Accuracy of the Anatomage Table in detecting extranodal extension in head and neck cancer: a pilot study

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Abstract

Purpose: To assess whether the three-dimensional reconstructions of preoperative computed tomography (CT) scans are helpful for establishing extranodal extension (ENE) in head and neck carcinoma.

Approach: Patients with a histological diagnosis of ENE (pENE+) were considered "cases" and patients with negative histological examination for ENE (pENE−) were considered "controls." Cases and controls were divided into two groups: a major nodes (MaN) group (lymph nodes on CT > 15 mm) and a minor nodes (MiN) group (lymph nodes on CT ≤ 15 mm). The preoperative CT scans were uploaded to the Anatomage Table and were randomly and blindly provided to the radiologist for assessment. The findings at the Anatomage Table were compared with those of CT and magnetic resonance imaging (MRI) scans.

Results: Analysis of data from the MaN group showed that the Anatomage Table had a higher percentage of concordance with histopathological examination (90%) than the CT and MRI scans. The Anatomage Table had 100% sensitivity in identifying all pENE+ patients, associated with a lower specificity. The negative predictive value of 100% allowed identification of pENE− patients. In the MiN group, on the other hand, sensitivity was lower, related to a high number of false-negative results.

Conclusions: The Anatomage Table could represent a useful tool for preoperatively establishing the extranodal extension of cervical lymph node metastasis.

1 Introduction

Nodal involvement is the most important prognostic factor in squamous cell carcinoma of the head and neck district. The clinical evaluation of lymph nodal stations of the neck allows classification of nodal status on a clinical basis, and this is a fundamental step to outline the therapeutic approach and the prognosis on patients with head and neck cancer.[1–3]

Extranodal extension (ENE) refers to the spread of a nodal metastasis beyond the lymph node capsule and correlates with the patient's prognosis.[4] The 2017 update of the tumor-nodes-

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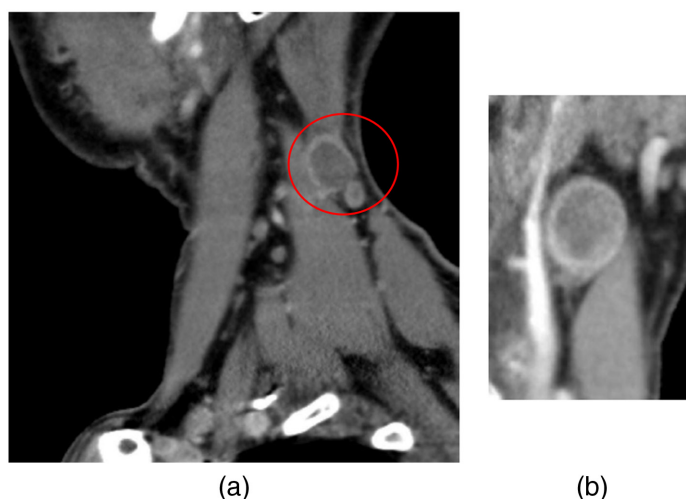(a)   (b)

Fig. 1 (a) CT image, sagittal view, of an ENE+ laterocervical lymph node. (b) CT selected image of an ENE− laterocervical lymph node.

metastases classification introduced ENE as a variable for classifying lymph nodal metastases, with a finding of ENE (ENE+) directly increasing the N stage to stage 3b.[5] Exceptions are human papilloma virus (HPV)-positive oropharyngeal neoplasms, in which the presence of ENE (ENE+) does not correlate directly with the prognosis.[6,7] Furthermore, ENE status influences the type of surgical nodal dissection (radical versus modified radical), and allows, in particular cases, the use of neoadjuvant chemotherapy or radio/chemotherapy as the first or only treatment.[8,9]

ENE+ status can be established on a clinical basis (cENE+) due to unequivocal data (signs of capsular encroachment such as skin invasion and nerve invasion) or during surgical dissection in cases showing evident spread of the nodal metastases to the surrounding tissues.[8] Given that most patients do not present clinical evidence of ENE+, the only way to assess ENE status before treatment is through the use of imaging techniques. However, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography are not sensitive enough to evaluate capsular involvement of the lymph nodes (Fig. 1), which explains why several authors discourage from developing treatments on the sole basis of the imaging findings.[10–12]

In the literature, three-dimensional (3D) post-processing of images of the head and neck district is controversial. In fact, although it has been shown to help radiologists provide additional views, with the exception of the larynx and hypopharynx, the technique is not routinely used.[13]

The 3D reconstructions of the head and neck district are not used routinely in tumor staging and no published study to date has investigated the application of 3D post-processing in the assessment of ENE.

The Anatomage Table Software (Anatomage, Inc., Santa Clara, California) allows 3D visualization of anatomy by performing reconstructions of images already preloaded mainly for educational purposes.[14] The system also allows the processing of data acquired by CT or MRI scans but, despite recent proposals to apply the technique to routine clinical practice, its clinical use is still not clearly described (Fig. 2).[15–17]

In view of the importance recently attributed to the ENE parameter and the difficulty in assessing it preoperatively, this study has been designed to assess whether the Anatomage Table could be a valid tool for the preoperative evaluation of ENE in clinical practice.

2 Materials and Methods

This study was conducted as a blind prospective study on a retrospective cohort and was designed with the aim of exploring the accuracy of the Anatomage Table in evaluating capsule integrity of metastatic lymph nodes in head and neck tumors. All the 66 selected patients were staged and subsequently treated as indicated by the most recent version of the National Comprehensive Cancer Network (NCCN) guidelines.[8]

Fig. 2 Anatomage Table 3D reconstructions. From left to right: bone window, vessels window, and muscles window

2.1 Inclusion Criteria

This study considered patients diagnosed with head and neck squamous cell carcinoma and treated in our department between 2012 and 2018. They were all subjected to neck dissection (ND), which showed the presence of extracapsular extension on pathological examination (pN + ENE+). As controls, we selected an equal number of patients, whose histopathological examination after ND showed metastatic nodal involvement without signs of extracapsular extension (pN + ENE−).

To be included in this study, patients from both groups had to undergo a preoperative contrast-enhanced CT scan evaluated by radiologists skilled in head and neck imaging.

The two groups were further divided into two subgroups based on the CT measurement of the long axis diameter of the lymph nodes, setting a cutoff value of 15 mm. These subgroups were named "major nodes" (MaN) (lymph nodes >15 mm on CT) and "minor nodes" (MiN) (lymph nodes ≤15 mm on CT). The chosen cutoff identifies the minimum CT size for a lymph node to be considered pathological, regardless of localization and other specific characteristics. Furthermore, according to the literature, the smaller a lymph node is, the lower the specificity of the CT is.[18]

2.2 Exclusion Criteria

All patients who had undergone previous radiotherapy or surgery of the neck were excluded. Patients whose 3D reconstructions were not performed accurately and those whose clinical data were not strictly objectifiable were also excluded.

2.3 Radiological Assessment

All patients included in the two groups were initially studied by CT at our hospital, and their scans were evaluated by radiologists experienced in head and neck imaging. The CT scans were performed with a Toshiba Aquilion scanner (model TSX-101A, 64 slices). The images were acquired after intravenous administration of 110 ml of iomeprol 350 mg/ml (Iomeron, Bracco Imaging Italia S.r.l.) followed by 20 ml of saline solution at a flow rate of 1.6 ml/s.

About 46 patients also underwent a contrast-enhanced MRI scan with a Philips Ingenia 1.5T scanner.

2.4 Anatomage Table

The Anatomage Table is a digital anatomy visualization platform which consists of two touch screens working with an Intel Core i7-4790 processor (3.60 GHz) with 32 GB RAM and
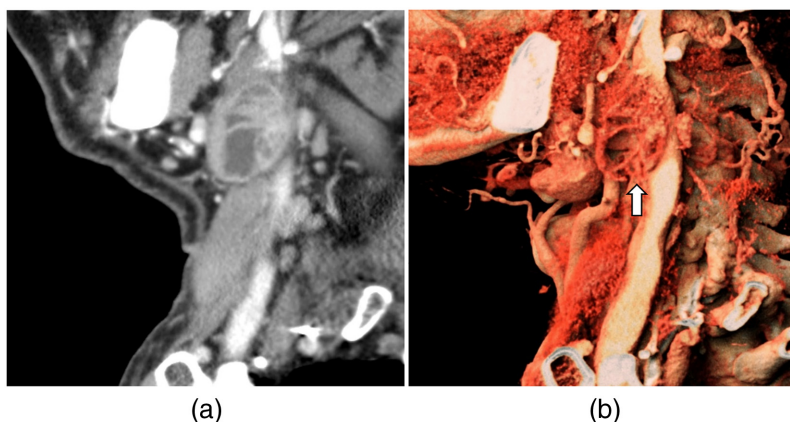
Fig. 3 (a) CT image, sagittal view of an ENE+ lymph node. Capsular interruption is not clearly visible. (b) 3D Anatomage Table Software reconstruction of CT images. The arrow shows the capsular interruption in the caudal pole of the lymph node.

NVIDIA GeForce RTX 2070 graphics card. The operating system is Windows 7 Professional, on which Table Educational runs, the software that allows 3D reconstruction, updated to version 6.0.3. The uniqueness of the software is that it allows interactive visualization of 3D anatomy with an operating/dissection table form factor, with a life-size touch screen permitting dissection of the 3D volume as precise as, or perhaps even more precise than, a true cadaver dissection can offer. The CT scans of the patients selected for the study were uploaded to the Anatomage Table, and 3D reconstructions were then performed for the contrast-enhanced CT scans of the head and neck district. (Fig. 3) The Anatomage Table is the only system displaying real, completely segmented, and 3D human anatomy. It enables users to view the anatomy exactly as they would on a real cadaver, through high-definition detailed 3D reconstructions of each structure with a level of accuracy and precision equal to the anatomy. The software is compatible with all medical imaging systems such as CT and MRI, it can be incorporated into picture archiving and communications systems and serve as a radiological review system for clinical and educational applications.

2.5 *Evaluation of 3D Reconstructions at the Anatomage Table*

All 3D reconstructions were randomly presented to the radiologist, who reviewed the reconstructions blinded to lymph node size and pENE status, and characteristics of patients, their clinical condition and their disease. The window/level combination was set for optimal visualization of muscle tissue, to allow the radiologist to analyse the capsule and the cleavage planes around the lymph nodes. The radiologist was asked to express a judgment as to whether or not capsular involvement was present (ENE+ or ENE−). The results obtained with the 3D reconstructions of the Anatomage Table were then compared with the CT, MRI, and histology reports to determine the accuracy of the Anatomage Table as a preoperative tool for analysis. The cost of the Anatomage Table and the time required for evaluation of each 3D reconstruction by the radiologist were also taken into account.

2.6 *N Parameter*

In a clinical context, the N parameter categorizes the status of lymph node involvement by a head and neck cancer. At our institution, we follow the NCCN guidelines, namely:[8]

1. Nx Regional lymph nodes cannot be assessed
2. N0 No regional lymph node metastasis
3. N1 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension ENE(−)
4. N2a Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension, and ENE(−)

5. N2b Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(−)

6. N2c Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(−)

7. N3a Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)

8. N3b: Metastasis in any node(s) and clinically overt ENE(+), except for HPV+ oropharyngeal cancers.

3 Results

A total of 66 patients (43 men and 23 women; average age, 64 years; age range, 47 to 88) were included in this study. The patients were divided into two groups based on the CT size of the lymph nodes: 50 patients had lymph nodes >15 mm (MaN group) and 16 patients had lymph nodes smaller than or equal to 15 mm (MiN group). Based on the clinical findings, all patients were ENE−. The patients' data are summarized in Table 1, whereas the main tumor characteristics and the lymph node status of these patients are summarized in Table 2.

3.1 MaN Group Results

The percentage of agreement between the imaging techniques utilized and the pathological analysis in the evaluation of capsular involvement was: Anatomage Table 90% (45/50), CT 58% (29/50), and MRI 52.94% (18/34).

As shown in Table 3, CT had a sensitivity of 33%, a specificity of 95%, a positive predictive value (PPV) of 91% and a negative predictive value (NPV) of 49% in detecting extracapsular extension in the MaN group.

The radiologist's evaluation of the Anatomage Table 3D reconstructions identified extracapsular invasion with a sensitivity of 100%, a specificity of 75%, a PPVof 86%, and an NPV of 100%. In particular, the Anatomage Table enabled detection of all 30 patients who were pENE+ (sensitivity 100%): among them, three patients were cN1, 18 were cN2, and 9 were cN3.

MRI, on the other hand, showed a sensitivity of 38%, a specificity of 77%, a PPV of 73% and an NPV of 43% in detecting extracapsular extension in the MaN group (Figs. 4–7).

3.2 MiN Group Results

The percentage of agreement between the imaging techniques utilized and pathological analysis in the evaluation of capsular involvement was: Anatomage Table 50% (8/16), CT 56.25% (9/16), and MRI 72.73% (8/11).

In the MiN group, capsular involvement of the lymph nodes was detected by CT with a sensitivity of 0%, a specificity of 100%, a non-determinable PPV, and an NPV of 56%. The Anatomage Table showed a sensitivity of 14%, a specificity of 78%, a PPV of 33% and an NPV of 54%. In particular, the Anatomage Table enabled identification of only one of the seven patients who were pENE+ (sensitivity 14%); this patient was found to be cN2.

Finally, MRI exhibited a sensitivity of 0%, a specificity of 100%, a non-determinable PPV and an NPV of 73%.

Table 1 Patient characteristics.

Patient characteristics					
Gender		Age		CT evaluation of lymph nodes	
Male	43	Average	64	MaN group	50
Female	23	Range	47 to 88	MiN group	16
Total number of patients enrolled: 66					

Table 2 Characteristics of the tumors and nodal status of the patients.

Tumor characteristics	
Element analyzed	Number of patients
Site of primary tumor	
Oral cavity	21
Pharynx	21
Larynx	10
Skin	4
Unknown (T0)	10
cT stage	
T0	10
T1-2	22
T3-4	34
pT stage	
T0	9
T1-2	18
T3-4	39
cN stage	
N0	5
N1	11
N2	41
N3	9
pN stage	
N0	0
N1	16
N2	19
N3	31

Abbreviations: cT: clinical stage of primary tumor; pT: pathological stage of primary tumor; cN: clinical stage of lymph nodes; pN: pathological stage of lymph nodes.

3.3 *Calculation of Likelihood Ratios*

Based on these results, we were able to calculate the positive (LR+) and negative (LR−) likelihood ratios. CT had a LR+ of 6.6 and a LR− of 0.53 for the MaN group. In the MiN group, on the other hand, CT showed a non-determinable LR+ value (derived from 0% sensitivity and 100% specificity) and a LR− of 1. The Anatomage Table had a LR+ of 4 and a LR− of 0 for the MaN group; the results in the MiN group, on the other hand, showed a LR+ of 0.64 and a LR− of 1.1. The likelihood ratios for MRI were different, with an LR+ of 1.65 and an LR− of 0.81 for the MaN group, and a non-determinable LR+ (derived from 0% sensitivity and 100% specificity) and an LR− of 1 for the MiN group.

Table 3 Accuracy of anatomage, CT and MRI in evaluating the presence of ENE.

	Anatomage (%)	CT (%)	MRI (%)
	Lymph nodes >15 mm		
SENS[a]	100	33	38
SPEC[b]	75	95	77
PPV[c]	86	91	73
NPV[d]	100	49	43
	Lymph nodes ≤ 15 mm		
SENS	14	0	0
SPEC	78	100	100
PPV	33	Non determinable	Non determinable
NPV	54	56	73

[a]sensitivity;
[b]specificity;
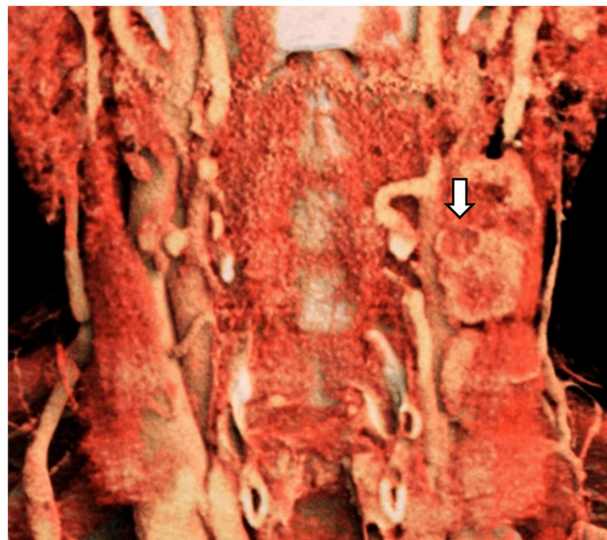[c]positive predictive value;
[d]negative predictive value.

Fig. 4 A 3D Anatomage Table Software reconstruction of CT images. The arrow shows the capsular interruption in the cranial pole of the lymph node.

4 Discussion

Nodal involvement is so closely correlated to patient prognosis that it represents the most important prognostic factor in squamous cell carcinoma of the head and neck region. Patients showing any evidence of ENE are classified as stage N3b, except for those with HPV-positive oropharyngeal neoplasms. The challenge is to establish capsular involvement before surgery, with a high degree of concordance with pathological analysis. Establishing capsular involvement before surgery would allow the physician to choose the best surgical approach (specifically radical ND versus modified radical ND) or to offer the possibility of chemotherapy or radiotherapy in particular cases. [8]
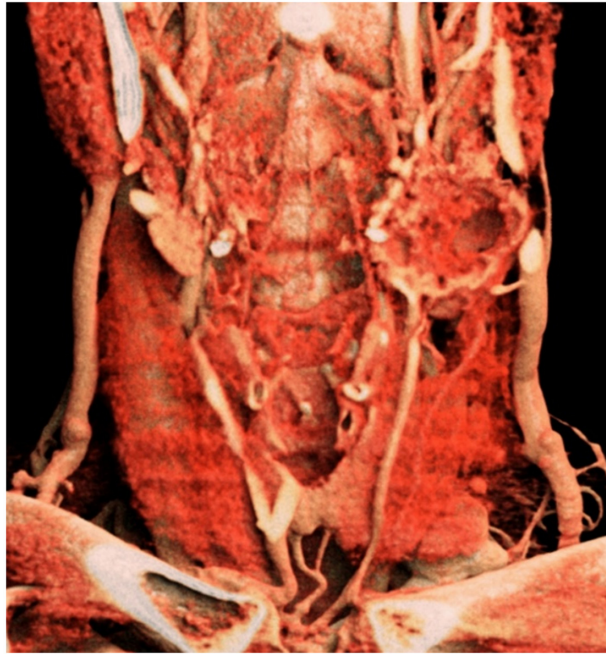
Fig. 5 A 3D Anatomage Table Software reconstruction of CT images. Multiple interruptions of the capsule can be noted.
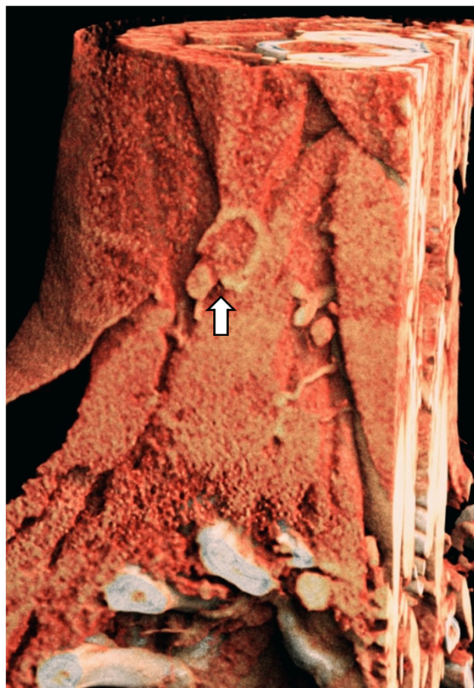

Fig. 6 A 3D Anatomage Table Software reconstruction of 2A CT images. The arrow shows the capsular interruption in the caudal pole of the lymph node.

Clinically, a painless cervical lymph node with increased volume must be viewed as a suspected metastasis.[12] The suspicious lymph node should be considered an expression of ENE+ when clear signs of capsular encroachment are present, such as skin and nerve invasion.

According to McMullen et al.,[19] the following criteria characterize the presence of a suspicious node on both CT and MRI: "(1) retropharyngeal nodes 0.8 cm or larger in the longest
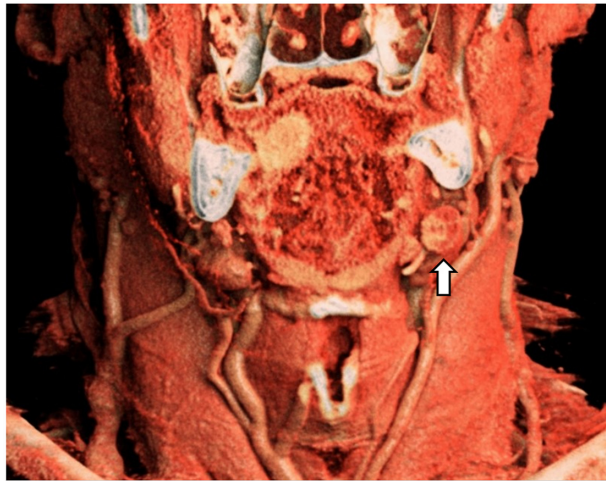
Fig. 7 A 3D Anatomage Table Software reconstruction of CT images. The arrow shows an ENE− lymph node. Integrity of the lymph node capsule can be observed.

dimension in the axial plane; (2) jugulodigastric chain and level 1b nodes 1.5 cm or larger; (3) nodes in all other levels 1 cm or larger; (4) nodes with cystic or necrotic components of any size; (5) nodes with a rounded rather than ovoid shape of any size; and (6) asymmetric clustering of nodes and loss of fatty hilum." Specifically, according to the literature, a lymph node is considered ENE+ in the case of poor definition of its boundaries (absence of peri-lymph node fat) and/or in the case of matted nodes (soft tissue invasion or distortion).[20,21]

With regard to imaging techniques, the literature establishes that the absence of a perinodal fat plane on CT provides the highest sensitivity for detecting ENE+.[20] For MRI analysis, the morphological information from T2-weighted imaging and the functional data from diffusion tensor imaging should be interpreted together to assess the presence of ENE more successfully.[22] Ultrasonographic analysis of ENE+, compared to ENE−, shows more frequent node matting, microcalcifications, cystic appearance and disproportions of the lymph nodes (increase in diameter).[23]

However, the literature recommends to avoid devising treatments based on the imaging findings alone, given that current technology is not sufficiently precise to demonstrate the presence or absence of ENE prior to pathological examination.[10–12] For example, in cases of HPV+ oropharyngeal carcinoma, the PPV of the radiological assessment of ENE is too low to be considered a starting point for clinical decisions.[24]

In our study, the distinction between the two groups (MaN and MiN) was based on CT measurements of the lymph nodes, choosing 15 mm as a cutoff value. The choice was made considering the relationship between nodal size and CT accuracy,[18,19] and because no studies to date have reported on the accuracy of the Anatomage Table in evaluating such small elements as lymph nodes. In fact, if a different cutoff had been chosen, based for example on the CT criteria for pathological lymph nodes, pathological elements with different CT dimension would have been compared. Since the accuracy of the Anatomage Table is not known, the comparison between pathological elements of different size becomes very challenging. In addition, the chosen 15-mm cutoff allowed us to state that all patients in the MaN group had pathological lymph nodes on CT, regardless of their location and other specific characteristics.

Data from the MaN group demonstrate that the Anatomage Table software and CT are superior to MRI, except for MRI sensitivity which is higher than CT. However, it must be considered that not all enrolled patients underwent MRI. This data also shows that the positive and NPVs of the Anatomage Table are higher than those obtained with CT.

Furthermore, several considerations can be made about sensitivity and specificity, analysing the LR+ and LR- values in the MaN group. A LR+ value of 4 for the Anatomage Table shows that this examination had high sensitivity, associated with a relatively high false-positive rate. The LR+ value of 6.6 for CT shows that CT has a lower false-positive rate than the Anatomage

Table, but lower sensitivity. The LR− value of 0 for the Anatomage Table indicates a good ability to identify pENE− patients, in which it performs better than CT (LR− = 0.53). Finally, a 100% NPV for the Anatomage Table means that a patient who is ENE− at the Anatomage Table is also pENE−.

As regards the MRI evaluation of the MaN group, its low LR+ value (1.65) and high LR− value (0.81) do not support the use of MRI for detecting ENE+. As stated, it should be considered that only 45 patients (68.18% of all the patients) underwent MRI.

In the MiN group, the small dimensions of the lymph nodes prevented the study of capsular involvement with CT and MRI. Specifically, the radiologist was unable to recognize any lymph node with ENE: this demonstrates that CT does not allow the detection of pENE+ patients in the MiN group. This results in a high false-negative rate, given that the CT reports always define small lymph nodes as ENE−. In this context, MRI has similar accuracy to CT, but a higher NPV, which means that MRI yields fewer false-negative results than CT.

As for the Anatomage Table, its efficiency in avoiding false-negative results and in detecting pENE+ is lost in the MiN group.

The radiologist's accuracy in evaluating capsular integrity depends on several factors. First, the dimensions of the lymph nodes: lymph nodes with a long axis diameter lower than or equal to 15 mm are considered too small for a reliable radiological evaluation on the Anatomage Table (same spatial resolution limit as non-thin CT scans). Second, it is important to set the correct window/level combination, especially based on muscle visualization: the possibility to change this parameter proved crucial in solving many doubtful cases. Finally, the possibility of 360° viewing of 3D reconstructions facilitates the assessment of complex geometrical structures such as lymph nodes.

To design future studies on the ability of the Anatomage Table to evaluate ENE, our data should be analyzed by calculating a 95% confidence interval (CI), in accordance with inferential statistics. All the data summarized in Table 4 shows a range of values reflecting the true values of a larger population with 95% CI. Future studies on larger patient populations would be able to demonstrate the accuracy of the Anatomage Table more precisely, decreasing the range of collected values and lowering the 15-mm cutoff. In fact, if our results were to be confirmed with double the number of patients, then the CI range would be narrower than observed.

Our study has some strengths and limitations. One point of strength is that the analysis was performed blinded: the radiologist had no information about the patients or their diseases. Another strength is that, to our knowledge, this is the first study using the Anatomage Table for evaluation of ENE in the head and neck region, and one of the first investigating the introduction of the Anatomage Table into a clinical context.

Nowadays just nine papers describe the use of the Anatomage Table and only five of them describe possible uses in clinical contests. More precisely two works describe the use of the Anatomage Table for anatomical studies, two describe its use for pre- and post-operative assessment and only one for diagnostic purpose.[15,17,25–27] It should be noted that the latest work was published more than two year after the conception of our study.[27] Very few studies have used the Anatomage Table in the head and neck region. Among them, the study of Strantzias et al. traced the course of the marginal nerve, an anatomical structure for which it is difficult to find safe anatomical landmarks.[17,28,29] One limitation of this study is the small number of patients enrolled. Future studies with larger patient populations will make it possible to better establish the accuracy of the Anatomage Table in evaluating capsular involvement, especially in the MiN group. A second limitation may be that the reports were read by a single radiologist, although it should be recalled that this was a pilot study. Furthermore, the Anatomage Table was unable to evaluate the MRI 3D reconstructions. In fact, although 3D post-processing reconstruction of MRI images is feasible, it was not possible to obtain clear 3D images with the Anatomage Table because of technical limitations of both instruments.

Finally, this study showed that in patients with small lymph nodes (≤15 mm) the ability of the Anatomage Table to avoid false-negative results and detect pENE+ proved to be inadequate. On the other hand, in patients with larger lymph nodes (>15 mm), the Anatomage Table had very high sensitivity closely associated with a relevant false-positive rate. However, it was always able to identify pENE− patients.

Table 4 Accuracy of anatomage, CT, and MRI in evaluating the presence of ENE calculated with a 95% confidence interval.

		95% confidence interval		
		Anatomage	CT	MRI
Lymph nodes >15 mm	SENS[a]	88.43% to 100%	17.29% to 52.81%	18.11% to 61.56%
	SPEC[b]	50.90% to 91.34%	75.13% to 99.87%	46.19% to 94.96%
	PPV[c]	73.74% to 92.76%	58.09% to 98.63%	46.22% to 89.22%
	NPV[d]	Non-determinable	41.98% to 55.50%	32.94% to 54.64%
	PLR[e]	1.87 to 8.55	0.92 to 48.10	0.53 to 5.12
	NLR[f]	Non-determinable	0.53 to 0.92	0.51 to 1.26
Lymph nodes ≤15 mm	SENS	0.36% to 57.87%	0% to 40.96%	0% to 70.76%
	SPEC	39.99% to 97.19%	66.37% to 100%	63.06% to 100%
	PPV	5.31% to 81.68%	Non-determinable	Non-determinable
	NPV	42.36% to 64.93%	56.25% to 56.25%	72.73% to 72.73%
	PLR	0.07 to 5.73	Non-determinable	Non-determinable
	NLR	0.69 to 1.75	1 to 1	1 to 1

The data from Table 3 were recalculated with a 95% confidence interval. Non-determinable values do not reflect the real prevalence of the disease, therefore, these values cannot be estimated.
[a]sensitivity;
[b]specificity;
[c]positive predictive value;
[d]negative predictive value;
[e]positive likelihood ratio;
[f]negative likelihood ratio.

5 Conclusions

In conclusion, the Anatomage Table can be a valid tool to establish the preoperative nodal status in patients with squamous cell carcinoma of the head and neck. However, further studies are necessary to determine whether the Anatomage Table could change the therapeutic approach to patients with squamous cell carcinoma of the head and neck.

Disclosure

The authors have no conflicts of interest to disclose.

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