Positron-emission tomography in head and neck cancer

Tomografia por emissão de pósitrons em tumores malignos de cabeça e pescoço

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ABSTRACT

Head and neck cancer is considered a public health problem worldwide, given its high morbidity and mortality. The more advanced is the histopathologic grade, the more aggressive may be the therapies. The development of health policies, diagnosis and treatments lead to better prognostic perspectives. This paper aimed to review the literature regarding the application of positron emission tomography in head and neck cancer, including its impact in the diagnosis, image principles, radiotracers, positron emission tomography / computed tomography image fusion and other advantages. The review was performed following systematized search strategies reported in the literature. It could be observed that the use of positron emission tomography improves the diagnostic approach of the patients, especially when positron emission tomography is allied to computed tomography. As it provides physiological information, positron emission tomography also benefits the prognostic and reduces the morbidity related to the treatment of head and neck cancer.

Indexing terms*: Carcinoma, squamous cell. Head and neck cancer. Positron-emission tomography.*

RESUMO

Apresentando-se como um problema de saúde pública em todo o mundo, o câncer de cabeça e pescoço caracteriza-se por sua alta morbidade e mortalidade. Quanto mais avançado o grau de diferenciação tumoral, mais mutiladoras tendem a ser as terapias empregadas. Desta forma, os avanços nos âmbitos da promoção de saúde, diagnóstico e tratamento são extremamente benéficos ao prognóstico. Esta revista da literatura tem por objetivo discorrer sobre a aplicação da tomografia por emissão de pósitrons no diagnóstico e planejamento terapêutico de pacientes portadores de tumores malignos de cabeça e pescoço, princípios de formação da imagem, radiofármacos utilizados, fusão de imagens tomografia por emissão de pósitrons e tomografia computadorizada e suas contribuições. O levantamento bibliográfico foi efetuado segundo estratégias sistematizadas relatadas em literatura. Fornecendo informações relativas à fisiologia das lesões através da administração de radiofármacos, pode ser observado que a tomografia por emissão de pósitrons, especialmente quando aliada à tomografia computadorizada, maximiza as possibilidades diagnósticas em determinadas indicações, favorecendo ao prognóstico e sugerindo redução na morbidade decorrente do tratamento no câncer de cabeça e pescoço.

Termos de Indexação: Carcinoma de células escamosas. Neoplasias de cabeça e pescoço. Tomografia por emissão de pósitrons.

INTRODUCTION

The National Cancer Institute (NCI) defines head and neck cancer as the type of disease that affects the nasal cavity, paranasal sinuses, lips, mouth, salivary glands, oropharynx and nasopharynx. According to the World Health Organization (WHO), it corresponds to the 5th most common neoplasia worldwide, being the Squamous Cell Carcinoma (SCC) the most common malignancy. In the context of public health, oral cancer represents one of the most aggravating conditions of oral health, representing 5% of all neoplasms. The Brazilian National Cancer Institute (INCA) estimated 14,120 new carcinoma cases of the oral cavity for the year 2010[1].

The impact of head and neck cancer on the quality of life of affected patients is undeniable. Thus, in addition to actions for health promotion, technological advances in the fields of diagnosis and therapy can result in better

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prognosis and reduction of the impact on the quality of life of these patients. Given the high mortality and morbidity, early diagnosis is a major ally in minimizing mutilating treatments, resulting in better survival rates[2]. In this sense, it is worth noting the important role of imaging tests such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), nuclear medicine (NM) and more recently positron-emission tomography (PET), also applied to other types of tumors.

The development of PET/CT image fusion has maximized the diagnostic ability of these two techniques, combining morphological data provided by CT to physiological data obtained through PET scan. The findings reported in the literature show a reduction in the amount of false positive and false negative diagnosis, suggesting a promising use of this technique in head and neck cancer.

METHODS

The searches for the literature review related to PET and PET/CT were conducted in the MEDLINE database according to the strategy reported by Facey et al.[3], also using terms of Mijnhout[4]. Comments, letters, editorials and case reports were excluded. The research was limited to studies involving humans, published in the last 10 years.

Computed tomography

Introduced by Hounsfield in 1972, the CT has become essential in the diagnosis and treatment planning of cancer patients, considering its high sensitivity and specificity in evaluating multiple systems through a single exam[5-6], in addition to the remarkable skill in delineating the tumor and its anatomical relations[7]. For these reasons, this is currently the standard imaging method used in surgical and radiotherapy planning.

In head and neck cancer, CT allows an accurate assessment of bone destruction, medullary extension and cortical and soft tissue involvement. The 3D reconstruction of the acquisition is didactic and helps in the therapeutic planning[8]. The CT contributions in clinical staging, measurement of tumor volumes and determination of therapeutic responses are also reported in the literature[9-10]. Furthermore, the detection of metastasis from primary head and neck tumors is favored by CT, as it allows the analysis of small changes in the morphology of multiple organs and systems in a single test.

Despite highly accurate morphological data is obtained, imaging tests as CT and MRI do not provide information related to the metabolism of lesions. In this sense, the advancement of NM contributed significantly to fill this gap.

Positron-emission tomography

NM is a diagnostic imaging and therapy modality, which was initiated in the late 1940s, NM is based on the detection of pharmacological substances linked to radioactive isotopes - the radiopharmaceuticals - according to their biological distribution in the organism. Most of them are a combination of a radioactive component that allows the detection of a biologically active portion or drug component that is responsible for biodistribution. For some agents, such as radioactive inert gases, radioiodines, gallium-67 and thallium-201, the atoms themselves have the desired properties for the location, so there is no need for higher chemicals. The most used are 99mTc (Technetium) and 131I (Iodine).

Radiopharmaceuticals have affinity for specific organs of the body, and for this reason, are used to transport radioactive substance to the specific organ or system. Among the main radiopharmaceuticals, there are Tc99-MDP (used to obtain images of the skeleton), Tc99-SESTAMIBI (heart images and research of tumors), Tc99-DISIDA (biliary analysis), Tc99-ECD and Tc99-HMPAO (brain perfusion scintigraphy). Most radiopharmaceuticals are generated in particle accelerator devices called cyclotrons.

The PET constitutes a non-invasive imaging technique based on the exploration of systems through its metabolism by administering a radiopharmaceutical[11]. Its oncological application was proposed as positron emitting radioisotopes - such as Carbon 11, Nitrogen 13 and Fluorine 18 - were produced in cyclotrons in 1951 and became available[12]. The development of computer science and electronics technology in the 1970s made possible the establishment of the foundations for the contemporary use of PET. After the 1980s, the introduction of small cyclotron devices allowed hospitals and clinics to produce radiopharmaceuticals and use them immediately on their patients' examinations.

The devices that perform PET scans can be classified into two types: non-dedicated (hybrid PET/SPECT) and dedicated. In the first device, non-dedicated scintillation cameras perform all nuclear medicine examinations, using 2 or 3 sodium iodide detectors. However, the dedicated devices only perform double-headed gamma camera examinations, as PET, with the advantage of better

resolution due to the presence of thousands BGO (bismuth germanate) or LSO (lutetium oxyorthosilicate) detectors.

Qualitative analysis of data provided by PET can be performed based on the experience of the examiner, or by adopting systematized indices as the SUV (standardized uptake value). The SUV consists in the ratio of the radioactivity concentration found in the lesion and the average radioactivity concentration across the whole body[3].

Radiopharmaceuticals in oncology

In the study of head and neck cancers by PET, the most widely used radiopharmaceutical is 18F-FDG (Fluorine 18 added to Fluorodeoxyglucose, an analogue of the glucose molecule). Its use is based on the work of Warburg, in the decade of 1936, who observed that the tumor cells showed an increased metabolism of glucose compared to the normal cells. Thus, the analogue glucose 2-deoxy-D-glucose (DG) is phosphorylated into DG-6-phosphatase, which is not metabolized and remains in the body. The dephosphorylating process is slow due to the low permeability of the cell membrane. This feature is favorable to the working time with the material still in time for the exam, being the physical half-life equivalent to 109 minutes. During this period, the radionuclides disintegrate and emit positrons that go across a 2 to 8 mm path, on average. After losing its kinetic energy, these positrons can interact with the electrons of the tissues atoms, emitting two gamma photons in opposite directions (180°) of 511keV energy[11]. The opposed detectors of a device similar to a tomographic unit record the gamma photons by means of coincidence techniques known as electronic collimation. Thus, the image is generated in a separate workstation, where it can be manipulated and analyzed.

The uptake of 18F-FDG is directly related to tumor histology. Thus, a higher concentration of the radiopharmaceutical is associated with a more active glucose metabolism, which is the characteristic of a tumor with a high grade of histological differentiation. The size of lesions detected by PET depends on several factors, including the safe limits of FDG dose, the spatial resolution of the scanner, besides the physics of positron emission[3].

As stated previously, the accumulation of 18F-FGD occurs where glucose metabolism is high, occurring high uptake in tumor lesions throughout the body. However, there are other tissues and conditions which also generate high-uptake foci without any presence of neoplastic lesion. Tissues such as skeletal muscle, heart muscle, brain and tissues involved by an inflammatory process can be marked as high-uptake areas ("hot spots"). In patients with high blood glucose, as in decompensated diabetics, the accumulation of FDG is reduced.

The high number of false positive diagnosis related to physiological hot spots motivated the search for new radiopharmaceuticals with different mechanisms. The 18-FLT (Fluorine-18 added to 3-deoxy-3-fluorothymidine) is a thymidine analog which allows identification of typical cell proliferation of tumor lesions[13]. The thymidine is a nucleoside used in DNA replication. The 18-FLT participates in the synthesis of DNA but does not incorporate into it, being accumulated in the cell cytoplasm and enabling the uptake through the PET. The results of preliminary studies with 18-FLT-PET have not demonstrated a remarkable superiority to 18-FDG-PET for staging head and neck tumors. However, regarding the evaluation of the therapies that were used, a superior ability of 18-FLT-PET to predict recurrence has been suggested. In spite of that, future studies with larger samples and robust methodology will be able to give more accurate conclusions[14].

Radiopharmaceutical drugs analogues of amino acids have also been studied recently due to the tumoral characteristic of high rate of protein synthesis. Examples are: 18-FET (Fluorine-18 added to O-2-fluoro-ethyl-tyrosine), 18-FMT (Fluorine-18 added to 3-fluoro-a-methyl tyrosine) and 11C-MET (Carbon-11 added to methionine)[3]. A potential advantage of these radiopharmaceuticals would be greater specificity, since the amino acid accumulation in inflammatory cells (non-tumor) is reduced when compared to glucose. However, the diagnostic values found are similar to 18-FDG-PET. Though, studies suggest the use of analogues of amino acids on suspicious false positive cases coming from the 18-FDG-PET, as in post-therapeutic evaluation[14].

An important factor to be considered in the evaluation of resistance to therapy is the hypoxia. Tumors with lower oxygenation are more resistant to chemotherapy and radiotherapy[15], requiring a cautious approach. The most widely used radiopharmaceutical for hypoxia is the 18-FMISO (Fluorine-18 added to fluoromisonidazole). Recent studies have shown detection rates of tumor hypoxia ranging from 71 to 87%. However, it remains longer in the intracellular environment given its lipophilic characteristics, with the disadvantage of low contrast in relation to the tissues adjacent to the tumor. Thus, new hydrophilic radiopharmaceuticals, such as 18- FETNIM (Fluoroeritronitroimidazole), EF3 [2-(2-nitromidazole-1-yl)-N-(3,3,3-trifluoropropyl) acetamido] and EF5 [2-(2-nitro-1H-midazol-1-yl)-N-(2,2,3,3,3-pentafluoropropane) acetamido], all labeled with Fluorine-18 are under

clinical investigation[14]. Other promising agents for the identification of tumor hypoxia are the 18F-FAZA (18F connected to Fluoro Azomycin arabinoside) and the complex diacetyl-2,3-bis(N4-Methyl-3-thiosemicarbazone) labeled by Copper-60 or Copper-64. The half-life of Copper-60 and Copper-64 are respectively 23,7 minutes and 12,7 hours, being the last one highly superior to those radiopharmaceuticals labeled by Fluorine-18 (109 minutes) [14-15].

In addition to these radiopharmaceuticals, the labeling of antibodies by elements such as Iodine-124, Zirconium-89 and Gallium-68 constitutes the basis of immuno-PET. This imaging modality provides information about the molecular tumor targets, being useful in the selection of the most appropriate therapy and individualized treatment[15].

PET/CT Image fusion

As PET does not provide morphological data, exams such as CT or MRI are frequently used as a guide to determine the anatomical location of uptake sites. This can be done visually or by fusing images on specific software. This fusion can be performed using two acquisitions made in separate equipment at different times, or two acquisitions obtained on the same scanner that acquired PET and CT images.

For the first situation, there are many reports in the literature proposing methods to standardize the position of the patient in both acquisitions, in such a way that the two images can be obtained with the maximum similarity as possible. One of the tools suggested for this standardization is the use of radiotherapy masks[16-17]. However, the PET/CT scanners have become extremely promising to significantly reduce the possibility of patient motion during acquisitions, and perform them in just one session, 30-40% faster[18].

Concerning the production of artifacts, studies report that, when using a PET/CT image, CT promotes attenuation and correction of PET images. However, image artifacts such as those produced by the presence of metallic materials, respiration, contrast and difference in the fields of view (FOV) of PET and CT scans are replicated in the images[18]. On the other hand, some authors reported that artifacts produced by metallic implants were present in both examinations, PET and PET/CT exams, and had not compromised the view of any of the neoplastic lesions involved in their study[19].

Clinical aplications

Staging

When inserted in the TNM staging system, PET allows the scanning of the entire body, providing information of the primary tumor (T), cervical lymph nodes involved (N) and distant metastasis or secondary tumors (M) at their early stages. When compared to CT, the literature shows that PET has a higher sensitivity (87% versus 62%) and specificity (89% versus 73%) in clinical staging. The application of PET/CT image fusion has even a greater impact at clinical stating than PET alone[20].

In the primary tumor staging, the results of PET are similar to or higher than CT and MRI. However, the replacement of these techniques is infeasible because of the better spatial resolution and anatomical detail of CT and MRI over PET. A recent study showed better results when using the PET/CT image fusion in relation to CT and MRI of oral cavity tumors due to the presence of metal artifacts, especially in deeper tumors[20].

The superiority of PET and PET/CT in relation to the staging of cervical lymph nodes is extensively reported and discussed in the literature. In most studies, the sensitivity and specificity values are higher than those of CT and MRI. However, N0 patients are a challenge for PET and PET/CT as a high number of false-positive and false-negative results are related, being not conclusive in the decision of neck dissection[15,20].

In the diagnosis of distant metastasis, the superiority of PET and PET/CT compared to conventional techniques is reported in the literature. This is one of the main advantages of the technique, mainly for allowing a whole-body scanning[20].

Diagnosis of hidden primary tumors

The CUP syndrome (carcinoma of unknown primary) consists of a microscopic or cell confirmation of the disease, without knowing its site. It is estimated that its incidence ranges from 3 to 9% of head and neck tumors[21]. In most cases, the primary tumor cannot be identified by conventional imaging techniques[20], increasing the risk of distant metastasis, if it is not already present. Additionally, the therapy in these patients usually involves extensive radiotherapy target areas, increasing tissue morbidity and occurrence of sequelae resulting from radiotherapy.

The PET and PET/CT show higher sensitivity values than CT and MRI in the diagnosis of occult primary tumors. Meta-analysis studies showed that 25-37% of tumors can be localized by PET and PET/CT[20,22-23]. The

best results are obtained with PET/CT, especially when combined with panendoscopy[24]. However, a negative result for the presence of tumor by PET should not discard the panendoscopy due to the possibility of false-negative results, especially in regions like the base of the tongue and the tonsils[25].

Treatment planning

In treatment planning, the biggest advantages of PET and PET/CT are in the delineation of the target area to be irradiated through intensity-modulated radiotherapy. This treatment modality allows escalation of the radiation dose, with higher doses in tumor regions where the metabolism is more active or less oxygenated, through the use of radiopharmaceuticals for hypoxia. Another important point of whole-body PET is the ability to diagnose distant metastasis more efficiently, causing significant changes in the treatment plan.

Despite some studies have found no statistically significant differences, the results show a more selective trend of PET/CT in the delineation of a tumor when compared to the conventional techniques. Several studies demonstrated alterations in tumor volume, at higher or lower levels[20]. Thus, the proper treatment planning of patients with malignant head and neck tumors can allow a more conservative treatment, and therefore, with less side effects, promoting a better prognosis and quality of life[26-30].

CONCLUSION

The evidences indicate that the use of PET and, especially, PET/CT image fusion in the diagnosis and treatment planning of malignant head and neck tumors provides superior sensitivity and specificity when compared to CT31-33. In Brazil, the accessibility of PET or PET/CT examinations is restricted. Few centers perform these tests due to its high cost and logistics in the production and distribution of radiopharmaceutical 18F-FDG. Since the 18F-FDG half-life is up to 109 minutes, PET scans can hardly be performed in places far away from the center where the radiotracer is produced.

REFERENCES

1. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Instituto Nacional de Câncer. Coordenação de Prevenção e Vigilância de Câncer. Estimativas 2010: incidência de câncer no Brasil. Rio de Janeiro: INCA, 2011 [citado 2011 Mar 20]. Disponível em: < http://www.inca.gov.br/estimativa/2010/index.asp?link=conteudo_view.asp&ID=2>.

2. Scully C, Porter S. ABC of oral health: oral cancer. BMJ. 2000;321(7253):97-100.

3. Facey K, Bradbury I, Laking G, Payne E. Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers. Health Technol Assess. 2007;11(44):3-4.

4. Mijnhout GS, Hooft L, van Tulder MW, Devillé WL, Teule GJ, Hoekstra OS. How to perform a comprehensive search for FDG-PET literature. Eur J Nucl Med. 2000;27(1):91-7.

5. Fox SH, Lawrence NT, Ackelsberg S, Hsieh J. Future directions in CT technology. Neuroimaging Clin N Am. 1998;8(3):497-513.

6. Franca C, Levin-Plotnik D, Sehgal V, Chen GTY, Ramsey RG. Use of three-dimensional spiral computed tomography imaging for staging and surgical planning of head and neck cancer. J Dig Imag. 2000;13(Suppl 1):24-32. doi: 10.1007/BF03167619.

7. Leopoldino DD, Marques EF, Chjoniak R. Imagem em oncologia. In: Kowalski LP, Anelli A, Salvajoli JV, Lopes LF. Manual de condutas diagnósticas e terapêuticas em oncologia. 2ª ed. São Paulo: Âmbito; 2002. p. 64-9.

8. Cavalcanti MGP, Varnier MW. The role of three-dimensional spiral computed tomography in oral metastases. Dentomaxillofacial Radiol. 1998;27(4):203-8.

9. Cavalcanti MP, Santos DT. 3D-CT computer graphics protocols in the evaluation of maxillofacial tumors. In: Proceedings of the 89th Annual Meeting of Radiological Society of North America; 2003.

10. Leslie A, Fyfe E, Guest P, Goddard P, Kabala JE. Staging of squamous cell carcinoma of the oral cavity and oropharynx: a comparison of MRI and CT in T-and N-staging. J Comput Assist Tomogr. 1999;23(1):43-9.

11. Carranza-Pelegrina D, Lomeña-Caballero F, Soler-Peter M, Berini-Aytés L, Gay-Escoda C. The diagnostic possibilities of positron emission tomography (PET). Med Oral Patol Oral Cir Bucal. 2005;10(4):331-42.

12. Lima ENP. Aspectos práticos de medicina nuclear em Oncologia. In: Kowalski LP, Anelli A, Salvajoli JV, Lopes LF. Manual de condutas diagnósticas e terapêuticas em oncologia. 2ª ed. São Paulo: Âmbito; 2002. p. 69-75.

13. Troost EG, Bussink J, Hoffmann AL, Boerman OC, Oyen WJ, Kaanders JH. 18F-FLT PET/CT for early response monitoring and dose escalation in oropharyngeal tumors. J Nucl Med. 2010;51(6):866-74. doi: 10.2967/jnumed.109.069310.

14. Heuveling DA, de Bree R, van Dongen GA. The potential role of non-FDG-PET in the management of head and neck cancer. Oral Oncol. 2011;47(1):2-7. doi: 10.1016/j.oraloncology.2010.10.008.

15. Hustinx R, Lucignani G. PET/CT in head and neck cancer: an update. Eur J Nucl Med Mol Imaging. 2010;37(3):645-51.

16. Lavely WC, Scarfone C, Cevikalp H, Li R, Byrne DW, Cmelak AJ, et al. Phantom validation of coregistration of PET and CT for image-guided radiotherapy. Med Phys. 2004;31(5):1083-92. doi: 10.1118/1.1688041.

17. Vogel WV, Schinagl DAX, van Dalen JA, Kaanders JHAM, Oyen WJG. Validated image fusion of dedicated PET and CT for external beam radiation therapy in the head and neck area. QJ Nucl Med Mol Imaging. 2008;52(1):74-83.

18. Sureshbabu W, Mawlawi O. PET/CT imaging artifacts. J Nucl Med Technol. 2005;33(3):156-61.

19. Goerres GW, Hany TF, Kamel E, von Schulthess GK, Buck A. Head and neck imaging with PET and PET/CT: artifacts from dental metallic implants. Eur J Nucl Med Mol Imaging. 2002;29(3):367-70.

20. Al-Ibraheem A, Buck A, Krause BJ, Scheidhauer K, Schwaiger M. Clinical applications of FDG PET and PET/CT in head and neck cancer. J Oncol. 2009;2009:208725. doi: 10.1155/2009/208725.

21. Cerezo L, Raboso E, Ballesteros AI. Unknown primary cancer of the head and neck: a multidisciplinary approach. Clin Transl Oncol. 2011;13(2):88-97. doi: 10.1007/s12094-011-0624-y.

22. Rusthoven KE, Kosky M, Paulino AC. The role of fluorodeoxyglucose positron emission tomography in cervical lymph node metastases from an unknown primary tumor. Cancer. 2004;101(11):2641-9.

23. Kwee TC, Kwee RM. Combined FDG-PET/CT for the detection of unknown primary tumors: systematic review and a meta-analysis. Eur Radiol. 2009;19(3):731-44. doi: 10.1007/s00330-008-1194-4.

24. Waltonen JD, Ozer E, Hall NC, Schuller DE, Agrawal A. Metastatic carcinoma of the neck of unknown primary origin: evolution and efficacy of the modern workup. Arch Otolaryngol Head Neck Surg. 2009;135(10):1024-9. doi: 10.1001/archoto.2009.145.

25. Miller FR, Karnad AB, Eng T, Hussey DH, Stan McGuff H, Otto RA. Management of the unknown primary carcinoma: long-term follow-up on a negative PET scan and negative panendoscopy. Head Neck. 2008;30(1):28-34. doi: 10.1002/hed.20654.

26. Ciernik IF, Dizendorf E, Baumert BG, Reiner B, Burger C, Davis JB, et al. Radiation treatment planning with an integrated positron emission and computed tomography (PET/CT): a feasibility study. Int J Radiat Oncol Biol Phys. 2003;57(3):853-63. doi: 10.1016/S0360-3016(03)00346-8.

27. Deantonio L, Beldì D, Gambaro G, Loi G, Brambilla M, Inglese E, et al. FDG-PET/CT imaging for staging and radiotherapy treatment planning of head and neck carcinoma. Rad Oncol. 2008;3:29. doi: 10.1186/1748-717X-3-29.

28. Paulino AC, Koshy M, Howell R, Schuster D, Davis LW. Comparison of CT- and FDG-PETdefined gross tumor volume in intensitymodulated radiotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2005;61(5):1385-92. doi: 10.1016/j.ijrobp.2004.08.037.

29. Santos DT. Mapeamento topográfico metabólico de carcinomas espinocelulares de cabeça e pescoço utilizando a fusão de imagens 18F-FDG-PET- TC [tese]. São Paulo: Universidade de São Paulo; 2005.

30. Guido A, Fuccio L, Rombi B, Castellucci P, Cecconi A, Bunkheila F, et al. Combined 18F-FDG-PET/CT imaging in radiotherapy target delineation for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2009;73(3):759-63. doi: 10.1016/j.ijrobp.2008.04.059.

31. Branstetter BF, Blodgett TM, Zimmer LA, Snyderman CH, Johnson JT, Raman S, et al. Head and neck malignancy: is PET/CT more accurate than PET or CT alone? Radiology. 2005;235(2):580-6.

32. Freudenberg LS, Fischer M, Antoch G, Jentzen W, Gutzeit A, Rosenbaum SJ, et al. Dual modality of 18F-fluorodeoxyglucose-positron emission tomography/computed tomography in patients with cervical carcinoma of unknown primary. Med Princ Pract. 2005;14(3):155-60. doi: 10.1159/000084632.

33. Schöder H, Yeung HW, Gonen M, Kraus D, Larson SM. Head and neck cancer: clinical usefulness and accuracy of PET/CT image fusion. Radiology. 2004;231(1):65-72. doi: 10.1148/radiol.2311030271.

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