to identify relevant publications. A total of 102 records were identified for the defined search period. We included only studies comparing cartilage invasion detected on CT to final pathological examination. Studies that included patients with non-radical treatments (i.e. larynx preservation) were excluded due to the impossibility of objectively confirming the radiological findings in these cases. Finally, a total of 15 studies were included (Table 6).

In the last decade, numerous studies have been performed to assess and compare the value of different imaging techniques in the evaluation of cartilage invasion [7, 10–23]. However, most of those studies have significant drawbacks, mainly small sample sizes. In addition, direct comparison of findings is questionable given the heterogeneity among those studies (e.g. in the larynx sites evaluated) (Table 6). By contrast, the present study includes a large population of patients for whom complete radiological and histopathological data were available.

While CT findings depend on the specific criteria used to define invasion, this technique is most accurate in cartilage-penetrating tumours [4]. A recent systematic review of CT imaging found that the PPV and NPV for detecting cartilage invasion ranged from 44% to 87% and 56% to 100%, respectively [4]. Our overall results for PPV (65.6%) and NPV (63.8%) are consistent with those ranges, indicating that CT is not optimal to confirm or rule out cartilage invasion.

False positives are an important issue because they can lead to possible overtreatment (e.g. total laryngectomy instead of organ preservation strategy). In many cases, false positives are due to cartilage ossification, because the non-ossified tissue can mimic cancer invasion [4]. In our study, 44 (18.9%) of the larynges that underwent surgery were false positives on CT for cartilage invasion. Most of these patients (41/44; 93.2%)

Table 6. Summary of studies published from 2010 investigating the CT performance in detecting cartilage invasion

Author	Year	Country	No. of patients	Surgery	Diagnostic test	Thyroid cartilage					Cricoid cartilage					Arytenoid cartilage					All cartilages				
						Se	Sp	PPV	NPV	Acc	Se	Sp	PPV	NPV	Acc	Se	Sp	PPV	NPV	Acc	Se	Sp	PPV	NPV	Acc
Wojtera *et al.* (present study)	2022	Poland	233	Primary or salvage TL	CE-CT	61.2	72.6	68.9	65.4	66.9	85.7	81.9	12.8	99.5	82	100	86.6	3.1	99.5	86.7	68.9	60.4	65.6	63.8	64.8
Lee *et al.* [23]	2022	USA	91	Primary TL	CE-CT	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	60.6–80.3	48–84	80.3–90.9	44.7–48	–
Guo *et al.* [19]	2020	China	265	Primary TL	CE-CT	74.4	69.98	–	–	71.3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Pietragalla *et al.* [10]	2020	Italy	40	Primary or salvage TL	CE-CT	64.3–77.8	87.1–100	63.6–100	54.5–93.1	75–85	100	100	100	100	100	71.4	66.7	31.2	91.7	67.5	–	–	–	–	–
Paone *et al.* [11]	2019	Switzerland	27	TL	CE-CT	70	86	93	50	74	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Weselik *et al.* [12]	2019	Poland	21	TL	CE-CT	61.5	60	80	37.5	–	80	60	66.7	75	–	100	60	50	100	–	–	–	–	–	–
Lucioni *et al.* [22]	2018	Italy	100	OPHL	CE-CT	–	–	–	–	–	–	–	–	–	–	81	63	29	94	–	–	–	–	–	–
Kuno *et al.* [13]	2018	Japan	55	TL or pharyngo-laryngectomy	DE-CT	89	100	100	95	96.4[a]	75	98	86	96	94.5[a]	67	97	67	97	94.5[a]	81	98	88	96	95[a]
Harris *et al.* [20]	2018	United Kingdom	79	Primary or salvage TL	CE-CT	100	88.6	52.9	100	89.9	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Dankbaar *et al.* [14]	2017	The Netherlands	14	TL	DCE-CT	75[a]	86.7[a]	69.2[a]	89.6[a]	83.3[a]	100[a]	91.7[a]	66.7[a]	100[a]	92.8[a]	51.7[a]	95.2[a]	80[a]	86.9[a]	85.7[a]	67	90	70	89	–
					CE-CT	91.7[a]	93.3	84.6[a]	96.5[a]	92.8[a]	100[a]	91.7[a]	66.7[a]	100[a]	92.8[a]	71.4[a]	90.5[a]	71.4[a]	90.5[a]	85.7[a]	86	92	78	95	–
Dhoot *et al.* [15]	2017	India	58	Surgical resection	CE-CT	90.7	75	98	37.5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Koopmann *et al.* [7]	2016	Germany	120	Primary TL	CE-CT	46	89	76	69	70.8[a]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Xia *et al.* [21]	2013	China	72	Surgical resection	CE-CT	75	94.6	80[a]	93[a]	90.3[a]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Han *et al.* [16]	2013	Republic of Korea	32	Salvage TL after RT failure	CE-CT	71.1	94.4	88.9	73.9	78.1	50	89.3	40	92.6	84.4	33.3	75.9	12.5	91.7	71.9	–	–	–	–	–
Hartl *et al.* [17]	2013	France	236	Primary open partial laryngectomy	CE-CT	10.5	94	13	92	87	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Li *et al.* [18]	2011	USA	61	TL	MDCT	85	75	63	92	78.7	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

[a]*Parameters were calculated based on raw data from the studies: true positives, false positives, true negatives, false negatives.*

Se – sensitivity, Sp – specificity, PPV – positive predictive value, NPV – negative predictive value, Acc – accuracy, TL – total laryngectomy, OPHL – open partial horizontal laryngectomy, RT – radiotherapy, CE-CT – contrast-enhanced computed tomography, DE-CT – dual-energy computed tomography, DCE-CT – dynamic contrast-enhanced computed tomography, MDCT – multidetector computed tomography.

could have been offered larynx preservation therapy because they presented with primary cancer.

In our review of the literature, the reported sensitivity and specificity of CT to detect cartilage invasion ranged from 10.5% to 100% and 48% to 100%, respectively (Table 6). In our cohort, the sensitivity of 68.39% and specificity of 60.4% were in line with previous reports. In a recent study, Lee *et al.* [23] compared the clear invasion cartilage in CT with the gestalt judgment of the radiologist, which resulted in higher sensitivity (60.6% vs. 80.3%) and lower specificity (84% vs. 48%).

Pietragalla *et al.* compared primary and recurrent tumours evaluated by CT, reporting no differences in detection rates for cartilage invasion [10]. Our findings were largely in line with those results, although we found that staging was generally less accurate in recurrent tumours (57% accurate staging in primary tumours vs. 38% in recurrent tumours).

Our data show that the time interval from the CT scan to surgical resection has a significant impact on CT performance (Table 1, Figure 1). Surgeries performed up to 14 days after imaging had a better sensitivity and NPV (82.1% for both parameters). This finding is interesting given that the CT-to-surgery interval has received scant attention in the literature. Although it seems obvious that surgery should be performed as soon after CT as possible, no widely accepted guidelines are available. Moreover, surgery is frequently delayed due to the need for additional diagnostic testing, the presence of other comorbidities, evaluation by a multidisciplinary team, administrative issues, or patient-related personal matters. Nonetheless, our findings clearly indicate that this is an important variable that needs to be considered when planning diagnostics and surgery.

If the presence of cartilage invasion on the CT image is indeterminate, additional imaging tests should be considered. In this regard, one study found that combining CT with MRI could improve the accuracy of detecting cartilage invasion [24]. In another study, Lim et al. assessed the sensitivity, specificity, PPV, NPV, and accuracy of CT combined with MRI, reporting excellent results: 88%, 89%, 44%, 98%, and 84.9%, respectively [25].

Other imaging tests can also be used to evaluate cartilage invasion. Paone *et al.* found that PET/CT improves the detection of cartilage invasion and overall staging [11]. Dual-energy CT has been shown to improve the accuracy of cartilage invasion imaging By contrast, dynamic contrast-enhanced CT does not appear to improve diagnostic accuracy in assessing cartilage invasion [14].

Ultrasound has also been used for laryngeal cancer staging [26]. In the study by Xia *et al.* [21], the authors concluded that ultrasound may be more accurate than CT in evaluating invasion of the paraglottic space and thyroid cartilage, thus making it an effective complement to CT imaging. A recent preliminary study showed that contrast-enhanced ultrasound appears promising and may become another reliable tool for staging of laryngeal cancer [27].

The limited performance of human assessment of radiological scans led to the development of radiomics and has increased interest in machine learning. While some data suggest these techniques could improve the accuracy of detecting cartilage invasion, the results published to date are contradictory [19, 28].

The main limitation of this study is the retrospective study design. Another limitation is the potential bias associated with the study population, which was limited to patients who underwent total laryngectomy. This is relevant given that cartilage invasion is less prevalent in the whole population of patients with laryngeal cancer versus those who undergo radical treatment, which means that the true PPV and NPV rates are probably lower and higher, respectively, than those observed in the present study. A final limitation is the involvement of various radiologists and pathologists, which could have impacted the interpretation of the CT scans and the histopathologic evaluations.

Conclusions

The time interval from CT examination to surgery is a crucial factor in determining the diagnostic efficiency of CT imaging in detecting cartilage invasion in patients with laryngeal cancer. Our results suggest that laryngectomy should be performed within 14 days of the CT scan to maintain the best diagnostic power of the scan, which is a novel finding. Furthermore, we recommend consideration of performing additional CT prior to the surgery if the previous imaging was performed more than 14 days before the day of the operation. Additionally, surgeons should be aware of the limited capacity of CT to accurately detect cartilage invasion. In ambiguous cases, complementary imaging techniques such as MRI and/or ultrasound should be considered.

Conflict of interest

The authors declare no conflict of interest.

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