REVIEW ARTICLE

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The Effectiveness of PET scan Technology in Diagnosis and Treatment of Non-Small Cell Lung Carcinoma (NSCLC) and Lymphoma:

A Systematic Review of Literature

Hamid Ravaghi[1], Ali Akbari Sari[2,*], Sima Sarvari[3]
Mohammad Reza Mobinizadeh[4]

ABSTRACT

Background: Positron emission tomography (PET) scan is a non-invasive, complicated and expensive medical imaging technology used for diagnosis and treatment of various diseases including cancers. This study aimed to evaluate the safety and effectiveness of this technology in Iran.

Methods: The major medical electronic databases including Cochrane Library, Google Scholar, MEDLINE and IranMedex were searched. Studies that compared PET scan with another diagnostic method in terms of sensitivity, specificity and safety were used.

Findings: PET scan has been found to be a non-invasive and safe procedure for diagnosing metastatic NSCLC with a sensitivity and specificity of 74% to 95% and 81% to 97%, respectively. On the other hand, the sensitivity and specificity of computed tomography (CT) scan have been reported as 60% to 67% and 73% to 77%, respectively. The corresponding values for mediastinoscopy have been 78% and 100%. In lymphoma, the specificity and sensitivity of PET scan (90% and 79% to 100%, respectively) have been higher than those of gamma scan. Although PET scan is not an appropriate method for screening and diagnosing cancer, it can contribute to staging and follow-up processes in cases of NSCLC and lymphoma. This technology adds 0.046 years (about 17 days) to the patient's life.

Conclusion: PET scan is a safe technology that has better diagnostic performance compared to similar technologies. The application of this method in staging and follow-up of NSCLC and lymphoma can prevent unnecessary surgeries and adds a few years to patients' longevity and quality of life.

Keywords: PET scan, NSCLC, Lymphoma, Imaging .

1. Assistant Professor, Department of Health Service Management, School of Management and Medical Information Services, Tehran University of Medical Sciences, Tehran, Iran.
2. Assistant Professor, Department of Health Management and Economics, School of Public Health, And Knowledge Utilization Research Center, Tehran University of Medical Sciences, Tehran, Iran.
3. Medical Lecturer, Medical College, Shantou University, China.
4. Health Technology Assessment (HTA) Office, Deputy of Curative Affairs, Ministry of Health and Medical Education, Tehran, Iran.

***Corresponding Author:**
Ali Akbari Sari,
Assistant Professor,
Department of Health Management and Economics,
School of Public Health, And Knowledge Utilization Research Center,
Tehran University of Medical Sciences, Tehran, Iran
Email: akbarisari@tums.ac.ir

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Introduction

In recent years, the use of medical technologies has had dramatic and accelerated growth in the diagnosis and treatment of diseases. Proper use of these technologies can help the diagnosis and treatment of diseases effectively. However, unrestricted and unsupervised entry of these technologies may result in induced demand from service providers and excessive and irrational use of the services. This problem has been created in many developed and developing countries and led to highly increased costs. Therefore, some countries meticulously evaluate new technologies before importing in a systematic fashion and the import permission and their usage are investigated so that available resources can be used as optimally as possible.[1] Positron emission tomography (PET) scan technology is a non-invasive, complicated and expensive medical imaging technology introduced in 1950s, was developed over time and now is rapidly developing. Today, this technology is commonly and increasingly used in many countries and is applied in the diagnosis and treatment of several diseases including various kinds of cancer, cardiovascular and neurological diseases. In this method, a tracer or radiopharmaceutical is injected to the patient's body. Various body tissues uptake different amounts of this substance due to the amount of blood flow and their cellular and chemical metabolism. This absorbed substance emits an invisible light that can be received by the imaging device. Healthy and diseased tissues in the patient's body have different cellular metabolism, so the amount of radiopharmaceutical absorbed and consequently the amount of radiation from these tissues is different. Therefore, normal and abnormal tissues are characterized by different color tones.

Cancer tissues often uptake more of this substance and are observed as hot spots in images. In this way, various tumors and diseases can be detected due to their higher radiopharmaceutical uptake and radiation as compared to normal tissues. Thus, three-dimensional imaging with PET scan can provide valuable information about the biological activity of body tissues.[2] This research was conducted by the recommendation of Health Technology Assessment Unit of the Ministry of Health, Treatment and Medical Education with the main objective to evaluate the safety and effectiveness of the technology regarding the status of the country and to provide a solution for import and use of this technology.

Materials and methods

To obtain the related studies, the most appropriate and important medical electronic databases including Cochrane library (DARE, NHS EEDs, Cochrane systematic reviews), Google scholar, MEDLINE and IranMedex until the end of 2008 were systematically searched. With reference to studies obtained from electronic search and by reviewing their references, other related articles were searched. Then, required information was completed by manual search in relevant websites and if necessary by contacting with experts in this field. Due to limited resources and time and no possibility to translate non-English papers, only articles in English and Persian were used. Also, given the limited time and resources, the main focus was on the report of health technology assessment (HTA) and most of these studies were used. Particularly, the major attention focused on the studies that were as comprehensive as possible, recently conducted, up-to-date, high quality and able to help answer part of the questions in this evaluation. In addition, if a question could not be answered using these HTAs in each part, we attempted to use other types of studies (systematic review, economic assessment and randomized controlled study) that could help in this area (**Table 1**).

First, a health technology assessment report in Scotland was selected and used as a model due to the fact that it met most of the requirements including being up-to-date, comprehensiveness and high quality.[3] Then the main and required information was extracted from this report and reviewed and compared in detail with findings of other studies in terms of similarities and differences particularly the study of Hicks et al. in Australia.[18] Then, based on questions raised in this project, proper and relevant information was combined and qualitative analysis was performed comparatively in two safety and effectiveness subgroups. In this regard, inclusion criteria included studies that PET scan was used to assess patients with non-small cell lung carcinoma and lymphoma and compared with other diagnostic methods to assess outcomes such as sensitivity, specificity and safety.

Table2. Characteristics of studies reviewed in this study.		
The kind of study	**Title**	**Author**
Health Technology Assessment	Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers	Facey et al.[3]
Systematic Review	Role of operation in lung cancer [Persian].	Abbasidezfuli et al.[4]
Health Technology Assessment	Positron emission tomography [Part 2(ii)].	Medicare services advisory Committee[5]
Health Technology Assessment	American Cancer Society- Web Info Revised: 10/31/2007	American Cancer Society[6]
Health Technology Assessment	HTA Tomographie par Emission de Positrons en Belgique; KCE reports..	Cleemput et al.[7]
Health Technology Assessment	Institute for Clinical Evaluative S. Health technology assessment of positron emission tomography in oncology - a systematic review.	Laupacis[8]
Health Technology Assessment	Positron emission tomography (PET) with 18-F- fluorodeoxyglucose (FDG). A literature review of evidence for clinical use in the fields of oncology, cardiology and neurology.	DACEHTA[9]
Health Technology Assessment	Recommendations for clinical practice: Standards, Options and Recommendations for utilization of positron emission tomography with [18F]-FDG (FDGPET) in oncology (full report)	Bourguet et al.[10]
Health Technology Assessment	Positron emission tomography (PET) imaging in cancer management.	HTBS-HTA[11]
Health Technology Assessment	Positron emission tomography in Quebec. Montreal; 2003	Danish Centre for Evaluation and Health Technology Assessment[12]
Randomized controlled evaluation	FDG-PET is superior to gallium scintigraphy in staging and more sensitive in the follow-up of patients with de novo Hodgkin lymphoma: a blinded comparison.	Friedberg et al.[13]
Randomized controlled evaluation	Early detection of relapse by whole-body positron emission tomography in the follow-up of patients with Hodgkin's disease.	Jerusalem et al.[14]
Randomized controlled evaluation	Positron emission tomography in patients with Hodgkin's disease: correlation to histopathologic subtypes.	Dobert et al.[15]
Randomized controlled evaluation	Agressive large cell lymphoma: Early assessment of therapeutic efficacy by positron emission tomography.	Itti et al.[16]
Randomized controlled evaluation	Advantages of positron emission tomography (PET) with respect to computed tomography in the follow-up of lymphoma patients with abdominal presentation.	Zinzani et al.[17]
Economic evaluation (cost – effectiveness)	Positron emission tomography (PET): experience with a large-field-of-view three dimensional PET scanner.	Hicks et al.[18]
Health Technology Assessment	Positron emission tomography (PET) imaging in cancer management; Understanding HTBS Advice; Use of PET imaging for cancer in Scotland	NHS Quality Improvement Scotland[19]

Findings

The results obtained from the included studies were divided in two subgroups: Safety: PET scan is a noninvasive technology. In this technology, radiopharmaceutical substances are used. One of the most common radiopharmaceuticals is a radioactive glucose derivative called FDG (2-[18-F]-fluoro-2-deoxy-D-glucose) which is used at very low amounts in microgram. Thus, in normal circumstances, there is not a significant risk in using this technology. In a retrospective study conducted at 22 centers in the U.S., no complications and unfavorable reactions were observed for the use of FDG.[2] However, the

use of FDG is not recommended for pregnant women. In addition, some patients may feel anxious before performing this test, and anxiety may increase glucose uptake and lead to distorted image in PET scan. So, it is recommended patients be provided with some information about the non-invasive nature and process of PET scan at least 4 hours before the test to minimize their anxiety. In sum, although this technology is generally safe, it is necessary to observe the following points carefully: after the test, the patient should stay away from his young children for a few hours, FDG should be cautiously used for patients with glucose intolerance, very obese patients (more than 158 kg) cannot enter the machine, claustrophobic patients cannot use this technology because of being enclosed in its chamber, there is potentially the risk of injury for employees who work with the PET scan machine, and it is necessary to observe rules carefully required for preparing and using radiopharmaceutical matters and their transport.[3]

Effectiveness

This technology is primarily used for two diseases including lung cancer and lymphoma. However, due to its cost it is not appropriate for screening and is applied in staging and follow-up of the disease.[3] There are often two main types of lung cancer: small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC). If both small and non-small lung cells are involved it is called mixed small and large cell carcinoma. NSCLC comprises the majority of lung cancers and if its location is found, its surgery may be possible. Typically, experiments and procedures of searching, diagnosis and grading of cancer are often performed simultaneously. Physical examination and medical history, chest x-ray, CT scan, PET scan, sputum cytology, lung biopsy through fine-needle aspiration (FNA), bronchoscopy, thoracoscopy and thoracocentesis are examinations and tests performed for diagnosis and staging of this type of cancer.[6]

Although imaging may lead to the diagnosis of the disease, it is not definitive and for definitive diagnosis cytologic or histologic criteria are necessary. The diagnosis of solitary lung tumor, differentiation of primary lung cancer and solitary metastasis from a benign lesion, disease staging, detection of mediastinal, hilar and extrathoracic metastases in early stages of NSCLC, monitoring treatment course, and evaluation of treatment response (chemotherapy or radiotherapy), evaluation of possible relapse of the disease and planning to perform surgery due to lung metastasis are potential applications of PET scan in lung cancer.[7] Danish Center for Evaluation and Health Technology Assessment based on the results of a systematic review stated that some studies have reported the sensitivity of 100% for PET scan or PET/CT on initial diagnosis of NSCLC.[9] However, based on the results of health technology assessment report of MSAC, sensitivity and specificity of PET scan compared to biopsy were reported 61% to 98% and 81% to 100%, respectively.[5] Cleemput et al. in a health technology assessment report regarding large differences in sensitivity and specificity reported in various studies, summarized the conclusion based on a receiver operating characteristic (ROC) curve. According to ROC curve obtained in their study, with a median specificity of 77%, the sensitivity was 94.6%. In addition, they stated that generally, the probability of malignancy in a solitary nodule before PET scan is 15% to 75%. If we consider the median of 40% for the probability of malignancy before the PET scan, the probability of malignancy with a positive PET scan reaches about 75%. If there is a negative result in PET scan, the probability of malignancy will reach 4.5%. However, in one of their systematic review studies, the probability of malignancy was reported 2.7% by ROC curve.[7] In studies considered for the initial staging of NSCLC, the reported sensitivity of PET scan to assess local disease was 61% to 100% and the specificity was 64% to 100%, while the sensitivity of CT scan was between 20% and 83% and the specificity was 25% to 100%, which can be compared.[8-10] Based on two reports, the PET scan has the sensitivity of 70% to 100% and the specificity of 61% to 100%.[10-11] In the staging process, CT scan is considered a conventional method that presents morphological details, the initial tumor, lymph node metastasis and its expansion (for example, metastasis to chest wall or liver). Enlarged mediastinal lymph nodes more than one cm is often considered positive for malignancy. But because there is the risk of benign enlargement (for example, in reactive lymphadenopathy), the histological proof of accessible lymph nodes is necessary.[3] Based on three meta-analyses of patients with negative CT scan for lymph nodes, PET scan had the sensitivity of 86% (CI: 79% to 86%) and the speci-

ficity of 90% (CI: 87% to 93%). In patients with positive CT scan for lymph nodes, the sensitivity of PET scan was 92% (CI: 87% to 95%) and the specificity was 76% (CI: 69% to 82%).[11] In the UK, two economic models have been designed that evaluated the use of FDG-PET in the staging of NSCLC before and after surgery.[19] Both models showed that after diagnosis of lung cancer was confirmed by conventional methods such as biopsy and CT scan, the use of FDG-PET is cost– effective in the assessment of the rate of spread of malignancy in NSCLC before surgery particularly in patients with negative CT scan. However, the Scottish study showed that the use of PET scan is cost–effective only if there is a willingness to pay £60,000 per QALY.[19] A study in Australia also showed that the use of PET scan for detection of mediastinal involvement, increases an average of $ 189 per added 0.046 year (about 17 days) to patient's life. This means that a one-year increase in survival incurs $ 41,087 of extra cost.[5] Lymphoma refers to a cluster of related cancers developed because of malignant lymphocytes. Several types of lymphoma are divided into two main groups of Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). There are subgroups for each group. However, according to the World Health Organization classification, lymphoma can be divided into different groups: Hodgkin's lymphoma, B-cell non-Hodgkin's lymphoma, follicular non-Hodgkin's lymphoma. There is a significant difference between HD and NHL, and these differences are involved in the diagnosis and treatment. PET scan is not used for all patients with lymphoma and today is limited to a selected population of patients. Overall, PET scan can be applied for initial diagnosis, staging and the diagnosis of disease relapse, assessment of the residual tumor (at the end of treatment) and determination of prognosis and response to therapy (after primary treatment).[7] Due to the need for histologic diagnosis of lymphoma, the role of PET scan is very limited in the early diagnosis of lymphoma.[3] Facey et al. believed that there is a low probability that the PET scan is commonly used for diagnosis.[3] PET scan has a better role than CT scan in the initial staging of the disease based on non-invasive assessment of lymph node, the rate of lymph node involvement and determining appropriate site for accurate biopsy.[7] In a study by Bourguet et al. for the above purpose, the sensitivity and specificity of PET scan were 99.2% and 100%, respectively, compared to those of CT scan that were 83.2% and 99.8%, respectively.[10] The report of MSAC (Medicare Services Advisory Committee) evaluated the evidence from seven studies on 369 patients with HL or NHL.[5] These studies showed that the PET scan had the sensitivity of 79% to 100% and specificity of 90% to 100%. To evaluate the residual tumor, the sensitivity and specificity of PET scan was 43% to 100% and 69% to 100%, respectively, compared to the sensitivity of 71% to 100% and specificity of 17% to 65% of the CT scan. The positive predictive value of the PET scan was reported 44% to 100% and the negative predictive value was reported 67% to 100%. These values for the CT scan are 19% to 60% and 50% to 100%, respectively.[10] If PET scan is positive, one-year survival rate is 20%±18% and two-year survival rate is 0% to 4% with the possible relapse of 100%. If PET scan is negative, one-year survival rate is 87%±7% to 100% and two-year survival rate is 68%±11% to 100% with the possible relapse of 17%.[10] Therefore, in the case of very high FDG uptake during initial staging and for the quick evaluation of treatment response, PET scan should be applied for the diagnosis of residual disease, especially in HD and follicular or progressive NHL.[8,10]

Studies have been also conducted on Hodgkin's lymphoma. Friedberg et al. compared PET scan and gallium scintigraphy on 36 patients. The study indicated that PET scan had a higher validity in prediction of the next relapse ($P<0.04$) with a positive predictive value of 0.49 versus 0.65 of gallium scintigraphy. At the end of treatment, negative predictive value of the PET scan compared to gallium scintigraphy was also 0.96 versus 0.9. In addition, the sensitivity of the PET scan and gallium at the end of treatment was estimated 0.8 and 0.4, respectively .[13] Another study by Jerusalem et al. conducted on 36 patients showed that PET scan can become positive 9 months before histologic proof with asymptomatic relapse and 5 cases were reported with relapse in 11 patients with the positive PET scan and none among patients with negative PET scan.[14] Dabert et al. compared PET scan with bone marrow biopsy and concluded that bone marrow biopsy cannot be replaced by PET scan, but the latter can provide a proper location to perform bone marrow biopsy.[15]

Itti et al. compared PET scan with a CT scan in 50 patients with aggressive NHL and concluded that the

survival of patient can be predicted through the results of PET scan following two courses of chemotherapy (P<0.001, Kaplan-Meier).[16] The fifth study was conducted by Zinzani et al. on 59 patients (16 patients with HD and 43 patients with aggressive NHL) and they compared the diagnostic accuracy of PET scan and CT scan in the detection of relapse after chemotherapy. PET scan had a sensitivity of 82% and specificity of 92%, while they were 73% and 15%., for CT scan, respectively. Local relapse or disease progression was found in 70% of patients with a positive PET scan and only in two patients with negative PET scan (P<0.001).[17] The study conducted in Scotland used a decision model with five main strategies for the evaluation of PET scan in chemotherapy process of patients with lymphoma. The study showed that CT scan without PET scan leads to simultaneously increase survival and also lower costs. However, this strategy led to unnecessary radiotherapy and other treatments in 36% of patients. In contrast, when FDG-PET was used alone and without CT scan, the figure was reduced to 4%. In addition, on average it led to the average increase of 0.7-year survival and the reduction of £ 236 expenditure per patient.[5]

Discussion

In total, PET scan is a non-invasive and safe process that has little use in screening and even initial diagnosis of various types of cancers because it is a complicated and expensive technology. However, in many malignancies after the diagnosis of tumor is confirmed by conventional and less expensive methods, it can be helpful in the evaluation of expansion of the lesion, better planning for treatment and follow-up of the disease and re-evaluation of disease spread after initial treatment. On two indications examined in this study, this technology has a better performance than similar technologies for diagnosis of metastases due to NSCLC and lymphoma in that the sensitivity and specificity for NSCLC are 74% to 95%, and 81% to 97%, respectively. The sensitivity and specificity of this method for lymphoma were 79% to 100% and more than 90%, respectively. These figures explain that although PET scan is not appropriate for diagnosis of NSCLC and differentiation of benign tumors from malignant tumors (without biopsy) in lymphoma, its use in staging and follow-up of these two types of cancers can prevent the number of unnecessary surgeries and increase patient's survival (about 17 days) and quality of life.

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