

Positron Emission Tomography (PET) in the staging of head neck cancer: comparison between PET and CT

Utilità della Tomografia ad Emissione di Positroni (PET) nella stadiazione clinica dei carcinomi della regione testa collo: confronto dell'imaging PET con l'imaging TC

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Key words

Head and neck cancer • Diagnosis • Imaging • PET

Parole chiave

Tumori testa-collo • Diagnosi • Imaging • PET

Summary

Standard pre-treatment clinical staging (TNM) of head and neck squamous cell carcinoma includes clinical and instrumental objective examination of primary tumour and of the cervical lymph nodes (inspection, palpation of neck, panendoscopy, biopsy of tumour, fine needle aspiration of nodes) and computed tomography or magnetic resonance imaging. Albeit, this procedure presents diagnostic limitations in the identification of approximately 1/3 of T1, of small sized nodes and in the diagnosis of metastases. Positron emission tomography-fluorodesoxy-glucose imaging, in the diagnostic workup of these cases, appears to offer an important contribution, however, its use is limited due to poor availability of this equipment and the high cost of the examination. In the present study, a comparison is made of results of standard clinical staging and positron emission tomography-fluorodesoxy-glucose in 22 patients with head and neck carcinoma prior to surgical treatment, with the results of pathological staging (pTNM) carried out on surgical specimens. In the staging of the tumour, computed tomography shows a sensitivity of 71% and positron emission tomography of 81%. In the staging of nodes, computed tomography imaging shows a sensitivity of 73%, a specificity of 57% and an accuracy of 68%, whereas positron emission tomography shows a sensitivity of 93%, a specificity of 100% and an accuracy of 95%. Furthermore, positron emission tomography identified 1/5 occult tumours and one tumour revealed at objective endoscopic examination, but not by computed tomography. The risk of occult nodes following positron emission tomography was found to be 7%. Overall, these results are in keeping with those reported in the literature, thus confirming the usefulness of positron emission tomography-fluorodesoxy-glucose in identifying occult tumours and nodes, in which computed tomography appears to be limited. Indications of positron emission tomography-fluorodesoxy-glucose may play a role in the choice of therapeutic options for the clinically N0 neck.

Riassunto

La stadiazione clinica standard pretrattamento (TNM) dei carcinomi a cellule squamose del distretto testa-collo (HNC) comprende l'esame obiettivo clinico e strumentale di T e di N (ispezione, palpazione del collo, panendoscopia, biopsia di T, citologia per agoaspirato di N) e l'imaging TC od MR. Tuttavia presenta limiti diagnostici per l'identificazione di circa 1/3 dei T1, degli N di piccole dimensioni e per la diagnosi di M. Il contributo dell'imaging PET-FDG in queste diagnosi appare rilevante, ma il suo impiego è limitato dalla scarsa disponibilità delle apparecchiature e dai costi elevati dell'esame. Nel nostro studio vengono messi a confronto i dati della stadiazione clinica standard e della PET-FDG di 22 pazienti affetti da HNC prima del trattamento chirurgico, con i risultati della stadiazione patologica (pTNM) effettuata sui pezzi operatori. Nella stadiazione di T l'imaging TC ha una sensibilità del 71% e l'imaging PET dell'81%. Nella stadiazione di N l'imaging TC ha una sensibilità del 73%, una specificità del 57% ed una accuratezza del 68%, mentre l'imaging PET ha una sensibilità del 93%, una specificità del 100% ed una accuratezza del 95%. La PET inoltre ha identificato 1/5 tumori occulti e 1 tumore evidenziato dall'esame obiettivo endoscopico, ma non dalla TC. Il rischio di N occulti dopo imaging PET è risultato del 7%. Nel complesso questi risultati si allineano a quelli già presenti nella letteratura, confermando l'utilità della PET-FDG nella identificazione di T ed N occulti, dove la TC presenta delle limitazioni. Le indicazioni della PET-FDG possono incidere sulla opzione terapeutica nel collo clinicamente N0.

Introduction

In the clinical staging of the head and neck cancer (HNC), besides objective clinical and instrumental

examination of the primary tumour (T) and cervical lymph nodes (N) (inspection, neck palpation, endoscopy, biopsy of T, fine needle cytology of N), it is necessary to perform imaging examinations – com-

puted tomography (CT) and/or magnetic resonance (MR) – for the identification and morphological definition of T and N (size, extension to soft tissues, bone, cartilage or vessel infiltration) and for diagnosis of distant metastases (M)¹. Objective clinical and endoscopic examinations lead to correct staging only in 50% of T and 60-70% of N, whilst identification of some T and small sized N as well as the morphological definition of many T and larger N remain uncertain²⁻⁴. CT or MR imaging contribute to the identification of some 50% of occult N at objective examination and to correct staging of the majority of large T (T2-T4), showing limitations in the identification of approximately 1/3 of T1 and small N^{2-4,6}. Another diagnostic problem concerns the detection of M which requires, in asymptomatic forms, total body CT, not usually included in staging.

These diagnostic limits suggested the use of scintigraphic imaging methods such as single proton emission computed tomography (SPECT) and, more recently, the use of positron emission tomography with 2-(¹⁸F)-fluorodesoxyglucose (PET-FDG), with the first clinical use of PET-FDG imaging in HNC being performed in 1992⁷. This procedure was later used both in staging and follow-up, with specific indications, in which CT and MR imaging were found to have diagnostic limits, such as identification of occult T and synchronous T⁸⁻¹¹, in staging of the N0 neck¹²⁻¹⁶, in the diagnosis of a recurrence of T and/or N following surgery and/or radiotherapy^{10,15,17,18}. Albeit, considering the complexity and the poor availability of these tools and the high costs of the examination, PET imaging has so far been limited to few Nuclear Medicine centres, and the studies on HNC are still, today, relatively few in number and often refer to a limited number of cases.

In order to contribute to the evaluation of the usefulness of the method, an analysis has been made of our population of HNC patients prior to surgical treatment, comparing CT imaging data and those of PET-FDG imaging with post-operative pathological staging (pTNM).

Patients and methods

PATIENTS

The patient population comprised 22 patients (19 male, 3 female), mean age 62.27±8.8 years (range 46-79), (mean body weight: 67.87±11.9 kg), (mean height 168±7.9 cm) consecutively admitted to the ENT Division of Azienda Ospedaliera Pisana, Pisa with a diagnosis of squamous cell carcinoma (SCC) of head and neck. None of the patients were diabetic. Site of the primary tumour (T) was larynx in 8, oropharynx in 5, oral cavity in 4, whilst the site of the

tumour was not identified in 4 (occult primary tumour). Furthermore, one patient had previously been submitted to surgery for primary tumour of the head skin (T0) (Table I). In all patients, pre-operative staging of tumour included, besides the objective clinical examination (inspection, neck palpation, panendoscopy and biopsy of T), CT of head-neck region and total body PET-FDG. All patients were submitted to surgical treatment of the primary tumour and regional lymph nodes. Written informed consent to the diagnostic-therapeutic procedures was obtained prior to commencement from all patients, in accordance with the regulations of the Ethics Committee of the Azienda Ospedaliera Pisana.

HISTOPATHOLOGY

Pathological staging of patients (pTNM) was performed by means of macro- and microscopic examination of surgical specimens^{7,19}. From measurements of T, in the three dimensions, the volume of the tumour was calculated in cm³ according to the formula $V = \pi/6 \times A \times B \times C$, (with A, B and C being the three dimensions)¹⁴. The number of nodes removed and number of pathological nodes were also calculated. To measure lymph nodes, the maximal diameter of the greatest node was taken into consideration (Table I).

POSITRON EMISSION TOMOGRAPHY-FLUORODESOXY-GLUCOSE

Glucose consumption of the primary neoplastic lesion and of the metastatic lesions was evaluated by means of PET with FDG, as metabolic tracer. Patients were studied in fasting conditions for at least 6 hours, and serum glucose levels were also determined. An i.v. infusion of 370 MBq of 2-(¹⁸F)-Fluorodesoxyglucose was then given. Tomoscintigraphic imaging was performed using a total body ECAT HR + (Siemens/CTI) tomograph with a theoretic spatial resolution of 5 mm FWHM. The instrument is equipped with 32 rings with a bismuth germanate detector which provides, simultaneously, 63 planes of scanning in a 15 cm field of investigation. Consecutive multiple 3-D scans, with the use of a sliding couch, enabled us to obtain total body scans. Data obtained, corrected for random detection, system dead time, attenuation and scatter, were recomposed using an iterative algorithm (FORE-SEM). After recomposition on the coronal, sagittal and transverse planes, tomoscintigraphic scans were interpreted qualitatively, and semiquantitatively by calculating the absorption value of the relative tracer (Standardized Uptake Value, SUV). On transaxial images, in which the primary or secondary neoplastic mass was better represented, a region of interest (ROI) was manually detected (10 mm around the pixel with highest activity), in order to calculate the maximal and mean SUV values, using Siemens Statistical Analysis software according to the formula:

Table I. Patients enrolled and related anatomico-histopathological data of T and N according to CT and PET-FDG diagnosis of T and N.

N.	Age	Sex	T site	Pathological TNM		CT diagnosis		PET diagnosis		T cm ³ (#)	N cm (S)	Total nodes (n.)	Metastatic nodes (n.) (S§)
				T	N	T	N	T	N				
1	73	M	Larynx	2	2b	+	+	+	+	1.099	4	22	3
2	69	F	Larynx	3	2b	+	+	+	+	6.911	2	24	4
3	51	M	Oropharynx	1	2a	+	+	+	+	0.164	3.2	10	1
4	58	M	Larynx	4	2a	+	+	+	+	40.317	3.5	24	1
5	53	M	Larynx	3	2b	+	+	+	+	7.917	2.2	15	3
6**	58	M	Skin	0	0	-	+	-	-		1.5	28	0
7	79	M	Oropharynx	3	2b	+	+	+	+	6.283	2.3	16	3
8	46	M	Oral cavity	2	0	+	-	+	-	3.77	0.8	7	0
9*	78	M		x	2b	-	+	-	+		3	16	2
10	47	M	Larynx	2	0	+	-	+	-	11.729	1	12	0
11	61	M	Larynx	3	0	+	+	+	-	5.97	1.2	10	0
12	56	F	Oropharynx	1	0	-	+	+	-	0.208	1.5	8	0
13*	79	F		x	2a	-	+	-	+		4	15	1
14	59	M	Larynx	2	1	+	-	+	-	6.963	0.9	12	1
15	57	M	Larynx	2	0	+	-	+	-	6.597	0.6	9	0
16*	46	M		x	2a	-	+	-	+		5	14	1
17	79	M	Oral cavity	4	1	+	-	+	+	37.699	0.9	21	1
18	55	M	Oropharynx	2	0	+	-	+	-	11.781	0.8	41	0
19	63	M	Oropharynx	3	1	+	+	+	+	13.744	1.9	19	1
20	75	M	Oral cavity	2	1	+	-	+	+	7.54	1.2	22	1
21*	60	M		x	2b	-	+	-	+		4	24	6
22	60	M	Oral cavity	2	1	+	-	+	+	6.597	0.9	26	1

(*) Patients with occult T; (**) Patient already submitted to surgery for skin T; (&) 1-well differentiated, 2-moderately differentiated, 3-poorly differentiated; (#) Volume of T in cm³; (S) Diameter of node of greater size; (§§) Histological diagnosis.

$$\text{SUV} = \frac{\text{Dose corrected for decay/cm}^3 \text{ of tumour}}{\text{Dose injected/weight of patient in grams}}$$

A mean SUV value >3 was considered indicative of an increased regional metabolism.

COMPUTED TOMOGRAPHY

All patients were submitted to neck and mediastinum CT. Baseline scans were obtained with CT/i Hi Speed spiral scanner (GE Medical Systems, Milwaukee, WI, USA) which extended from the mandibular arch to the aortic arch. Iohexol (Omnipaque 350, Nycomed Amersham, Princeton, NJ, USA) was injected iv in a single bolus (100 ml). Spiral images were repeated after 30 seconds using a collimation of 5 mm.

STATISTICAL ANALYSIS

Values are expressed as mean ± standard deviation (SD). Data are expressed in terms of sensitivity, specificity, accuracy, and positive and negative predictive values.

Youden (J) index was used to calculate global diagnostic performance both for FDG-PET and CT. Jandel SigmaStat software was used in the statistical analysis.

Results

STAGING OF T

The 22 patients have been classified (pTNM) as 4 Tx (occult primary tumours), 1 T0 (primary tumour of the skin of the head already operated upon prior to staging), 2 T1, 8 T2, 5 T3 and 2 T4. The volume of operated T varied from 0.164 cm³ to 40.317 cm³ (mean 10.311 ± 11.451 cm³) (Table I). The 4 Tx have been thus classified since clinical staging and PET imaging did not allow their identification. The 2 T1 in the palatine tonsil were identified by PET but not by CT. The smallest neoplasia (patient n. 3, Table I) was 0.164 cm³ in volume (maximal diameter of 0.9 cm) and was "occult" until identification with PET (Tables I, II). Also the second T1 (patient n.12, Table I) was located in the palatine tonsil and was identified with objective examination and PET, but not with CT. The other T+ (T2, T3, T4) varied in volume between 1099 cm³ and 40.317 cm³ and all were identified both with CT and PET.

Excluding T0 (primary tumour previously operated upon), CT identified overall 15/21 (71%) T with 6 false negative (29%) and no false positives (sensitivity 71%), whilst PET identified 17/21 (81%) T with 4 false negatives (19%) and no false positives (sensitivity 81%) (Table IV).

Table II. Primary tumours correctly staged according to the T class (T0 not shown).

T class	Histology	CT	PET
Tx	4	0	0
T0	-	-	-
T1	2	0	2
T2	8	8	8
T3	5	5	5
T4	2	2	2
	21	15	17

Table III. Neck node metastases correctly staged according to N class.

N class	Histology	CT	PET
N0	7	4	7
N1	5	1	4
N2a	4	4	4
N2b	6	6	6
	22	15	21

Table IV. Results of use of PET and CT in diagnosis of T.

	PET	CT
Sensitivity	80.95%	71.43%
Specificity	n.f.*	n.f.*
Accuracy	80.95%	71.42%
False positive	n.f.*	n.f.*
False negative	19.04%	28.57%

*n.f. - not feasible

STAGING OF N

In 22 operations, overall 395 nodes were removed, of which 30 were the site of metastases. The neck nodes removed varied in diameter from 0.6 cm to 5.0 cm (2.11 ± 1.32 cm). Pathologic nodes ranged in diameter between 0.9 and 5.0 cm (2.60 ± 1.33 cm).

The 22 patients were classified (pTNM) as 7 N0, 5 N1, 4 N2a and 6 N2b. In 7 N0 the diameter of the nodes ranged from 0.6 to 1.5 cm (1.06 ± 0.35 cm), in 5 N1 from 0.9 to 1.9 cm (1.16 ± 0.43 cm), whilst in 10 N2 from 2.0 to 5.0 cm (3.32 ± 0.96 cm) (Table I). In the 7 N0, CT diagnosis corresponded to pathological staging in 4 patients with 3 false positives, whereas PET diagnosis was in accordance in all 7 pa-

tients. In 5 N1, CT corresponded to pathologic staging in 1 patient with 4 false negatives, whilst PET diagnosis was in accordance in 4 patients with 1 false negative. In 10 N2, CT and PET diagnosis corresponded to pathological staging in all patients (Table III).

The smallest pathological nodes identified with PET were 0.9 cm in diameter (patients n. 14, 17, 22, Table I), whereas the smallest node metastasis identified by CT was 1.9 cm in diameter (patient n.19, Table I). Overall, CT correctly staged neck nodes in 15/22 (68%) patients with 3/7 (43%) false positives and 4/15 (27%) false negatives, whilst PET correctly staged in 21/22 (95%) patients with only one false negative (1/15-7%) and no false positive.

CT imaging in the staging of N shows a sensitivity of 73%, a specificity of 57% and an accuracy of 68%, with Youden index = 0.30, a positive predictive value of 79% and a negative predictive value of 50% (Table IV).

PET imaging in the staging of N shows a sensitivity of 93%, a specificity of 100% and an accuracy of 95%, with Youden index = 0.93, a positive predictive value of 100% and a negative predictive value of 87.5% (Table V).

Table V. Results of use of PET and CT in diagnosis of N.

	PET	CT
Sensitivity	93.3%	73.33%
Specificity	100%	57.14%
Accuracy	95.45%	68.18%
False positive	0.00%	42.86%
False negative	6.67%	26.67%

Discussion

Clinical staging of primary tumour (T) includes not only the objective clinical and instrumental examination (inspection, panendoscopy, biopsy) but also CT or MR imaging¹.

Objective and endoscopic examination results in correct staging of T in only 50% of cases, even if it appears to be more sensitive than radiological imaging, CT and MR, in the identification of small T (T1)^{2,5}. CT or MR imaging is employed to define the limits of T, and extension to adjacent tissues, involvement of bones, cartilages or vessels. This contribution allows adequate staging in 77-84% of T^{2,5,14,15}. Indeed, correct staging was achieved in all T4, T3, many T2, whereas many small sized T1 were not identified (occult T)^{2,5}.

The reasons for lack of identification, besides small

size, were superficial spread of the neoplasia in certain sites such as glottis and pharynx, where slight structural alterations are not detected at morphologic imaging².

In this regard, PET imaging offers certain advantages, since identification of T depends exclusively upon the FDG uptake. In fact, with PET-FDG, 22-50% of the very small sized occult T are identified^{8,10}. The smallest T detected by PET, located in pharynx (rhinopharynx, palatine tonsil, base of the tongue), was between 0.3 and 0.6 cm in diameter^{10,11}. Overall, PET imaging, in staging of T, shows a specificity of 83-100% and a sensitivity of 90-100%, which is approximately 15% greater than that of CT or MR imaging^{8,14,15,17,20}.

Uptake of FDG was related to the proliferative activity and development of tumour²¹. In non-treated T, the marked uptake was associated with more advanced stages of the tumour with worse prognosis²². A relationship was found between hypercaptation and higher grading, without, however, reaching statistical significance²².

In our patient population, all primary tumours <cm³ in volume (8 T2, 5 T3 and 2 T4) were correctly staged both with CT and PET, while the 2 T1 were identified only with PET. The smallest of these T1, located in palatine tonsil was 0.164 cm³ in volume (maximal diameter 0.9 cm) and was "occult" until identification with PET, whilst the other T1 a little larger in volume (0.208 cm³), also localised in palatine tonsil was detected both at the objective clinical examination and at PET (Fig. 1). A total of 4 primary tumours were not identified (Tx), following clinical staging and PET imaging. In our series, CT imaging showed a sensitivity of 71%, with 29% of false negative cases (occult T). PET imaging showed a sensitivity of 81%. PET imaging, thus, shows 10% greater sensitivity than CT.

These results are in agreement with those reported in the patient populations of most Authors²³⁻²⁵, which, moreover, vary considerably with each other due to the different number of T1 and Tx in each series, the problem of identification being limited to small T1, which, in effect, determines the sensitivity of the diagnostic method.

Clinical staging of neck node metastases relies mainly upon palpation of the neck and CT and/or MR imaging, with ultrasound being more frequently employed in follow-up¹. Neck palpation is considered part of the overall objective clinical examination, but is not very accurate: sensitivity and specificity being between 60-70%, thus 30-40% of necks, negative at palpation (clinically N0 necks), are at risk of occult metastases^{3,4}. This risk depends upon the size and site of the primary tumour (T): in T of the glottis, this is relatively low, while in many T of the oral cavity and pharynx, the risk of occult metastases is about 30-50%⁴. As far as concerns the poor diagnostic sen-

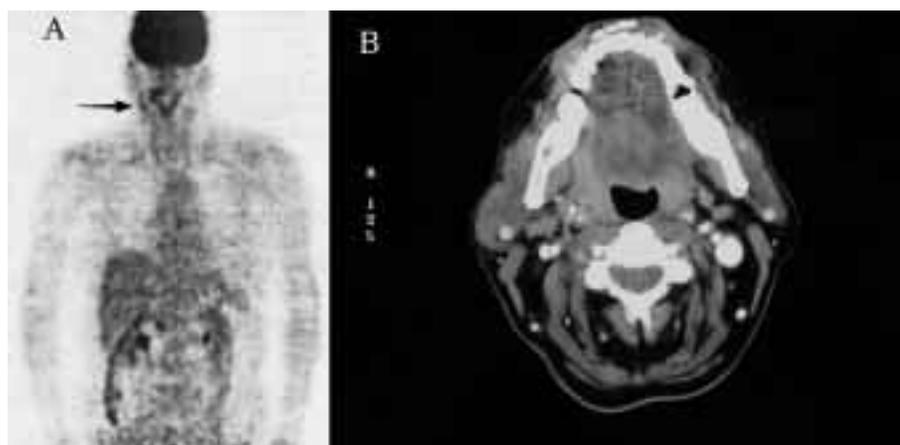


Fig. 1. Patient n. 12. A) Total body PET: primary tumour of oropharynx right lateral wall. B) Axial CT scan after i.v. contrast infusion: at tonsil cavity level, no asymmetry of air lumen is seen, nor imaging of expansion.

sitivity of palpation preventive surgical treatment is usually carried out on the N0 neck, if the risk of occult metastases is high, according to the site of the primary tumour⁴.

CT or MR imaging stages, with reasonable accuracy, clinically N+ neck with hyperplastic nodes, reaching a sensitivity of 81-100% and a specificity of 75-86%^{2,4,5}. The fairly high number of false positive is due to the difficulty in distinguishing, on the basis of morphological findings, inflammatory hyperplastic nodes from node metastases⁴. This difficulty increases considerably in small nodes of clinically N0 necks. In these patients, sensitivity of CT or MR staging is reduced by 40%-68%, whilst specificity remains in the region of 78%-92%^{4,6}. Of the two imaging techniques, CT has a slightly higher sensitivity and specificity, the difference, however, not being statistically significant from RM⁴. Overall, CT or MR staging allows identification of >40% occult metastases upon palpation, albeit the risk of residual occult metastases in clinically N0 necks is still too high (32-60%) since CT or MR may play a role in the choice of surgical procedure. PET imaging allows identification of very small pathological nodes: the smallest metastatic node detected was 0.4 cm in diameter⁷. In staging of N, PET-FDG shows a sensitivity of 84-91% and a specificity of 88-94%^{12-14,16}, being significantly greater than that of CT or MR in these conditions i.e., the clinically N0 necks¹²⁻¹⁶.

In our series, many pathological nodes were of small size. In 12 patients, classified as N0 and N1 (pTNM), the maximal diameter of the greatest pathological node ranged between 0.6 and 1.9 cm, whereas in the other 10 patients, classified as N2a and N2b, this var-

ied between 2 and 5 cm. CT imaging correctly staged only 5/12 (42%) patients N0 and N1, with 4/5 (80%) false negatives and 3/7 (43%) false positives (Fig. 2), whereas PET-FDG correctly staged 11/12 (92%), with only 1 false negative (1/5-20%). All 10 patients classified as N2a and N2b were correctly staged both by CT and PET-FDG. Overall, in our patient population, CT imaging, in the staging of N showed a sensitivity of 73%, a specificity of 57%, whilst PET-FDG showed a sensitivity of 93%, a specificity of 100%.

The present investigation confirms the usefulness of the two imaging methods in staging of N >2 cm and the diagnostic limits of CT in the detection of small node metastases, for which PET showed, on the contrary, high sensitivity and specificity. Only in 1/12 patients classified as N0-N1 (pTNM) with nodes with a mean diameter of about 1 cm, did PET fail to identify one metastatic node of 0.9 cm. The risk of residual occult metastases after PET staging in our patients was 7% (false negatives).

Conclusions

In the pre-treatment clinical staging of HNC, CT is still the imaging technique of choice for the morphological definition of T and N (size, extent in adjacent tissues, bone, cartilages or vessel infiltration). However, the technique fails to identify many small T1 of larynx and pharynx and diagnostic accuracy in N0 neck is not sufficient to have an effect upon the therapeutic choice. PET-FDG imaging identifies a mean of 1/3 of clinically occult T and shows a very high diagnostic accuracy in the clinically N0 neck, with a

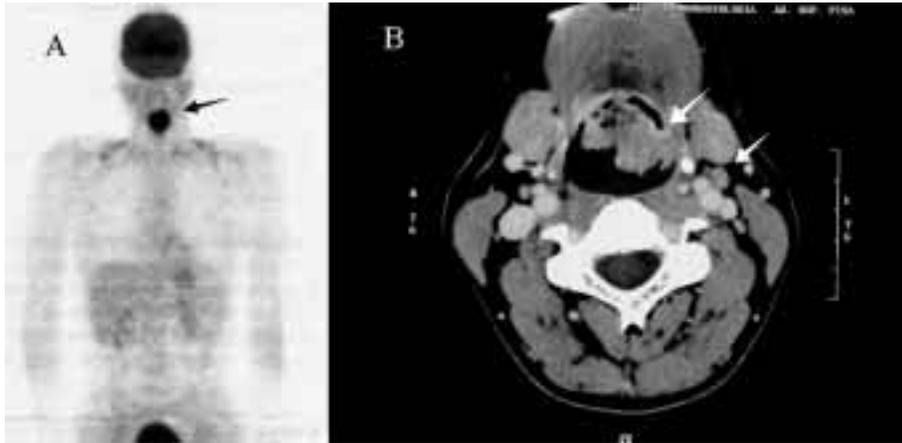


Fig. 2. Patient n. 11. A) Total body PET: larynx tumour without pathological neck nodes. B) Axial CT scan of neck after i.v. contrast infusion: bulky exophytic supra-glottic lesion occupying air lumen; in left latero-cervical site, in correspondence to carotid bifurcation, presence of false positive lymph node.

risk of residual occult metastases of about 10%. In clinically N0 necks, indications of PET-FDG may be supported both by the “wait and see” option, as well

as the choice of the side upon which to operate (monolateral, rather than bilateral neck dissection), or the levels to be submitted to neck dissection.

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