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PET/CT in Staging and Treatment Evaluation of Non-Small Cell Lung Cancer

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Abstract: Lung cancer relatively common in Peru. PET/CT is a useful tool in the staging and follow-up of the treatment of lung tumors. There is currently enough evidence to affirm that this technology helps in adjusting treatment and increasing the survival rate of the patients. A descriptive review of the relevant articles recently published on the subject was carried out. It is concluded that PET/CT is useful in the staging and follow-up of the proposed treatment for patients with non-small cell lung cancer. This malignant tumor is also often discovered and diagnosed at an advanced stage.

Keywords: Non-small cell lung cancer; PET/CT; Treatment; Non-invasive surgery; Radiomics; Computed tomography

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1. Introduction

Approximately 80-85% of lung neoplasms are non-small cell tumors, with the main types being adenocarcinoma, squamous cell carcinoma and large cell carcinoma [1,2]. They are grouped together because they behave similarly and respond in the same way to treatment. According to the latest statistical reports, non-small lung tumors have the highest mortality rate in the world [3], with an overall survival rate of 17.4%. In Peru, it occupies third place in incidence and fifth place in frequency in Peru, among all types of malignant neoplasms [4].

Non-small cell lung cancer occurs equally in men and women, is aggressive, and has a higher mortality rate, mainly due to the fact that the diagnosis is made in advanced stages, and it continues to spread [5]. The proportion of new cancer cases diagnosed in less developed countries is expected to increase more than 60% of the world total by 2030, due to increase in cancer rates and expected increases in life expectancy and population growth. Only 10% of stage IV patients exceed 60 months of survival after diagnosis.

Positron emission tomography linked to tomography (PET/CT) is important to the precision medicine in patients with lung cancer, and it is crucial for optimal patient management and determining initial staging. The therapeutic approach of about one third of lung cancer patients was changed after evaluation with PET/CT. This allows an appropriate re-staging of the disease, detection of residual disease and its recurrence; it also evaluates the therapeutic response and aids the patient's prognosis [6].

PET/CT is also important in the planning of radiotherapy by determining the extent of active disease and functional tumor volume [7]. Recent advances suggest that therapeutic response criteria in the near

future will be based on metabolic characteristics and will include assessment of the biological characteristics of tumors to further improve the efficacy of precision medicine in lung cancer, thus producing better patient outcomes with less morbidity [8].

Therefore, PET/CT should be highlighted so that a more accurate diagnosis can be made, the extent of disease (staging) can be better assessed, and a more suitable follow-up treatment can be selected for a given patient.

2. Methodology of the literature search

Databases (PubMed, Elsevier, Scopus, Cochrane Reviews, Google Scholar) were consulted, and original articles related to non-small cell lung cancer were reviewed. In addition, we also searched for papers that clarifies some issues of staging of non-small cell lung cancer and positron emission tomography technology (PET/CT).

3. Establishment of the search strategy

The keywords used were PET/CT, NSCLC, staging, non-small cell lung cancer, non-invasive therapy, thoracotomy, mortality, response to treatment, radiotherapy, and chemotherapy.

Articles that were published in the last ten years were included in this paper, including some older articles because of their importance and relevance. Studies with less than 20 patients were so that this review will be more relevant.

4. Selection of results

We selected original articles that involved the use of PET/CT in the initial diagnosis and staging of non-small cell lung cancer and those that had information on the patients' follow-up after treatment.

Eighteen articles that met the selection criteria: title related to the topic, clear and specific summary of the study topic, relevant results, study delimitation statement and appropriate number of cases, (including two meta-analyses) were reviewed, in addition to multicenter studies. An additional 5 studies that provided statistical data or general concepts to clarify the review topic were also included in this review.

The results of the studies reviewed, which adequately measure the effect of using PET/CT in non-small cell lung cancer, at various stages, with various treatments, such as curative or palliative surgery, chemotherapy or radiotherapy in different modalities were reliable. The reliability was determined based on the soundness of the work and the methodology used.

5. Development of the topic

A descriptive review was carried out on the literature we compiled. Some authors such as Farsad [2] say that PET/CT cannot determine the parameters of the tumor although it is very useful in determining the nodal involvement and predicting the outcome of treatment. Fischer [1] stated that there was no significant contribution in the evaluation of nodal involvement, an aspect in which progress has been made in the last decade.

The staging of non-small cell lung cancer is a multidisciplinary process that involves a set of imaging studies and endoscopic and surgical components [9]. PET/CT studies are non-invasive and have been shown to have a relevant negative predictive value, which makes invasive studies unnecessary for the evaluation of mediastinal nodes. In the case of being positive, it requires the other studies for its confirmation. There are authors who recommend using PET/CT, CT, and invasive studies altogether to achieve an adequate staging [10–15].

6. Preoperative staging

There is a previous review of the subject carried out in 2015 by Hochhegger *et al*. [16], in which they schematize the TNM methodology to evaluate the usefulness of PET/CT in evaluating tumors (T), lymph nodes (N) and metastases (M).

In other studies, such as the meta-analysis performed by Zhao et al [17], the study of the nodal component (N) in the mediastinum and in other locations has been shown to be more precise. This study confirms that PET/CT has good specificity but lacks sensitivity.

A study carried out by Osman and Korashi [18] in the year 2020 stated that PET/CT is most useful in reviewing the T component, is when performing staging of patients with T2 (using the nomenclature of the 8th version of the TNM that is currently in force) [19]; a tumor stage in which it allows elucidation of the tumor region of the adjacent inflammatory region.

This same finding has been found in another publication [20], in which De Cecco and coworkers studied the inflammatory involvement around the primary tumor, before and after radiotherapy.

There is a study on the evaluation of the metabolic parameters of PET-CT (total tumor volume, SUV_{max}, total glycolysis of the lesion) in determining whether a patient has second primary synchronous or metachronous tumors following non-small cell lung cancer, which is relatively common [21]. Zhu *et al.* [22] mentioned that these parameters can be used to predict the overall survival of the patient with acceptable accuracy regardless of age, type of treatment, tumor histology and TNM stage.

Similar observations were found in a study by Dashevsky *et al* [23], who reported what was found in a T3B stage, specifically in non-small cell lung cancer; they concluded that the total tumor volume marker is a prognostic marker of stage 3B of the neoplasm, regardless of age, gender, treatment or tumor histology.

Artificial intelligence plays a role in imaging studies. Borreli *et al* [24] studied the use of artificial intelligence in the management of patients with lung cancer. Their study showed that artificial intelligence allows a a more precise diagnosis of small and medium-sized lesions.

Finkle *et al.* [25] found that numerical indices that allow quantitative calculations in PET/CT provide an approximation to risk calculation in patients with non-small cell lung cancer. They did their work by applying the staging rules of the eighth edition of the TNM system [26]. They state that the indices allow the health care team to incorporate concepts such as prognostic value, associated with total tumor volume and TNM-calculated stage, which can serve to improve the accuracy of predicting overall survival.

These findings were corroborated in a recent study conducted by Tosi's group [27] in patients with stage I non-small cell lung cancer. Their research confirms that SUV_{max} and TLG - total tumor glycolysis measurements correlate adequately with the recurrence-free rate in patients with lung adenocarcinoma who have undergone lobectomy.

7. Use of quantitative

Positron emission tomography studies began in the 1970s. With the use of PET/CT, it is possible to carry out a metabolic study of tumors and to reach numerical conclusions that allow quantitative evaluation of what is found in patients with neoplasms. Lammertsma states not to use semiquantitative indexes indiscriminately, but to base oneself on clinical judgment and careful and meticulous inspection of the images [28]. This effort is possible if the patient had been examined previously. In PET/CT studies, it is common practice to compare the latest results with the previous examinations to evaluate the efficacy of various treatments.

Hua et al. [29] consider that numerical parameters are extremely important when evaluating the possibility of mediastinal lymph node metastasis. In this work they mention that PET-CT with ^{18}F-FDG has a sensitivity of 81.3% and specificity of 79.4% for detecting mediastinal metastatic lymph nodes, with a SUV_{max} value of 2.5 as a cut-off point; however, the false positive rate is relatively high, which is up to

61.1 %.

Therefore, the authors evaluated several morphological and metabolic parameters in 206 mediastinal lymph nodes of 156 patients with non-small cell lung cancer, concluding that the combined parameters, such as SUV ratio (SUV_{max} node/SUV_{max} mediastinum), COV (coefficient of variation of heterogeneity) and D_{min} (maximum short diameter) showed better diagnostic performance for detecting metastatic mediastinal lymph nodes, with 87.38%, 81.55%, 84.47%, 82.57%, and 86.6% for sensitivity, specificity, accuracy, positive predictive value, and negative predictive value respectively. They conclude that their results have limitations because the sample size was small, but multicenter studies may be carried out in the future.

Lee *et al.* [30] used a double check-in time (early and late study) of PET/CT images and concluded that they have an adequate diagnostic system for the detection of metastases in mediastinal nodes in patients with non-small cell lung cancer with the same accuracy in the early and late study. They suggested that multicenter studies should be carried out with this methodology to firmly establish the usefulness of the late images.

8. Evaluation of the effect of selected treatment for non-small cell cancer and follow-up of patients

Eze *et al.* [31] have studied the status of the method, limitations, and possible future uses of hybrid imaging such as PET/CT to evaluate the treatment efficacy and toxicity of some new drugs, such as immunotherapy in patients with locally advanced, inoperable, and metastatic non-small cell lung cancer. They concluded that as new forms of immunotherapy are developed for locally advanced lung cancer, new patterns of response, disease progression and side effects of these drugs are being seen. They mentioned that adding PET/CT to existing imaging techniques can provide clinical support and more morphological information, allowing early detection of side effects and effective decision-making.

Gamal reported in his study which consisted of 63 patients that [32] PET/CT plays an important role in distinguishing post-treatment changes in patients with non-small cell lung cancer from tumor recurrence. He emphasizes the value of the study for calculating the patient's overall survival, and stated that multicenter studies with a larger number of cases are needed to draw conclusions regarding the predictive value of the study.

Zheng *et al.* [33] studied the application of radiomics in the PET/CT evaluation of 716 patients with non-small cell lung cancer, with pre- and post-surgery evaluation of mediastinal nodes. They conclude that a radiomics model applied to this technology and the analysis of the data is useful in the evaluation of mediastinal node staging in patients with non-small cell lung cancer. This evaluation method allows for a better treatment plan according to the preoperative prediction and to offer alternatives of less radical surgery or stereotactic body radiotherapy in selected cases. All this effort requires a very strict quality control of the equipment to be used.

Jahangiri et al. [34] determined that the inflammatory component can be seen following radiotherapy of patients with non-small cell lung cancer. The changes in PET/CT images before and after receiving radiotherapy were evaluated in the form of proton therapy in order to quantify the inflammatory response in patients with advanced stage lung cancer.

Being able to diagnose this inflammatory response suggests that PET/CT parameters could serve as biomarkers of radiation pneumonitis in these cases and guide subsequent therapeutic management.

Fledelius *et al.* [35] found that the outcome of adjuvant chemotherapy can be assessed in patients with non-small cell lung cancer prior to radiotherapy, suggesting that a quantitative method (in this case Positron Emission Tomography Response Criteria [PERCIST]) be used instead of visual assessments alone. Further studies are required to reach definitive conclusions. What is clear is the usefulness of PET/CT in the follow-up of these patients, before, during, and after selected treatment.

There are ongoing controlled clinical trials that have reported that pretreatment tumor volume can maybe predict the response to chemo- and radiotherapy. However, a recent study contradicts this claim. Guberina *et al.* [36] state that quantitative PET/CT values after induction chemotherapy are better predictors of survival than pretreatment findings.

Therefore, it can be affirmed that a decrease in SUV (numerical value of PET/CT) serves to predict survival in patients with stage III non-small cell lung cancer without being able to draw conclusions or extrapolate results to other stages or to the stage prior to chemotherapy, and these studies still require validation with larger series.

Horn and his team [37] studied the application of PET/CT in chemo-radiotherapy regimens, since it would be possible to find susceptible areas of treatment that have not responded to initial chemotherapy. They acknowledged that there are limitations and that the results of ongoing work in various parts of the world are still required. They emphasized that quantitative parameters should be simplified, which can be applicable to various brands of PET/CT equipment.

9. Recent advances based on the metabolic characteristics of the tumor

In recent years, immune therapy-based on immune checkpoint inhibitors targeting the programmed death-1 (PD-1) axis and programmed death ligand 1 (PD-L1) has been incorporated into the field of therapy. However, the evaluation of immunohistochemical biomarkers for targeted therapy, as well as the scoring of the proportion of PD-L1 in the tumor, have had serious limitations in terms of interobserver reproducibility, clones, and epitopes used for their evaluation, and automated biomarker processing systems. Zhou *et al* [38] have presented a model for predicting response to immunotherapy that takes into account the correlation between PD-L1 and PET/CT findings in patients with non-small cell lung cancer. They stated that FDG-PET/CT radiomic features are sufficient to predict the presence of tumor immune types, indicating that quantitative PET/CT could be used to guide candidates for immunotherapy. Similar conclusions were also drawn by a study by Valentinuzzi *et al.* [39], who suggest combining iRECIST parameters with PET/CT radiomic parameters in order to determine the response to immunotherapy.

Studies have affirmed that immunotherapy is an established treatment for malignant tumors, particularly in advanced cases, in which progression-free survival was improved [41]. Therefore, there is great room for research and therapeutic management to offer a better quality of life to patients with non-small cell lung cancer.

10. Cost-effectiveness studies

Much effort has been put into using available technology and reducing costs to make diagnosis prior to and after treatment for non-small cell lung cancer more affordable.

Han et al. [41] from China have designed 4 models for the management of mediastinal lymph node involvement in non-small cell lung cancer, regarding the use of diagnostic images: Model A consisted of using CT only, Model B used PET/CT only if the CT was negative, model C involved both methods, and model D, is PET/CT only. Using various economic indicators, they concluded that Model C was more cost-effective in the country where the study was performed, and that method was introduced to aid staging strategies, reduce surgical mortality, and extend survival expectancy.

Johnson's team [42] in Australia has published a study in which, by studying the timing of PET/CT in patients with non-small cell lung cancer, they determine that, against the "CT first" system, it may be decided to perform FDG-PET/CT first, prior to biopsy attempts, which may reduce the number of patients who will need more than one biopsy. However, they acknowledge that the clinical significance and a prospective evaluation of the overall cost-benefit of this type of patient management still needs to be further studied.

Several limitations were reviewed in the studies. For example, in terms of the waiting time to perform imaging studies, long waiting periods could be detrimental to the health of patients with non-small cell lung cancer because of its aggressive nature. On the other hand, in terms of diagnostic samples, little tissue is obtained in some cases, which greatly limits the diagnosis and follow-up in spite of all the imaging studies. There remains fertile ground for study in these topics, even more so in issues that have not been addressed, such as the prediction of the type of pathological markers associated with PET/CT iin advanced immunotherapy, which is very expensive but apparently effective in other latitudes.

11. Conclusion

In conclusion, PET/CT study is useful in the staging and follow-up of the proposed treatment for patients with non-small cell lung cancer. This malignant tumor is often diagnosed at the advanced stage. It is crucial to determine the lines of research and further study the treatments available in Peru and utilize the best of the technology available. Much progress has been made and numerical data are available to support a coordinated and systematic study. The lines of research can be oriented towards improving the conditions of the equipment in use, so that quantitative parameters can be calculated accurately, and personalized treatments can be offered, thus prognosis of each individual patient can be improved.

Another line of research proposed is prospective studies of patients with non-small cell lung cancer, having PET/CT images after each therapy they receive and disseminate articles that have an impact on the framework of prevention and early diagnosis, to ensure that this tumor is diagnosed at earlier stages, which will allow better management and survival; in other words, changing the history of the patient with non-small cell lung cancer in Peru.

Disclosure statement

The authors declare no conflict of interest.

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