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# ADVANCED DIAGNOSTIC TECHNIQUES OF METASTATIC NECK LYMPH NODES

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The development of advanced technologies including computerized tomography devices of new generation (MSCT) and MRI devices has enabled the application of high quality techniques that are used for functional analysis of head and neck tumors. Therefore, the role of conventional CT and MR imaging techniques relating to anatomical domain has been transferred to functional level thus enabling better understanding of biological characteristics of the tumor tissue and better differentiation of benign and malignant neck lymph nodes.

Positron emissin tomography (PET) is a functional technique that can detect metastatic neck lesions on the basis of increased glucose metabolism in tumor cells. However, due to poor anatomical resolution some hybrid methods (PET / CT and PET / MR) have been designed that provide morphological and functional information about the tumor tissue and thus are considered to be superior in comparison to conventional PET. Perfusion techniques have proved to be beneficial in the diagnosis of head and neck tumors, especially in the diagnosis of recurrent disease after radiotherapy and for the characterization of the lymph nodes. Diffusion weighted imaging (DWI) is very useful in the diagnosis of malignant lymph nodes smaller than 10 mm that are otherwise difficult to diagnose by means of conventional methods.

The paper describes the role of high quality techniques including positron emission tomography PET in combination with CT or MRI (PET / CT and PET / MR) in the diagnostics of metastatic neck lymph nodes, possibilities of perfusion imaging techniques (MSCT / MRI) in the analysis of tumor tissues, as well as possibilities of diffusion MR imaging (DWI-MRI) and MRI with nanoparticles of iron oxide in the differentiation of benign and malignant neck lymph nodes. *Acta Medica Medianae 2013;52(4):53-57.*

***Key words:*** *neck lymph nodes, head and neck tumours, PET, CT perfusion, DWI-MR*

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## Introduction

The presence of metastatic lymph nodes on the neck alters the surgical procedure plan and generally indicates a poorer prognosis in patients with head and neck tumors. Therefore, it is of primary importance to become acquainted with these findings before therapy planning (1).

In clinical practice, computerized tomography (CT) and magnetic resonance imaging (MRI) are most frequently used radiological methods in the diagnostics of metastatic lymph nodes on the neck prior to surgical treatment.

The direct sign of lymph nodes malignancy using CT and MRI is the presence of necrosis and extracapsular expansion, as well as the absence of fatty hilum. However, a large number of neck lymph nodes do not show these direct signs of malignancy. In this case, the only applicable criterion is the lymph node size. Generally, diameter greater than 10 mm (2) is taken as the criterion for the malignancy assessment. However, it has been shown to be insufficiently sensitive, taking into account the fact that even the sub-centimeter lymph nodes may be malignant as well.

The technology advancement has resulted in development of high quality imaging techniques that enabled both morphological and functional analysis of tumor tissue. Positron emission tomography (PET) combined with CT and MR (PET/CT and PET/MR) provides anatomical and functional analysis of metastatic lymph nodes on the neck (1,2).

Other advanced techniques used in the differentiation of benign and malignant lymph nodes on the neck include perfusion imaging techniques (MSCT and MRI), diffusion MR imaging (DWI) and MR with nanoparticles.

## Hybrid methods (PET/CT and PET/MR)

PET represents a functional technique which can detect metastatic neck lesions on the basis of increased glucose metabolism in tumor cells (2) being registered after the administration of radiopharmaceuticals of 2-fluoro-2-Deoxo-D-glucose (FDG). The glucose analog is transported

in metabolically active cells by means of a facilitated glucose transport (using glucose transporter). Therefore, FDG accumulates in malignant cells because they have a larger number of glucose transporters such as hexokinase, the enzyme that phosphorylates glucose. After phosphorylation, FDG continues to accumulate in the altered metastatic lymph nodes, which allows the detection of PET (3,4).

PET is better in comparison to conventional methods in the detection of metastatic neck lesions with normal morphology. Available literature data indicate wide range of sensitivity and specificity. Thus, different authors report that PET sensitivity in the diagnostics of malignant lymph nodes on the neck ranges from 67% to 96%, and specificity of 82% to 100% (5-7).

Poor anatomical resolution is considered to be the greatest disadvantage of PET. Therefore, new methods have been developed combining PET with CT or MR imaging techniques (PET/CT and PET/MR) having good anatomical resolution and providing information about altered metabolism. These methods have shown to be superior and more accurate in detecting neck metastases in comparison with PET as an independent method, as well as in comparison with conventional imaging techniques, because they provide simultaneous functional and morphological information (8).

However, restricted availability and high cost of examination are considered to be disadvantages of these hybrid methods.

**Perfusion imaging techniques (MSCT and MR perfusion)**

They are used for differentiation of normal and metastatic lymph nodes on the neck. Perfusion is the volume of blood transferred to capillary system of a tissue in a unit of time calculated per 100 g of tissue.

Perfusion imaging techniques performed either in conjunction with CT or MRI device show the changes in the microcirculation of a lymph node (8). This is achieved by measuring the amount of contrast agent which accumulates in the lymph node in a function of time after intravenous administration of contrast agent.

Changes in the intensity and density of tissue after administration of contrast agent, blood flow, blood volume, and transition time are measured (9). In comparison to normal node, metastatic nodes have longer time to achieve maximum contrast accumulation, reduced maximum post-contrast enhancement, reduced slope of accumulation curve and reduced slope of leaching curve. Neoplastic tissue shows changes in perfusion characteristics with the volume increase and blood flow, and with the transition time drop in comparison to normal tissue (11).

Perfusion techniques are not generally used in routine clinical practice for the diagnostics of head and neck tumors. Studies have shown the benefits of these techniques in the diagnostics of head and neck tumors, especially in the diagnosis of recurrent disease after radiotherapy and for the characterization of the lymph nodes. Postradiation sequelae (post-contrast enhancement due to inflammation or fibrosis) may simulate the presence of pathological substrates which cannot be differentiated by conventional CT and MRI. In addition, it is at times impossible to detect metastatic lymph nodes particularly when they are not enlarged using conven-tional techniques.

**Difffusion MR (DWI-MR)**

At the beginning, DWI was used for the evaluation of intracranial diseases, but with MR imaging advancement this method has been used more frequently for extracranial applications. More precisely, DWI is nowadays being widely used for differentiation of benign and malignant lymph nodes on the neck (12).

The advanced, non-invasive MRI technique enables tissue characterization based on differences in Brown's motion of water molecules. Quantification of DWI is established using the diffusion coefficient ADC which combines the effects of capillary perfusion and water diffusion in the extracellular, extravascular space. The value of ADC varies, depending on the selected b-value. When only low b-values are used, ADC represents only microperfusion and microcirculation and has a limited influence on diffusion, while a high b-value reflects ADC that represents real diffusion in the tissue. This selection is an important prerequisite for proper application and interpretation of DWI.

Hypercellular tissues present in malignant tumors show low diffusion coefficient (ADC). Non-cancer tissue changes like edema, inflammation, fibrosis or necrosis have low cellularity, contrary to the tumor tissue and show high diffusion coefficient. This inverse correlation between the value of the diffusion coefficient ADC and tumor cellularity was proved both experimentally and clinically (13).

DWI is very useful in the diagnostics of malignant lymph nodes smaller than 10 mm which are difficult to diagnose by conventional methods. De Bondt RB et al. investigated the values of ADC in small lymph nodes (smaller than 10mm) in SCC with a border ADC value of 1.0 × 10-3 $mm^2/s$., and found sensitivity of 92.3% and specificity of 83.9% (14).

In the head and neck region this technique shows diffusion restriction in planocellular carcinomas due to its high cellularity, and shows greater sensitivity and specificity than conventional CT and MR examinations in the differentiation of lymph nodes of planocellular carcinomas (14). Diffusion coefficient of metastatic lymph nodes is greater than that of the benign lymph nodes. In addition, the diffusion coefficient is greater in high or moderate differentiated carcinomas than in poorly differentiated carcinomas. This technique has a positive predictive value of 87.8% and a negative predictive value of 76.1% (16).

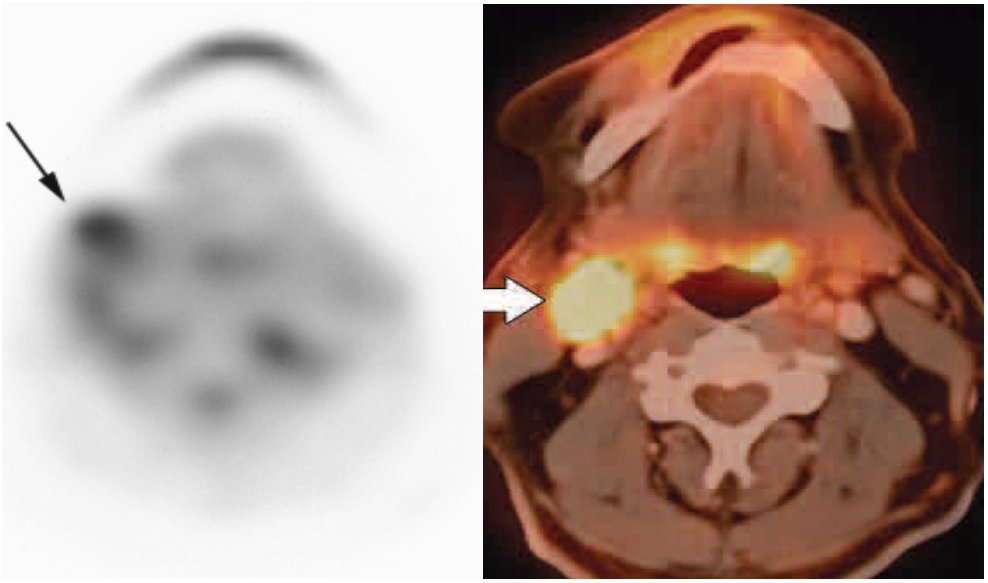

*Figure 1. Tomogram from PET with poor anatomical resolution and tomogram with PET-CT-a combining morphological information and information about increased metabolism: metastatic lymph node of pyriform sinus cancer on the right side of the neck (arrow)(8).*

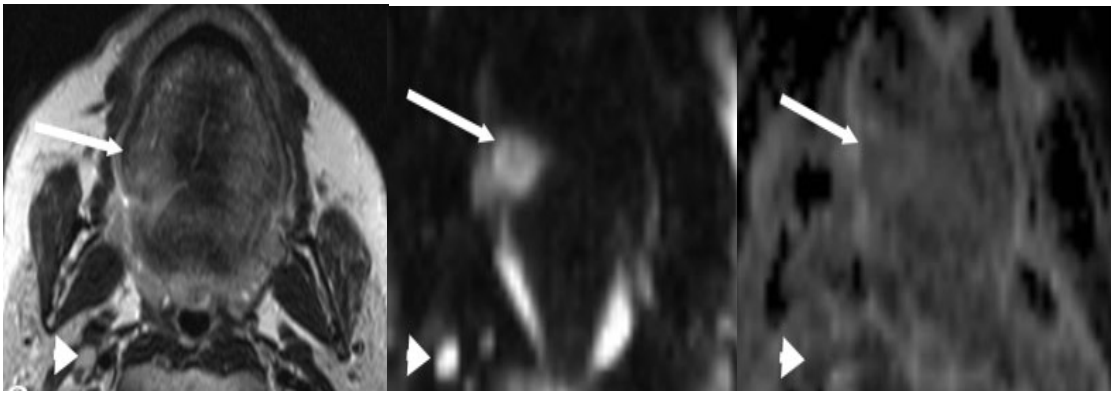

*Figure 2. Axial T2w tomogram with tumour change on tongue body and small lymph node of 4mm in diameter on level II on the right side of the neck (arrows), diffusion restriction (tomogram in the middle), diffusion map (the last tomogram in a raw). Diffusion coefficient value for lymph node is 0.74x10-3mm$^2$/s. Pathohistological finding showed squamocellular carcinoma on the tongue with metastatic lymph node on the neck (15).*

**MR with contrast agent of iron oxide - nanoparticles (Nanoparticle-enhanced MRI)**

The new contrast in MR diagnostics includes ultra small supramagnetic particles of iron oxide ((USPIO) classified as nanoparticles (with medium diameter of 30 nm) composed of nucleus of iron oxide (17-19).

The application of this contrast requires two MR scanning processes within 24 hours. At first, precontrast X-ray is taken to identify the localization of lymph node, then contrast is injected intravenously, and after 24 hours the second postcontrast X-ray is taken where contrast enhancement is observed in already identified lymph node. The standard protocol for MR scanning with nanoparticles consists of the following aquisition parameters: gradient echo sequence (GRE) T1W, fast spin-echo sequence (FSE) T2W and GRE T2*W. The identical protocol is used for pre- and postcontrast scanning (18).

By intravenous USPIO application normal lymph node phagocytizes particles and becomes black on T2 and T2W after 24 hours. If a part of lymph node is tumour infiltrated, that part of lymph node will not accept USPIO and will not turn black. The size of black zone on postponed MR examination is inversely proportional to the presence of tumour tissue in the node. If 50% of the node is black, then it is 80% possible that the node contains tumour.

If this is found in the lymph node that is morphologically normal on conventional MRI, then it is a step forward in the diagnostics. False-negative results are mainly due to microscopic tumor infiltration which is below spatial resolution of existing MRI devices, while the false positive findings are found in reactive hyperplasia, granulomatous disease and nodal lipomatosis (17,19). Although this technique may increase the accuracy in the detection of metastatic lymph nodes, the cost of USPIO and problems due to

the need for scan postponement after 24 hours prevent widespread use of this technique.

## Conclusion

The role of conventional CT and MR imaging techniques relating to anatomical domain has been transferred to functional level due to the development of advanced technologies, thus enabling better understanding of biological characteristics of the tumor tissue and better differentiation of benign and malignant lymph nodes on the neck.

PET is a functional technique that can detect metastatic lesions on the neck on the basis of increased glucose metabolism in tumor cells. However, due to poor anatomical resolution some hybrid methods (PET/CT and PET/MR) have been designed that provide morphological and functional information about the tumor tissue and thus are considered to be superior in comparison to conventional PET. Perfusion techniques have proved to be beneficial in the diagnosis of head and neck tumors, especially in the diagnosis of recurrent disease after radiotherapy and for the characterization of the lymph nodes. DWI is very useful in the diagnosis of malignant lymph nodes smaller than 10 mm that are otherwise difficult to diagnose by means of conventional methods.

Nowadays, the advanced techniques including PET/CT and PET/MR, perfusion imaging techniques, DWI-MRI and MRI with nanoparticles are considered to be the most accurate diagnostic modalities. The only disadvantages include restricted availability and high cost of examination.

Neck dissections with thorough histopathological examination still represent the gold standard in the detection of metastatic lymph nodes on the neck.

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# NAPREDNE TEHNIKE U DIJAGNOSTICI METASTATSKIH LIMFNIH ČVOROVA NA VRATU

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Razvoj naprednih tehnologija, nove generacije aparata za kompjuterizovanu tomografiju (MSCT) i MR aparata, omogućio je i primenu naprednih tehnika kojima se vrši funkcionalna analiza tumora glave i vrata. Uloga konvencionalnih slikovnih tehnika CT-a i MR-a, koja je u anatomskom domenu, razvojem naprednih tehnologija prebačena i na funkcionalni nivo, čime je omogućeno bolje sagledavanje bioloških karakteristika tumorskog tkiva i bolja diferencijacija benignih od malignih limfnih čvorova na vratu.

Pozitron-emisiona tomografija (PET) je funkcionalna tehnika kojom mogu da se detektuju metastatske lezije na vratu na osnovu povišenog metabolizma glukoze u tumorskim ćelijama, međutim, zbog loše anatomske rezolucije, osmišljene su hibridne metode (PET/CT i PET/MR), koje daju morfološke i funkcionalne informacije o tumorskom tkivu i time su postale superiornije u poređenju sa konvencionalnim PET-om. Perfuzione tehnike pokazale su benefite u dijagnostici tumora glave i vrata, posebno u dijagnostici rekurentne bolesti nakon radioterapije i za karakterizaciju limfnih čvorova. Diffusion weighted imaging (DWI) je jako korisna u dijagnostici malih malignih limfonodusa, manjih od 10 mm, koje je teško dijagnostikovati konvencionalnim metodama.

Rad opisuje ulogu naprednih tehnika, poput pozitron-emisione tomografije (PET) u kombinaciji sa CT-om ili MR-om (PET/CT i PET/MR) u dijagnostici metastatskih limfnih čvorova na vratu, mogućnosti perfuzionih slikovnih tehnika (MSCT/MR) u analizi tumorskog tkiva, kao i mogućnosti difuzionog MR imidžinga (DWI/MR) i MR sa nanopartikulama oksida gvožđa u diferencijaciji benignih od malignih limfnih čvorova na vratu. *Acta Medica Medianae 2013;52(4):53-57.*

***Ključne reči:*** *limfni čvorovi vrata, tumori glave i vrata, PET, CT perfuzija, DWI/MR*

 