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ORIGINAL ARTICLE

PET-SUV Max and Upstaging of Lung Cancer

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Background Lung cancers managed surgically with curative intent are sometimes upstaged postoperatively. The potential contributions from surgical waiting time and primary tumour ^{18}F-FDG avidity on positron emission tomography (PET)/computed tomography (CT) are unknown.

Methods We reviewed the records of 153 Royal Adelaide Hospital surgical patients with primary lung cancers from 2013 to 2016 who had preoperative staging combining CT, ^{18}F-FDG PET/CT and biopsy. Subjects were divided into two cohorts: postoperative Tumour, Node, Metastases (TNM) upstaged (US) and not upstaged (UN). The parameters of standardised uptake value (SUV max), pre-scan blood glucose level (BGL), the time interval between staging and surgery were analysed using a two-tailed Mann-Whitney U test.

Results Subjects were aged 31 to 85 years; 75 were male. Ninety-three had adenocarcinoma (AC), 42 had squamous cell carcinoma (SCC). Sixty-four were upstaged after surgery, 40 AC and 18 SCC.
For AC, US SUV max was significantly higher (mean US 6.4 (SD 4.6) vs. UN 4.6 (SD 3.4), p = 0.03) but not time to surgery (mean US 55 (SEM 7.1) vs. UN 71 (SEM 14.8) days p = 0.74). Upstaged were mainly T (imaging and histopathology discordance) and N (unexpected mediastinal or hilar nodal metastases).
For SCC, US vs. UN SUV max (mean US 12.0 (SD 5.6) vs. UN 9.4 (SD 5.6), p = 0.08) and time to surgery (mean US 48 (SEM 5.3) vs. UN 47 (SEM 5.0) days p = 0.66) were not significantly different.
Standardised uptake value max and surgical waiting time were not analysed for other tumour types due to small numbers.
Pre-PET BGL US vs. UN was not significantly different for all (p = 0.52), AC (p = 0.32) and SCC (p = 0.37) subjects, thus not a confounding factor.

Conclusions For lung cancers assigned to curative surgery, high primary tumour SUV max of AC but not SCC may predict surgical upstaging with implications for ^{18}F-FDG PET/CT nodal assessments. Surgical waiting time appears not to be a predictor for both tumour types.

Keywords PET • Lung cancer • SUV max • Adenocarcinoma • Upstaging

Background

Lung cancer is the leading cause of cancer mortality for both the male and female population of Australia and accounted for the highest number of deaths from cancer in Australia in 2013 and 2016 [1].

For cases of non-small cell lung cancer (NSCLC), whereby management is with curative intent, the preoperative imaging includes CT scan and ^{18}F-FDG PET/CT scan. The preoperative staging is based on the Tumour, Node, Metastases (TNM) system, which takes into account tumour size and location, nodal disease and distant metastasis.

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Postoperatively, some patients are upstaged based on the operative and the histological findings. Upstaging may reflect the inherent limitations of the preoperative staging tests. Disease progression during the course of workup is another potential cause of postoperative upstaging [2].

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) is now routinely used [3]. Combined ^{18}F-FDG PET/CT is more accurate than single modality PET and standard CT for accurate description of T-staging [4,5] lung cancers. The most significant factor in treatment planning is mediastinal staging. PET, if negative for mediastinal disease, helps to reduce the rates of invasive mediastinal nodal sampling, which may be performed via endobronchial ultrasound or with mediastinoscopy. There is data to suggest that performing routine mediastinoscopy for all patients with non-small cell lung cancer (NSCLC) does not significantly preclude patients from unnecessary thoracotomy [6]. The indications for mediastinal nodal staging are patients with central tumours, enlarged lymph nodes on CT and/or N1 disease on ^{18}F-FDG PET/CT [7].

Although several previous studies have reported the usefulness of ^{18}F-FDG PET/CT in the preoperative staging for NSCLC [8,9], there are also reports suggesting the rate of thoracotomies are not affected by this imaging modality [10,11].

Standardised uptake value (SUV max), is a commonly used semi quantitative parameter in ^{18}F-FDG PET/CT evaluations. It reflects the degree of radiotracer avidity within the defined region of interest. It is easily derived in most proprietary reporting stations and is commonly used.

We preformed an audit on patients treated surgically for NSCLC with curative intent in our institution to evaluate the possible role of primary tumour ^{18}F-FDG PET/CT SUV max and surgical waiting time as predictive factors for postoperative upstaging.

Methods

The records of all patients who had lung surgery at the Royal Adelaide Hospital from January 2013 to December 2016 were reviewed. Subjects were known or were strongly suspected to have primary lung cancer based on imaging and biopsy results. Surgery was performed with curative intent. The protocol of our surgeons is to do systemic nodal sampling — station 4, 7 and 10 nodes for right-sided tumours; station 5, 6, 7 and 10 nodes for left sided tumours. In addition, 38 patients also had mediastinal lymph node sampling intraoperatively. All patients had preoperative staging tests that consisted of standard chest CT scan and ^{18}F-FDG PET/CT. A total of 153 subjects had all of the relevant data and were included in this audit. In three of these subjects, the SUV max was not reported and was determined retrospectively.

Computed tomographic scans were performed at different institutions depending on the source of the patient referral.

The ^{18}F-FDG PET/CT scans were performed at one of two centres:

1. The Royal Adelaide Hospital, using a Philips Gemini GXL 16–DS PET/CT scanner (Philips Healthcare, Port Melbourne, Vic, Australia). The studies were acquired in the standard protocol (minimum 4-hour fast; average ^{18}F FDG dose of 285 MBq; acquisition time at 60 minutes; 3 minute per bed position; two dimensional (2D) high sensitivity mode; 15 cm axial field of view; 256 × 256 matrix; iterative reconstruction of 128 × 128 matrix; concomitant low energy CT). Studies were processed and reviewed on a Hermes workstation (Hermes Medical Solutions, Wollongong, NSW, Australia).
2. Dr. Jones and partners Medical Imaging (a private imaging provider), using a Siemens biograph True Point, 16 slice, PET/CT camera (Siemens Healthcare, Bayswater, Vic, Australia). This centre had a similar scanning protocol to the Royal Adelaide Hospital. Studies were reviewed on an Inteleviewer workstation (Intelerad Medical Systems, Southbank, Vic, Australia).

The surgical specimens were analysed by SA Pathology (formerly the Institute of Medical and Veterinarian Science, Adelaide, SA, Australia) and histological type categorised according to the WHO classification system from 2011 [11].

The clinical and surgical data for all patients were obtained from the electronic medical record system of the Cardiothoracic Surgery Department of the Royal Adelaide Hospital. For the purpose of this audit the 7th edition of the TNM staging system was used [12].

The study endpoints were:

1. ^{18}F-FDG PET/CT SUV max of the primary tumour.
2. Time interval from PET scan to surgery.
3. Pre ^{18}F-FDG PET/CT blood glucose level.

To simplify analysis, subjects were divided into two cohorts: TNM upstaged (US) and not upstaged (UN). The UN group also included patients who were down-staged postoperatively. The data were analysed using a two-tailed Mann-Whitney U test.

The Royal Adelaide Hospital Ethics committee approved the study.

Results

Between January 2013 and December 2016, 160 patients underwent surgical procedure with curative intent for primary lung cancer by the cardiothoracic surgery unit at the Royal Adelaide Hospital. The data of 153 of these patients were reviewed retrospectively.

Seven patients were excluded:

- four were for metastasectomy (two with colorectal carcinoma and two with sarcoma)
- two had missing data
- one with no PET images available

Table 1 **Demographic.**

	Total	Average (Age)	Max (Age)	Min (Age)	SD	Male (%)
Upstaged	64 (42%)	68.4	85	46	9.9	51
Unchanged	89 (58%)	67	83	42	8.5	49

Abbreviation: SD, Standard Deviation.

In three of the remaining 153 subjects the SUV max was not reported and was determined retrospectively but still included in the review.

There were 75 male (49%) and 78 female (51%). The mean age of the study sample was 67.4 (SD 9.6) years.

Out of 153 patients, 42% were TNM upstaged postoperatively. This cohort had a mean age of 68.4 years and 51% were males (Table 1).

The tumour characteristics of the subjects are summarised in Table 2. The most common primary tumour type was adenocarcinoma noted in 60%. Twenty-seven (27%) per cent had squamous cell carcinoma. The remainder had different tumour types, including small cell carcinoma. The number of subjects in this miscellaneous group was too small for any meaningful statistical evaluation and has also been excluded in some of the sub-analyses.

Comparing SUV max of the US vs. UN groups, there was a statistically significant difference when all tumour types were considered collectively (mean US 8.2 (SD 5.5) vs. UN 6.4 (SD 5.3), p = 0.02). In a subgroup analysis, the US vs. UN SUV max was only significantly different for adenocarcinoma (mean US 6.4 (SD 4.6) vs. UN 4.6 (SD 3.4), p = 0.03). For the SCC subgroup the US vs. UN SUV max was not significantly different (mean US 12.0 (SD 5.6) vs. UN 9.4 (SD

Table 2 **Tumour characteristics.**

Tumour Type	Tissue Type	N
NSCLC	Adenocarcinoma	93 (60%)
	Squamous Cell Carcinoma	42 (27%)
	Large Cell Carcinoma	4
SCLC	Small Cell Carcinoma	4
Carcinoid		8
Others	Spindle Cell and Mesothelioma	2

Abbreviation: NSCLC, Non Small Cell Lung Cancer.

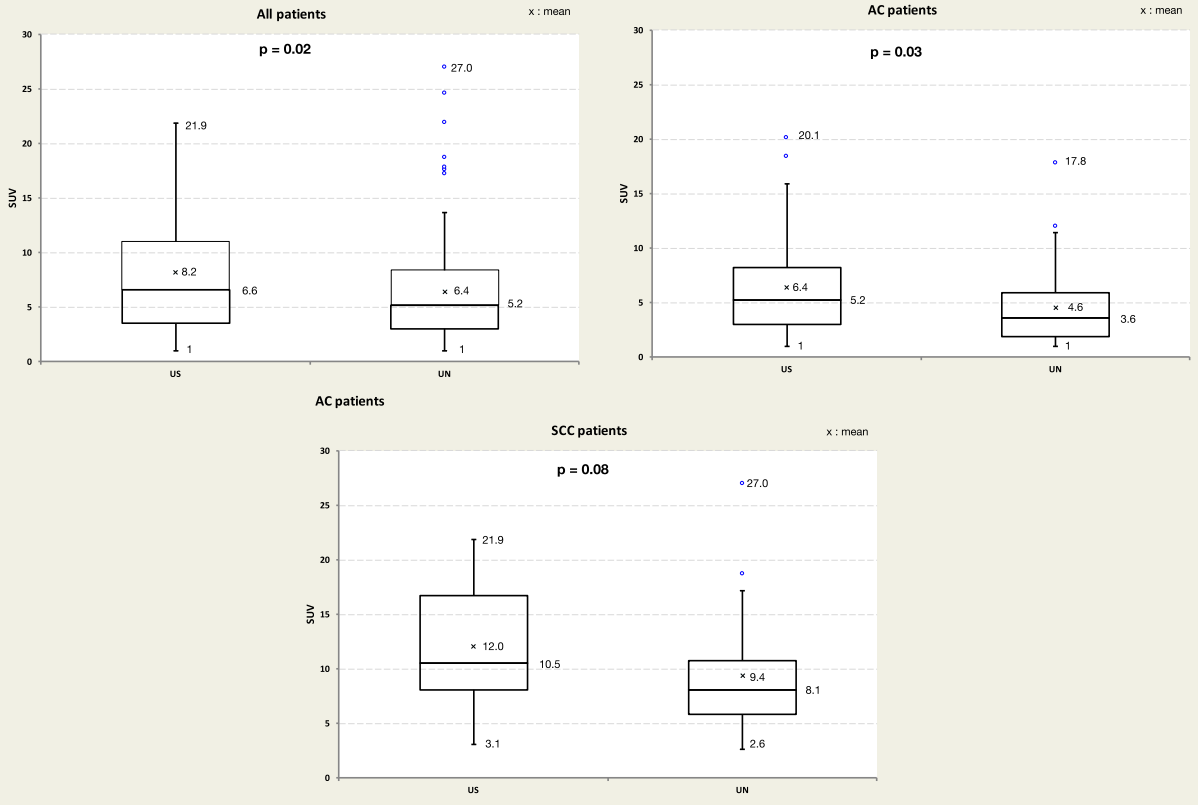

Figure 1 SUV max of upstage (US) vs unchanged (UN) subjects for all, adenocarcinoma (AC) and squamous cell carcinoma (SCC) groups.

Table 3 Time to surgery (Days).

	Mean	Median	Range	Standard Error
(A) All Patients (p = 0.59)				
US	53	50	5–298	4.8
UN	63	47	7–718	9.1
(B) Adenocarcinoma (p = 0.74)				
	Mean	**Median**	**Range**	**Standard Error**
US	55	51	5–298	7.1
UN	71	47	8–718	14.8
(C) SCC (p = 0.66)				
	Mean	**Median**	**Range**	**Standard Error**
US	48	49	13–96	5.3
UN	47	43	7–108	5.0

Abbreviations: US, Upstaged; UN, Not Upstaged.

Table 4 Pre-PET BGL (mmols/L).

	Mean	Median	Range	Standard Deviation
(A) All Patients (p = 0.52)				
US	6.4	6.1	4–15.7	1.8
UN	6.4	6.1	4.1–12.4	1.5
(B) Adenocarcinoma (p = 0.32)				
	Mean	**Median**	**Range**	**Standard Deviation**
US	6.4	5.9	4–15.7	2.1
UN	6.3	6.1	4.1–12.2	1.3
(C) SCC (p = 0.37)				
	Mean	**Median**	**Range**	**Standard Deviation**
US	6.1	6.2	5.1–7.9	0.8
UN	6.7	6.2	4.9–12.4	1.7

Abbreviations: US, Upstaged; UN, Not Upstaged.

5.6), p = 0.08) (Figure 1). The numbers of subjects in the other tumour types were too small for meaningful subgroup analyses. Comparing the two largest groups, SUV max was significantly higher for SCC than adenocarcinoma in both the US and UN groups (US: mean SUV max 6.4 for AC vs. 12.0 for SCC, $p < 0.001$; UN mean SUV max 4.6 for AC vs. 9.4 for SCC, $p < 0.001$).

The time intervals from staging to surgery are outlined in Table 3. The range of results were noted to be quite large, thus mean +/− standard error is reported instead of standard deviation. Comparing the US vs. UN groups there was no significant difference for all subjects collectively (mean US 53 (SEM 4.8) vs. UN 63 (SEM 9.1) days p = 0.59), for adenocarcinoma (mean US 55 (SEM 7.1) vs. UN 71 (SEM 14.8) days p = 0.74) and for SCC (mean US 48 (SEM 5.3) vs. UN 47 (SEM 5.0) days p = 0.66).

Pre ^{18}F-FDG PET/CT blood glucose levels are outlined in Table 4. Comparing US vs. UN there was no significant difference for all subjects collectively, for adenocarcinoma and for SCC.

Among the subjects who were upstaged, Table 5 outlines the reason for the upstage for each tumour type. Table 6 outlines the final postoperative staging. Among those who were upstaged to stage 3A or higher Table 7 outlines their preoperative staging. Of note there were five with adenocarcinoma and two with SCC who were upstaged to stage IV and were deemed inoperable at surgery.

Table 5 TNM staging in upstaged lung cancer patients.

	n	T	N	M	TN	NM	TNM
Adenocarcinoma	40	24	9	3	2	1	1
SCC	18	5	8	2	3	0	0

Abbreviation: SCC, squamous cell carcinoma.

Discussion

Despite best preoperative clinical staging, lung cancer patients operated on with curative intent are sometimes upstaged postoperatively. This was well described in 2,994 patients, where concordance between clinical and pathologic stage was 47% for the primary tumour and 47% for regional lymph nodes [13]. Surgical upstaging can occur due to multiple, complex interlinking factors that can arise from the inherent limitations of clinical staging, sensitivity and specificity of the imaging tools, disease progression during the

Table 6 Post surgical upstaging.

	Total Upstage	Stage IB	Stage II	Stage IIIA	Stage IIIb/IV
Adenocarcinoma	40	20	7	8	5
SCC	18	4	9	3	2

Abbreviation: SCC, squamous cell carcinoma.

Table 7 Upstage – pre vs. postoperative stage.

Stage	Preoperative			
	IA	IB	IIA	IIB
Postoperative				
Adenocarcinoma				
III A	4	1	1	2
III B	0	0	0	0
IV	3	1	1	0
SCC				
III A	0	2	0	1
III B	0	0	0	0
IV	0	0	0	2

Abbreviation: SCC, squamous cell carcinoma.

course of workup, flare of unrelated comorbidity, theatre lists and some unexplained causes [14].

The purpose of the study was to see if the primary tumour ^{18}F-FDG PET/CT SUV max and surgical waiting time are the predictive factors for postoperative upstaging with the hope of reducing the incidence of postoperative upstaging.

In our audit, the patients who were referred for surgery had mainly non-small cell lung cancers (NSCLC). The majority had adenocarcinoma followed by squamous cell carcinoma. Patients referred for staging ^{18}F-FDG PET/CT were mainly suspected NSCLC that did not demonstrate distant metastasis on CT scan and also in select borderline populations who may be operable (e.g. CT stage IA to IIIA disease).

Duan XY et al. reported that tumour pathologic type and differentiated grade were significantly related to SUV max [15]. From our analysis, SUV max as a predictor of postoperative upstaging was significant only in patients with histology diagnosis of adenocarcinoma. Adenocarcinoma is characterised by significant heterogeneity as determined by the presence of multiple subtype patterns of varying prognostic significance [16,17]. Our study also demonstrates this heterogeneity with respect to the SUV max values in the adenocarcinoma group, where upstaged patients had higher primary tumour SUV max compared to the patients whose staging remained stable postoperatively.

T Staging

In our study, the majority of the patients who were upstaged were a result of T staging (50% of the total upstaged SCC and AC population). Spatial resolution of current multi-detector CT's allows accurate assessment of tumour dimensions, and ^{18}F-FDG PET/CT complements this assessment when the edge of the tumour is blurred by adjacent collapse or consolidation. ^{18}F-FDG PET/CT can also help to determine if a tumour is invading the chest wall or the mediastinum [18]. However, all modalities of imaging cannot match the final pathological measurements of the excised tumour and the microscopic determination of tumour margins and extent. The discordant T staging reflects the limitations of current imaging techniques.

N Staging

There were 17 subjects (nine AC and eight SCC) who were upstaged purely from operative detection of nodal involvement. Another seven patients had nodal upstage in addition to T and M disease (AC: two with TN, one with NM, one with TNM; SCC three with TN) (Table 6). Thus a total of 24 subjects, or 17.7%, had nodal disease that was not classified preoperatively. This would have included the cohort of patients who may have had equivocal nodal appearances on CT and/or PET/CT. These patients may have had preoperative nodal sampling via endobronchial ultrasound/EBUS. If the nodes sampled were positive on the contralateral side, thus an N3 node then surgery would have been cancelled and this cohort would not have been captured in this series. If the nodal biopsy was negative or equivocal (e.g. with micro metastasis), then the patient might still have been given the benefit of the doubt and surgery might still be performed.

The identification of nodal involvement is vital to select candidates for curative surgery. Various studies report relatively low rates of false negative for mediastinal staging for NSCLC [19]. Within the limitations of a retrospective study, our study has raised concerns about possible underestimation of occult nodal involvement in cases of adenocarcinoma with a high primary tumour SUV max. The results of our nodal findings are supported by literature on occult nodal metastasis by Al-Sarraf et al. and other authors who have quoted an even higher false negative rate [6,19]. The results of this audit may have implications with respect to the evaluation of mediastinal and hilar nodes. For the adenocarcinoma group with SUV max >6.4 there may be a risk of underestimating the nodal staging and perhaps preoperative nodal sampling would be beneficial.

Of note, we found SCC to be a more FDG avid tumour as evidenced by statistically higher SUV max than adenocarcinoma in this audit. The total number of SCC subjects who were N upstaged were 11 (8N + 3TN), or 26% (11/42) of those with this tumour type. In comparison, the number of adenocarcinoma subjects who were N upstaged was 13 (9N + 2TN + 1NM + 1TNM), or 14% (13/93) of those with this tumour type (Table 5). The SUV max of the primary SCC was not a predictor of postoperative upstage. This could possibly be explained by the SCC subjects who did not proceed to surgery because of a positive contralateral mediastinal node (i.e. at least stage IIIB), a cohort that is beyond the scope of this audit. N3 nodes, if present, may have been more obvious with SCC, therefore treated non-surgically.

M Staging

The combined benefits of high spatial resolution of multi-detector CT and high contrast resolution of ^{18}F-FDG PET/CT result in effective detection of metastatic disease. Our study

reported seven patients, (five adenocarcinoma and two SCC) who underwent thoracotomies and were M upstaged (Table 5). Amongst these, two patients had tumours that were strongly adherent to the chest wall in such a manner that would have required substantial chest wall resection, and therefore could lead to significant operative morbidity and mortality, noting that there was parietal pleura infiltration. Three patients had parietal pleural surface invasion, one had malignant pleural effusion and one had a combination of chest wall invasion and multiple firm pleural nodules. Although ^{18}F-FDG PET/CT was performed before operation in these five patients with unexpected intraoperative pleural metastasis, no increased pleural uptake was found.

Final Postoperative Staging

Among the population in our series with adenocarcinoma and SCC, a total of 64 out of 135 subjects or 47% were upstaged. However, surgery with curative intent is still possible in select cases for up to stage IIIA that means no worse than T3N2M0 or T4N1M0 according to the 7th edition of the TNM staging. In our series, there were five with adenocarcinoma and two with SCC who were upstaged to IV and none to stage IIIB, thus only 5% were deemed inoperable (Tables 6 and 7). For adenocarcinoma all five were upstaged to stage IV, three of whom were preoperative stage IA. For SCC both were stage IIB preoperatively. All seven patients were M upstaged because of combination of chest-wall and/or pleural involvement.

Operative Waiting Time

Our study showed no significant difference for time to surgery irrespective of tumour type. This is not surprising as the surgical waiting times (Table 3) were below the tumour doubling time, which for a typical lung adenocarcinoma is approximately 221.6 days and 115.2 days for squamous cell carcinoma [20].

Blood Glucose Level

Blood glucose levels can have a significant influence on tumour ^{18}F-FDG uptake. Our study showed no significant difference in BGL in upstaged verses unchanged groups. Therefore, BGL was not a confounder for SUV values in this series (Table 4).

Our study has significant limitations. First, this is a retrospective review compiled from cardiothoracic database. There are inherent deficiencies of a retrospective review relating to patient selection bias (e.g. patients with potentially curable disease but who were not fit for surgery were not captured by this audit) and missing data. The variability of the reporting styles of the CT and the ^{18}F-FDG PET/CT scans are also potential confounding factors. Second, the reliability of SUV max as a measure is affected by multiple factors apart from pre-test BGL. The ^{18}F-FDG PET/CT was performed in two centres with different equipment, which could potentially add to the uncertainty of the reproducibility of the measured SUV max. A prospective study will be required to more confidently assess SUV max as a predictor of postoperative upstaging of NSCLC.

Conclusions

In our audit of patients with non-small cell lung cancer who were operated on with curative intent in our institution, preoperative ^{18}F-FDG PET/CT SUV max of the primary tumour was found to potentially be a predictor of postoperative upstaging in those with adenocarcinoma but not for those with squamous cell carcinoma. This may have implications for the interpretation of lymph nodes with equivocal ^{18}F-FDG uptake and the need for preoperative nodal sampling for adenocarcinomas with very high metabolic activity. Operative waiting time was not a predictor of upstaging in both tumour types.

References

[1] Australian Institute of Health and Welfare. Australian Cancer Incidence and Mortality (ACIM) books: lung cancer. Canberra: AIHW; 2016 [Accessed February 2017].

[2] Liberman Moishe, Liberman Dan, Sampalis John S, Mulder David S. Delays to surgery in non-small-cell lung cancer. Can J Surg 2006;49 (February (1)):31–6.

[3] Al-Sarraf N, Aziz R, Gately K, Lucey J, Wilson L, McGovern E, et al. Pattern and predictors of occult mediastinal lymph node involvement in non-small cell lung cancer patients with negative mediastinal uptake on positron emission tomography. Eur J Cardiothorac Surg 2008;33:104–9.

[4] Juweid ME, Cheson BD. Positron-emission tomography and assessment of cancer therapy. N Engl J Med 2006;354:496–507.

[5] Herrmann K, Benz MR, Krause BJ, Pomykala KL, Buck AK, Czernin J. (18)F-FDG-PET/CT in evaluating response to therapy in solid tumors: where we are and where we can go. J Nucl Med Mol Imaging 2011;55:620–32.

[6] Al-Sarraf N, Aziz R, Gately K, Lucey J, Wilson L, McGovern E, Young V. Pattern and predictors of occult mediastinal lymph node involvement in non-small cell lung cancer patients with negative mediastinal uptake on positron emission tomography. Eur J Cardiothorac Surg 2008;33:104–9.

[7] Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2013;143(Suppl. 5):e166S–90S.

[8] Fischer B, Lassen U, Mortensen J, Loft A, Bertelsen A, Ravn J, et al. Preoperative staging of lung cancer with combined PET/CT. N Engl J Med 2009;361:32.

[9] Van Tinteren H, Hoekstra OS, Smit EF, Van den Bergh JH, Schreurs AJ, Stallaert RA, et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. Lancet 2002;359:1388.

[10] Pozo-Rodríguez F, Martín de Nicolás JL, Sánchez-Nistal MA, Maldonado A, García de Barajas S, Calero-García R, et al. Accuracy of helical computed tomography and [^{18F}] fluorodeoxyglucose positron emission tomography for identifying lymph node mediastinal metastases in potentially resectable non-small-cell lung cancer. J Clin Oncol 2005;23:8348.

[11] Herder GJ, Kramer H, Hoekstra OS, Smith EF, Pruim J, Van Tinteren H, et al. Traditional versus up-front [18F] fluorodeoxyglucose-positron emission tomography staging of non-small-cell lung cancer: a Dutch cooperative randomized study. J Clin Oncol 2006;24:1800.

[12] Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. J Thorac Oncol 2016;11:39.

[13] López-Encuentra A, García-Luján R, Rivas JJ, Rodríguez-Rodríguez J, Torres-Lanza J, Varela-Simo G, et al. Comparison between clinical and

pathologic staging in 2,994 cases of lung cancer. Ann Thorac Surg 2005;79:974.
[14] Silvestri GA, Gould MK, Margolis ML, Tanoue LT, McCrory D, Toloza E, et al. Noninvasive staging of non-small cell lung cancer: ACCP evidenced-based clinical practice guidelines (2nd edition). Chest 2007;132 (Suppl. 3):178S–201S.
[15] Duan X-Y, Wang W, Li M, Li Y, Guo Y-M. Predictive significance of standardized uptake value parameters of FDG-PET in patients with non-small cell lung carcinoma. Braz J Med Biol Res 2015;48(3):267–72.
[16] Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6(2):244–85.
[17] Russell PA, Wainer Z, Wright GM, Daniels M, Conron M, Williams RA, et al. Does lung adenocarcinoma subtype predict patient survival?: a clinicopathologic study based on the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary lung adenocarcinoma classification. J Thorac Oncol 2011;6(9):1496–504.
[18] Yousefi-Koma Abbas, Panah-Moghaddam Mojgan, Kalff Victor. The utility of metabolic imaging by ^{18}F-FDG PET/CT in lung cancer: impact on diagnosis and staging. Tanaffos 2013;12(1):16–25.
[19] Carnochan FM, Walker WS. Positron emission tomography may underestimate the extent of thoracic disease in lung cancer patients. Eur J Cardiothorac Surg 2009;35:781–4 [Discussion 784–785. Epub ahead of print March 2009].
[20] Arai Takashi, Kuroishi Tetsuo, Saito Yasuki, Kurita Yuzo, Naruke Tsuguo, Kaneko Masahiro. Tumor doubling time and prognosis in lung cancer patients: evaluation from chest films and clinical follow-up study. Jpn J Clin Oncol 1994;24(4):199–204.