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Clinical, ultrasound and histopathological correlation of clinically N0 neck nodes in patients with cancers of the pharynx and larynx

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Abstract

Background: The presence of metastatic cervical adenopathy is essential for treatment planning and prognosis assessment. Treatment of patients with head and neck cancer with clinically negative cervical lymphadenopathy (N0) remains controversial. Neck palpation, as the method used in tumor, node, metastasis (TNM) staging, has limitations and can provide false negative results in some cases. Lymph node metastases are associated with a reduced survival rate but at the same time, neck dissection for the patient with N0 neck is not without risks or complications. *Objectives*: In prospective study, we compared palpation, ultrasonography (US) examination of the neck and histopathological examination in patients with cancers of the pharynx and larynx. *Patients, Materials and Methods*: Forty-six patients with cancers of the pharynx and larynx that presented with a N0 neck were prospectively analyzed. They were divided in two groups: 23 patients operated with an external approach including the control of the lymph node areas, and a second group of 23 patients operated using endoscopy and carbon dioxide (CO_2) laser, no neck dissection – "watchful waiting policy". All patients have had a flexible endoscopy of the pharynx and larynx, US of the neck and all received surgical treatment for their primary tumor. Imaging was performed in selected cases. All the removed lymph nodes were sent for histopathology. US was also used as a follow-up method. The US features of the examined lymph nodes were: diameters [longitudinal (L) and transverse (T)]; the ratio of the two diameters (L/T); shape; lymph node area; central hypodensity; regular/irregular margins; aspect (homogeneous or not). *Results*: US has detected 25 lymph nodes in the open surgery group and intraoperatively, we excised 31 (sensitivity of 80.6%). Ten lymph nodes showed metastases, with 100% accuracy of US, which have been confirmed both pathologically and immuno-histochemically. US in the second group – patients treated with CO_2 laser – detected at four patients 10 cervical lymph nodes that did not presented any malignant features. At recurrence alone, the US confirmed 100% presence of nodes metastases. *Conclusions*: US was superior to palpation and this method can be recommended as a diagnostic tool in preoperative assessment of patients without palpable metastasis (N0).

Keywords: lymph nodes, palpation, ultrasonography, neck node metastasis.

Introduction

Malignant tumors are considered the first and most important problem of public healthcare, as their incidence has epidemic characteristics, they cause an immense burden on healthcare systems, they require large amounts of economic resources, they cause major social problems and seriously affect the individual and the family [1, 2]. The present epidemiological data show a tendency of increase in the incidence, prevalence, and mortality for the next 40 years [1, 3].

Head and neck cancers represent the sixth most frequent form of cancer world widely, with approximately 630 000 new patients diagnosed every year and over 350 000 deaths every year [4, 5]. Cancers located in the pharynx and larynx are the most frequent head and neck malignancies [6–8]. Smoking and alcohol intake represent major etiological factors for the pharynx and larynx cancer [9].

The incidence of laryngeal cancer varies a lot from one country to another, from 2.5 to 17.2 up to 100 000 per year and it represents approximately 3% of the new cases of malignant tumors diagnosed every year all over the world [10].

The hypopharynx cancer has a 3–5% morbidity of head and neck cancers, with a poor prognosis, as the tumor has an infiltrative progression alongside the pharynx mucosa, it has a low number of symptoms and gives early metastases, therefore when it is diagnosed, the cancer already presents metastases in the cervix ganglia [11, 12].

The therapy of pharyngeal and laryngeal cancer is decided according to the results of the clinical examination, endoscopy, and imaging. According to the location of the primary tumor and the tumor, node, metastasis (TNM) staging, either surgical or non-surgical treatment are considered. The decision is influenced by the presence or absence of the cervical lymph node metastasis. For laryngeal cancers, if the decision is to perform open surgery, the control of the lymph node areas is usually associated. If the decision is to perform endoscopic surgery – usually with lasers – than a "watchful waiting policy" is employed if no lymph nodes are palpable (N0) neck. Palpation of the neck is not a very reliable method and it depends on many factors – anatomy of the neck (short, thick neck), size and location of the lymph nodes, etc. Ultrasonography (US) is a well-established method for diagnosis of the lymph nodes in the head and neck area and can provide details regarding the characteristics of the lymph nodes (benign or malignant) [13–15]. This noninvasive method can be used for postoperative screening of the involved lymph node areas for both surgical and non-surgical patients, as it is cheap and well tolerated.

Aim

In the present study, we proposed to evaluate the role of US within the diagnosis of cervix ganglion metastases in the pharynx and larynx cancer, in the patients where the clinical examination did not show the presence of adenopathy (N0).

Patients, Materials and Methods

We included in the study 46 patients with cancers of the pharynx and larynx that presented with a N0 neck in Ear, Nose and Throat (ENT) Department of Timişoara, Romania, for three years, having a three-year period follow-up. They were divided in two groups: 23 patients operated with an external approach including the control of the lymph node areas, and a second group of 23 patients operated using endoscopy and carbon dioxide (CO_2) laser, no neck dissection – a "watchful waiting policy". All patients have had a flexible endoscopy of the pharynx and larynx, US of the neck and all received surgical treatment for their primary tumor. Imaging was performed in all selected cases. US was also used as a follow-up method. US of the neck areas was performed using a wide band transducer (frequency of 6–13 MHz) at a frequency of 7.5 MHz. The patient is in a supine position with the neck in extension and the head rotated towards the opposite side. We searched for the following features of the lymph nodes: size, shape, margins, location, structure, and relation to the nearby structures.

All tumors and all excised lymph nodes were sent to the Laboratory of Pathological Anatomy for histopathological (HP) and immunohistochemical (IHC) studies.

The biological material was fixed in 10% neutral buffered formalin and included in paraffin, according to the usual HP protocol. After the microtome sectioning, there was performed Hematoxylin–Eosin (HE) and green light trichrome, the Goldner–Szekely (GS) technique; for the IHC study, there were used the following antibodies: anti-Ki67 (monoclonal mouse anti-human Ki67, clone MIB-1, 1/50 dilution, Dako); anti-AE1/AE3 (monoclonal mouse anti-human cytokeratin, clone AE1/AE3, 1/100 dilution, Dako); anti-p53 (monoclonal mouse anti-human p53 protein, clone DO-7, 1/100 dilution, Dako).

Results

In our study, most patients were male, respectively 41, representing 89.1%. From the studied group, the women were in a small number, respectively five, representing 10.9%. The main symptoms were: dysphonia, which was present in 42 (91.3%) patients; dysphagia was found in eight (17.4%) patients; pain on swallowing was present in three (6.5%) patients, and significant weight loss was mentioned only in two (4.3%) patients. Palpation of the neck was carefully performed in all patients and only the N0 patients were included in the study. In our study, 45 (97.8%) patients had laryngeal tumors. One case presented a tumor located in the oropharynx, in the left tonsil, extending to the base of the tongue. The laryngeal tumors were located as follows: epiglottis – five (11.1%); extension beyond the epiglottis – two (4.4%); vocal cord – 14 (31.1%); vocal cord extended to anterior commissure – nine (20.1%); vocal cord extended to subglottic region – four (8.9%); vocal cord extended to the supraglottic region – 11 (24.4%). Staging was performed according to TNM Classification [*American Joint Committee on Cancer* (AJCC) and *Union for International Cancer Control* (UICC)] and is presented in Table 1. It can be seen that there are malignant laryngeal tumors that do not show lymphadenopathy even in advanced stages of the disease, respectively III and IV stages.

Table 1 – *N0 neck patients according to T staging*

Tumor (T) staging	No. of cases (%)
T I	18 (39.13%)
T II	8 (17.39%)
T III	6 (13.04%)
T IV	14 (30.43%)
Total	46 (100%)

Tumor (T) stage was the main factor in deciding which therapy was used. The open surgery was performed on a number of 23 (50%) patients, especially those in advanced (III and IV) stages of the disease (Table 2), while endoscopic surgery mainly in early (I and II) stages in 23 (50%) patients (Table 3).

Table 2 – *N0 neck patients treated with open surgery according to T staging*

Tumor (T) staging	No. of cases (%)
T I	1 (2.17%)
T II	2 (4.34%)
T III	6 (13.04%)
T IV	14 (30.45%)
Total	23 (50%)

Table 3 – *N0 neck patients treated with endoscopic CO_2 laser surgery according to T staging*

Tumor (T) staging	No. of cases (%)
T I	17 (36.96%)
T II	6 (13.04%)
T III	0
T IV	0
Total	23 (50%)

US was performed in all patients both preoperatively – to help planning, and postoperatively – for follow-up. US has detected 25 lymph nodes in the open surgery group and intraoperatively we excised 31 (sensitivity of 80.6%).

The US features of the examined lymph nodes were: diameters [longitudinal (L) and transverse (T)]; the ratio of the two diameters (L/T); shape; lymph node area; central hypodensity; regular/irregular margins; aspect (homogeneous or not) (Table 4). US features for metastatic lymph nodes were as follows: size larger than 1.2 cm; L/T ratio less than 2; round shape; clustering; central hypodensity; irregular margins; non-homogeneous aspect. Not all of these features were present in every patient we examined. The only feature with 100% appearance was the round shape, followed by central hypodensity (75%) and L/T ratio (66%). Irregular shape and clustering were inconclusive (25%). While size and L/T ratio produced an over evaluation of the number of cases all other features produced an under evaluation. Clustering, L/T ratio and shape of the lymph nodes were features with 100% accuracy, while central hypodensity (Figure 1) had an accuracy of only 75% (Table 5). Irregular margins had no significance on diagnosis. This can be explained by the small size of the lymph nodes.

Table 4 – *US features of the neck lymph nodes*

US features	No. of lymph nodes (%)
Minimal and maximal diameter [cm]	
▪ 0.8–1.2	25 (100%)
▪ >0.8–1.2	0
L/T ratio	
▪ >1.8	19 (76%)
▪ <1.8	6 (24%)
Shape	
▪ round	4 (16%)
▪ oval	21 (84%)
Lymph node clustering	
▪ one lymph node	6 (24%)
▪ two lymph nodes	18 (72%)
▪ three lymph nodes	1 (4%)
Central hypodensity	
▪ present	3 (12%)
▪ absent	22 (88%)
Margins	
▪ regular	24 (96%)
▪ irregular	1 (4%)
Structure	
▪ homogeneous	22 (88%)
▪ non-homogeneous	3 (12%)

L/T: Longitudinal/transverse; US: Ultrasonography.

Table 5 – *US features of the lymph node metastasis in patients with N0 neck*

Patient No.	Lymph node group	L/T ratio	Shape	Structure	Margins	Central hypodensity
1.	Two lymph nodes	1.12	Round	Hypodensity Non-homogenous	Regular	Present
2.	Three lymph nodes	1.14	Round	Hypodensity Non-homogenous	Regular	Present
3.	Two lymph nodes	1	Round	Hypodensity Homogeneous	Regular	Absent
4.	Three lymph nodes	1.11	Round	Hypodensity Non-homogenous	Regular	Present

L/T: Longitudinal/transverse; US: Ultrasonography.

US in the second group (patients treated with CO_2 laser) detected in four patients, 10 cervical lymph nodes that did not present any malignant features (Figures 2 and 3), and the attitude against them was a closed follow-up "watchful waiting policy" which revealed no change of the characteristics over time.

Only one patient in this group developed local recurrence and it was treated with open surgery with neck dissection.

On neck dissection, we excised two lymph nodes – previously detected on US with malignant features, confirmed with metastases on HP examinations.

HP and IHC examination of the primary tumor was performed in all cases and for all removed lymph nodes. All tumors were squamous cell carcinomas with varying degrees of differentiation; most cases were moderately differentiated squamous cell carcinomas (Figures 4 and 5).

IHC study showed that both primary tumors and lymph node metastases were positive, more or less intense, of anti-Ki67 antibody, depending on the degree of tumor differentiation, weakly or moderately differentiated tumors showing a more intense reaction compared to well-differentiated tumors (Figures 6 and 7).

Regarding the reaction to the anti-AE1/AE3 antibody, an intense reaction was noted, both in the primary tumor and in the lymph node metastases (Figures 8 and 9). Also, laryngeal tumors that responded positively to p53, also showed positive lymph node metastases to the same antibody (Figures 10 and 11).

Over three-year follow-up there was only one case (4.3%) with local recurrence so the "wait and see" policy was justified. The benefits of this approach are obvious: shorter operating time, good exposure with the operating microscope, no external scars, no wound related complications, less postoperative pain, shorter hospitalization, and lower costs.

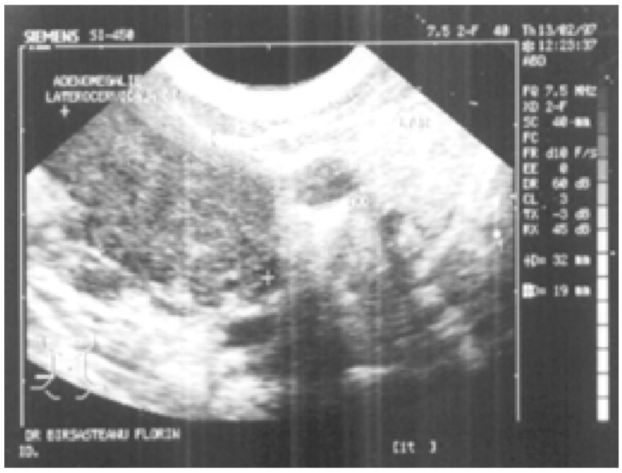

Figure 1 – ***Lymph node metastasis, non-homogeneous (areas of central and peripheral necrosis) size 50/40 mm, regular margins, adjacent to the external jugular vein.***

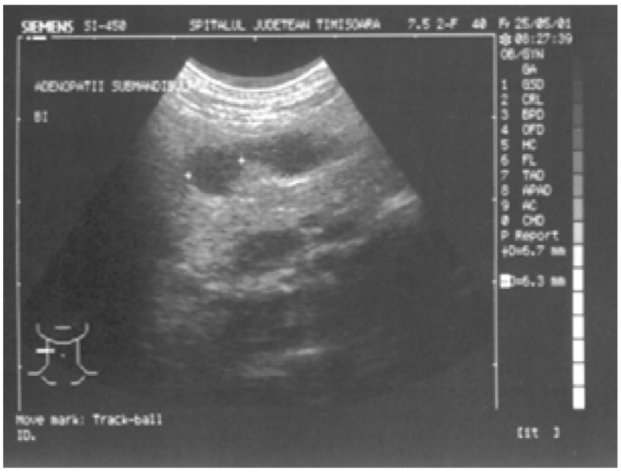

Figure 2 – ***Ultrasound of the neck: reactive lymph nodes.***

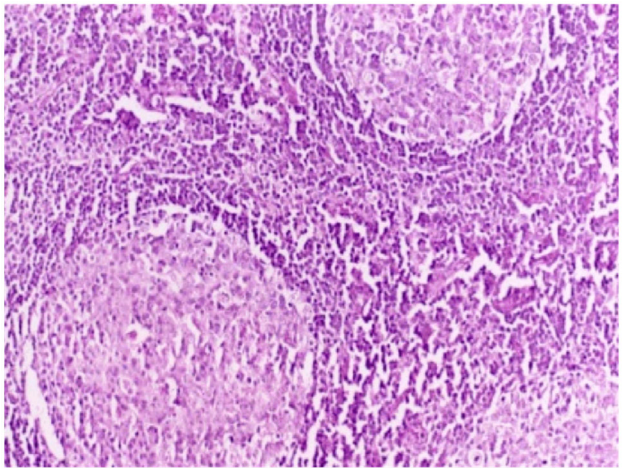

Figure 3 – ***Lymph node with hyperplastic secondary lymphatic follicles (HE staining, ×200).***

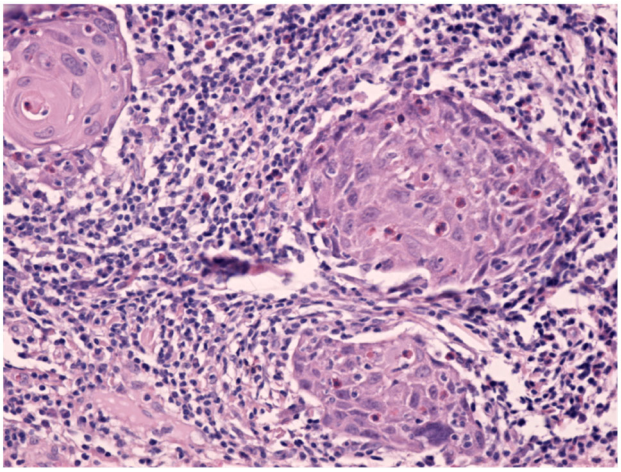

Figure 4 – ***Islands of moderately differentiated squamous cell carcinoma, with intense inflammatory reaction around, in a case of laryngeal carcinoma (HE staining, ×200).***

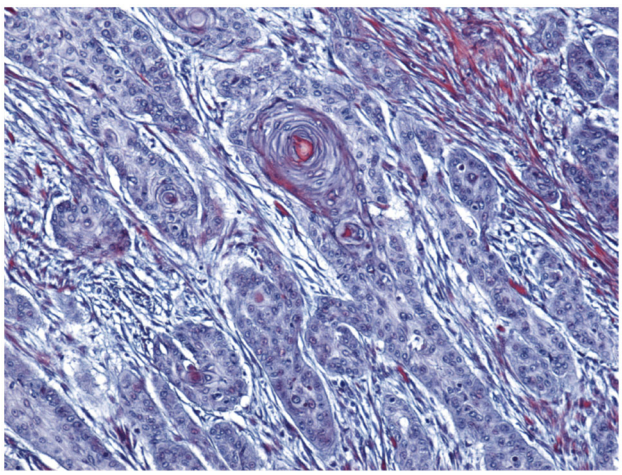

Figure 5 – ***Moderately differentiated squamous cell carcinoma, with tumor cells arranged in coordinates, separated by a desmoplastic stroma (GS trichrome staining, ×200).***

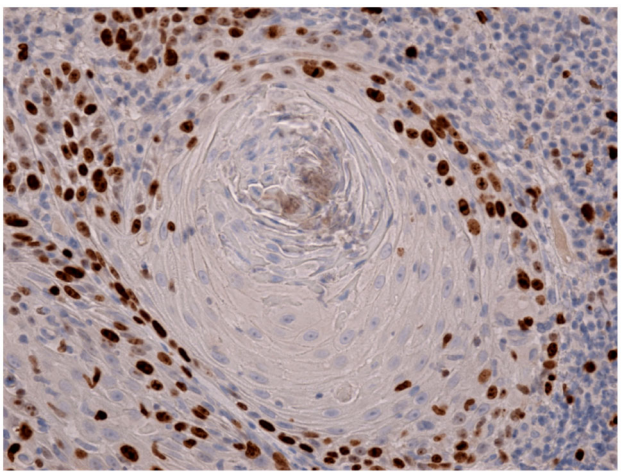

Figure 6 – ***Image of well-differentiated squamous cell carcinoma with moderately positive reaction to anti-Ki67 antibody (Immunostaining with anti-Ki67 antibody, ×200).***

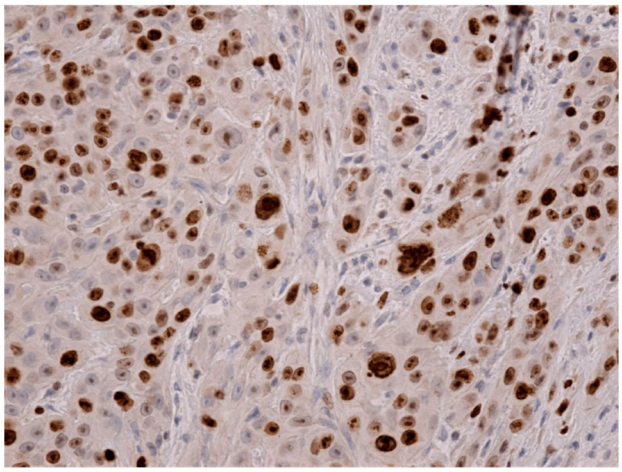

Figure 7 – ***Poorly differentiated laryngeal squamous cell carcinoma, with marked cellular and nuclear atypia, with intense reaction to anti-Ki67 antibody (Immunostaining with anti-Ki67 antibody, ×200).***

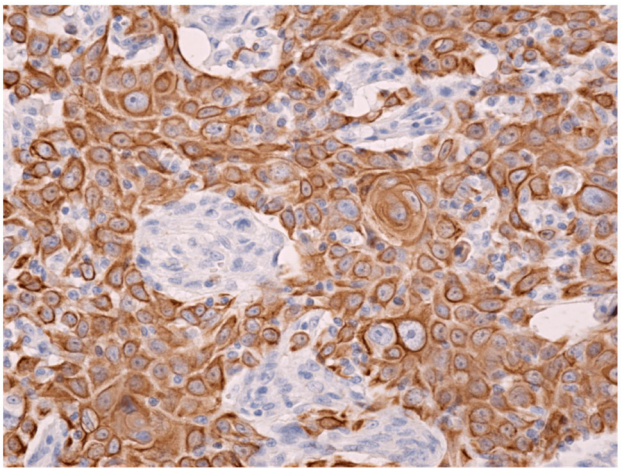

Figure 8 – ***Primitive laryngeal tumor, moderately differentiated, with intense reaction to anti-AE1/AE3 antibody (Immunostaining with anti-AE1/AE3 antibody, ×200).***

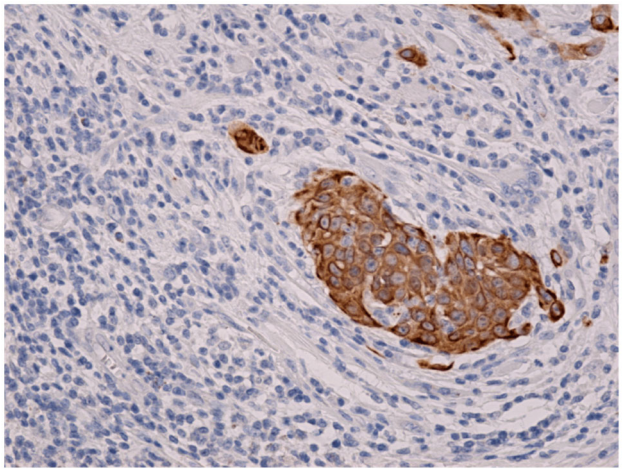

Figure 9 – ***Image of lymph node metastasis with intense reaction to anti-AE1/AE3 antibody (Immunostaining with anti-AE1/AE3 antibody, ×200).***

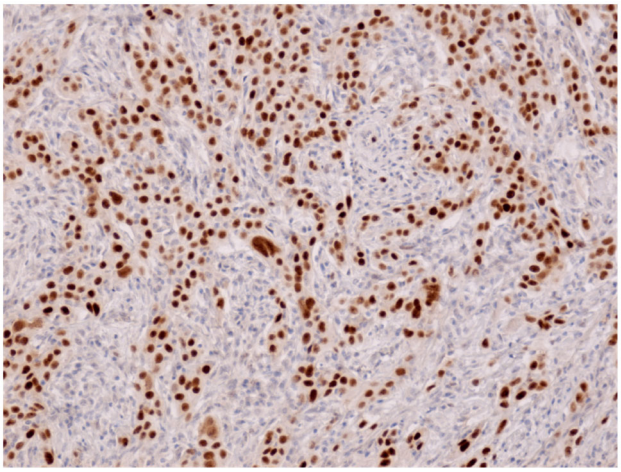

Figure 10 – ***Primitive laryngeal tumor: poorly differentiated squamous cell carcinoma, with intense reaction to anti-p53 antibody (Immunostaining with anti-p53 antibody, ×100).***

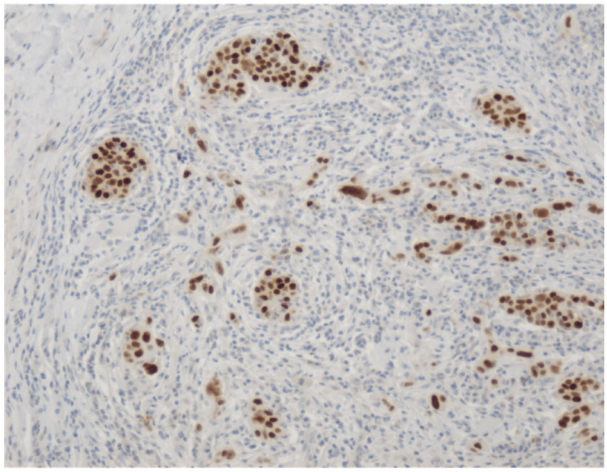

Figure 11 – ***Laterocervical ganglion metastasis consisting of cell islands or isolated cells, resulting from a moderately differentiated squamous laryngeal carcinoma (Immunostaining with anti-p53 antibody, ×100).***

Discussions

Over 50% of the head and neck malignancies have cervical lymph node involvement at presentation [16], and lymph node metastases are associated with a reduced survival rate [16, 17]. Palpation has its obvious limitations in detecting cervical metastasis. Sako *et al.* (1964) reported a 28% incidence of lymph node metastasis in 123 patients with head and neck tumors and N0 neck in which selective neck dissection was performed [18]. Szmeja *et al.* (1999) demonstrated the superiority of US over palpation in 810 patients with laryngeal cancer treated with either surgery or radiotherapy over a five-year period [19]. The same authors extended their study over seven years with 1120 patients with laryngeal cancer receiving surgical treatment. In the N0 group (505 cases), US examination detected 261 patients with lymph node involvement. Sixty-three (24.1%) patients had histology confirmation of metastatic lymph nodes. They found a correlation US–surgery of 95% and US–histology of 90% [20]. All the patients had US

of the neck as a part of their follow-up. One hundred thirty-six patients developed lymph node recurrences and 117 presented initially with N0 neck (105 histologically confirmed). The authors recommend US as a very useful diagnostic tool and for the follow-up period. Schipper *et al.* (1999) [21] presented a study of 101 early (T1 and T2, N0) stage head and neck patients receiving US examination as part of their diagnostic procedure and 18–36 months follow-up period. US detected lymph node involvement in 30 cases and they received neck dissection as part of the treatment. Eight patients out of 30 presented with metastatic lymph nodes. The conclusion of the study was that the "watchful waiting policy" does not alter the prognosis and they recommend US for the follow-up in head and neck patients. Yoshida *et al.* (1998) perform histology in 117 lymph nodes detected by US in head and neck patients and find 26 (22.2%) metastases, so the sensitivity is 83% and sensibility is 97% with an accuracy of 95% [22]. In other study, an L/T ratio ≤2, non-hilar vascular pattern, parenchymal granular echoes, necrosis, and the presence of groups of three or more otherwise normal nodes in a high-risk area were considered good indicators of metastatic disease [23]. Wang *et al.* (2019), examining 89 patients with hypopharyngeal cancer showed that US plays an important role in the preoperative detection of tumor metastases in the cervical lymph nodes [24]. US diagnostic [13] criteria in the US differentiation of benign and malignant nodes of the neck are very useful (Table 6) as US is an important tool in the follow-up protocol in head and neck patients.

Table 6 – *US diagnostic criteria in the US differentiation of benign and malignant nodes of the neck*

Type	*Benign*	*Malignant*
Form	Oval	Round
Boundary	Sharp	Blurred
Hilar sign	Hyperechoic hilum	No hilum
Vessels	Hilar vascularization	Tangential vascularization
Dynamic behavior	Stationary	Increase of size
Intranodal necrosis	Without	Anechoic central region in heterogeneous lymph node texture

US: Ultrasonography.

US of the neck was also successfully used as a follow-up method in oral cancers with only one patient out of 32 presenting a lymph node metastasis six months post-operatively [25]. US can be used for specifically monitoring of a certain lymph node area – the risk ones – jugulo-digastric (JDG) and jugulo-omohyoid (JO). 31.6% were not elliptical, more of the JO than the JDG nodes were round; there was a significant difference in roundness index between them ($p<0.05$) and significantly more of the lymph nodes with roundness index <2 lacked a visible echogenic hilum [26, 27]. The follow-up for patients with N0 neck – especially in pharyngeal and laryngeal cancers – is of paramount importance as selective neck dissection is still controversial. Reports are still controversial: Birkeland *et al.* (2016), in 35 patients found 17% histology positive lymph nodes [28]. However, Deganello *et al.* (2014) [29] and Pezier *et al.* (2014) [30] found almost no lymph node involvement and recommend a conservative approach over the lymph nodes. When considering recurrence in laryngeal cancers neck dissection is mandatory in all cases of squamous cell carcinomas recurrence with N^+, and routine elective neck dissection is recommended for recurrent supraglottic and transglottic cancers [31]. US can be also used intraoperatively in head and neck tumors. Stieve *et al.* (2012) in a study on 115 cases concluded that US was helpful providing information about the size of the tumor and involvement of the adjacent areas [32].

Conclusions

Selective neck dissection in N0 pharyngo-laryngeal cancers is still controversial. Palpation is an inaccurate method for detection of lymph node involvement in head and neck patients and depends highly on surgeon's experience. US of the neck is a cheap, reliable, and very well tolerated method of investigation for the lymph node involvement in the cervical area both for diagnostic and follow-up purposes. HP and IHC examinations represent the most important methods of positive and differential diagnosis, but also for assessing the prognosis.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Gheorghe Iovănescu and Eugen Horaţiu Ştefănescu have equal contributions to this paper.

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