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Volumetric evaluation of pulmonary nodular lesions at multi-slice CT – preliminary assessment of usefulness of the method

The number of chest CT examinations performed for various reasons is increasingly higher and therefore the problem of small nodules detected within the pulmonary parenchyma is more often faced. Such incidental nodules are more and more frequent- they are detected (at least one) in 23–66% of patients in various CT screening programs of lung cancer (4, 13).

Generally, morphological features of a small pulmonary mass (smaller than 10 mm) do not allow explicit evaluation of its nature. The nodules containing fat and calcifications are most likely to suggest their benignity while those with spiculated contours and partially solid structure most often suggest malignancy. However, in the group of patients undergoing screening such explicit nodules are rare- about 30%, the remaining 70% of nodules are those which are not differentiated by their morphological features (11). Moreover, it is known that in patients without neoplastic history only 1% of nodules smaller than 5 mm is found to be malignant, 23% in the 5–10 mm group and 33% in the 11–20 mm group (4).

The long-term prognosis in lung cancer depends on the disease stage on detection – 60–70% of 5-year-survival in stage T1 (1) and therefore, the determination of neoplastic nature of the smallest lung nodules is extremely important. Small lesions, however, are often difficult to verify with imaging methods – PET, contrast CT as well as with operative procedures, e.g. a biopsy through the chest wall (2,8,12). The only, generally accepted option is to repeat the CT examination (under the same conditions of acquisition and reconstruction as those in baseline examination) and to assess the lesions growth – as the growth is one of the main indices of malignancy (7).

The nodule growth index defined as the doubling time (DT) was introduced about 50 years ago (3, 10) and used in comparative measurements of linear focal lesions on successive X-ray images. A similar approach was applied in CT evaluation of lesions – initially 2D measurements in successive examinations were performed and recently – 3D volumetric measurements, which are becoming a reference standard for nodule growth evaluation (6).

The study was to differentiate the nature of small nodular lesions in the lungs in at least two successive CT examinations by determining their volume and growth dynamics (doubling time) and to evaluate the volume change of metastases to the lungs in patients with extrapulmonary location of primary neoplastic proliferation during successive cycles of chemotherapy in order to assess its effectiveness.

MATERIAL AND METHODS

The analysis included the findings of volumetric evaluation of 182 focal solid lesions of the lungs in two groups of patients examined in the years 2002-2004. Every patient underwent at least two CT examinations; the interval between them was 42–165 days (average 96). The first group consisted of 72 patients with nodules detected incidentally at CT or chest X-ray (without calcifica-

tions, fatty tissue or spiculated contours) whose size was smaller than 1.0 cm. Fifty-nine patients were found to have one nodule, 11 two lesions and the remaining two – 3 small pulmonary foci- altogether, in this group 87 nodules were evaluated comparatively to determine their possible malignancy. The second group consisted of 19 patients with numerous pulmonary metastases. In every patient at least 5 target nodules were selected for analysis in the next CT- altogether 95 lesions were evaluated volumetrically to determine the effects of cytostatic therapy.

CT examinations were performed with the spiral, 8-row tomograph , Light Speed Ultra (GE Medical Systems, Milwaukee, Wisc); in both series the parameters of scanning and collimation were comparable – slice thickness – 1.25–2.5 mm, pitch 1.2–1.5:1, 120–140 kV, 80–120 mAs (depending on the patient's weight). The acquisition was performed with the breath held. The volumetric evaluation of nodules was performed with workstations Advantage 4.1 and 4.2 (GE) and Advanced Lung Analysis (ALA) software designed for automatic summing up of the volumes of small, solid pulmonary foci. The volumetric analysis was performed twice (by two radiologists independently) in order to determine repeatability of volume measurements (a disagreeing result – if, at least once different from the rest in a series of four independent measurements), to assess doubling time (DT) and possibilities of automatic segmentation of solid lesions and adjacent anatomical structures – vessels or pleura. The only manual activity of the radiologist was to localize and mark the selected nodule for ALA evaluation. No manual linear measurements of lesions were made – thus the results could not have been affected by subjective errors of size interpretation made by radiologists performing CT examinations.

One of three algorhythms was automatically computed depending on the location of the marked nodule – juxtapleural for nodule adjacent to the pleura, juxtavascular for the lesion largely connected with vessels and circumscribed when no solid anatomical elements were present near the lesion, only air pulmonary parenchyma. Each type of automatic segmentation was displayed enabling the radiologist to assess the extent and borders of the real area of every nodule finally chosen for volumetric evaluation – some segmentations were unsuccessful – when automatic separation of the marked lesion and surroundings was impossible.

After calculations (when segmentation was successful) all data from CT examinations were automatically compiled in the form of a report containing the most important information for patients – i.e. interval between both CT examinations, evaluation of the change in nodular volume (in %), and doubling time if the nodule increased.

RESULTS

In the first group, 87 nodules were assessed on the basis of volume change and doubling time in order to determine their nature. Automatic segmentation was successful in 83 out of 87 nodules (95.4%), 4 nodules were not separated from the pleura due to high adherence (small lesions – 3–4 mm in size). Among 83 nodules which could be further analyzed, 23 were juxtapleural (28%), 42 circumscribed (50%), 18 juxtavascular (22%). Fourfold assessment of repeatability of volume measurements (two times by two radiologists) showed full, 100% agreement of measurements in circumscribed nodules, 98% agreement in juxtavascular lesions and 86% agreement in juxtapleural nodules. The variations in volume measurements when one of four measurements, was different were small – up to 4.3% and did not significantly affect the finally calculated doubling time of the nodule.

DT was determined for 61 nodules; in the remaining 22 nodules DT was not determined due to their decrease at the second CT. Out of 61 nodules, 42 were defined by the software as benign (Fig. 1a-d)– DT in this group ranged from 4 to 176 years; the remaining 19 nodules were defined as malignant – the range of DT – 44–236 days. Verification of 14 out of 19 malignant nodules (thoracotomy) confirmed that 11 of them were primary lung cancers (Fig. 2 a-d) and 3 were metastatic lesions. The remaining 5 nodules were not verified by operative procedures as their metastatic nature was confirmed by the development of further dissemination foci at the second CT or by the detection of extrapulmonary localization of primary neoplasm during some other examinations.

The doubling time for 8 metastatic lesions was shorter than that in 11 primary lung cancers; 44–49 days and 87–236 days, respectively.

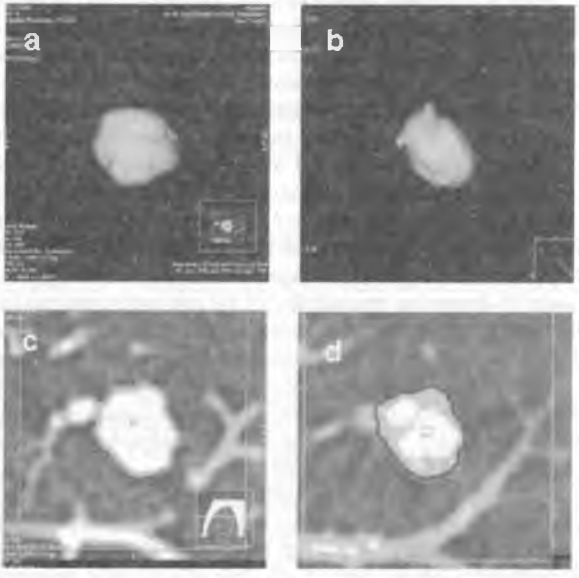

Fig. 1a–d. Images of benign nodule obtained with the 3D volumetric CT software (Advanced Lung Analysis) in a 48-year-old woman; 1a, c – volume rendering and transverse reconstructions at the first examination, 1b, d – the measured volume has decreased by 13% at the second CT presentation

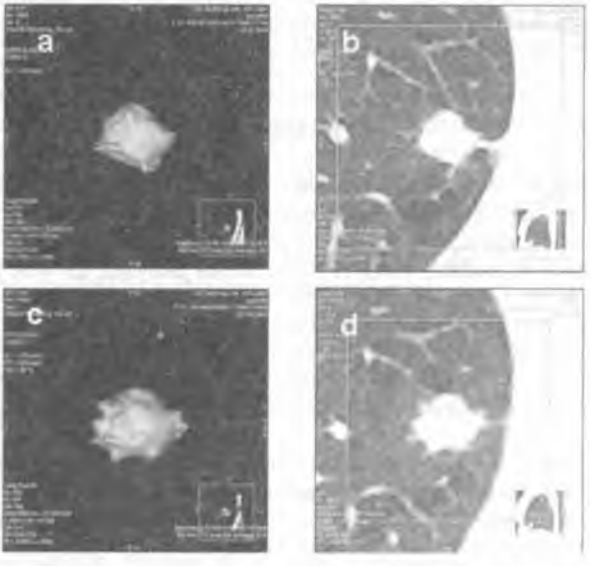

Fig. 2 a–d. Images of a malignant nodule obtained with 3D volumetric CT software in a 71-year-old female patient; 2 a, b – the first CT examination findings, 2 c, d – 119 days later the measured volume has increased by 66%. It corresponds to calculated doubling time of 164 days

In the second group, the volume change was assessed in 95 target metastatic nodules in order to determine the response to cytostatic therapy (Fig 3 a, b). The volume change was found in 75 nodules of this group – 54 (73%) decreased and 20 (27%) increased their volumes. The mean decrease in volume was 53%, while the mean volume increase was 44%. In 21 out of 95 nodules, the volume change was not determined due to unsuccessful segmentations of some lesions at the second CT, contour overlapping of target nodules or other new nodules found at the second CT. In such cases the software summed up the volumes of several lesions or informed about unsuccessful segmentation. Some results were difficult to interpret due to another reason – some nodules in the same patient increased their volume, other decreased – in 5 patients (26%).

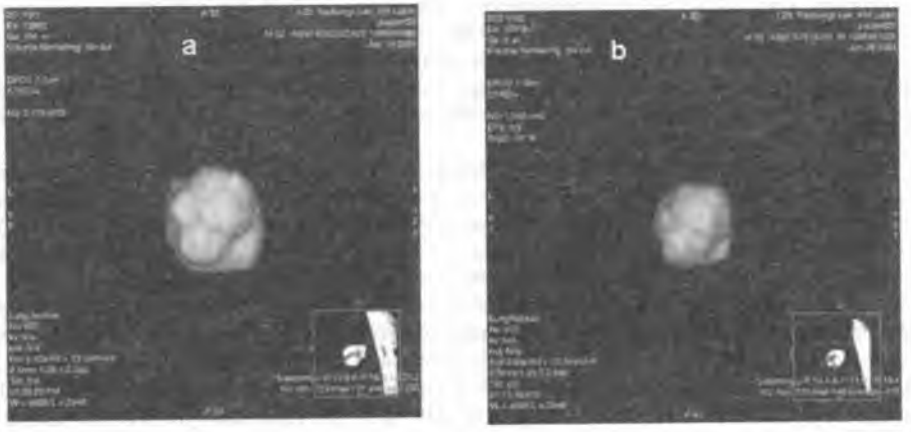

Fig. 3 a, b. Images of a metastatic nodule in a 52-year-old man obtained with the 3D volumetric software; a – the first CT findings, b – 56 days later, the measured volume has decreased by 41%

DISCUSSION

Lung cancer is one of the most common neoplasms; moreover its prognosis is poor. An early detection of small malignant nodules of the lungs is associated with smaller progression of the disease, which greatly increases the effectiveness of treatment and reduces mortality.

The detection of small (<10 mm) lesions has become possible when spiral, multi-slice tomographs were introduced, which enable acquisition of data with thin slices during a single breath hold; this in turn allows us to obtain full 3D volumetric reconstruction of examined structures at the clinically acceptable level thanks to accurate evaluation of even small nodules. Since the availability of spiral CT has increased, small 5–10-mm nodules (sometimes even smaller than 3 mm) are detected in the lungs both in lung cancer screening and incidentally during examinations for various medical reasons. Radiologists are faced with the challenge of determining their potential malignancy by using imaging methods as the detected lesions are often so small that they cannot be directly qualified for histological verification (6, 16). Likewise, the detection of multiple morphologically dubious small nodules or lack of patient's consent to a biopsy is another indication for repeating CT and estimating the nodule's growth to confirm its malignancy.

Initially, linear measurements (2 D) of the nodule were commonly used – measuring its maximum diameter at two successive CT examinations – manually or using computer programs (6). However, the linear dimension was found to be insufficient as the nodule growth is a three-dimensional phenomenon and direct measurements of the volume are more accurate than those of its diameter (11). The majority of nodules are spherically shaped, in consequence the growth of, for example, the 10-mm lesion by 1 mm (10% enlargement in 2D) results in 38% volume growth in 3D, thus the volume increase is easier detected in cases of spherical lesions (14). An increase in

the sphere diameter by 26% causes a 100% increase in its volume – this corresponds to linear enlargement of 10-mm nodules by 2.6 mm, of 5 mm ones by 1.3 mm and of 2.5-mm lesions by 0.65 mm. Even a small error of the 2D measurements results in a big error in nodule volume evaluation, which shows that such measurements are not a sufficient criterion of the nodule growth (11, 14). Another argument indicating that 2D measurements should be abandoned is their unreliability in irregular, asymmetrically growing nodules – their doubling times were found to be typical benign tumors when 2D measurements were used, while 3D measurements demonstrated their malignant nature (15). In general, the literature reports (5, 6, 15) question the repeatability of manual linear measurements of small nodules – e.g. according to R e v e l et al. (11), the variations of such measurements performed by 3 experienced radiologists with the Advantage Window workstation were 1.32–1.5–1.5 (inconsistency coefficients) – which for a 10-mm nodule corresponds to 170 days of volume doubling. Jennings et al. recommend volumetric measurements as the reference standard for evaluation of small nodule growth; they stress however that most of radiologists still use the maximum lesion diameter in two successive CT examinations, despite the fact that such manual measurements provide improper classification of the nodule growth compared to volume measurements (6).

The results of the present study are comparable to the literature data. The 95.4% effectiveness of segmentation is similar to that in the study performed by R e v e l et al. (11) – 96%, in which the separation of some juxtapleural small nodules from the surrounding structures was also difficult. Likewise, the repeatability of volume measurements in the Revel's study – compared 9 times for every nodule, was similar – 100% for 67% of the evaluated nodules; 33% of nodules had at least one different result – the difference in volume measurement was small – 2.26% (the acceptable error limit – 6.38%) (3). Assessing the accuracy of volume measurements, the author states that to keep this accuracy measuring the linear dimensions of nodules, one should measure the 5-10 and 15-mm nodules with accuracy of 0.1–0.2 and 0.3 mm, respectively, which is virtually impossible in 2D manual measurements (11). In our study, the repeatability of volume measurements performed four-times was 100.98 and 86% for the lesions surrounded by air parenchyma, those adjacent to vessels and juxtapleural lesions, respectively; the measurement differences were also small – 2.6% and 4.3% in the last two categories of lesions. Such high accuracy of volume measurements minimizes even the effects of the marker's placement in the module selected by the radiologist – by calculating and determining its centre. The variations of volume measurements are likely to result from the nodule edges, which especially concerns juxtapleural nodules. Therefore, the measurement variations were observed mainly in this category of nodules.

The doubling times in our study – 4–176 years for benign lesions and 44–236 days for malignant nodules – were within the range of the literature values. According the R e v e l et al. (3), the DT value for malignant lesions is 100 days on average- although for metastatic lesions this time is usually shorter (several dozen days); however, the dynamics of malignant nodule growth in elderly patients is slower – even 180–360 days (17). According to W a n g et al., the DT range for malignant nodules is 30–490 days (12), most often – one hundred, one hundred and several dozen days. Therefore, R a v e l et al. recommend a 90-day interval between CT examinations to differentiate the nature of small pulmonary nodules – if the nodule is malignant its volume should increase by 90%.

No comparable literature data were found for the second group of nodules – metastatic lesions evaluated volumetrically in the present study to assess the effects of cytostatic therapy. It seems that in various oncological programs, the 2D linear measurements predominate, with all their negative consequences of evaluation – as presented above. The use of analysis of volume changes in metastases requires, however, further studies in larger populations – the evaluation results in our study were difficult to interpret, particularly in patients with multiple lesions in whom the nodule contours often overlapped and 3D measurements were not possible or in patients with some nodules increasing and some decreasing their volume.

In conclusion, it should be stressed that the volumetric measurement is a more accurate index differentiating the nodule growth as the information is collected from all data concerning the evaluated nodule and not only from the scan with a maximum cross section of the nodule, which is

the case in linear measurements. There is an agreement that the measurements of nodule changes in repeatable conditions are a reliable, non-invasive method of predicting the nodule malignancy (9).

As a result, short doubling time demands histological verification of nodules while long DT suggests their benignity, which can be confirmed by CT follow-ups. The use of the program of automatic volume assessment of small nodules in the lungs should shorten the time of making a final decision about the patient's treatment.

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SUMMARY

The aim of the present study was to differentiate the nature of small focal lesions of the lungs (smaller than 10 mm) in two successive CT examinations by determining their volume and growth dynamics - defined by the doubling time (DT) – and to assess the volume changes in pulmonary metastases in patients undergoing chemotherapy in order to define the effectiveness of cytostatic treatment. Two radiologists evaluated 182 small nodular lesions of the lungs in patients with indeterminate focal lesions (I group) and pulmonary metastases (II group). All the patients underwent

two CT examinations in the same conditions of acquisition and reconstruction, the interval between examinations was 42–165 days. The examinations were performed using the 8-row, spiral tomograph LightSpeed Ultra (GE Medical System). Nodules were evaluated volumetrically using workstations – Advantage Window 4.2 with the software automatically assessing volumes of lung solid lesions – Advanced Lung Analysis (ALA). In I group, automatic segmentation of nodules was successful in 83/87 lesions (95.4%). The repeatability of volume measurements (4 times, independently) was extremely high – 100-98-86% depending on the location of the nodule in relation to adjacent anatomical structures; measurement variations were small – 4.3% and did not significantly affect the DT calculations. DT was calculated for 61 nodules – 42 of them were diagnosed as benign lesions – DT 4–176 years, 19 were found to be malignant – DT range - 44–276 days. In the second group, 54/75 nodules decreased (73%) and 20/75 increased (27%); in 21/75 nodules (22%) the changes in volume were not determined due to unsuccessful segmentation at second CT. The program for automatic assessment of volume changes of small lung nodules was found to be highly useful for differentiating their nature. The volumetric measurement provides more accurate evaluation of growth dynamics of the pulmonary focus than the manual linear mea-surement (2D). Further studies are needed to determine the usefulness of metastatic lesion volumetry for evaluating the effectiveness of cytostatic therapy.

Ocena wolumetryczna zmian ogniskowych płuc w wielorzędowej tomografii komputerowej– wstępna ocena przydatności metody

Celem pracy była próba zróżnicowania charakteru drobnych zmian ogniskowych płuc (mniejszych od 10 mm) w dwu kolejnych badaniach CT na podstawie określenia ich objętości i dynamiki wzrostu – wskaźnikiem czasu podwojenia (DT), oraz ocena zmian objętości przerzutów do płuc u chorych poddanych chemioterapii w badaniu skuteczności leczenia cytostatycznego. Dwóch radiologów oceniło 182 drobne zmiany guzkowe płuc u chorych z niejednoznaczną zmianą ogniskową (I grupa) oraz z przerzutami do płuc (II grupa). Każdy pacjent miał dwukrotnie wykonane badanie CT w tych samych warunkach akwizycji i rekonstrukcji, odstęp między badaniami wyniósł 42–165 dni. Badania wykonano 8-rzędowym, spiralnym tomografem Ligot Speed Ultra (GE Medical System). Ocenę objętościową guzków wykonano przy użyciu konsoli Advantage Window 4.1 i 4.2 z oprogramowaniem automatycznej oceny objętości zmian litych płuc *Advanced Lung Analysis* (ALA). W pierwszej grupie automatyczna segmentacja guzków od otoczenia była udana wobec 83/87 zmian (95,4%). Uzyskano bardzo dużą powtarzalność pomiaru objętości przez program (4-krotny, niezależny pomiar) – 100–98–86% zależnie od lokalizacji guzka wobec przylegających struktur anatomicznych, odchylenie pomiaru objętości było niewielkie – 4,3% i nie wpłynęło istotnie na wyliczenie czasów podwojenia. DT wyliczono dla 61 guzków – 42 z nich na podstawie wyników program uznano za łagodne – DT 4–176 lat, 19 zostały określonych jako złośliwe – zakres DT 44–276 dni. W drugiej grupie 54/75 guzków zmniejszyło objętość (73%), 20/75 powiększyło się (27%), dla 21/75 guzków (22%) nie udało się ustalić zmiany objętości ze względu na nieudane segmentacje w drugim badaniu CT. Stwierdzono dużą przydatność programu automatycznej oceny zmiany objętości małych guzków płuc w różnicowaniu ich charakteru. Pomiar wolumetryczny dokładniej określa dynamikę wzrostu ogniska płucnego w porównaniu z ręcznym pomiarem liniowym (2D). Dalszych badań wymaga określenie przydatności wolumetrii zmian przerzutowych w ocenie skuteczności leczenia cytostatycznego.