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Correlation between MDCT and postoperative histopathology in the staging of laryngeal carcinoma

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► ***Original article***

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ABSTRACT

Background: Laryngeal squamous cell carcinoma (LSCC) originates from the laryngeal mucosal epithelium. Multidetector contrast-enhanced computerized tomography (MDCT) is valuable staging tool for various cancers. Objectives are evaluation of the performance of preoperative staging of LSCC according to the interpretation of MDCT imaging compared to pathological staging of the surgically excised specimens. ***Materials and Methods:*** MDCT scanning was performed by 64-detector, multi-slice CT device, and injection of contrast material (Lohexal 75%). Surgically excised laryngeal specimens were examined pathologically and staged. The study outcome was the performance of the CT scanning versus pathological findings. ***Results:*** Excellent agreement was detected for most laryngeal regions with Kappa values >0.9. In terms of tumor staging, CT showed good agreement with pathology stagings (Kappa=0.557). Overall, CT shows excellent diagnostic utility, with accuracy rates of 73.3% to 96.7% with ≥90% sensitivity and 100% for LSCC in subglottic, paraglottic, preepiglottic, aryepiglottic folds, and vocal cord regions. ***Conclusion:*** Preoperative MDCT scanning for LSCC patients might accurately detect and stage lesions across the laryngeal regions. MDCT imaging could detect extra-laryngeal space invasion with perfect agreement with pathological staging.

INTRODUCTION

Head and neck squamous cell carcinomas are highly heterogeneous in terms of their progression behavior and the outcomes of various treatment modalities, primarily due to the heterogeneity of their molecular pathophysiology [1]. Laryngeal squamous cell carcinoma (LSCC) is a common malignancy that originates from the laryngeal mucosal epithelium [2] and is the widely prevalent malignant tumor of the upper respiratory tract [3].

Cervical lymph node metastasis in glottic LSCC increases the possibility of recurrence with a subsequent deleterious impact on the prognosis. Cervical occult metastasis, which may be missed during clinical examination, was significantly encountered during surgery for glottic LSCC and worsens the surgical outcomes [4].

Multidetector contrast-enhanced computerized tomography (MDCT) is a valuable initial staging tool for various body cancers [5]. The esophageal wall thickness on CT showed a 60% positive prediction of the esophageal squamous cell carcinoma T stage [6]. In case of HPV-positive oropharyngeal squamous cell carcinoma, CT showed high sensitivity, specificity, and negative predictive value for extranodal extension [7]. MDCT for T1/T2 gastric cancer helps better select patients for upfront surgery versus perioperative chemotherapy [5]. Implementing MDCT, as a diagnostic modality for breast cancer within a dedicated breast protocol, showed high agreement and reliability with breast MRI for locoregional staging of newly diagnosed breast cancer [6].

The current work aims to define the performance of preoperative staging of laryngeal carcinoma (LC) according to the interpretation of the MDCT images compared to pathological staging of the surgically excised specimens.

MATERIALS AND METHODS

Patients, irrespective of age or gender, with LC who were assigned for total or partial laryngectomy were eligible for evaluation of their demographic and clinical data, and for enrollment criteria. The Ethical Committee at the Faculty of Medicine, Ain Shams University, approved the study protocol with the number: FWA 000017585.

Inclusion criteria

Patients with settled clinical and histopathological diagnoses of laryngeal squamous cell carcinoma (LSCC), who received no previous treatment, ASA grade of I or II, and signed a written informed consent to apply the study protocol, were enrolled in the study.

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Exclusion criteria

Patients had histopathological diagnoses other than LSCC, distant metastasis, with a history of previous or synchronous head and neck malignancy, uncompensated medical disorders, received or maintained on therapies other, ASA grade >II, or refused surgical intervention or to sign the informed consent

Clinical evaluation

This entailed otorhinolaryngological (ORL) examination, including history taking, external examination of the neck, particularly lymph node assessment, indirect and fiberoptic laryngoscopy to assess subglottic, anterior commissure extension, and vocal cord mobility.

Patients were prepared to undergo direct laryngoscopy under intravenous anesthesia to map the tumor extensions and biopsy taking for histopathological examination. Hopkin endoscopes were combined with the laryngoscope to assess and measure subglottic extension. The tumor was staged according to the TNM staging system based on the clinical, endoscopic, and radiologic findings.

Radiologic workup

Patients were asked to attend the CT unit fasting for >4. Patients were positioned supine during the procedure. CT scanning was performed by a 64-detector, multi-slice CT device (Aquillion 64, Toshiba, Tokyo, Japan). Fifty ml of Lohexal 75% contrast material (Omnipaque 300; Amsterdam Health, Cork, Ireland) was injected intravenously through the median cubital vein via an injector (2-ml/sec), under strict observation. CT protocol: 64x0.5 mm collimation, 0.5 seconds rotation time, 3.5 cm/sec table movement at gantry rotation, 225 mA, and 120 kV. Volumetric acquisition with a 0.5 mm interval slice thickness was performed with coverage starting at the skull base, down to the level of the aortic arch. Interpretation: the volume images on the workstation (Dell Base-unit, program; Vitrea) from the soft tissue and bone windows on axial slices were interpreted by two radiologists independently and blindly about the diagnoses. All the anatomical constituents of the larynx, mucosa, and surrounding soft tissue were evaluated. CT images for three cases are shown in figures 1-3.

Surgical procedure

After preoperative lab adjustment and preparation for blood transfusion, if required, preanesthetic preparation was ensured. Surgeries were performed under general total intravenous anesthesia. The surgical procedure was planned based on the predetermined TNM staging.

Pathological work-up

The excised specimens were fixed in 4% formaldehyde for 72 hours and decalcified by De-cal-Histol. Decalcif agent for two weeks. Axial whole organ slices were cut at a thickness of 1 to 3 mm, and at least one slice for each level was prepared and hematoxylin/eosin stained to determine the pathological diagnosis and staging.

Study outpoints

The study outcome was the performance of the CT scanning for the final diagnosis compared to the pathological findings on examination of the excised specimens as a gold standard comparative item.

Statistical analysis

The extent of agreement between the interpretations of the MDCT imaging and the findings of the histopathological examination of the excised specimens was measured by the Cohen's Kappa (ƙ) coefficient, along with 95% confidence intervals (CI) and was used to measure agreement between CT and pathological findings; where ƙ-value ranging between slight (ƙ coefficient = 0–0.20) to perfect (ƙ value=0.81 –1). The diagnostic performance characteristics of the MDCT for LSCC staging were calculated. Data descriptions were shown as numbers and percentages. Statistical analysis was done using SPSS, Version 25 (Armonk, NY: IBM Corp; 2017). P<0.05 indicated significance.

Case presentation

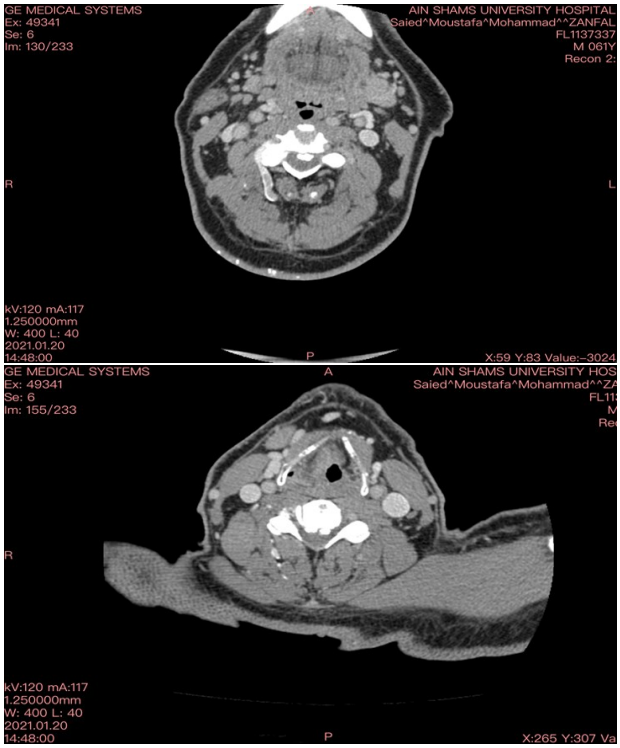

Figure 1. Case 1: A 53-year-old male presented with hoarseness of voice, cough, and difficulty in swallowing. CT scan showed thyroid cartilage invasion, involvement of the aryepiglottic fold with extra-laryngeal spread.

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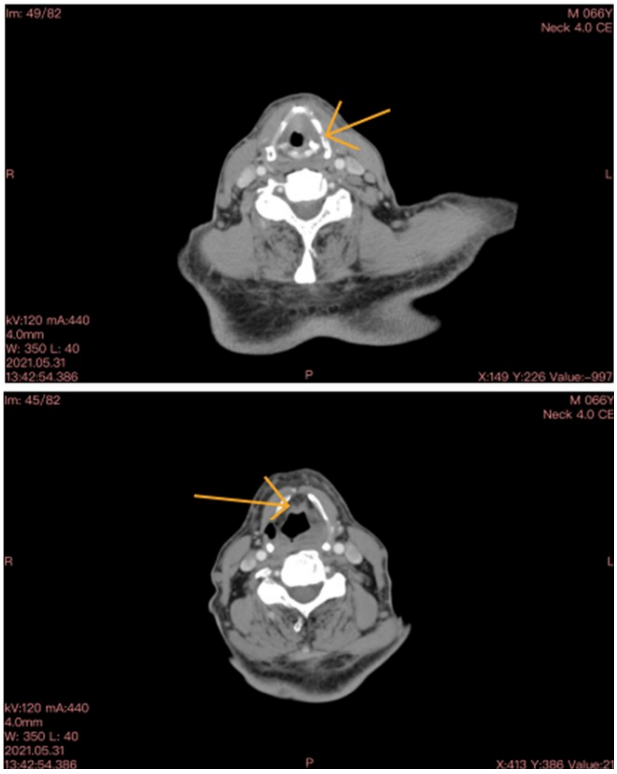

Figure 2. Case 2: A 65-year-old male patient presented with hoarseness of voice, cough, and neck pain that occurred occasionally. CT showed involvement of the anterior commissure and thyroid cartilage invasion.

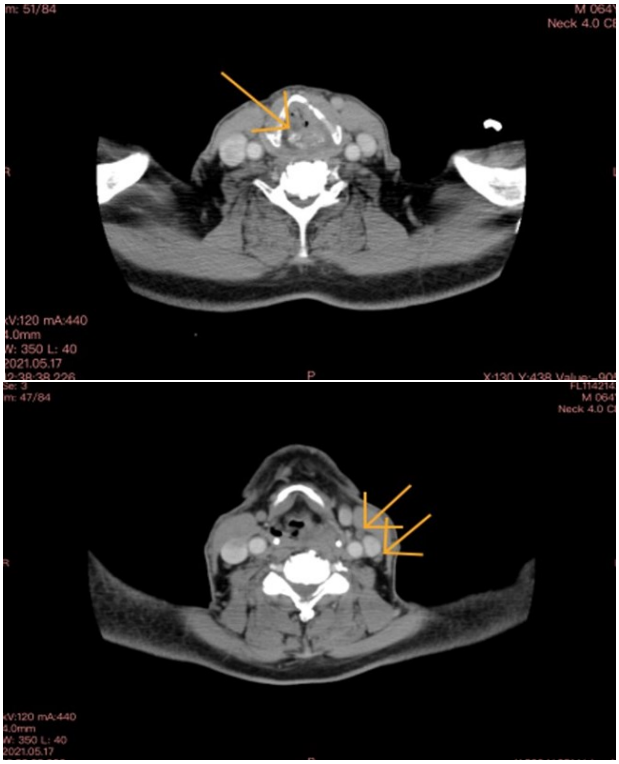

Figure 3. Case 3: A 64-year-old male patient presented with voice hoarseness, neck pain, and swelling. CT showed definite cartilage invasion; however, it was confirmed that the lymph nodes were involved.

RESULTS

During the initial patients' evaluation, 5 patients were excluded for being unfit for surgery; three because of uncontrolled medical disorders, and two had an advanced LSCC. After MDCT imaging, two patients did not attend for surgical intervention and were also excluded from the study (figure 4).

Thirty male patients underwent the study protocol. Their mean age was 57.6 (±13) years, and the age range was 34-81 years. The mean body mass index (BMI) was 29.3 (±2.3), and the range was 24.8 to 34.4 kg/m^2. Twelve patients (40%) were obese, 10 patients were overweight, 6 (20%) were average weight, and two patients were underweighted. Twenty-one patients (70%) were current smokers, and five patients (16.7%) were ex-smokers, while only four patients had never smoked previously. The major presenting symptoms were hoarseness of voice and persistent cough, reported in 22 patients (73.3%). Ten patients presented with sore throat and/or difficulty swallowing, and occasional pain was the complaint of 5 patients (13.3%). The total presenting symptoms were 37 for 1.2 complaints per patient (table 1).

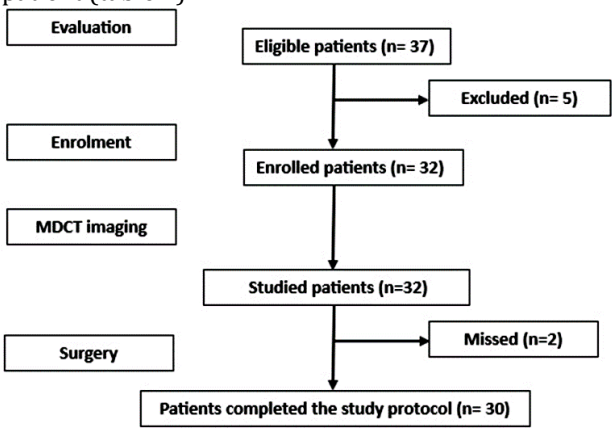

Figure 4. The study flowchart.

Table 1. The enrollment data.

Data		Findings
Age (years)		**57.6±13 (34-81)**
Body mass index (kg/m^2)	Underweight	2 (6.7%)
	Average weight	6 (20%)
	Overweight	10 (33.%)
	Obesity grade I	7 (23.3%)
	Obesity grade II	5 (16.7%)
	Average	29.3±2.3 (24.8-34.4)
Smokers	Non	4 (13.3%)
	Current	21 (70%)
	Ex	5 (16.7%)
Presenting symptoms	Hoarseness of voice	13 (43.3%)
	persistent cough	9 (30%)
	sore throat	6 (20%)
	Difficult swallowing	4 (13.3%)
	occasional pain	5 (16.7%)

Endoscopic examination detected a vocal cord nodule in 13 patients (43.3%), a cauliflower mass in 6 patients (20%), an abnormal mucosal band was the finding in five patients (16.7%), and 6 patients (20%)

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had either an ulcerative lesion or excessive exudate. Fourteen lesions (46.7%) were supraglottic, thirteen lesions (43.3%) were glottic, and three lesions (10%) were subglottic. Eleven lesions (36.7%) were left epicenter, thirteen lesions (43.3%) were right epicenter, and 6 lesions (20%) were central epicenter (table 2).

Table 2. The endoscopic findings of the enrolled patients.

Data		Number	Percentage
Type of lesion	Vocal cold nodule	13	43.3
	Cauliflower mass	6	20
	Abnormal mucosal band	5	16.7
	Exudate	3	10
	Ulcer	3	10
Site of lesion	Supraglottic	14	46.7
	Glottic	13	43.3
	Subglottic	3	10
Lesion epicenter	Left	11	36.7
	Right	13	43.3
	Central	6	20

The evaluation of diagnostic agreement between the interpretations of the MDCT images and the results of histopathological examinations across the various anatomical subsites in LSCC patients defined good agreement (Kappa = 0.500) for cartilage invasion, excellent agreement (Kappa = 0.718) for lesions in the anterior commissure, and almost perfect agreement (Kappa = 0.831) for extra-laryngeal space invasion. Excellent agreement was observed for the remaining laryngeal regions with Kappa values >0.9 (table 3).

Table 3. The agreement between the interpretations of MDCT findings and the results of pathologic examination across the different cancer sites.

Lesion site	Modality	CT		Patho-logical		Kappa agreement (95% CI)	P-value	sig
	Result	No	%	No	%			
Subglottic	Negative	21	70	20	66.7	0.923 (0.775-1.000)	0.001	HS
	Positive	9	30	10	33.3			
Paraglottic	Negative	12	40	11	36.7	0.930 (0.794-1.000)	0.001	HS
	Positive	18	60	19	63.3			
Preepiglottic space	Negative	20	66.7	21	70	0.923 (0.775-1.000)	0.001	HS
	Positive	10	33.3	9	30			
Aryepiglottic fold	Negative	23	76.7	24	80	0.902 (0.714-1.000)	0.001	HS
	Positive	7	23.3	6	20			
Vocal Cords	Negative	7	23.3	6	20	0.902 (0.714-1.000)	0.001	HS
	Positive	23	76.7	24	80			
Anterior Commissure	Negative	21	70	17	56.7	0.718 (0.472-0.965)	0.001	HS
	Positive	9	30	13	43.3			
Cartilage invasion	Negative	20	66.7	12	40	0.500 (0.243-0.757)	0.001	HS
	Positive	10	33.3	18	60			
Extralaryngeal space invasion	Negative	23	76.67	21	70	0.831 (0.607- 1.000)	0.001	HS
	Positive	7	23.3	9	30			

In terms of tumor staging, CT showed correct staging in 22 cases (73.3%), while overstating 5 cases (16.7%), and understating 3 cases (10%). This resulted in a good agreement between CT and pathology classifications (Kappa = 0.557) as shown in table 4.

Overall, CT shows excellent diagnostic utility, with accuracy rates ranging from 73.3% to 96.7%. The subglottic, paraglottic, preepiglottic, aryepiglottic folds, and vocal cords regions all show high sensitivity (≥90%) and perfect specificity (100%), with overall accuracy (96.7%). The anterior commissure has a lower sensitivity (69.2%), and perfect specificity (100%) with a reduced accuracy of 86.7%. Cartilage invasion shows the lowest sensitivity (55.6%), although perfect specificity (100%) with an overall accuracy equal 73.3%. In contrast, extralaryngeal invasion demonstrates good sensitivity (77.8%) and perfect specificity, with a high accuracy of 93.3% (table 5).

Table 4. The agreement between the MDCT staging and the pathologic staging.

	Pathological staging						Kappa Agreement (95% CI)	P-value	sig
	Stage 1		Stage 2		Stage 3				
CT staging	No.	%	No.	%	No.	%			
Stage 1	2	50	0	0	0	0	0.557 (0.284 - 0.831)	0.0001	HS
Stage 2	2	50	14	82.4	3	33.3			
Stage 3	0	0	3	17.6	6	66.7			

Table 5. The diagnostic performance of CT findings compared to Pathological findings based on the lesion's site.

Site Parameter	Sensitivity	Specificity	PPV	NPV	Accuracy
Subglottic	90%	100%	100%	95.2%	96.7%
Paraglottic	94.7%	100%	100%	91.7%	96.7%
Preepiglottic space	100%	95.2%	90%	100%	96.7%
Aryepiglottic fold	100%	95.8%	85.7%	100%	96.7%
Vocal Cords	95.8%	100%	100%	85.7%	96.7%
Anterior Commissure	69.2%	100%	100%	81%	86.7%
Cartilage invasion	55.6%	100%	100%	60%	73.3%
Extralaryngeal space invasion	77.8%	100%	100%	91.3%	93.3%

DISCUSSION

The obtained results confirmed the study endpoint, and CT imaging showed excellent diagnostic performance in identifying LC, with accurate staging ranging from 73.3% to 96.7% across different anatomical sites in the larynx.

The detected performance of CT for the detection and staging of LC align with Pietragalla *et al.* [9] who documented substantial (67.5%) to perfect (100%) diagnostic performance of CT for primary LC of arytenoid and cricoid cartilage invasion, respectively with good identification of cancer in thyroid in general, and accurate prediction of extra-laryngeal soft-tissue extra-laryngeal tissues without difference between primary and recurrent lesions.

Zhang *et al.* [10] suggested that laryngeal high-resolution CT and bone density testing of the arytenoid cartilage may be an essential diagnostic and prognostic modality for evaluating patients with laryngeal contact granuloma, based on detecting a greater risk of granuloma size and recurrence. Ferrari *et al.* [11] compared the coordination of clinical assessment of the vocal cord-arytenoid unit on video laryngoscopy and radiologic analysis of posterior laryngeal extension in CT imaging studies, and found

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that radiologic assessment of vocal cord-arytenoid unit mobility and posterior extension of LSCC was characterized by very high intra-rater agreement.

Dizdar *et al.* [12] documented that implementing a new quantitative measure for radiodensity during interpreting thyroid CT images significantly improved the CT determining ability for involvement of the pre-epiglottic space, with a good agreement coefficient with a ƙ value of 59.5%. Montenegro *et al.* [13] retrospectively analyzed preoperative CT of patients who had total laryngectomy for advanced LSCC to quantify the volume of cartilage infiltration, as a prognosticator for disease-free survival intervals, and reported an inverse relation between higher volume of infiltration and these intervals

Hernandez *et al.* [14] found cricoid cartilage (CC) involvement by either erosion or invasion and evidence of involvement of the thyroid gland (TG) on CT scan indicated such involvement during the histopathological examination of the excised LSCC specimen, and indicated thyroidectomy to ensure good margins of resection. Ganesan *et al.* [15] also detected individual likelihood ratios of 2.58 and 3.23 for CC erosion and TG involvement in CT scans, with reasonable agreement with histopathological findings, and defining both findings in CT scans resulted in an 8.23 likelihood with a fair agreement with histopathological findings. Ganesan *et al.* [15] based on their results concluded that preoperative detection of CC erosion with TG involvement in a CT scan might be considered as a preoperative indicator favoring a decision for thyroidectomy. Recently, Xie *et al.* [16] constructed a new predictor for invasion of TG by invading LC in the lower part of thyroid cartilage based on preoperative combined imaging by CT and MRI, and found this predictor exhibited sensitivity and NPP of 88.2 and 95%, respectively, and advice its application for patients with laryngeal cartilage cancer, especially in its lower third cancer to detect invasion of thyroid gland to spare routine thyroidectomy during total laryngectomy.

Ling *et al.* [17] tried defining the preoperative indicator for the oncological outcomes of selective partial laryngectomy on preoperative CT imaging and documented that for patients with T3 glottic LSCC, detection of posterior invasion and subglottic extension in preoperative CT imaging are independent indicators for recurrence after partial laryngectomy. Further, detection of inclusion of the dorsal plate of CC is associated with laryngeal stenosis after surgery. Ling *et al.* [17] concluded that selected partial laryngectomy can allow better oncological outcomes, but the invasion pattern of LC on preoperative CT may aid in the selection of a more individualized treatment strategy.

However, Hintze *et al.* [18] documented that salvage surgery is a predictor of poor outcome, while margin status insignificantly impacts survival or recurrence. Rocha *et al.* [19] documented the efficacy of the horizontal partial laryngectomy for patients with pT2 and pT3, and allowed adequate rates of local control and overall survival, with resumption of oral feeding in 89% of patients, and 86.4% were recurrence-free, and 83.7% survived disease-free.

CONCLUSION

Preoperative MDCT scanning for LSCC patients might accurately detect and stage lesions across the laryngeal regions. MDCT imaging could detect extra-laryngeal space invasion with perfect agreement with pathological staging.

***Limitations*:** The study's limitations included the studies number of patients was small and comparisons versus other diagnostic utilities is missing.

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***Ethical considerations*:** The Ethical Committee at the Faculty of Medicine, Ain Shams University, approved the study protocol with the number: FWA 000017585.

***Author contribution*:** All authors were involved equally in all aspects of research and read and approved final version of manuscript for submission.

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