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ORJİNAL MAKALE / ORIGINAL ARTICLE

Laryngeal Cancer: Radiological Staging by Multislice Computed Tomography and Pathological Correlation

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ABSTRACT: To evaluate the accuracy of multislice computed tomography (MSCT) in staging of laryngeal cancer and comparison with histopathological findings. Twenty- eight patients diagnosed with laryngeal cancer and underwent surgical treatment were staged according to radiological and histopathological examination. The diagnostic accuracy of computed tomography (CT) for detecting cartilage involvement was as follows: sensitivity, 89 %; specificity, 80%. For detection of preepiglottic and paraglottic space invasion, MSCT has a sensitivity; 100% and 100 %, respectively, and a specificity; 55 % and 63%, respectively. Sensitivities and specifities of CT assessment for supraglottic mucosa, glottic mucosa and subglottic mucosa were 100 %, 100 % and 100 % respectively, 83 %, 85 % and 86 %, respectively. The high sensitivity value (100%) for the evaluation of the vocal cords may due to the images obtained during phonation. MSCT is a good, non-invasive imaging modality in staging of laryngeal cancer. The present study showed that CT was highly sensitive, but with relatively low specificity due to an increase in false positive values. The images obtained during phonation should be added to the neck CT protocol of the larynx cancer patients for improved evaluation of the glottic region, in particular.
KEYWORDS: laryngeal cancer, staging, multislice computed tomography

LARINGEAL KANSER: MULTIDEDEKTÖR BILGISAYARLI TOMOGRAFI ILE RADYOLOJIK EVRELEME VE PATOLOJIK KORELASYON

ÖZET: Multidedektörlü bilgisayarlı tomografinin (MDBT) laringeal kanser evrelemesinde doğruluğunu değerlendirmek ve histopatolojik bulgularla kıyaslamak. Laringeal kanser tanısı alan ve cerrahi tedavi uygulanan 28 hasta radyolojik ve histopatolojik inceleme sonuçlarına göre evrelendi. Bilgisayarlı tomografinin (BT) kartilaj tutulumunu saptamada tanısal doğruluğunun sensitivitesi 89%; spesifitesi, 80%'dir. Preepiglottik ve paraglottik boşluk invazyonunun saptanmasında, MDBT'nin sırayla sensitivitesi 100%, 100%; spesitivitesi sırayla 55% ve 63% bulunmuştur. Supraglottik mukoza, glottik mukoza ve subglottik mukoza tutulumunun değerlendirilmesinde BT'nin sensitivite ve spesifite değerleri sırayla 100%,100% ve 100%, 83%,85% ve %86 idi. Vokal kordların değerlendirilmesindeki yüksek sensitivite değerleri 100%) fonasyon sırasında elde edilen imajlardan kaynaklanabilir. MDBT laringeal kanser evrelemesinde güvenilir ve non-invaziv bir görüntüleme metodudur. Çalışmamız gösterdi ki BT yüksek sensitivite değerlerine sahiptir. Ancak yalancı pozitif sonuçlardan dolayı nispeten düşük spesifite değerleri mevcuttur. Fonasyon sırasında elde olunan görüntüler, larinks kanserli hastalarda glottik bölgenin daha iyi değerlendirilmesi için boyun BT protokollerine eklenmelidir.
ANAHTAR KELIMELER: laringeal kanser, evreleme, multiddektörlü bilgisayarlı tomografi

1. Introduction

The accurate staging of laryngeal cancer has been the most critical factor guiding treatment decisions in patients with laryngeal cancer (1-3). For example, patients with early-stage (stage I,II) cancers can be treated with laser excision or primary radiation whereas patients with more-advanced cancers (stage III, IV) have been treated with total laryngectomy with or without adjuvant radiotherapy (2).

Clinical examination (including endoscopy and biopsy) of the larynx is most accurate in evaluating the superficial spread of neoplasm. However, pathologic involvement of the deep spaces of the larynx is greatly underestimated by the clinical examination. Imaging conversely cannot sufficiently assess to detect superficial mucosal disease and tends to overestimate the deep extent of tumor. The combination of information from cross-sectional imaging when taken together with information gleaned from clinical examination provides the most accurate pretreatment staging of laryngeal cancer (3-5).

We conducted this study to determine the diagnostic accuracy of MSCT to pathological findings in staging of laryngeal cancer with the focus on subanatomical regions infiltration.

2. Materials and Methods

Patients

Between March 2009 and November 2010, a total of 73 patients with histologically proven laryngeal cancer, established by endoscopy and biopsy were studied prospectively. Informed consent was obtained from all patients. The study was approved by local ethic committee. Each patient underwent preoperative staging with MSCT at our radiology department.Cases with a history of larynx surgery, a history of previous chemotherapy or radiotherapy were not included into the study. Fourty-five patients who refused surgery or whose primary treatment decision was radiotherapy were excluded from the study. Finally, 28 patients were enrolled into the study.

For tumor staging, the TNM classification developed by American Joint Committee of Cancer in 2009 was used (6). T1 tumor is with tumor limited to one subsite of supraglottic or vocal cord or subglottic. When tumor is located to glottic and limited to one vocal cord it is staged as T1a. When tumor involves both vocal cords, it is staged as T1b. A tumor is staged T2 when supraglottic tumor invades mucosa of more than one adjacent subsite of supraglottic or region outside the supraglottic. The cases of glottic tumor extending to supraglottic and/or subglottic or subglottic tumor extending to vocal cords are also staged T2. T3 is staged tumor limited to larynx with vocal cord fixation. Invasion of tissue beyond the larynx is staged as T4. Tumor invading through the outer cortex invasion is classified as T4, whereas inner cortex invasion with intact outer cortex is classified as T3. Neoplastic infiltration of arytenoid does not effect the staging.

Clinical examination

Preoperative clinical examination comprised physical examination, flexible endoscopic examination and direct laryngoscopic examination. Flexible endoscopic and direct laryngoscopies were performed by an experienced head and neck surgeon.

CT imaging and histopathological analysis

All patients underwent CT scanning performed using a 64 detector, multi-interval CT device (Aquillion 64, Toshiba, Tokyo, Japan) at 64x0.5 mm collimation, 0.5 seconds rotation time, 3.5 cm/sec table movement at gantry rotation, 225 mA (adjusted by the automatic exposure control system according to individuals) and 120 kV. Contrast material injection was performed automatically with the CT injector (Ulrich Missouri CT injection system). Injection was performed from the veins of the frontal arms, with a total of 75 ml in two phases at a rate of 2ml/sec, under the supervision of a physician. 75% iohexal was used as contrast material for all patients (Omnipaque 300; Amsterdam Health, Cork, Ireland). In the first phase, 40 ml of contrast material was injected, and approximately 90 sec later, a second phase of 35 ml was further injected. In this way, optimum contrast for both soft tissues and vascular structures was achieved. Scanning with a 0.5mm interval slice thickness was performed at the skull base, up to the level of the arcus aorta. Following awaiting period of approximately 9 sec, scanning was performed during phonation

by patients (making the "e" sound) to better visualize the level of the vocal cords, from the hyoid bone to the lower level of the cricoid cartilage so as to also include the level of the larynx. This scan was also performed with 0.5mm interval slice thickness. Radiological assessments were performed 2 experienced radiologists who are blinded to the endoscopic and laryngoscopy findings, and they performed initially standard and phonation evaluations on the axial plane. Then, these examined multiplanar reconstruction images on 3 planes, and a consensus decision was reached for each case. All evaluations were performed on volume images (Vital Images) on the work station (HP XW8200 base unit, program vitrea). Images were evaluated from the soft tissue window and the bone window. Paraglottic space, and preepiglottic spaces, supraglottic mucosa, aryepiglottic fold, anterior commissure, glottic and subglottic mucosa, prelaryngeal tissue and cartilages (thyroid, cricoid, and arytenoid cartilages) were evaluated for tumor invasion.

The patients went on to surgery within maximum 3 weeks. The final T assignments were based on histopathological interpretations of surgical specimens.

Statistical Analysis

Statistical analyses were performed by the NCSS 2007 package program. The evaluation of the data was performed with descriptive statistical methods (mean, standard deviation, frequency distribution, percentage distribution). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and test likelihood ration (LR) were calculated to assess the accuracy of CT scans by comparing with results of histopathology. Agreements between the perceived preoperative findings of LC as determined by clinical/endoscopic examination and CT imaging, and the postoperative histopathological assessment were determined using the Kappa weighted test (κw). For all tests, p value was considered to indicate a statistically significant difference.

3. Results

There were 27 males and 1 females with a mean age 59.57 (range; 36-77). There were 13 supraglottic, 4 glottic, 5 glotto-subglottic, 6 transglottic tumors. Sixteen patients underwent total laryngectomy, 9 patients underwent supraglottic laryngectomy, 3 patients underwent frontolateral laryngectomy.

Details of sensitivity, specificity, positive predictive value, and negative predictive value for CT assessment in involvement of subanatomical areas are listed in Table 1. Assessment of cartilage invasion

Neoplastic invasion was present in 10 of 28 thyroid cartilages and CT diagnosed all those invasion correctly. The cricoid cartilage was invaded in 6 out of 16 cricoid cartilage. 3 out of 41 arytenoid cartilage, neoplastic invasion was found. Statistical results in CT assessment for thyroid, cricoid and arytenoid cartilage were as follows: False negative results were detected in 0, 2 and 0 cartilage, respectively. False positive results were detected in 1, 2, 10 cartilage, respectively "(Figure 1)".

Sensitivities were 100 %, 67 % and 100 % respectively. Specificities were 94 %, 80 % and 74 % respectively. PPVs were 91 %, 67 % and 23 % respectively. NPVs were 100 %, 75 % and 100 % respectively. Neoplastic invasion was present at 19 of 85 cartilages. The diagnostic accuracy of CT for detecting cartilage invasion was as follows: sensitivity, 89 %; specificity, 80%; PPV, 57%; and NPV, 96%.

Assessment of preepiglottic space

Preepiglottic space was assessed, except in 3 cases in whom tissue sampling could not be performed due to frontolateral laryngectomy. CT showed the presence of preepiglottic space invasion with a sensitivity of 100 %, a specificity of 55%, a PPV of 74 %, a NPV of 100 %, accuracy 80 % "(Figure 2)".

Tablo 1

The comparison between radiological and pathologic involvement of subanatomical areas and the diagnostic value of CT in detecting involvement of the tumor

	Pathological involvement (+) (n)	Radiological Involvement (+) (n)	Pathological involvement (-) (n)	Radiological involvement (-) (n)	Diagnostic value of CT						
					Sensitivity	Specificity	PPV	NPV	Accuracy	LR(+)	LR(-)
Thyroid cartilage	10	11	18	17	1.00	0.94	0.91	1.00	0.96	18	0.00
Cricoid cartilage	6	6	10	10	0.67	0.80	0.67	0.80	0.75	3.33	0.42
Arytenoid cartilage	3	13	38	28	1.00	0.74	0.23	1.00	0.76	3.80	0.00
Preepiglottic space	14	19	11	6	1.00	0.55	0.74	1.00	0.80	2.20	0.00
Paraglottic space	19	22	8	5	1.00	0.63	0.86	1.00	0.89	2.67	0.00
Supraglottic mucosa	19	20	6	5	1.00	0.83	0.95	1.00	0.96	6.00	0.00
Glottic mucosa	23	28	33	28	1.00	0.85	0.82	1.00	0.91	6.60	0.00
Subglottic mucosa	14	12	3	5	0.86	1.00	1.00	0.60	0.88	-	0.14
Arvepiglottic folds	27	29	23	21	0.96	0.87	0.90	0.95	0.92	7.38	0.04
Anterior commissure	13	14	9	8	0.92	0.78	0.86	0.88	0.86	4.15	0.10
Prelaryngeal tissue	9	9	7	7	0,89	0,89	0,89	0,89	0,94	8,09	0,12

* Number (n), positive predictive value (PPV), negative predictive value (NPV), likelihood ration (LR)

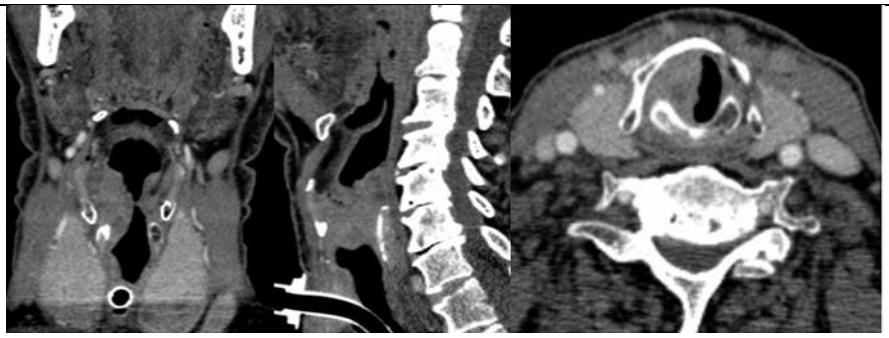

Figure 1. *a-c. 75 year old male patient, with transglottic lesion mass involving supraglottic region, the right vocal cord, the right paraglottic space and the anterior commissure, extending into the subglottic region. In MSCT images for contrast-enhanced soft tissue window coronal (a), sagittal (b), and axial (c) images. The coronal section shows paraglottic region invasion on the right side and normal paraglottic space on the left (a). The transglottic lesion mass is seen on sagittal image (b). The axial image passing subglottic region shows sclerosis on the right part of the cricoid cartilage which is pathologically normal and thickening of the subglottic mucosa (c).*

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Assessment of preepiglottic space

Preepiglottic space was assessed, except in 3 cases in whom tissue sampling could not be performed due to frontolateral laryngectomy. CT showed the presence of preepiglottic space invasion with a sensitivity of 100 %, a specificity of 55%, a PPV of 74 %, a NPV of 100 %, accuracy 80 % "(Figure 2)".

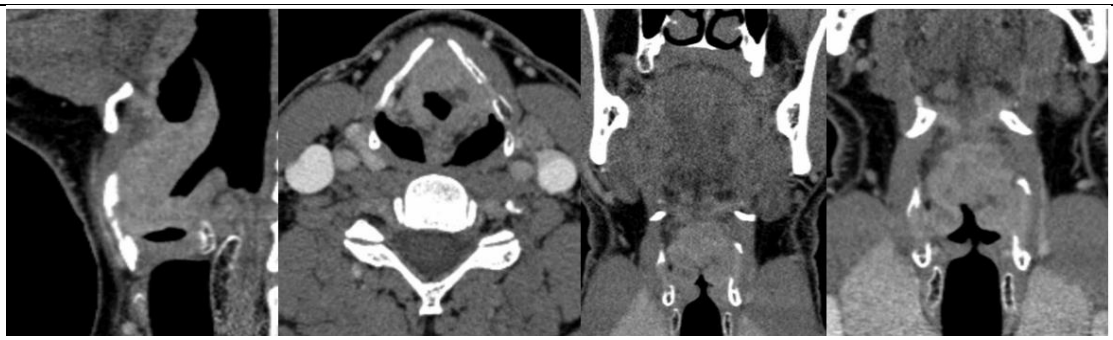

Figure 2. *a-d. 48 year old male patient, with lesion mass filling the preepiglottic space, and causing thickening at the epiglottic and aryepiglottic folds. Sagittal (a), axial (b), pre-phonation coronal (c), post-phonation coronal (d) contrast-enhanced soft tissue MSCT slices. Thickening at the epiglottis (a) and thickening of both aryepiglottic folds (b) are seen. While bilateral vocal cords might be interpreted as thick at pre-phonation image (c), after phonation, both ventricles and the vocal cords are observed as being normal (d). Preepiglottic space and aryepiglottic folds involvement was pathologically confirmed.*

Assessment of paraglottic space

Paraglottic space was not evaluated in one patient in whom tissue sampling could not be performed due to frontolateral laryngectomy. CT in evaluation of paraglottic space invasion showed a sensitivity of 100 %, a specificity of 63 %, a PPV of 86 %, and a NPV of 100 %, a accuracy of 89 %.

Assessment of supraglottic mucosal invasion

CT showed the presence of supraglottic mucosal invasion with a sensitivity of 100 % and a specificity of 83 %. PPV for CT was 95 % and the NPV was 100 %.

Assessment of aryepiglottic fold invasion

Fifty aryepiglottic fold invasion was evaluated in 25 patients. Three patients who underwent frontolateral laryngectomy were not evaluated for aryepiglottic fold invasion. CT was found to be 96 % sensitive, 87 % specific and 92 % accurate for aryepiglottic fold involvement while PPV and NPV were 90 % and 95 % respectively.

Assessment of anterior commissure invasion

Anterior commissure invasion on CT had a sensitivity and specificity of 92 % and 78 %, respectively. PPV was 86 %, while NPV was 88 %.

Assessment of glottic mucosal invasion

Fifty-six glottic mucosa were evaluated for invasion by CT. The diagnostic accuracy of CT for detecting glottic mucosal invasion was as follows: sensitivity, 100 %; specificity, 85 %; PPV value, 82 %; NPV, 100 %; accuracy of 91 %.

Assessment of subglottic involvement

Subglottic area was evaluated in 17 patients (16 patients underwent total laryngectomy and one patient was performed subglottic biopsy during frontolateral laryngectomy). CT showed the presence of subglottic mucosal invasion with a sensitivity of 86 %, a specificity of 100 %, a PPV of 100 %, a NPV of 60 %, accuracy 88 %.

Assessment of staging of tumor infiltration

Histopathological examination of the surgical specimens revealed 2 patients (7.1 %) with T 1a, 3 (10.7 %) with T 2, 14 (50 %) with T3 and 9 (32.2 %) with T4a. When compared with pathologic stage, clinical/endoscopic classification was correct in 4 (14%). Twenty-four cases were underestimated by clinical/endoscopic evaluation. The agreement between clinical/endoscopic stage and histopathological stage was fair ($\kappa w = 0.06$).

The T stage was correctly determined by CT scan in 23 (82 1%) of cases. The agreement between perceived T stage by CT and histopathological analysis was good ($\kappa w = 0.773$). Overestimation of CT was present in

4 (14.2 %) (2T4a, 2T3) of cases and underestimation in 1 (3 %) (1T1).

Table 2 shows clinical/endoscopic, radiological and pathological T stage. Table 3 shows comparison of pathological stage and clinical/endoscopic and radiological stage

Table 2

T stages by clinical/endoscopic radiological and pathological examinations

T Stages of the tumor	Clinical/endoscopic Examination n (%)	Radiological Examination n(%)	Pathological examination n(%)
T1	4 (14.3)	-	-
For glottic cancers - T1a	4 (14.3)	3 (10.7)	2 (7.1)
T2	18 (64.3)	-	3 (10.7)
T3	2 (7.1)	14 (50)	14 (50.0)
T4a	-	11 (39.3)	9 (32.2)

Table 3

The relationship and concordance between pathologic staging and staging created by physical, clinico-radiologic and intraoperative examination

		Pathologic staging			
		T1 (n)	T2 (n)	T3 (n)	T4a (n)
Staging by	T1 (n)	2	2	3	1
clinical/endoscopic	T2 (n)	-	1	10	7
physical	T3 (n)	-	-	1	1
examination	T4 (n)	-	-	-	-
	T1a (n)	2	1	-	-
	T2 (n)	-	-	-	-
CT staging	T3 (n)	-	2	12	-
	T4 (n)				
	T4a (n)	-	-	2	9

4. Discussion

The proper staging of laryngeal cancer requires accurate information about the invasion of the primary tumor to subanatomical areas of larynx and cartilages. The usefulness of CT in the pretherapeutic staging of laryngeal cancer was emphasized in many cases, however, a few studies focused on involvement of subanatomical areas of larynx. (2, 3, 7-11).

The radiological appearance of the laryngeal cartilage may change according to the degree of ossification or the amount of fatty bone marrow in the medullar region (12). Several studies in the literature descrıbe that especially in the presence of extralaryngeal spread of tumor, CT can also visualize gross cartilage invasion, and that it not successful in imaging minor cartilage invasion (13,14,15). In the literature sensitivity values of 46-67% and specificity values 87-91% were reported for CT visualization of cartilage retention (3,15,16). Generally the presence of tumor on both sides of the tyhroid cartilage in CT is the only criterion accepted for the verification of neoplastic cartilage invasion (14,17,18). However this findings is visible only in advanced stages of neoplastic invasion. For early identification of cartilage invasion some authors have suggested new criteria to increase the sensitivity of CT procedures. In his studies with 111 cases of larynx cancer, Becker et al. (7)described four CT criteria(extralaryngeal spread, sclerosis,erosion and lysis) with high sensitivity and specificity for the identification of neoplastic cartilage invasion. In our study cartilage invasion was identified in 10 out of 85 cartilages. In histopathologically proven 2 cases, CT was unsuccessful in showing cricoid cartilage invasion. In eleven case, on the other hand, there were false positives on the CT. At our study, to accept the positive involvement of cartilage, we use the criterias of

extralaryngeal spread, erosion, lysis and sclerosis. In our study based on 28 cases, we found a sensitivity of 89 % and a specificity of 80 %, positive predictive value, 57%; and negative predictive value, 96%.When compared to the studies in the literature our sensitivity values for cartilage invasion are high, while our specificity values were lower (3,15,16,19). In a study of 36 larynx carcinoma cases by Nix et al (20), the sensitivity and the specifity rates of CT in demonstrating isolated cartilage involvement were 62% and 42% , respectively. In our study, CT evaluation of the sclerotic cartilages that didn't have any evidence of histopathological tumoral involvement revealed that the tumors in these cases were advanced as far as just by the side of the cartilage, without demonstrating any signs of cartilage invasion however. Since the finding of isolated cartilage sclerosis on CT may actually be a result of an ongoing reactive inflammation, it is possible to assume that the false positive assessment rates would increase when isolated cartilage sclerosis is used as the sole criterion for the cartilage involvement.

Accurate assessment of preepiglottic and paraglottic is mandatory for a correct staging, supraglottic tumors progress into T3 tumors if the PES and/or PGS is involved (3). The significance of paraglottic space lies especially in the determination of extension and accurate stage of transglottic cancers, because transglottic cancers invading paraglottic space have a high incidence of laryngeal skeleton invasion and cervical metastasis. The significance of preepiglottic space also lies in determination of surgical margins of the base of the tongue and whether the hyoid bone must be resected or not which are required in the supracricoid surgeries(21). In the present study, sensitivity and specificity values for the diagnosis of the preepiglottic invasion were 100% and 55% respectively, and sensitivity and specificity values for the diagnosis of the paraglottic invasion were 100% and 63% respectively. When compared previous studies (3, 22), the reason of higher sensitivity rate in the present study may be because of the use of thin sections (0.5mm slice thickness) and the lower specificity values than results of the literature may be due to the inability of CT to distinguish reactive changes and inflammation from tumor invasion.

Tumor arising at the aryepiglottic fold may spread to the preepiglottic space, epiglottic and the upper edge of the thyroid cartilage (21).Thus, aryepiglottic fold plays indirectly an important role for tumor prognosis, and it must carefully evaluated pretreatment. In the present study, MSCT had high accuracy value (92%) for the evaluation of aryepiglottic folds, and our result was consistent with the literature (8,23).

In the present study, laryngeal mucosa was structured into three parts: supraglottic mucosa, glottic mucosa and subglottic mucosa. CT showed the presence of supraglottic mucosal involvement with a sensitivity of 100 % and a specificity of 83 %. The diagnostic accuracy of CT for detecting glottic mucosal involvement was as follows: sensitivity, 100 %; specificity, 85 %. The high sensitivity value for the evaluation of the vocal fold mucosa in our study may also be due to evaluation by combining the images obtained during breath-holding and phonation. The subglottic region and the anterior comissure may be hidden by bulky tumors and cannot be evaluated by endoscopy (3). The invasion of subglottic region has significant surgical implication; the patients having the cancer with subglottic invasion lost the chance of partial laryngectomy (3). Our result of CT assessment for the subglottic involvement is similar to the results described in the literature (3, 4, 11). Anterior commissure involvement on CT had a sensitivity and specificity of 92 % and 78 %, respectively in our study.

The limitation of clinical/endoscopic tumor evaluation to assess the exact tumor extension of LC is well recognized (3). In the present study, clinical/endoscopicevaluation failed in 24 of 28 case. All clinical/endoscopic staging errors occured from underestimation caused by a failure to clinically identify invasion of the paraglottic and preepiglottic space and laryngeal cartilaginous structures. Agada et al reported the accuracy of CT staging compared with pathologic specimens, demonstrating that 45% of patients were overstaged and 10% were understaged by CT (24). In our study, overestimation of stage was present in 14.2 % of cases and underestimation in 3 %. This

improvement may be attributable to current technology allowing thinner slice thickness.

The limitation of our study is the low number of patient included. Another limitation is related to the multıpl biopsies performed to evaluate the areas outside the surgical site in the cases of partial laryngectomy.

5. Conclusion

MSCT is a good, accurate and non-invasive imaging modality in staging of LC with high sensitivity rates. However, MSCT has relatively low specificity due to an increase in false positive values. The images obtained during phonation should be added to the neck CT protocol of the larynx cancer patients for improved evaluation of the glottic region, in particular.

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