

## PET/CT and brain MRI role in staging NSCLC: prospective assessment of the accuracy, reliability and cost-effectiveness

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**Aim:** To determine whether PET/CT and brain MRI used in staging NSCLC can be accurate, reliable and cost-effective tools. NSCLC represents 80–85% of lung cancer and adequate information on the initial tumor staging is critical for planning an optimal therapeutic strategy. **Patients & methods:** Data from 30 newly diagnosed NSCLC patients in Greece were collected and prospectively recorded. Patients with potential resectable disease were evaluated to ensure that there are no detectable metastases that would rule out the possibility of a curative surgery. **Results:** Divergence occurred in 50% of cases of staging with CT or PET/CT alone, while metastases undetectable by the CT were revealed using PET/CT. Unnecessary thoracotomies were avoided by 10% of patients and another 10% was operated on after chemotherapy with a better prognosis. **Conclusion:** PET/CT and brain MRI combined are reliable for correct staging, reducing avoidable thoracotomies, morbidity rates and costs.

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### Lung cancer

Lung cancer is a major health problem worldwide accounting for 13% of all cancer cases and causing over 1.5 million deaths per year, as shown in GLOBOCAN PROJECT 2012 by the International Agency for Research on Cancer of WHO [1]. In Europe, lung cancer is third in cancer incidence (12%) and it is the number one cause of deaths with over 20% of all cancer mortality [1]. In Greece, lung cancer is the first in both new incidents and deaths per year and it grows at an almost 10% rate as the future burden of lung cancer is estimated for 2020 [1].

Lung cancer is mainly differentiated into small-cell lung cancer (SCLC), accounting for 10–15% of all cases, and non-small-cell lung cancer (NSCLC), accounting for about 80–85% of all cases [2]. Almost 60% of NSCLC is adenocarcinoma and occurs mainly in current or former smokers, but it is also the most common type of lung cancer seen in nonsmokers. Squamous-cell lung cancer accounts for about 30% of NSCLC and is more strongly associated with smoking [3].

### Diagnosis

Initial diagnosis of each NSCLC patient should be performed by a multidisciplinary medical team who will assess the patient's diagnostic tests, plan the optimal treatment and ultimately improve the quality of the prognosis [4].

An appropriate differentiation between patients with potentially curable disease and those with palliative therapy is therefore of utmost importance. For the most advantageous management of each case, precise information about the initial tumor staging is mandatory. If cancer is diagnosed at an early stage, the treatment of choice usually includes complete resection of the tumor. However, if the tumor has already reached distant organs, a cure is usually not possible.

CT scans show the size, shape and position of any lung tumor and can detect unfiltered lymph nodes with cancer cells [2]. Although CT is considered the conventional way used (CWU) for NSCLC staging, PET/CT is becoming

a useful tool. PET/CT is a hybrid technique that combines anatomic information from CT and metabolic details from PET [5]. CT provides adequate information for T staging but if there is an atelectasis, then PET can accurately determine the exact location of the tumor and its extent [6].

Although PET/CT represents a highly sensitive diagnostic test to screen for metastatic tumor deposits in the entire body that may be missed by CWU, it has a limited ability to detect brain metastases and brain MRI is required to rule out brain lesions. Thus, their combination has become standard practice in the NSCLC staging [7].

There is robust evidence in the literature which states that the addition of PET to CWU reduces the frequency of unnecessary thoracotomies by 20% [8,9]. The benefit of PET/CT has been estimated to increase the odds of identifying metastases at those uncommon sites by 5–29% [10].

### NSCLC surgery

Nearly 30% of all NSCLC patients will undergo surgery [11]. In some cases of NSCLC, neoadjuvant chemotherapy precedes the surgery aiming to shrink the tumor and facilitate thoracic surgeons with removing the tumor [2]. The purpose of the surgery is to achieve total removal of the primary tumor with a total lack of volume macroscopically and clear limits microscopically [12].

Different surgical operations are used to treat NSCLC, such as pneumonectomy, lobectomy, segmentectomy or wedge resection, sleeve resection and video-assisted-thoracic-surgery [2]. Generally, after surgery, hospitalization is needed for 5–7 days [2]. However, the risk of complications after such a surgery is very high [13]. Biological age, which is based on physical condition and co-morbidity, rather than chronological age, is a more important factor in the course of a thoracotomy. A thoracotomy can be averted either because it is performed on patients with a benign lung lesion or on patients with unresectable advanced-stage cancer [12].

### Prognosis

Prognosis is clearly better when diagnosis is made at an early stage of the disease and a curative intervention is possible. Patients at the same stage do not have the same survival rates, and recurrence of the disease after a full surgical removal occurs more often as a distant metastasis (65%) and less frequently as a local relapse (35%) [7]. The spread of the disease based on the TNM staging system, the overall performance status (PS) of the patient, gender, age over 70 and weight-loss are the most prominent predictors of survival time [12]. The size of the tumor and PET/CT findings at the initial staging as well as restaging appear to be important prognostic factors for patients' survival [2]. The exact staging of N is a powerful factor and crucial for choosing the best treatment option. The presence of lymphadenopathy of mediastinum is vital and determines the possibility of surgical removal of the cancer [7]. Different meta-analysis studies have pointed out that PET is more accurate than CT for demonstrating nodal metastases and is superior for mediastinal staging [13,14].

Unsuccessful surgery is unlikely to lead to a cure [12]. Five-year survival of patients in relation to postoperative staging (pTNM), after histological examination of the removed pulmonary parenchyma and lymph nodes, is lessened from 70 to 0% as the TNM stage grows [16], with a total 5-year survival for stage III, less than 15% [17]. The TNM Classification of Malignant Tumours (TNM) is a notation system that describes the stage of a cancer which originates from a solid tumour with alphanumeric codes. T describes the size of the original (primary) tumour and whether it has invaded nearby tissue, N describes nearby (regional) lymph nodes that are involved, and M describes distant metastasis (spread of cancer from one part of the body to another).

### Health economics

Health economics is about improving the health of the population through effective use of available resources. Guidelines should be based on clinical efficiency and cost-effectiveness. The goal is not only to save money but to rationalize resources, increase life expectancy, improve quality of life (QoL) and reduce overall treatment costs.

From an economic point of view, the data differentiate between costs incurred for treating the patient (direct medical expenses such as hospital or medicine costs) and other indirect costs due to the illness that are not related to the actual treatment (such as loss of productivity due to absence from work). When calculating the direct cost on the economic assessments of diagnostic tests, consideration should be given to the costs of potential treatment in addition to the cost of the diagnostic tests and the comparison of the costs and consequences of alternative methods [17].

Specifically for NSCLC, staging by CT or PET/CT can lead to therapeutic resection or palliative treatment with subsequent costs and results. In locally advanced tumors (IIIB) or metastatic disease (IV), patients are considered

inoperable. Patients who seem to have an operable disease should be evaluated to ensure that there are no detectable metastases that will rule out the possibility of a curative surgery [18].

Randomized clinical trials have established the value of PET/CT over conventional CT for NSCLC staging and have analyzed its cost–effectiveness for NSCLC preoperative staging as it leads to significant reductions in the number of avoidable thoracotomies and costs associated with the diagnosis and treatment of lung cancer. NSCLC patients who receive the appropriate treatment have a better QoL [17]. Different studies [8,17] concluded that for every five NSCLC patients who were staged with PET/CT, one unnecessary surgical procedure was prevented. Despite the additional cost of PET/CT, overall costs were lower when PET/CT was used, mainly due to the reduction of unnecessary interventions and days of hospitalization, particularly in the hospital ICU [19].

### Purpose & contribution of this study

NSCLC is the most common type of lung cancer and the greatest cause of morbidity and mortality in Greece. The prognosis of NSCLC is based significantly on early diagnosis and selection of the optimal therapeutic approach. The avoidance of unnecessary invasive and noninvasive procedures contributes to the maximum maintenance of the patient's well-being and the improvement of his/her life expectancy. The primary objective of this study is to evaluate whether PET/CT in combination with brain MRI as the sole tool of staging NSCLC is a capable imaging source in terms of accuracy and reliability. At a period when health economics is a major issue, this study also examines whether or not this combined imaging tool is cost-effective. Although there is a robust bibliography on this topic in general, for Greece in particular, this paper features an original case study as no other published research that combines scientific and economic evaluation for comparing staging and treatment options for NSCLC patients after CT and PET/CT scans exists.

## Patients & methods

### Study design & follow-up

For the purpose of this research, we studied 30 newly diagnosed NSCLC patients, from December 2014 until November 2016, who were referred for oncological assessment and treatment to the Oncology Unit of the 3rd Department of Medicine of National and Kapodistrian University of Athens Medical School, hosted in the General Hospital of Thoracic Diseases of Athens 'Sotiria'. The study protocol was approved by the Committee of the Medical Faculty of the National and Kapodistrian University of Athens and the Scientific Advisory Board of 'Sotiria.'

Data were derived from the Oncology Unit's medical records. Recording and follow-up of incidents was done using records of the patients' files. The diagnostic and treatment process was followed until the day recording was completed. We collected all NSCLC patients' treatment diaries and their imaging and laboratory tests from the first day they visited their general practitioner until the day their oncologist planned their treatment, as well as later data from their surgical and/or nonsurgical interventions.

### Patients & inclusion/exclusion criteria

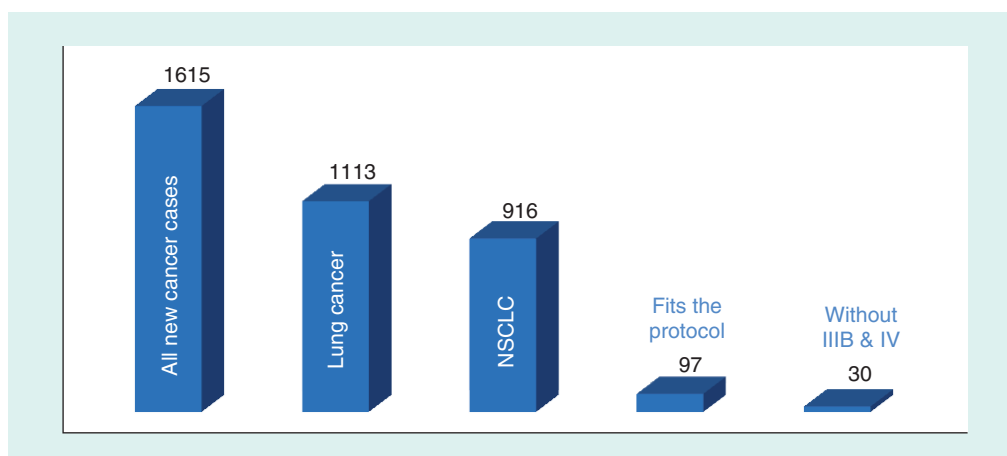
The inclusion criteria for participation in the study were the following:

- Newly diagnosed NSCLC
- Patient visited oncologist directly after visiting a pneumonologist
- Age more than 18 years old
- NSCLC clinical staging based on thoracic CT from IA to IIIA
- Short time period between CT and PET/CT scan for the initial staging (no longer than 30 days)
- Short time period between PET/CT and brain MRI for the initial staging (no longer than 7 days)
- PS: 0–1

The exclusion criteria for participation in the study were the following:

- Positive brain MRI
- Positive bones scintigraphy
- Successful or unsuccessful lung cancer resection
- Previous treatment therapy for NSCLC

The following data were collected:



**Figure 1.** Classification of newly diagnosed cases of the Oncology Unit (December 2014–November 2016).

- Demographic information for each patient
- Dates, diagnostic and treatment tools for each patient
- Separate and cumulative costs for diagnosis, nonsurgical treatment and/or surgical procedures

Diagnostic costs were based on the national reference price list for diagnostic procedures, the reimbursement of the diagnosis-related groups for nonoperative treatment and surgical interventions and the national price list for medical practices for the years 2015–2016. The pathology staging was included in cases of intended curative surgery. All the patients had echo-endoscopy and/or mediastinoscopy and their histological subtype was determined prior to the decision of choosing surgery as treatment.

### Statistical analysis

Quantitative variables are expressed as mean values and standard deviation (SD). Qualitative variables are expressed as absolute and relative frequencies. For the comparison of proportions, Chi-square and Fisher's exact tests were used. Student's *t*-tests were used for the comparison of continuous variables between two groups, and analysis of variance was used for the comparison of continuous variables between more than two groups. All *p*-values reported are two-tailed. Statistical significance was set at 0.05 and analyses were conducted using SPSS statistical software (version 19.0).

## Results

### Study collective

From December 2014 until November 2016, 1615 new patients visited the oncology unit (Figure 1), of which 502 had a type of malignancy other than lung cancer and 197 were diagnosed with small-cell lung cancer (SCLC). From the remaining 916, almost 90% were automatically excluded due to a prior surgical intervention as well as those whose PET/CT and brain MRI scan were not used at the initial staging or had too many weeks between CT and PET/CT scans, or whose primary CT staging was IIIB and IV. Another 67 persons were excluded from the study for meeting one or more of the remaining exclusion criteria.

### Patients' demographic data, pathologic-anatomical characteristics & costs

Characteristics of 30 samples were recorded (seven patients undergoing surgery after PET/CT [group 1], nine patients undergoing surgery after neoadjuvant chemotherapy [group 2] and 14 patients undergoing chemotherapy without surgery [group 3]) with a mean age of 66.8 years old (SD = 8.4). In all groups, the majority of the patients were over 60 years old. Ten patients from groups 2 and 3, received radiotherapy concurrently or sequentially with chemotherapy, while two patients from groups 1 and 2 continued with radiotherapy alone or concurrently with chemotherapy after their surgery.

Demographics and clinical characteristics of the study groups are presented in Table 1. The majority of patients

Table 1. Demographics and clinical characteristics by study groups.

	Group 1: patients undergoing surgery after PET/CT (n = 7)		Group 2: patients undergoing surgery after neoadjuvant chemotherapy (n = 9)		Group 3: patients undergoing chemotherapy without surgery (n = 14)		p-value	
	n	%	n	%	n	%		
Age, mean (SD)	71.6 (6.9)		67.7 (7.1)		63.9 (9.3)		0.142 <sup>†</sup>	
Sex	Women	3	42.9	1	11.1	1	7.1	0.114 <sup>‡</sup>
	Men	4	57.1	8	88.9	13	92.9	
Smoking	No	3	42.9	0	0.0	1	7.1	0.132 <sup>‡</sup>
	Yes and recent quitters	3	42.9	8	88.9	9	64.3	
	Ex-smoker	1	14.3	1	11.1	4	28.6	
Localization (based on PET/CT)	Right lung	3	42.9	6	66.7	8	57.1	0.863 <sup>‡</sup>
	Left lung	4	57.1	3	33.3	5	35.7	
	Both lungs	0	0.0	0	0.0	1	7.1	
Histological subtype	NOS	0	0.0	0	0.0	1	7.1	0.092 <sup>‡</sup>
	Adenocarcinoma	3	42.9	0	0.0	5	35.7	
	Squamous	4	57.1	9	100.0	8	57.1	
Age (2016)	40–49 y.o.	0	0.0	0	0.0	2	14.3	0.802 <sup>‡</sup>
	50–59 y.o.	0	0.0	1	11.1	2	14.3	
	60–69 y.o.	3	42.9	3	33.3	5	35.7	
	70–79 y.o.	3	42.9	5	55.5	5	35.7	
	80+ y.o.	1	14.2	0	0.0	0	0.0	

<sup>†</sup> ANOVA.  
<sup>‡</sup> Fisher's exact test.  
ANOVA: Analysis of variance; NOS: Not otherwise specified; SD: Standard deviation; y.o.: Years old.

Table 2. Clinical stage according to CT, PET/CT and pathological findings for the three study groups.

Stage	Group 1: patients undergoing surgery after PET/CT			Group 2: patients undergoing surgery after neoadjuvant chemotherapy			Group 3: patients undergoing chemotherapy without surgery	
	CT	PET/CT	Histology	CT	PET/CT	Histology	CT	PET/CT
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
IA	1 (14.3)	1 (14.3)	1 (14.3)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)
IB	0 (0.0)	0 (0.0)	0 (0)	3 (33.3)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)
IIA	3 (42.9)	1 (14.3)	3 (42.9)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)
IIB	1 (14.3)	3 (42.9)	1 (14.3)	0 (0.0)	0 (0.0)	1 (11.1)	4 (28.6)	1 (7.1)
IIIA	2 (28.6)	1 (14.3)	2 (28.6)	5 (55.6)	6 (66.7)	0 (0.0)	10 (71.4)	8 (57.1)
IIIB	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	2 (22.2)	1 (11.1)	0 (0.0)	2 (14.3)
IV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (21.4)
No disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)
TXNOMO	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)

in all groups had squamous cancer (70%), 26.7% of the sample had adenocarcinoma and 3.3% were not otherwise specified.

Regarding the sex of the patients, in group 1, 42.9% were women, while in groups 2 and 3 the proportion was 11.1 and 7.1%, respectively. One woman had adenocarcinoma (group 1), and the other four had squamous cancer. As for the location of the tumor, the majority of the patients had the tumor in the right lung. In addition, 42.9% of the patients from group 1 were smokers or recent quitters. Respectively, the proportion for group 2 was 88.9% and for group 3, 61.5%. In group 2, there were no nonsmokers.

Table 2 shows clinical stage according to CT, PET/CT and pathology findings for the three study groups.

**Table 3. Agreement of CT, PET/CT and pathology concerning staging.**

		Group 1: patients undergoing surgery after PET/CT		Group 2: patients undergoing surgery after neoadjuvant chemotherapy		Group 3: patients undergoing chemotherapy without surgery	
		n	%	n	%	n	%
CT versus PET/CT	Understaging	3	42.9	4	44.4	7	50.0
	Same	3	42.9	5	55.6	7	50.0
	Overstaging	1	14.3	0	0.0	0	0.0
CT versus pathology	Understaging	1	14.3	4	44.4	-	-
	Same	4	57.1	2	22.2	-	-
	Overstaging	2	28.6	3	33.3	-	-
PET/CT versus pathology	Understaging	0	0.0	4	44.4	-	-
	Same	4	57.1	0	0.0	-	-
	Overstaging	3	42.9	5	55.6	-	-

**Table 4. Agreement of CT, PET/CT and pathology concerning staging.**

		Group 1: patients undergoing surgery after PET/CT		Group 2: patients undergoing surgery after neoadjuvant chemotherapy		Group 3: patients undergoing chemotherapy without surgery		p-value
		Mean time	SD	Mean time	SD	Mean time	SD	
Total days from first CT until surgery		48.7	19.8	178.9	52.7	-	-	0.001*
Total days from first CT until surgery: number of patients (%)	<2 months	5 (71.4%)		0 (0.0%)		-		0.005†
	>2 months	2 (28.6%)		9 (100.0%)		-		
Total days from PET/CT (First for the 1st group, or second for the 2nd group of patients) until surgery		20.9	7.7	26.2	21.2	-	-	0.958*
Total days from surgery until the beginning of chemotherapy		36.6	20.1	-	-	-	-	
Total days from first PET/CT until the beginning of chemotherapy		-	-	19.1	16.0	22.5	15.6	0.629*

† Student's t-test.  
\* Pearson's  $\chi^2$  test.  
SD: Standard deviation.

Agreement of CT and PET/CT (Table 3) was 42.9% in group 1, 55.6% in group 2 and 50.0% in group 3 with no significant difference between the three groups ( $p > 0.05$ ). In group 1, the agreement of CT and pathological staging was equal to 57.1%, similar to the agreement between PET/CT and pathological staging. In the aforementioned group, the proportion of understaging was 14.3% for CT and 0.0% for PET/CT. In group 2, the agreement of CT and pathological staging was similar ( $p > 0.05$ ) and equal to 22.2%, while the agreement between PET/CT and pathological staging was equal to 0.0%. In group 2, the proportion of understaging was 44.4% for both CT and PET/CT and the proportion of overstaging was greater in PET/CT as compared with CT ( $p = 0.020$ ).

For the second group of patients, pathological understaging versus clinical staging was favorable as this showed that neoadjuvant chemotherapy was selected wisely.

In group 1, there was a divergence in CT versus PET/CT staging in four out of seven cases, mainly due to a difference in N. Pathology staging confirmed PET/CT staging in four out of seven patients. Based on CT staging, only three patients were directly operable without PET/CT. In group 2, there was also a divergence in staging in five out of nine cases, with an underestimation of I–IV stages. This was mainly due to a difference in N, while in three cases, there was a difference in T. Neoadjuvant chemotherapy improved the pathologic anatomical staging in eight out of nine patients. Lastly, in group 3, there was a divergence in CT versus PET/CT staging in nine out of 14 cases, seven of which had an underestimated N. For two of these patients, PET/CT showed stage IIIB. In addition, in three patients, PET/CT revealed a distant metastasis and these patients received mainly palliative care. Based on CT staging, three out of 14 patients could directly be operated on without PET/CT, while two patients were stage IIIB and IV and were inoperable.

Table 4 shows the days between CT and PET/CT until surgery or the beginning of chemotherapy, for each group separately. The mean time from CT until surgery was 48.7 days (SD = 19.8) for group 1 and 178.9 days (SD = 52.7) for group 2 ( $p = 0.001$ ). In group 2, there was a significant delay from the patients' first CT until surgery as neoadjuvant chemotherapy had to be done first. However, for group 2, 26.2 days (SD = 21.2) passed

Table 5. Cost of treatments for the three study groups.

	Group 1: patients undergoing surgery after PET/CT		Group 2: patients undergoing surgery after neoadjuvant chemotherapy		Group 3: patients undergoing chemotherapy without surgery		p-value <sup>†</sup> (Groups 1 vs 2)	p-value <sup>†</sup> (Groups 1 vs 3)	p-value <sup>†</sup> (Groups 2 vs 3)
	Mean (€)	SD	Mean (€)	SD	Mean (€)	SD			
Cost of diagnostic tests	1649.30	114.20	1739.00	144.40	1823.70	508.70	0.200	0.387	0.634
Cost of nonsurgical treatment	1523.20	918.50	1955.50	544.80	2227.50	1461.00	0.259	0.261	0.601
Cost of surgical treatment	4416.40	1923.30	4609.00	1629.00	–	–	0.831	–	–
Total cost until surgery	6065.80	1979.10	9068.20	1614.40	–	–	<b>0.005</b>	–	–
Total cost till the end of recording	7701.00	2369.30	9476.90	1445.30	5109.10	1864.40	0.084	<b>0.013</b>	<b>&lt;0.001</b>

<sup>†</sup>Student's *t*-test.  
p-values < 0.05 are in bold.

from the second PET/CT (or the second CT) until surgery. The time from the first CT until surgery was more than 2 months in only 28.6% of group 1, while 100% in group 2. The mean time from PET/CT until surgery was 20.9 days (SD = 7.7) for group 1 and 26.2 days (SD = 21.2) for group 2 ( $p = 0.958$ ). The time needed from the first PET/CT until surgery for the first group was similar to the time needed from the second PET/CT (restaging) until surgery for the second group. Adjuvant chemotherapy started 36.6 days after surgery for group 1. Also, groups 2 and 3 started neoadjuvant chemotherapy closely after PET/CT (19.1 and 22.5 days, respectively).

Table 5 shows the cost of treatment for the three study groups. Mean cost of diagnostic tests was €1649.30 (SD = 114.2) in group 1, €1739 (SD = 144.4) in group 2 and €1823.70 (SD = 508.7) in group 3, and it was not significantly different between the three groups ( $p > 0.05$ ). Similarly, the cost of nonsurgical treatment was not different between the three groups. Total cost until surgery was greater and equal to €9068.2 (SD = 1614.4) for those that underwent surgery after neoadjuvant chemotherapy as compared with those that underwent surgery after PET/CT. The total treatment cost was €7701.0 (SD = 2369.3) in group 1, €9476.9 (SD = 1445.3) in group 2 and €5109.1 (SD = 1864.4) in group 3, and as it was expected that the total treatment cost was significantly lower in the group 3 that did not have a surgery.

Total diagnostic costs for the second and third groups were elevated (€2870.1 and €2493.8, respectively), as after neoadjuvant chemotherapy, the patients had to be restaged in order to exclude those who could not undergo a thoracotomy. The cost of surgery and upcoming hospitalization in ICU and a surgical chamber were similar in the first and second groups.

## Discussion

In early-stage NSCLC patients, a PET/CT scan can prevent harmful interventions [20] as well as costly and unnecessary treatments and their associated side effects [17]. Overall, PET/CT has the potential to increase a patient's quality-adjusted life years and reduce the cost burden on the healthcare system by helping with the identification of the most appropriate treatment [17].

In this study, deviation existed between CT and PET/CT staging, in nine patients for T and in 15 patients for N. It is worth mentioning that CT showed T3 in four patients, which was verified by the PET/CT only in two of them, while the other two patients had, in reality, a smaller T. In addition, there were another three patients whose T based on PET/CT was T3 and another with T4, which was understaged by the CT. Finally, PET/CT revealed distant metastases in three cases.

When assessing PET/CT clinical benefit, it is important to distinguish it between direct and indirect. If PET/CT can replace an alternative invasive procedure such as surgery, then it has an immediate clinical benefit of avoiding the possible side effects and complications of that intervention. In such cases, PET/CT may be performed in

addition to CWU in each patient to confirm that its diagnostic accuracy is better. If instead PET/CT replaces another imaging tool, then it has an indirect benefit if it provides both greater diagnostic accuracy and improved health outcomes [17]. A positive change of 19–41% in curative treatment is shown by studies when PET/CT is added to the diagnostic algorithm. In 10–14% of patients, detection of distant metastases led to the prevention of surgery [13].

In one of the best known cost–effectiveness studies (PLUS trial [21]), researchers reported that in patients evaluated with the CWU, 41% were subjected to an avoidable thoracotomy. On the contrary, when PET/CT was added, only 21% had an unnecessary thoracotomy. Researchers concluded that the extra cost of PET/CT was worth the savings achieved by limiting unnecessary surgeries (~€1289 per patient) [22].

In this study, the average PET/CT cost was €1100 (total cost for the imaging and the quantity of radiopharmaceutical  $^{18}\text{F}$ -FDG used) for all patients, while the average cost for the patients who underwent surgery was €4500. Based on PET/CT staging, 10% of thoracotomies that would have been performed if staging was based on CT alone were averted. The economic benefit was €13,500, a much larger amount than the cost of running PET/CT. In addition, PET/CT staging led another 10% of patients to neoadjuvant chemotherapy instead of directly to an anatomical resection that CT staging was suggesting. For those patients, prognostic imaging was greatly improved.

Regarding restaging, timely and accurate detection of a relapse is vital to initiate retreatment or palliative care with the overall goal of increasing survival and QoL for patients [23]. In this research, only seven patients had a thoracotomy directly after PET/CT, while 23 followed neoadjuvant chemotherapy and they were then restaged. Restaging showed that only nine patients could undergo a thoracotomy, while the remaining 14 continued to receive chemotherapy or palliative treatment. From the nine patients that were operated on, seven had a PET/CT restaging and all seven of them had successful thoracotomies. The other two patients had only a CT restaging and unfortunately, one of them had an unnecessary resection, as his disease had worsened.

Beyond the financial benefits of limiting unnecessary surgeries, the effect on the patient's psychological condition must be taken into account. The QoL of a patient diagnosed with lung cancer can be greatly aggravated by the expected anxiety and emotional instability faced in the time leading up to the surgery, while at the same time being particularly vulnerable to the illness. It is also even worse to be informed after the surgery that it was, unfortunately, futile [24].

The patient's age is not a criterion of inoperability for cases of NSCLC [25,26]. Due to age, there is a slight increase in surgical morbidity and mortality [23], but if there is rigorous application of the surgical criteria [27] and careful patient selection according to their general condition, a thoracotomy can provide a good postoperative effect [28]. The use of PET/CT actually allows for a better allocation of resources (economic, material and human) within the healthcare system [29].

In this study, there were two cases that showed that individual PS plays a key role in influencing patient management decisions and may alter the usual treatment. In one case – for a patient with IIIB – who, by protocol would be considered inoperable, the multidisciplinary medical team judged that an operation would be beneficial for him and he had surgery after PET/CT scan. The findings of his Video-Assisted Mediastinoscopic Surgery (VAMS) proved that the anatomical resection was correctly chosen for this patient as there was only a single malignant lymph node disease (N2). After surgery, he underwent chemotherapy and targeted radiotherapy at his mediastinal and the hilar of his left lung. In a different case where a patient had IIB disease and very poor respiratory function, it was decided that he would have been unable to survive a thoracotomy. He had neoadjuvant chemotherapy instead and, after the four cycles, he was able to undergo radiotherapy. His condition was then re-evaluated but he was still in an inoperable state.

In the British NHS, doctors attempt to help patients detect cancer early and aim for 85% of those cases to start treatment within 62 days of the day of the first screening to confirm the cancer [30]. In this study, the approach followed by the oncology unit – from early suspicion of the existence of cancer until the diagnosis with PET/CT staging and the choice of the appropriate therapeutic scheme – was initiated in good time and within the desired time limits.

One limitation of this research is that the sample size was relatively small. However, this study was conducted with a prospective recording of patients' data rather than a retrospective recording, which might have increased the sample size. This is justified by the fact that although there were more than 900 new NSCLC patients in the oncology unit for the recording period, only 10.6% of them fit the initial protocol of this study. (i.e., newly diagnosed lung cancer, having consulted an oncologist directly after visiting a pneumonologist, and having no previous treatment for NSCLC). It is worth mentioning that in Greece, every year there are approximately 6500



newly diagnosed patients with lung cancer. At this thoracic oncology center, over 12% of these newly diagnosed lung cancer patients are referred to have an oncology assessment and treatment. This University Oncologic Center has a great reputation for its scientific work and the effective treatment of its patients who are not only citizens of Athens but come from other cities of Greece in order to get the best diagnosis. The cases that this oncology unit takes on are thus quite representative of the general image of lung cancer incidents in Greece.

A strong point of this research is that this Oncology Unit – as a part of a University Internal Medicine Department – can offer a multidisciplinary medical approach to the disease by the specialists in its various health departments (pneumonology, oncology, radiology, pathology, nuclear medicine, radiotherapy, thoracic surgery). Such an approach plays a key role in choosing the best therapeutic approach by invasive or noninvasive techniques. Another strong point of this research is that its economic data did not have to be calculated by bibliographical information, as almost all cost information were provided by the administration/financial department of the hospital (except for PET/CT and brain MRI scans that are not done in-house and their costs were based on the current price list for medical practices) and reflect the genuine picture of the cost for each patient.

Undoubtedly, the use of PET/CT has much to offer in medical science and in particular in the diagnosis of various forms of cancer. Trivial variations of PET/CT with different radiolabeled substances have already been used. One of these variants considered to play a particular role in the staging of lung cancer is F-DOPA PET, which has the potential, after one examination only to precisely and sensitively combine the benefits of a PET/CT with a brain MRI [31].

## Conclusion

PET/CT was proved an important tool for staging and restaging NSCLC. It seems reasonable to use it for helping with the designation of an optimal treatment strategy (surgical or not, with neoadjuvant or postsurgical chemotherapy) and improving patient prognosis. Not only from a financial standpoint but also by taking into consideration the possible complications during and soon after surgery as well as that overall survival from lung cancer surgery typically takes weeks to months. The combination of PET/CT and brain MRI can provide a reliable method for tumor and nodal staging plus distant metastasis detecting, reducing needless thoracotomies and their associated morbidity rates and costs.

This study shows that:

- Divergence among staging with CT alone or PET/CT alone occurred in 50% of the cases
- By using PET/CT, metastases were revealed that were undetectable by CT (20%) or nodal metastases that were underestimated (26.7%), as well as differentiation in T staging (30%)
- For the seven patients that proceeded to surgery directly after PET/CT staging, no thoracotomy was unnecessary
- For the patients that underwent neoadjuvant chemotherapy before surgery, a significant improvement was observed in patient imaging, and for all the cases where PET/CT was used for restaging, there was no futile thoracotomy
- 10% of unnecessary thoracotomies were avoided, while another 10% of cases underwent surgery after neoadjuvant chemotherapy and had a better prognostic imaging
- The average cost of initial staging with PET/CT was €1100, while the average cost of a surgical resection was €4500.

## Future perspective

Undoubtedly, the use of PET/CT has much to offer in medical science and in particular in the diagnosis of various forms of cancer. Minor variations of PET/CT with different radiolabeled substances have already been used. One of these variants, considered to play a particular role in the staging of lung cancer, is F-DOPA PET, which has the potential, after one examination only to precisely and sensitively combine the benefits of a PET/CT with a brain MRI [31].

## Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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### Summary points

- The PET/CT has proved to be an important tool for staging and restaging NSCLC in various studies and its contribution to medical science is significant. Surgery is the best attempt to treat the early-stage tumors of NSCLC, but as it is a severe intervention with various complications, it is not the ideal therapeutic strategy for every patient with NSCLC.
- In this study, we show that the PET/CT is an accurate and reliable method to help designate an optimal treatment strategy (surgical or not, with neoadjuvant or postsurgical chemotherapy). The exact staging of N is a powerful factor and crucial for choosing the best treatment option. Deviation existed between CT and PET/CT staging in 50% of the research sample for N or T and PET/CT revealed distant metastases in 10% of the cases.
- PET/CT also improves patient prognosis and cost-effectiveness, saving 10% of NSCLC patients from undergoing preventable surgeries. In another 10% of cases, anatomical resectomy followed neoadjuvant chemotherapy and the prognostic imaging biomarkers were also better. The average cost for a PET/CT is less than 25% of the average cost of a thoracotomy and it seems reasonable to add it in the conventional way used and design the optimal treatment.

### Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

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