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ORIGINAL ARTICLE

Impact Of PET/CT On Treatment In Patients With Head And Neck Squamous Cell Carcinoma

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT:

Introduction: Although PET/CT is effective for staging HNSCC, its impact on patient management is somewhat controversial. For this reason, we considered it necessary to carry out a study in order to verify whether PET/CT helps to improve the prognosis and treatment in patients. This study was designed to address the impact of PET-FDG imaging when used alongside CT in the staging and therapeutic management of patients with HNSCC.

Material and methods: Data was collected from 169 patients diagnosed with HNSCC with both CT and PET/CT (performed within a maximum of 30 days of each other). It was evaluated whether discrepancies in the diagnosis of the two imaging tests had impacted the treatment.

Results: The combined use of CT and PET/CT led to a change in the treatment of 67 patients, who represented 39.7% of the sample. In 27.2% of cases, it entailed a change in the type of treatment which the patient received. In 3.0% of the cases, using both diagnostic tests led to modifications of the therapeutic intention of our patients.

Conclusions: Using PET/CT in addition to the conventional imaging method in staging resulted in more successful staging and more appropriate therapeutic decision-making.

KEYWORDS: computed tomography (CT), head and neck squamous cell carcinoma (HNSCC), positron emission tomography–computed tomography (PET/CT), therapeutic impact

ABBREVIATIONS

AJCC – American Joint Committee on Cancer
CEICA – Committee of the Community of Aragón
CT – computed tomography
HNSCC – head and neck squamous cell carcinoma
MRI – magnetic resonance imaging
NPV – negative predictive value
PET/CT – positron emission tomography–computed tomography
PPV – positive predictive value

INTRODUCTION

The initial staging of head and neck squamous cell carcinoma (HNSCC) is based on clinical history, clinical examination of the respiratory tract using fibroscopy, and diagnostic imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) to evaluate the involvement of the lymph nodes, as well as the extension and infiltration of the tumor.

The current clinical guidelines recommend positron emission tomography-computed tomography (PET/CT) as an option in advanced-stage disease. However, it is not advised in the early stages of the disease, due to poor diagnostic yield in patients in stage I or II of the disease [1].

Nonetheless, the supplementary examination provided by PET/CT has improved staging, treatment evaluation, and recurrence detection in patients with HNSCC [2]. Some studies have analyzed the value of PET images in detecting pathological locoregional adenopathy. Two meta-analyses have demonstrated the excellent diagnostic performance of PET in pretreatment assessment, as well as the accuracy of PET/CT in the diagnosis of HNSCC, compared with CT alone [3]. In general, PET/CT scanning is not routinely indicated in patients with HNSCC [4]; however, in

Tab. I. Change in treatment using two diagnostic techniques.

CHANGE	YES	NO	TOTAL
	67	102	169
	39.7%	60.3%	100.0%

Tab. II. Impact on treatment using two diagnostic techniques.

IMPACT	NULL	LOW	MODERATE	HIGH	EXTREME	TOTAL
	81	21	16	46	5	169
	47.9%	12.4%	9.5%	27.2%	3.0%	100.0%

Tab. III. Variation in the diagnosis of the primary tumor.

T BY CT	T BY PET/CT	T FINAL	N
To	T1	T1	2
To	T1	To	1
To	T2	T2	4
To	T3	T3	5
To	T4a	T4a	2
T1	To	To	2
T2	To	To	7
T2	To	T2	3
T2	T3	T3	1
T3	To	To	10
T3	T4a	T4a	2
T4a	To	To	4

Patients correctly staged by CT
Patients correctly staged by PET/CT

patients considered to be at high risk of distant metastases, PET/CT scanning is currently recommended as the most effective screening technique [5], with no additional costs.

Although PET/CT has proved effective for staging HNSCC, its impact on patient management is somewhat controversial. While some authors have reported that using PET in addition to conventional imaging did not significantly alter clinical management [6], other research groups affirmed the opposite [7].

It is for the exposed facts that we consider it necessary to carry out a study in order to verify whether patients could benefit from PET/CT and to determine whether performing this test in patients with HNSCC has a significant impact on therapeutic decisions. In other words, the aim is to determine whether PET/CT helps to improve the prognosis and treatment of head and neck cancer patients.

MATERIAL AND METHODS

Data from 169 patients was collected from January 2012 to March 2020, under the approval of the Research Ethics Committee of the Community of Aragón (CEICA) and the management at Hospital Clínico Universitario Lozano Blesa of Zaragoza.

The inclusion criteria in the study were a history of HNSCC at any stage and in any location (paranasal sinuses, nasopharynx, oropharynx, hypopharynx, or larynx) and a CT and a PET/CT performed within 30 days of each other. All patients who did not meet these requirements were excluded.

The initial stage of the disease for the patients in our study was determined based on the classification in the American Joint Committee on Cancer (AJCC) Staging Manual (7th edition). More than half of the patients studied (51.0%) were diagnosed with stage IVa. The next most frequent stages were III (26.5%) and II (11.8%). The rest of the patients were in stage IVc (6.9%), IVb (2.0%), and I (2.0%).

This is a retrospective observational study conducted in a single tertiary center.

The imaging test protocol (CT and PET/CT) is described below.

A cervicothoracic CT scan was performed after iodine contrast was injected. The cervical study was focused on the head and neck region (from the base of the skull to the lung vertices with a slice thickness of 1 mm), while the thoracic study was performed from the lung vertices to the adrenal glands (thickness of 3 mm).

A PET/CT scan was performed on patients who had fasted for at least 6 h and who had been administered an intravenous injection of fluorodeoxyglucose 60 min before the test, at a dose of 3–4 MBq/kg. Images were captured from the head to the middle of the thighs in the axial plane. They were then reconstructed in the coronal and sagittal planes.

Once the two diagnostic test results were obtained, all the cases were presented to the Multidisciplinary Tumor Board of Hospital Clínico Universitario Lozano Blesa of Zaragoza. The Board is made up of otolaryngologists, medical oncologists, radiation oncologists, anatomy pathologists, nuclear medicine physicians, and radiologists. After each patient case was presented, with the exploration (performed by the otolaryngologist) and the diagnostic tests (evaluated by radiologists and nuclear medicine specialists, depending on whether it is CT or PET/CT, respectively), the TNM stage of the tumor was established according to the AJCC Staging Manual (7th edition).

The impact that the discrepancies between CT and PET/CT had on the treatment and the staging of the cases was also evaluated. For this purpose, the following coding was used:

- NULL: There was no variation between the stages;
- LOW: There was variation in the staging, but it had no impact on the treatment;
- MODERATE: The staging discrepancy resulted in a change in treatment, but within the same therapy modality, such as a different type of surgery, area to be irradiated, or number of chemotherapy cycles;
- HIGH: The variation in the staging led to a modification in the treatment modality (surgical treatment *vs*. organ-preserving treatment);
- EXTREME: The staging discrepancy generated a change in the intention of the treatment (curative *vs*. palliative).

Moreover, each case with discrepancies was assessed for variations in all the T, N, and M variables and for whether the error was attributed to CT or PET/CT. These results were corroborated by histological studies or follow-up examinations of the patients.

The data were analyzed using IBM SPSS 19.0 for Windows (IBM Corp., Armonk, NY, USA). The association between the different techniques was established using the likelihood-ratio test and was quantified using Somers' D. The alpha error was set to 0.05, which is equivalent to a 95% confidence interval.

RESULTS

The impact of the two imaging tests on the treatment was analyzed; that is, it was assessed how the use of both exploration techniques resulted in a change in the selected therapeutic modality. In the same way, the consequences that this entailed in the treatment of patients were evaluated. For this purpose, the coding mentioned in the methods section was used.

Afterwards, we established that the fact of using CT and PET/CT had led to a change in treatment in 67 patients, which represents 39.7% of the sample (Tab. I.). On the other hand, we analyzed the impact of these changes on the therapeutic management of the cases in our sample (Tab. II.) and in 47.9% of the cases the discrepancies between the two tests did not imply any change in the tumor stage.

In 12.4% of the cases, the impact was low: a change in the staging was observed, but without therapeutic repercussions (occurring most of the time due to the detection of adenopathy by PET/CT, which the CT was not able to reveal). In a few cases, PET/CT failures were detected, where there was an overestimation of the size of the primary tumor (1.2%) as well as an overestimation of locoregional adenopathy (0.6%).

In 9.5% of the cases, we observed a moderate impact; that is, the use of two imaging techniques had modified the treatment, but always within the same modality. In most of these cases (2.7%), the changes in the treatment were because a lesion was detected by PET/CT in the location of the primary tumor which CT was not able to distinguish. In 2.4% of the cases, it was because locoregional adenopathy was detected by PET/CT (undetectable by CT). In the same percentage of cases, PET/CT detected distant metastases. In 1.2% of the cases, pathological adenopathy was mistakenly indicated by PET/CT. In 0.6% of cases, there was an error on both the CT and PET/CT scans: not visualizing locoregional lymph node metastases which manifested later.

In 27.2% of the cases, the performance of both diagnostic techniques had a high impact on the treatment: it led to a modification in the therapeutic modality that the patient received. In most cases, there was a false positive on the CT scan, either of the primary tumor (10.7%) or of adenopathy (2.7%). CT detected distant metastases in 0.6% of cases, which proved to be false positives. Lesions were detected by CT in the area of the primary tumor that the PET/CT was unable to visualize in 1.8% of cases and positive adenopathy escaped the PET/CT diagnosis in 0.6% of cases. On the other hand, PET/CT was the only imaging technique able to detect the primary tumor or local recurrences in 2.4% of cases, locoregional metastatic lymph nodes in 1.8%, and distant metastases in 3.6%. Similarly, PET/CT led to false positive results when detecting local recurrences in 1.2% of cases and in 0.6% when detecting distant metastases. In 1.2% of cases, there was an error in both techniques: a lymph node recurrence was detected when there was none.

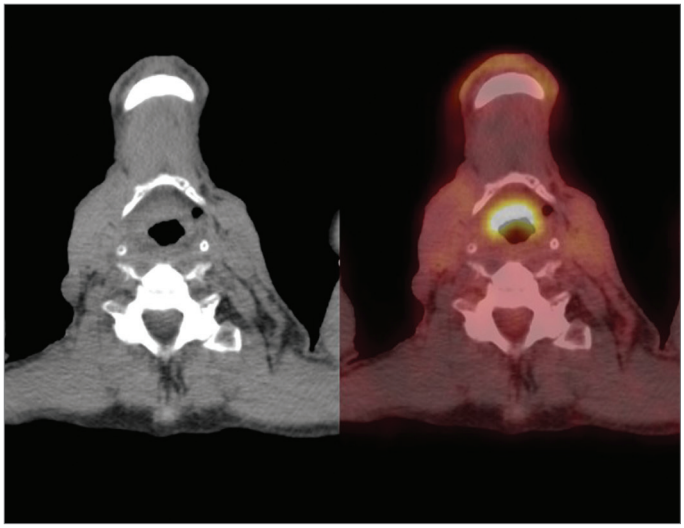

Fig. 1. Supraglottic hypermetabolism (SUV_{max}: 8.95), approximately 24 x 7 x 38 mm in maximum diameter, affecting the entire epiglottis from the base without causing obliteration of the airway, extending towards aryepiglottic folds and the pyriform sinus, mainly on the right side. No cervical, supraclavicular, axillary, mediastinal, hilar, abdominal, pelvic, or inguinal nodes suspicious of malignancy were detected.

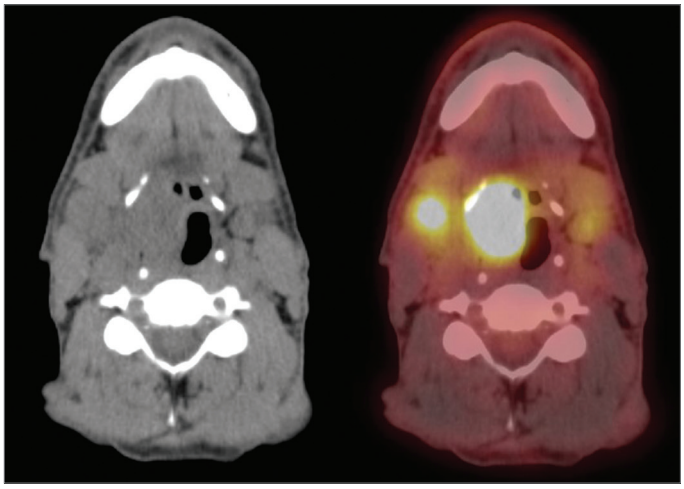

Fig. 2. Voluminous supraglottic hypermetabolic mass (SUV_{max}: 18.27 g/mL; metabolic dimensions: approximately 33 x 45 x 52 mm), extending from the right vallecula to the ipsilateral vocal cord and causing stenosis of the laryngeal lumen. Right lateral cervical hypermetabolic adenopathy IIA (SUV_{max}: 8.09 g/mL; 23 mm with a short axis).

In 3.0% of the cases, we observed an extreme impact on the treatment, since the use of CT and PET/CT changed the therapeutic intent: in 2.4% of the cases, PET/CT detected distant metastases that CT was unable to detect, while the opposite occurred in 0.6% of cases.

In the same way, we studied all the differences between the two imaging tests in the T, N, and M variables, breaking them down

Tab. IV. Variation in the diagnosis of regional lymph nodes.

N BY CT	N BY PET/CT	T FINAL	N
No	N1	N1	6
No	N2a	N2a	2
No	N2a	N2c	1
No	N2b	No	1
No	N2b	N2b	3
No	N2c	N2c	4
N1	No	No	5
N1	N2a	N2a	1
N1	N2c	N2c	3
N2a	No	N2a	1
N2a	N2b	N2b	1
N2b	No	No	1
N2b	N2a	N2a	1
N2b	N2c	N2c	6
N2c	No	No	2
N2c	N2b	N2b	1

Patients correctly staged by CT
Patients correctly staged by PET/CT
Patients incorrectly staged by PET/CT and CT

in Tab. III., IV., and V. We also obtained the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CT and PET/CT in staging for each of these variables (with 95% confidence intervals).

In the diagnosis of a primary tumor through the use of CT, the sensitivity, specificity, PPV, and NPV were 85.4% (78.1–92.7%), 67.5% (57.2–77.8%), 74.5% (66.1–83.0%), and 80.6% (71.1–90.1%), respectively. Likewise, the PET/CT diagnosis demonstrated a sensitivity of 95.8% (91.2–100.4%), a specificity of 99.0% (97.0–101.0%), a PPV of 98.6% (95.8–101.4%), and an NPV of 97.0% (93.6–100.3%).

In the case of lymph nodes, we obtained through CT a sensitivity of 66.2% (54.7–77.7%), a specificity of 89.4% (83.5–95.3%), a PPV of 79.6% (68.9–90.4%), and an NPV of 80.9% (73.7–88.1%). Using PET/CT, we obtained a sensitivity of 89.7% (82.5–96.9%), a specificity of 99.0% (97.1–100.9%), a PPV of 98.4% (95.3–101.5%), and an NPV of 93.5% (88.8–98.1%).

Finally, in the staging of distant metastases with CT, our study shows a sensitivity of 60.7% (42.6–78.8%), a specificity of 98.6% (96.6–100.5%), a PPV of 89.5% (75.7–103.3%), and an NPV of 92.7% (88.5–96.8%). With the use of PET/CT, the sensitivity, specificity, PPV, and NPV values were 96.2% (88.8–103.5%), 96.5% (93.5–99.5%),83.3% (70.0–96.7%), and 99.3% (97.9–100.7%), respectively. No statistically significant differences were found in a stratified analysis based on the location of the primary tumor.

It is worth mentioning that, in some patients, there were changes in more than one variable when using CT and PET/CT. In turn, we analyzed which of the two tests was more accurate, in terms of diagnosing the primary tumor, the cervical lymph nodes, and distant metastases.

DISCUSSION

There has been a debate about the optimal imaging method for staging HNSCC, since even though PET/CT has become a widely used test in pretreatment evaluation for many professionals, some have criticized it for its high cost and low specificity (Fig. 1.).

The sensitivity and specificity of PET/CT for the detection of malignant cervical lymph nodes (Fig. 2.) have been reported to range between 61–96% and 80–99%, respectively, while the sensitivity of combined CT/MRI is 53–82% and its specificity is 71–97% [8]. However, the radiotracer FDG used in PET imaging is not a tumor-specific biomarker and various inflammatory processes can lead to increased FDG uptake – and possible false-positive results [9].

Because most distant metastases in patients with HNSCC are located in the lung, some authors argue that a chest CT would be sufficient to identify distant metastases [10]. However, if treatment with curative intent is chosen in patients with metastases, a complete body imaging test, such as ^{18}FDG PET/CT, is necessary.

Several studies have analyzed the use of PET/CT in the diagnosis of patients with distant metastases. Senft et al. evaluated 92 patients diagnosed with HNSCC with high risk factors for metastasis and discovered that the use of PET/CT along with chest CT increased sensitivity from 37% to 63% [11]. Ng et al., in a study on 160 newly diagnosed HNSCC patients with negative results on chest radiography, liver ultrasound, and bone scintigraphy, concluded that for the detection of distant metastases and second primary tumors, the combination of PET/CT and chest CT resulted in greater sensitivity, increasing it from 50% to 81% [12]. Another prospective study of 307 patients with HNSCC which attempted to determine the detection rate of distant metastases and synchronous cancer, comparing diagnostic imaging methods, found a significantly higher detection rate of distant metastases and/or synchronous cancer, using PET/CT at diagnosis [13]. Due to its high spatial resolution, CT can serve as a complementary tool to PET/CT and can reduce the rate of false positives due to inflammatory processes [5].

Some authors have hypothesized that other tracers may improve the accuracy of PET [14]. For example, Hoshikawa et al. compared the diagnostic efficacy of ^{18}F-fluorothymidine (^{18}F-FLT PET/CT) with that of ^{18}FDG in a study of second primary tumors and distant metastases on 88 patients with HNSCC. FLT did not improve the sensitivity of PET compared to the use of FDG (78% and 90%, respectively). It was concluded that FLT should not replace FDG for the pretreatment staging of metastases in patients with HNSCC, due to its lower sensitivity and higher background activity in the liver and bone marrow [15].

Various studies have been published on the use of PET/CT in the management of HNSCC, most of which focused on determining the extent of the disease (detection of distant metastases) and surgical

or radiotherapy planning. However, few of them deal with the therapeutic repercussions of this imaging technique. In our study, we observed that PET/CT in the management of HNSCC influenced the treatment in 39.7% of the sample (Tab. I.), a somewhat higher figure than in other studies, such as the one carried out by Scott et al. [16], who, in a multicenter prospective study with 71 patients, demonstrated that PET modified the management of 33.8% of the sample. Fleming et al. reported a change in therapeutic decisions in 30.9% of the cases analyzed [6]. Cacicedo et al. carried out a study in which they observed a change in treatment in 26% of their patients [17]. However, these differences are even more noticeable when the data are compared with that of other studies, such as those carried out by Lonneux et al. [18], in which the impact rate was 13.8%; one possible explanation is the number of patients in early stages of the disease in their sample, with a lower risk of presenting distant metastases. However, Connel et al. found a change in treatment in 40% of the cases analyzed, even though close to 20% of their sample were in the early stages [19].

In another study by Cho et al. [20], 73 patients were studied using preoperative PET/CT and CT, with both tests being evaluated by three different specialists. In all patients, a cervical dissection was performed for the histological study of the regional lymph nodes. No significant differences in sensitivity or precision were found; however, CT had a higher specificity. Interestingly, the percentage concordances for pathologic N staging and PET/CT *versus* CT were 52% *versus* 55%. Although the authors did not study the impact that these differences might have had on treatment, the findings cast doubt on the accuracy of PET/CT for HNSCC staging. In addition, the authors noted that PET/CT tended to overstate the disease.

However, in our work, we observed greater precision of PET/CT when studying each of the variables. At the time of diagnosis of the primary tumor, for the 43 cases in which there was a discrepancy, we observed that the PET/CT reported a correct result in 39, while the CT did so in the remaining 4.

Tab. V. Variation in the diagnosis of distant metastases.

M BY CT	M BY PET/CT	M FINAL	N
Mo	M1	Mo	5
Mo	M1	M1	11
M1	Mo	Mo	2
M1	Mo	M1	1

Patients correctly staged by PET/CT

Patients correctly staged by CT

When we studied discrepancies in a regional lymph node analysis, we observed a correct PET/CT result in 31 of 39 cases, while CT showed a correct analysis in 7 of 39, with 1 case in which both tests failed.

During the analysis of distant metastases, we observed that the PET/CT reported a correct result in 13 of 19 cases, while the CT did so in the remaining 6.

In our experience, PET/CT can offer important information in patient evaluation, improving therapeutic planning. However, in some cases, discrepancies concerning other imaging techniques may increase the delay in treatment and require additional tests to assess whether the findings observed on PET/CT correspond to a malignant lesion or an incidental finding.

CONCLUSIONS

Despite the relatively small sample size, and even though the results should be interpreted with caution, our study has one of the largest sample sizes among published papers. According to our results and due to the characteristics of our sample, we can affirm that, in patients with HNSCC in advanced stages (III or IV), the addition of ^{18}F-FDG PET/CT to the conventional imaging method significantly increases appropriate therapeutic decision-making.

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