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Comparison of ^{18}F-FDG PET/CT and MDCT for staging/restaging of non-small cell lung cancer

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Multi-detector computed tomography (MDCT) is most commonly used for staging of non-small cell lung cancer (NSCLC). In recent years, ^{18}F- fluorodeoxyglucose positron emission tomography combined with computed tomography (^{18}F-FDG PET/CT) has also been used for the same purpose. Since studies comparing these two methods are scarce, our aim was to determine how the TNM classification and thereby staging of NSCLC compare between ^{18}F-FDG PET/CT and MDCT. ^{18}F-FDG PET/CT and MDCT were collected in 83 patients with NSCLC 3 to 30 days apart (median 17 days). The investigators interpreting ^{18}F-FDG PET/CT were unaware of MDCT results. The Cohen's kappa (κ) was calculated to determine the rate of agreement. The hypothesis was that the strength of agreement between the two methods will be at least moderate (κ>0.40) based on the adopted criteria (κ<0.20 poor; 0.21–0.40 fair; 0.41–0.60 moderate; 0.61–0.80 good; 0.81–1.00 very good agreement). The agreement was moderate for determining the T class (κ=0.45, overall agreement 58%), poor for the N class (κ=0.13, 42%) and fair for the M class (κ=0.22, 58%). The agreement for overall staging of NSCLC was poor (κ=0.20, 45%). The major source of disagreement was that metastases were present more frequently and/or in larger number on ^{18}F-FDG PET/CT than MDCT in the contralateral mediastinal, supraclavicular, and distant lymph nodes, as well as in the bones and suprarenal glands. Since ^{18}F-FDG PET/CT detected more regional and distant metastases than MDCT, we conclude that FDG PET/CT is useful for staging/restaging and planning treatment of patients with NSCLC.

Key words: non-small cell lung cancer, positron emission tomography, multidetector computed tomography, metastases detection

Lung cancer is the leading cause of cancer death worldwide [1, 2], with a non-small cell lung cancer (NSCLC) accounting for 75-80% of all cases. At the time of diagnosis, most NSCLC patients are in advanced stages of the disease with metastases in distant lymph nodes, bones, and adrenal glands [3, 4]. The most important prognostic factor is accurate staging of NSCLC based on TNM classification, which includes the assessment of tumor size and location (T), spread to regional lymph nodes (N), and presence or absence of distant metastases (M) [2].

The diagnosis, staging, and treatment of NSCLC requires a multidisciplinary approach [2]. Computed tomography (CT) is most commonly used for assessment of NSCLC but only the chest and upper abdomen (liver and adrenal glands) are typically scanned [5]. Also, CT has limited ability to distinguish between benign and malignant lesions [4]. Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is a non-invasive method increasingly used for diagnosis of different types of cancer [6]. ^{18}F-FDG PET evaluates the whole body and provides an insight into the intensity of glucose metabolism commonly increased in cancer cells. ^{18}F-FDG PET has been useful for the evaluation of unspecified lung metastases in mediastinal lymph nodes as well as the evaluation of local and distant metastases [7]. Although ^{18}F-FDG PET has proven useful for determining the stage of NSCLC [8], it suffers from poor spatial resolution [4]. Thus, combined ^{18}F-FDG PET and CT (PET/CT) has the potential to increase diagnostic reliability by providing information about the metabolic state in conjunction with a precise anatomic location, which is of interest for the proper diagnosis and staging of NSCLC [6, 9].

To our best knowledge, only two previous studies directly compared ^{18}F-FDG PET/CT to CT for detecting metastases in NSCLC patients [10, 11]. The results suggest that ^{18}F-FDG PET/CT is more accurate than CT for the staging of mediastinal lymph nodes. However, no direct comparison was made with respect to distant metastases, especially in the bones and adrenal glands. Thus, the purpose of our study was to compare the agreement between results of ^{18}F-FDG PET/CT and multi-detector CT (MDCT) in the detection of tumor size and location (T), the spread to regional lymph nodes (N), and the presence of distant metastases (M), particularly in the bones and adrenal glands, and thereby, the TNM staging of NSCLC.

Patients and methods

Between January 1st and December 31st 2012, 159 patients with NSCLC were examined at the PET Center of the Clinical Center of Serbia. The inclusion criteria were age over 18 years, histologically proven NSCLC, and MDCT and PET/CT performed within 30 days of each other. A total of 83 patients met the criteria. Their average age was 60 ± 8 years (range 44-79) and 49 (59%) were men. MDCT and PET/CT were done 3 to 30 days apart (median 17 days).

Data acquisition, reconstruction and image analysis. PET/CT imagining was performed with 64-slice Biograph True64 PET/CT scanner (Siemens Medical Solutions USA Inc.). The patients fasted for 6 to 8 hours before imaging. ^{18}F-FDG was administered in a dose of 5.5 MBq per kilogram of body weight (mean dose received 237 ± 38 MBq). Images were acquired at least 60 minutes after the ^{18}F-FDG administration (blood glucose level <11 mmol/l). PET acquisition was preceded by a low-dose MDCT for attenuation correction and topographic localization without contrast media, with 120 kV, 45 mAs, slice thickness 5 mm, pitch 1.5, and rotation time of 0.5 s. 3D PET images were acquired from the base of the skull to the upper third of the femur (6-7 fields of view, 3min/field). The collected data were reconstructed on the SYNGO workstation (Syngo 2008B, Siemens Medical Systems, Erlangen, Germany) and analyzed, including the individual PET and CT images, fused PET/CT images, and the display in 3D mode (maximum intensity projection).

PET/CT findings were considered positive for malignancy if the FDG uptake in the lesion was abnormal after excluding possible physiological causes and benign lesions. The semiquantitative analysis of F-18-FDG uptake was based on calculating a maximum standardized uptake value (SUVmax) per focus. The SUVmax was calculated as the activity concentration measured at the end of the scan and corrected for individual body weight and dose injected, as follows: SUVmax = Tissue Activity (counts/pixel/second) × Calibration Factor / Injected F-18-FDG Dose (MBq/kilogram body weight). The SUVmax >2.5 was used to differentiate benign from malignant lesions [12], except for the adrenal glands where SUVmax ≥3.1 was considered malignant [13]. The SUVmax was analyzed by a nuclear medicine physician unaware of other patient data.

PET/CT findings were interpreted by the study investigators and compared with the MDCT reports from medical records. The MDCT interpretation was based on the standard criteria for malignancy [11]. Lymph nodes were considered positive when the greatest diameter exceeded 10 mm [14]. The largest diameter of the lung lesion was considered the size of primary tumor. The seventh international TNM classification [15] was used for staging of NSCLC.

Statistical analysis. Demographic and clinical data were presented as frequencies, percentages, and means ± standard deviations (SD) for descriptive purposes. The agreement between PET/CT and MDCT was determined for the overall staging of NSCLC (0, I, II, III, IV), T classification (T0, T1, T2, T3, T4), N classification (N0, N1, N2, N3) and M classification (M0, M1a, M1b) of NSCLC, as well as the number of metastases in the bones and adrenal glands. The results are presented in cross-distribution tables showing frequencies of agreements and disagreements between PET/CT and MDCT. Each cross-distribution table was analyzed in three steps.

The first step included the calculation of overall agreement (sum of agreements along the table diagonal divided by total observations, %). This was followed by the calculation of agreement for each category (the category agreement divided by the category total, %).

In the second step, the Cohen's kappa test was used to determine the rate of agreement beyond the chance. We reported the observed kappa (κ) with the associated 95% confidence interval (95%CI) and the maximum kappa (κ_{max}). The unweighted kappa was chosen for brevity and because the results for weighted linear or quadratic kappa did not substantially differ. The hypothesis tested was that the strength of agreement between PET/CT and MDCT will be at least moderate (κ>0.40) based on the Altman criteria (<0.20 poor; 0.21–0.40 fair; 0.41–0.60 moderate; 0.61–0.80 good; 0.81–1.00 very good agreement) [16]. The outcome was determined after testing the null hypothesis that the upper limit of 95%CI will not fall in the moderate range or higher.

In the final step, two non-parametric McNemar tests were applied to facilitate the interpretation of the agreement/disagreement results. First, the McNemar test of independence was used for each category with Bonferroni adjustment for multiple testing (p=0.05/[total categories-1]). The null hypothesis was that the distribution within each category will differ between the two methods (i.e., row vs. column). This was followed by the McNemar test of bias (direction of change), with the null hypothesis that one method will not assign a significantly greater proportion of patients to higher categories compared to the other (comparison of proportions above and below the main diagonal, p<0.05).

Results

The characteristics of 83 patients are shown in Table 1. Adenocarcinoma and squamous cell carcinoma were the

Table 1. Characteristics of 83 patients with non-small cell lung cancer (NSCLC).

NSCLC Pathohistology	
Adenocarcinoma	28 (34%)
Squamous cell type	30 (36%)
Other types	9 (11%)
Unknown	16 (19%)
Bronchogenic tumors	24 (29%)
Surgery	31 (37%)
Chemotherapy	36 (43%)
Tumor recurrence	22 (27%)
Tumor size (mean ± SD)	
MDCT (cm)	3.2 ± 2.5
PET/CT (cm)	3.4 ± 2.6
SUVmax (mean ± SD)	10.2 ± 9.1

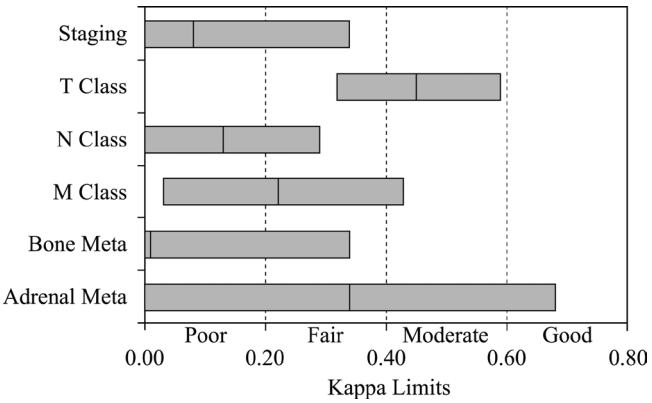

Figure 1. The 95% confidence intervals (horizontal bars) with the observed kappa values (vertical lines inside the bars) indicating agreement between PET/CT and MDCT for staging, TNM classification, and the number of metastases in the bones and adrenal glands.

most prevalent (70%). About 40% of patients had surgery and/or chemotherapy. The tumor recurrence was detected by both MDCT and PET/CT in 18 patients and only by PET/CT in 4 patients. No accumulation of ^{18}F-FDG was found in 6 patients who presented with atelectasis or enlarged lymph nodes on MDCT.

Frequency distribution by the stage of NSCLC (0, I, II, III, IV) for PET/CT and MDCT is shown in Table 2. The overall agreement was 43%. The category agreement was 23% for stage 0, 6% for stage I, 17% for stage II, 23% for stage III, and 42% for stage IV. The observed κ was 0.20 (95%CI=0.05-0.35, maximum κ=0.88), thus the hypothesis of at least moderate agreement between the two methods (κ>0.40) was rejected (95%CI range corresponding to poor-to-fair agreement). The McNemar test of independence was not significant for any of the five categories (p≥0.197, Bonferroni-adjusted criterion p<0.013), indicating that the two methods did not assign patients differently to any given category. Higher PET/CT than MDCT stage was assigned to 22 patients, whereas higher MDCT than PET/CT stage was assigned to 25 patients. Such directional change yielded the McNemar test of bias non-significant (p=0.662), indicating that one method did not assign proportionally more patients to a higher category than the other.

Frequency distribution by the size of primary tumor (T0, T1, T2, T3, T4) for PET/CT and MDCT is shown in Table 3. The overall agreement was 58% (Fig 1). The category agreement was 62% for T0, 37% for T1, 45% for T2, 35% for T3, and 14% for T4. The observed κ was 0.45 (95%CI=0.32-0.59, maximum κ=0.88), thus the hypothesis of at least moderate agreement between the two methods (κ>0.40) was accepted (95%CI range corresponding to fair-to-moderate agreement). The McNemar test of independence was not significant for categories T0-T3 (p≥0.275). Although 3 times more patients were assigned to T4 category by MDCT (n=12) than PET/CT (n=4), the difference was still not significant (p=0.021, Bonferroni-adjusted criterion p<0.013). Higher T class was assigned by PET/CT than MDCT to 11 patients, whereas higher T class was assigned by MDCT than PET/CT in more than twice as many patients (n=24). This proportional difference was significant (p=0.028, McNemar test of bias), indicating that MDCT more frequently suggested a larger tumor than PET/CT.

Table 2. Distribution of patients by the stage of disease based on ^{18}F-FDG PET/CT and MDCT findings (category agreement marked in bold).

		MDCT					
		0	I	II	III	IV	Total
PET/CT	0	**3**	1	0	4	1	9
	I	0	**1**	0	4	1	6
	II	0	1	**2**	2	1	6
	III	1	3	2	**9**	11	26
	IV	3	5	4	3	**21**	36
	Total	7	11	8	22	35	83

Observed κ=0.20 (95%CI 0.05-0.35); maximum κ=0.88; overall agreement=43%

Table 3. Distribution of patients by the T class based on ^{18}F-FDG PET/CT and MDCT findings (category agreement marked in bold).

		MDCT					
		T0	T1	T2	T3	T4	Total
PET/CT	T0	**13**	2	0	2	1	18
	T1	0	**7**	4	1	1	13
	T2	1	2	**17**	5	5	30
	T3	1	1	4	**9**	3	18
	T4	1	1	0	0	**2**	4
	Total	16	13	25	17	12	83

Observed κ=0.45 (95%CI 0.32-0.59); maximum κ=0.88; overall agreement=58%

Table 4. Distribution of patients by the N class based on ^{18}F-FDG PET/CT and MDCT findings (category agreement marked in bold).

		MDCT				
		N0	N1	N2	N3	Total
PET/CT	N0	**20**	1	5	6	32
	N1	2	**1**	1	0	4
	N2	11	2	**12**	0	25
	N3	14	0	6	**2**	22
	Total	47	4	24	8	83

Observed κ=0.13 (95%CI 0.00-0.29); maximum κ=0.73; overall agreement=42%

Table 5. Distribution of patients by the M class based on ^{18}F-FDG PET/CT and MDCT findings (category agreement marked in bold).

		MDCT			
		M0	M1a	M1b	Total
PET/CT	M0	**33**	1	13	47
	M1a	2	**1**	0	3
	M1b	13	6	**14**	33
	Total	48	8	27	83

Observed κ=0.22 (95%CI 0.03-0.43); maximum κ=0.87; overall agreement=58%

Table 6. Distribution of patients by the number of metastasis in the bone tissue based on ^{18}F-FDG PET/CT and MDCT findings (category agreement marked in bold).

		MDCT					
		0	1	2	3	>3	Total
PET/CT	0	**59**	3	0	0	0	62
	1	8	**0**	0	0	0	8
	2	4	0	**0**	0	0	4
	3	3	1	0	**0**	0	4
	>3	4	1	0	0	**0**	5
	Total	78	5	0	0	0	83

Observed κ=0.01 (95%CI 0.00-0.34); maximum κ=0.34; overall agreement=71%

Table 7. Distribution of patients by the amount of metastases in the adrenal glands based on ^{18}F-FDG PET/CT and MDCT examination (category agreement marked in bold).

		MDCT			
		0	1	2	Total
PET/CT	0	**67**	5	3	75
	1	2	**4**	0	6
	2	2	0	**0**	2
	Total	71	9	3	83

Observed κ=0.34 (95%CI 0.00-0.68); maximum κ=0.78; overall agreement=86%

The frequency distribution by the lymph nodes, affected (N0, N1, N2, N3) for PET/CT and MDCT, is shown in Table 4. The overall agreement was 42% (Fig.1). The category agreement was 34% for N0, 14% for N1, 32% for N2, 7% for N3. The observed κ was 0.13 (95%CI=0.00-0.29, maximum κ=0.73), thus rejecting the hypothesis of at least moderate agreement (κ >0.40) between the two methods (95%CI range corresponding to poor-to-fair agreement). Significantly more patients were placed in N0 class by MDCT (n=47) than by PET/CT (n=32, p=0.016, Bonferroni-adjusted criterion p<0.017), whereas the opposite was true for N3 class (MDCT n=8, PET/CT n=22, p=0.006). Higher N class was assigned by PET/CT than MDCT to 35 patients and the opposite was true in 13 patients. This proportional difference was significant on the McNemar test of bias (p=0.002), indicating that PET/CT more frequently suggested regional lymph node involvement than MDCT.

The frequency distribution by the spread of metastases (M0, M1a, M1b) for PET/CT and MDCT is shown in Table 5. The overall agreement was 58%. The category agreement was 53% for M0, 10% for M1a, and 30% for M1b. The observed κ was 0.22 (95%CI=0.03-0.43, maximum κ=0.88) (Fig.1), thus the hypothesis of at least moderate agreement (κ>40) was accepted given the 0.43 upper limit of 95%CI (range poor-to-moderate agreement). The McNemar test of independence was not significant for any of M category (p≥0.180, Bonferroni-adjusted criterion p<0.025). In 21 patients a higher M class was assigned by PET/CT than MDCT, whereas the opposite was true in 14 patients. This directional change was not significant (p=0.237).

The frequency distribution by the number of bone metastasis (0, 1, 2, 3, >3) detected by PET/CT and MDCT is shown in Table 6. The overall agreement was 71% (Fig.1). The category agreement was 73% for 0 metastasis but 0% for all other categories (1, 2, 3, >3). The observed κ was 0.01 (95%CI=0.00-0.34, maximum κ=0.34), thus the hypothesis of at least moderate agreement was rejected (range poor-to-fair agreement). Significantly more patients were found to be free of metastases by MDCT (n=78) than PET/CT (n=62, p=0.001, Bonferroni-adjusted criterion p<0.013). More than 1 bone metastasis was found in 11 patients on PET/CT but in none on MDCT. PET/CT detected more bone metastasis than MDCT in 12 patients. In only 3 patients MDCT detected one bone metastasis when PET/CT indicated none. This directional change was significant (p<0.001), suggesting that PET/CT detected more bone metastases than MDCT.

The frequency distribution by amount of metastases in the adrenal glands (0, 1, 2) for PET/CT and MDCT is shown in Table 7. The overall agreement was 86% (Fig. 1), with the category agreement of 85% for 0 metastasis, 36% for 1 metastasis, and 0% for 2 metastases. The observed κ was 0.34 (95%CI=0.00-0.68, maximum κ=0.78), thus accepting the hypothesis of at least moderate agreement (κ>40) given the 0.68 upper limit of 95%CI (range poor-to-good agreement). The distribution across each category was not significantly different (p≥0.248,

Bonferroni-adjusted criterion $p<0.025$) and neither was the directional change ($p>0.248$). This suggests the agreement between PET/CT and MDCT for detecting metastases in the adrenal glands.

Discussion

We compared the findings of ^{18}F-FDG PET/CT and MDCT in 83 patients with pathohistologicaly proven NSCLC to determine agreement between two methods with respect to the overall staging and TNM classification of NSCLC, as well as the presence of distant metastases in the bones and adrenal glands. The hypothesis of moderate agreement between the two methods was only partially confirmed. The agreement was moderate for detection of the tumor size/location (T0-T4), distant metastases (M0-M1b), and the number of adrenal gland metastases (0-2). On the other side, the agreement was poor-to-fair for the overall staging of NSCLC (0-IV) and detection of nodal metastases (N0-N3), and poor regarding the number of bone metastases (0->3). The disagreements were largely due to greater sensitivity of ^{18}F-FDG PET/CT than MDCT in detecting metastases in the regional lymph nodes, bones, and adrenal glands.

The agreement between poor-to-fair of PET/CT and MDCT in the overall staging of NSCLC is due to disagreements in TNM classification. Despite moderate agreement in determining the tumor size/location (T class), the two methods greatly differed with respect to the T4 class. This may be explained by better resolution of MDCT than PET/CT for detecting whether the tumor invaded blood vessels. However, MDCT may overestimate the size if the primary tumor is associated with atelectasis. This would rarely be the case with PET/CT, which is better than MDCT at distinguishing the primary tumor from atelectasis or benign lesions.

The largest disagreement between PET/CT and MDCT was regarding the spread of tumor to the regional lymph nodes (N class). Several observations may account for that. First, PET/CT findings were consistent with inflammation in the lungs or lymph nodes in 6 patients who underwent the surgery, but these changes were interpreted as a relapse on MDCT. Moreover, PET/CT detected metastases in the lymph nodes or distant organs in 4 patients after surgery, none of which were found on MDCT. This re-affirms the observations that ^{18}F-FDG PET/CT is more suitable for long-term monitoring of patients after surgery [17, 18]. Secondly, the greatest disagreement between the two methods was with respect to the assignment of different N classes. Specifically, PET/CT detected more metastasis in the ipsilateral and contralateral lymph nodes than MDCT. Thus, our results support previous findings that PET/CT is more sensitive than MDCT in detecting lymph node metastases [19] and more accurate in staging mediastinal lymph nodes [10]. Because lymph nodes may appear involved on PET/CT when the inflammation is present, histological verification of such findings is necessary [20].

At the time the lung cancer is diagnosed, more than half of patients already have distant metastases [21] and in almost 20% the metastases are in the adrenal glands [23]. Bone metastases are also frequent and may be located in any part of the skeleton [3]. Although our results suggest moderate agreement between PET/CT and MDCT in detecting distant metastases (M), the supportive evidence is rather weak because the upper limit of 95% confidence interval ($\kappa=0.43$) was just above the criterion level ($\kappa>40$). The agreement seemed better regarding the amount of metastases in the adrenal glands (poor-to-moderate), but the wide 95% confidence interval (0.00-0.68) suggests substantial uncertainty. This is because an isolated mass in the adrenal glands is necessarily a metastasis. Indeed, half of the masses detected on MDCT did not accumulate ^{18}F-FDG, consistent with findings that more than 60% of adrenal masses detected by MDCT in NSCLC patients are actually benign lesions [24]. The discrepancy between the two methods was the greatest when it comes to metastases in the bones (poor-to-fair agreement). This was mainly because PET/CT detected more bone metastases than MDCT. These findings are in line with the reported 94% sensitivity, 99% specificity, and 98% accuracy of ^{18}F-FDG PET/CT for detection of bone metastases [22].

Both MDCT and PET/CT have advantages and disadvantages. MDCT may be superior to PET/CT at T staging because MDCT can more accurately detect tumor infiltration in the thoracic wall or blood vessels. On the other side, MDCT is less capable of distinguishing the primary tumor from the atelectasis or post-treatment fibrosis and scarring from the relapse. Another limitation of MDCT is related to N staging because the presence of metastases in mediastinal lymph nodes is judged solely on the basis of nodal size [11]. However, metastases may be present in normal-sized lymph nodes and additional information on functional and molecular characteristics of lymph nodes is necessary for more accurate staging [25]. Indeed, PET/CT provides such structural and functional information and allows whole body scanning in one examination, thus, it is is more sensitive in detecting lymph node involvement [18]. However, PET/CT should not replace mediastinoscopy for mediastinal lymph node staging, especially in the case of suspected microscopic metastases in lymph nodes or moderately high SUV values [11, 25, 26]. PET/CT is also superior to MDCT in detecting unexpected distant metastases (M staging), but the accuracy of SUV measurement may be confounded by changes in body weight, blood glucose level, uptake period, and the type of region of interest [27].

This study has several limitations. The sample size of 83 may be perceived small given the number of categories within TNM classification. The nodal and distant organ metastases were not verified against pathological examination as the gold standard. Nonetheless, the overall results are consistent with the previous studies suggesting advantages of ^{18}F-FDG PET/CT compared to MDCT for monitoring patients with NSCLC [2, 10, 21, 22]. MDCT and ^{18}F-FDG PET/CT were performed up to 30 days apart (median 17 days), but this is consistent

with the previous literature [3]. Although MDCT was not done at one site and reports were used for comparison, all examinations were performed by board-certified radiologists using standard MDCT criteria for interpretation of findings [11]. As such, the study reflects a real clinical practice, which, in turn, may also be viewed as the strength of the study.

In conclusion, our results suggest that ^{18}F-FDG PET/CT is superior to MDCT for TNM classification and thus the overall staging of NSCLC. This pertains in particular to detecting regional metastases in the contralateral and supraclavicular lymph nodes as well as distant metastases in different organs, especially the bones. Thus, ^{18}F-FDG PET/CT may provide more accurate staging/restaging of NSCLC, which may greatly facilitate the treatment planning of these patients.

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