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The Possibilities and Limitations of Direct Digital Radiography, Ultrasound and Computed Tomography in Diagnosing Pleural Mesotelioma

Jelena Popić Ramač[1], Andrija Hebrang[1], Zlata Ivanovi-Herceg[2], Vinko Vidjak[1], Zoran Brnić[1], Karlo Novačić[1] and Ivan Fistonić[3]

[1] University of Zagreb, »Merkur« University Hospital, Departmet of Diagnostic and Interventional Radiology, Zagreb, Croatia
[2] University of Zagreb, Jordanovac Clinic of Lung Diseases, Department of Thoracic Radiology, Zagreb, Croatia
[3] Obstetrics and Gynecology Office, Zagreb, Croatia

A B S T R A C T

The goal of this study was to compare the possibilities and limitations of direct digital radiography of the chest (DDR), the use of ultrasound of the chest (US) and single slice computed tomography of the chest (CT) in diagnosing pleural mesothelioma. The study was conducted during the course of one year, on 80 patients who were successively referred to a specialized institution, under clinical suspicion of mesothelioma. The method of investigation was the comparison of findings, obtained by the reviewed methods of examination, with the pathohistologic results of a biopsy performed on each patient. The findings that were obtained by the enumerated methods were classified according to the radiologic signs that were found in each individual patient. We evaluated following radiological findings (signs), on each of the investigated methods: plaques, localized and generalized pleural thickenings, calcifications of the pleura, pleural effusions, parapneumonic effusions, pleural empyema, (round) atelectasis, pneumothorax, tumor mass or node, inflammatory infiltrate, elevation of the hemidiaphragm and osteolysis. The results of these were compared with pathohistologic findings and analyzed by means of standard statistical methods. The highest sensitivity was found for CT (94.4 %), followed by US (92.6%), and by DDR (90.7%). The highest specificity was obtained with DDR (46.2 %), followed by CT (35.5%) and US (23.8%). The comparison of these methods showed 90% diagnostic accuracy for DDR in relation to CT. CT as an individual method best satisfied most of the criteria for diagnosing mesothelioma. No pathognomonic radiologic sign for mesothelioma was found.

Key words: *pleural mesothelioma, malignant mesothelioma, diagnosing mesothelioma, sensitivity of imaging methods, specificity of imaging methods, diagnostic accuracy for DDR, US and CT*

Introduction

Malignant mesothelioma is primary tumor of the serous envelop, most common in costal, diaphragmal and mediastinal pleura[1]. Mesothelioma can appear in focal or diffuse form. Focal form is ussualy benign tumor, diffuse is commonly malignant. Malignant mesothelioma is strongly associated with asbestos exposure, with latency period of few to 35 years. The recognition of pleural disease, particularly mesothelioma leads to the consideration of variety of processes and involvement of physicians from many specialities. Diagnostic imaging has key role in detection, diagnosis and treatment of pleural mesothelioma. The rising number of radiologic imaging techniques and the development of new diagnostic methods presents a challenge in choosing the most appropriate means for establishing a definite diagnosis of malignant pleural mesothelioma. The methods having a key role in diagnosing it are: direct digital radiography of the chest (DDR), ultrasound of the chest (US) and single-slice or multi-slice chest computed tomography (CT). In the literature up to now there has been no unique stance in evaluating these radiologic diagnostic methods for this disease.

The aim of this study has been to highlight the strengths and weaknesses of the avaible imaging techniques and provide some guidance for their use. The aim has therefore been to establish the presence of character-

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istic radiologic signs, in each diagnostic method and compared with histopathological findings. Furthermore, the goal was to form, for each method separately, a model of the features, with positive and negative predictors, and combined models. We wanted to determine, on the basis of the obtained data, whether a pathognomonic radiologic sign for the diagnosis of mesothelioma exists, using the mentioned methods.

By means of calculations of: sensitivity, specificity, positive and negative predictive values, diagnostic accuracy, ratio between the probability for a positive and for a negative test and the diagnostic probability, to assess the possibilities and limitations in the application of each method in the detection of mesothelioma. And certainly, to compare the diagnostic accuracy of DDR, US and CT.

It was assumed that the obtained results could be a basis for a proposed algorhythm for examinations in diagnosing mesothelioma.

Patients and Methods

In a one year period, on 80 hospitalized patients (65 men and 15 women) with suspected mesothelioma, radiologic diagnostic procedures were performed (DDR, US, CT). The average age of the examinees was 56.8 (24–94) years. The average age of the men (57.6 years) did not differ statistically from the average age of the women (53.6 years).

The criteria for including the patients in this study required a previous clinical examination by a specialist in pulmology who had established a clinical suspicion of pleural disease that requested further radiological elaboration. The leading clinical symptoms were: chest pain, including referred pain localized to the shoulder, cough, dyspnea, and weight loos combined with finding of pleural effusion. Positive anamnesis of asbestos exposure was found in 43 patients. All patients had digital radiograms with two views of the thorax, except for partially mobile or immobile patients who had a supine or sitting frontal thoracic radiogram. Standard radiograms were followed by US and CT.

Direct digital radiography of the chest was performed on a Thoromat Siemens Thorax FD appliance. For ultrasonic diagnostics a SAOT ultrasound appliance was used, and for computed tomography, a spiral CT Shimadzu SCT 7800 TX.

In patients with pathologic changes in the peripheral thoracic zone discovered by DDR, ultrasound was applied using a 3.5MHz convex transducer. For diagnosing processes localized within the thoracic wall a linear 7.5 MHz transducer was used.

CT of the thoracic region was performed in the standard manner, with 7mm thick slices and 7mm intervals between them. The findings for each radiologic method were classified according to the radiologic signs that were found in each patient.

The pathologic specimens for pathohistologic analysis were obtained by biopsy with ultrasound guidance (in the case of superficially located changes) or under fluoroscopy monitoring (for changes located at a greater depth). We evaluated presence of the following radiological findings (signs), on each of the investigated methods: plaques, localized and generalized pleural thickenings, calcifications of the pleura, pleural effusions, parapneumonic effusions, pleural empyema, (round) atelectasis, pneumothorax, tumor mass or node, inflammatory infiltrate, elevation of the hemidiaphragm and osteolysis. These signs are already established as »classic« radiology findings that can suggest mesotehelioma[2].

The findings were observed by two independent radiologist one senior radiologist (20 years of experience) and another young radiologist (5 years of experience). Every reading was blinded to the findings of other methods. Each observer made report with positive or negative radiological signs found on DDR, US and CT (Table 1, 4, 7). Interobserver variability was 2.4% for DDR findings, 1.6% for CT of the chest and 3.2% for US findings. A third observer (15 years of experience) then evaluated the discordant findings.

Statistical analysis was performed using the Statistica for Windows, Release 6 (StatSoft, Inc. Tulsa, OK) statistical program package. For the description of age, arithmetic mean, standard deviation and range was used, and for comparison between genders the Student t-test was used. For comparison between categorical variables among the subgroups the χ^2 was used. Categorical variables were presented as frequency (%). In order to establish the link between individual variables that are categorical and their affiliation with the analyzed subgroups, a logistic regressive analysis was performed, including monovariant and multivariant models. Multivariant models were obtained on the basis of monovariant connections between individual variables. In order to compare the value of particular imaging presentations they were compared to a standard (pathohistologic analysis), and for them calculations were made: for sensitivity, specificity, positive (PPV) and negative (NPV) predictive value, diagnostic accuracy (DA), likelihood ratio (LR) and diagnostic odds (DO). For all parameters a 95% interval of reliability was calculated. In view of the small contribution of other diagnoses (other than mesothelioma), it was not possible to assess the diagnostic value of particular imaging presentations (US, X-ray, CT) or characteristic findings in each of these, in a way that would exclude the findings being chance results. As statistically significant, a $p<0.05$ level of significance was used.

Results

According to pathohistologic results a diagnosis of malignant mesothelioma was confirmed in 54 (67.5%) patients (45 men and 9 women), with an average age of 60.4 (39–80) years. The age of men and women did not differ with statistical significance in the whole group or in the group with a confirmed malignant mesothelioma diagnosis ($p>0.05$). The group of patients with malignant mesothelioma was statistically markedly older than

the remaining patients with suspected mesothelioma (60.4±9.9 in relation to 49.4±15.9 years; p=0.0003). Pathohistology confirmed diagnosis of mesothelial variant of malignant mesothelioma in 38 patients, sarcomatous in 11 patients and and mixed in 5 patients. Pathohistology did not confirmed diagnosis of benign mesothelioma in no one of our patients. Positive anamnesis of asbestos exposure was found in 43 (79.6%) patients with confirmed diagnosis of malignant mesothelioma. Among the patients in whom mesothelioma was excluded, nonspecific inflammatory pleural effusion was most frequent, in a total of 12 (15%) of patients (7M and 5F). The next most frequent finding was a primary tumor, in a total of 6 (7.5%) patients (6M, 0F), followed by metastatic tumors in 4 (5%) of patients (3M and 1F). In 2 (2.5%) patients a tuberculous inflammatory effusion was found.

One patient (1.3%) was diagnosed with inflammatory changes of pulmonary parenchyma, and another with malignant effusion (without confirmation of the primary tumor site).

No significant statistical difference was established between gender in relation to the prevalence of each particular enumerated diagnosis (p=0.4394).

Digital radiography findings

According to the results of examinations using the DDR technique, the most frequent radiologic signs in patients with mesothelioma were pleural thickening, plaque and calcification. In the group of patients with mesothelioma, a tumor mass or node (p=0.0146), pneumothorax (p=0.0213), and an inflammatory infiltrate (p=0.0057) were present significantly more infrequently. The most significant PPV of 100%, was found for plaque and calcification, with a NPV of 34.7%, but with low sensitivity of 9.3% and 100% specificity. The lowest PPV of 16.7% was found for inflammatory infiltrate, with a NPV of 28.4%, 1.9% sensitivity, and 80.8% specificity. No single characteristic radiologic sign found on DDR had a statistically significant higher frequency of appearance in the group of patients with mesothelioma. The results displaying the presence of characteristic radiologic signs in DDR findings, depending on the pathohistologic diagnosis, are shown in Table 1.

The results in Table 2 indicate the diagnostic value of characteristic digital radiography findings with a 95% reliability interval. Although pleural effusion is present in 96.3% mesothelioma cases, it is also present in 92.3% patients with other diagnoses. Pleural thickening which is present in 32.5% patients with mesothelioma is present also in 23.1% of other patients. A relatively small number of registered plaques and calcifications limits the diagnostic value of these signs. No single sign displays a diagnostic value in the positive prediction of mesothelioma. Regarding negative predictors (tumor mass or node, pneumothorax or inflammatory infiltrate), all exhibit a relatively high specificity (69.2%, 80.8%, 80.8%), and a significant DO (95% CI does not exceed 1).*

On the basis of the characteristics that individual signs exhibited, models were formed that included positive predictors (pleural thickening, plaque, calcification), negative predictors (tumor mass or node, pneumothorax, and inflammatory infiltrate), and also a model that combines positive and negative predictors for the diagnosis of mesothelioma, in order to verify their diagnostic value (Table 3).

The combined model (which includes positive and negative predictors for the diagnosis of mesothelioma) is best, with a statistically significant DO (8.4). In spite of relatively high sensitivity, PPV, NPV and DA, this model does not diagnose 5 (9.3%) patients with mesothelioma. It classifies 14 (53.8%) patients with other diagnoses in the mesothelioma group (Table 3).

US findings

According to the investigation results displayed in Table 4, not one characteristic US finding demonstrated a statistically significant more frequent or more infre-

TABLE 1
PRESENCE OF A SINGLE RADIOLOGIC SIGN ON DIGITAL RADIOGRAPHY DEPENDING ON THE PATHOHISTOLOGIC DIAGNOSIS

Characteristic finding	Total (N=80)	Mesothelioma (N=54)	Other diagnoses (N=26)	p-value*
X-ray - sign, number (%)				
Effusion	76 (95.0)	52 (96.3)	24 (92.3)	0.4433
Pleural thickening	25 (31.3)	19 (35.2)	6 (23.1)	0.2738
Plaque	5 (6.3)	5 (9.3)	0	0.1091
Calcification	5 (6.3)	5 (9.3)	0	0.1091
Osteolysis	0	0	0	0.9999
Tumor mass or node	13 (16.3)	5 (9.3)	8 (30.8)	0.0146
Pneumothorax	7 (8.8)	2 (3.7)	5 (19.2)	0.0213
Inflammatory infiltrate	6 (7.5)	1 (1.9)	5 (19.2)	0.0057
Elevation of hemidiaphragm	6 (7.5)	3 (5.6)	3 (11.5)	0.3413
Atelectasis	3 (3.8)	2 (3.7)	1 (3.9)	0.9749

*p-value for difference between diagnoses

TABLE 2
DIAGNOSTIC VALUES OF CHARACTERISTIC FINDINGS ON DIGITAL RADIOGRRAPHY WITH 95% INTERVALS OF RELIABILITY

Characteristic finding	Sensitivity	Specificity	PPV	NPV	DA	+LR	–LR	DO
Effusion	96.3% (87.5–98.9)	7.7% (2.1–24.1)	68.4% (57.3–77.8)	50% (15–85)	67.5% (56.6–76.8)	1.043 (0.96–1.13)	0.482 (0–164200)	2.167 (0.29–16.3)
Pleural thickening	35.2% (23.8–48.5)	76.9% (58–89)	76% (56.6–88.5)	36.4% (24.9–49.6)	48.8% (38.1–59.5)	1.525 (0.91–2.56)	0.843 (0.77–0.92)	1.81 (0.62–5.27)
Plaque	9.3% (4–19.9)	100% (87.1–100)	100% (56.6–100)	34.7% (24.9–46)	38.8% (28.8–49.7)	ND	0.907 (0.87–0.94)	ND
Calcification	9.3% (4–19.9)	100% (87.1–100)	100% (56.6–100)	34.7% (24.9–46)	38.8% (28.8–49.7)	ND	0.907 (0.87–0.94)	ND
Tumor mass or node	9.3% (4–19.9)	69.2% (50–83.5)	38.5% (17.7–64.5)	26.9% (17.7–38.5)	28.8% (20–39.5)	0.301 (0.01–17.9)	1.311 (1.2–1.43)	0.230 (0.07–0.79)
Pneumothorax	3.7% (1.02–12.5)	80.8% (62.1–91.5)	28.6% (8.2–64.1)	28.8% (19.7–40)	28.8% (20–39.5)	0.193 (0–?)	1.192 (1.12–1.27)	0.162 (0.03–0.9)
Inflammatory infiltrate	1.9% (0.3–9.8)	80.8% (62.1–91.5)	16.7% (3–56.4)	28.4% (19.4–39.5)	27.5% (18.9–38.1)	0.096 (0–?)	1.215 (1.15–1.29)	0.079 (0.01–0.72)
Elevation of hemidiaphragm	5.6% (1.9–15.1)	88.5% (71–96)	50% (18.8–81.2)	31.1% (21.7–42.3)	32.5% (23.2–43.4)	0.482 (0–61640)	1.068 (1.02–1.12)	0.451 (0.08–2.41)
Atelectasis	3.7% (1–12.5)	96.2% (81.1–99.3)	66.7% (20.8–93.9)	32.5% (23.1–43.5)	33.8% (24.4–44.6)	0.963 (0–?)	1.001 (0.96–1.04)	0.962 (0.08–11.1)

Legend: ND – non-defined, PPV – positive predictive value, NPV – negative predictive value, DA – diagnostic accuracy, +LR – likelihood ratio for a positive test, –LR – likelihood ratio for a negative test, DO – diagnostic odds

quent appearance in the group of patients with mesothelioma. This indicates that a single characteristic US finding pathognomonic for mesothelioma does not exist.

The most significant PPV was found for the presence of an anechogenic pleural effusion –74.5%, with NPV 44.8%, sensitivity 70.4%, and specificity 50%. Invasion of the thoracic wall had the lowest PPV of 0%, NPV 26%, sensitivity 0%, specificity 73.1%. The results for the diagnostic values of characteristic ultrasound findings with a 95% interval of reliability are displayed in Table 5.

On the basis of the characteristics that individual signs exhibited, models of US features, as well as for DDR, were formed. In spite of relatively high sensitivity, PPV and NPV, the combined model does not diagnose 4 (7.4%) patients with mesothelioma, and classifies 20 (76.9%) patients with other diagnoses in the mesothelioma group, exposing them to further diagnostic and therapeutic procedures (Table 6).

CT findings

According to the results (shown in Table 7) the most significant PPV for CT finding is the presence of plaque and calcification (PPV=100%, with a NPV of 37.7% and 35.1%), but with low sensitivity (20.4%, and 11.1%) and specificity 100%. The lowest PPV of 0% was found for pneumothorax, while it had a NPV of 29%, sensitivity 0% and specificity 84.6%.

Although pleural thickening and plaque have congruent diagnostic characteristics the independent presence of one of these signs in a maximum of 77.7% (the upper limit of 95% CI for pleural thickening) of patients is not sufficient to allow the independent use of any one of these signs in diagnosing this disease. Regarding negative predictors, (tumor mass or node, pneumothorax, inflammatory infiltrate) all exhibit relatively high specificity (69.2%, 84.6%, 80.8%), and significant DO (95%

TABLE 3
MODELS OF DDR FEATURES WITH 95% INTERVALS OF RELIABILITY

Model	Sensitivity	Specificity	PPV	NPV	DA	+LR	–LR	DO
Positive predictors	42.6% (30.3–55.8)	76.9% (58–89)	79.3% (61.6–90.2)	39.2% (27–52.9)	53.8% (42.9–64.3)	1.846 (1.19–2.87)	0.746 (0.68–0.82)	2.473 (0.86–7.14)
Negative predictors	14.8% (7.7–26.6)	42.3% (25.5–61.1)	34.8% (18.8–55.1)	19.3% (11.1–31.3)	23.8% (15.8–34.1)	0.257 (0.06–1.2)	2.013 (1.51–2.68)	0.128 (0.04–0.38)
Combined model	90.7% (80.1–96)	46.2% (28.8–64.5)	77.8% (66.1–86.3)	70.6% (46.9–86.7)	76.3% (65.9–84.2)	1.685 (1.46–1.95)	0.201 (0.11–0.36)	8.4 (2.53–27.9)

Legend: ND – non-defined, P – PV-positive predictive value, NPV – negative predictive value, DA – diagnostic accuracy, +LR – likelihood ratio for a positive test, –LR – likelihood ratio for a negative test, DO – diagnostic odds

TABLE 4
PRESENCE OF A SINGLE RADIOLOGIC SIGN ON US DEPENDING ON THE PATHOHISTOLOGIC DIAGNOSIS

Characteristic sign	Total (N=80)	Mesothelioma (N=54)	Other diagnoses (N=26)	p-value*
US-finding, number (%)				
Anechogenic effusion	51 (63.8)	38 (70.4)	13 (50.0)	0.0759
Complex non-loculated effusion	8 (10.0)	5 (9.3)	3 (11.5)	0.7503
Complex loculated effusion	6 (7.5)	4 (7.4)	2 (7.7)	0.9639
Homogenous echogenic effusion	7 (8.8)	3 (5.6)	4 (15.4)	0.1451
Incapsulated effusion	3 (3.8)	1 (1.9)	2 (7.7)	0.1978
Total effusion	74 (92.5)	51 (94.4)	23 (88.5)	0.3413
Nonspecific US finding or lesion undetectable by US	6 (7.5)	3 (5.6)	3 (11.5)	0.3413
Tumor mass or node	1 (1.3)	1 (1.9)	0	0.4850
Calcification	3 (3.8)	3 (5.6)	0	0.2206
Atelectasis	1 (1.3)	1 (1.9)	0	0.4850
Penetration into thoracic wall	7 (8.8)	0	7 (26.9)	0.0001

*p-value for difference between diagnoses

CI does not exceed 1). These results are presented in Table 8.

The combined model for CT (Table 9), which includes positive and negative predictors for the diagnosis of mesothelioma, is the best one with a statistically significantly highest DO (10.63). With high sensitivity, PPV, NPV, and DA that are statistically significantly higher (no overlap of 95% CI), this model does not diagnose only 3 (5.5%) patients with mesothelioma, but due to low specificity (38.3%) it includes 16 (61.5%) patients with other diagnoses into the mesothelioma group, maybe exposing them to unnecessary diagnostic and therapeutic procedures.

Discussion

Several important characteristics of the methods for diagnosing mesothelioma that were studied derive from the results that are presented:

TABLE 5
DIAGNOSTIC VALUES OF CHARACTERISTIC FINDINGS ON US EXAMINATIONS WITH 95% INTERVALS OF RELIABILITY

Characteristic finding	Sensitivity	Specificity	PPV	NPV	DA	+LR	–LR	DO
Anechogenic effusion	70.4% (57.2–80.1)	50% (32.1–67.9)	74.5% (61.1–84.5)	44.8% (28.4–62.5)	63.8% (52.8–73.4)	1.407 (1.18–1.67)	0.593 (0.45–0.78)	2.375 (0.90–6.24)
Complex non-loculated effusion	9.3% (4.0–19.9)	88.5% (71.0–96)	62.5% (30.6–86.3)	31.9% (22.3–43.4)	35% (25.5–45.9)	0.803 (0.01–71.9)	1.026 (0.97–1.08)	0.782 (0.17–3.56)
Complex loculated effusion	7.4% (2.9–17.6)	92.3% (75.9–97.9)	66.7% (30–90.3)	32.4% (22.9–43.7)	35% (25.5–45.9)	0.963 (0–1173)	1.003 (0.96–1.05)	0.96 (0.16–5.61)
Homogenous echogenic effusion	5.6% (1.9–15.1)	84.6% (66.5–93.9)	42.9% (15.8–74.9)	30.1% (20.8–41.4)	31.3% (22.2–42.1)	0.361 (0–39270)	1.116 (1.06–1.18)	0.324 (0.07–1.57)
Incapsulated effusion	1.9% (0.3–9.8)	92.3% (75.9–97.9)	33.3% (6.1–79.2)	31.2% (21.9–42.2)	31.3% (22.2–42.1)	0.241 (0–?)	1.063 (1.02–1.11)	0.226 (0.02–2.62)
Total effusion	94.4% (84.9–98.1)	11.5% (4.0–29)	68.9% (57.7–78.3)	50% (18.8–81.)	67.5% (56.6–76.8)	1.068 (0.98–1.17)	0.482 (0–138.6)	2.217 (0.42–11.8)
Non-specific US finding or lesion undetectable by US	5.6% (1.9–15.1)	88.5% (71–96)	50% (18.8–81.2)	31.1% (21.7–42.3)	32.5% (23.2–43.4)	0.482 (0–61640)	1.068 (1.02–1.12)	0.451 (0.08–2.41)
Tumor mass or node	1.9% (0.3–9.8)	100% (87.1–100)	100% (20.7–100)	32.9% (23.6–43.9)	33.8% (24.4–44.6)	ND	0.982 (0.95–1.02)	ND
Calcification	5.6% (1.9–15.1)	100% (87.1–100)	100% (43.9–100)	33.8% (24.2–44.9)	36.3% (26.6–47.2)	ND	0.944 (0.91–0.98)	ND
Atelectasis	1.9% (0.3–9.8)	100% (87.1–100)	100% (20.7–100)	32.9% (23.6–43.9)	33.8% (24.4–44.6)	ND	0.982 (0.95–1.02)	ND
Penetration into thoracic wall	0% (0.0–6.6)	73.1% (53.9–86.3)	0% (0.0–35.4)	26.0% (17.3–37.1)	23.8% (15.8–34.1)	0.09 (0.01–1.32)	1.37	0.059 (0–0.42)

Legend: ND – non-defined, PPV – positive predictive value, NPV – negative predictive value, DA – diagnostic accuracy, +LR – likelihood ratio for a positive test, –LR – likelihood ratio for a negative test, DO – diagnostic odds

TABLE 6
DIAGNOSTIC CHARACTERISTICS OF COMBINED MODELS OF US EXAMINATIONS WITH 95% INTERVALS OF RELIABILITY

Model	Sensitivity	Specificity	PPV	NPV	DA	+LR	–LR	DO
Positive predictors	70.4% (57.2–80.1)	50% (32.1–67.9)	74.5% (61.1–84.5)	44.8% (28.4–62.5)	63.8% (52.8–73.4)	1.407 (1.18–1.67)	0.593 (0.45–0.78)	2.375 (0.90–6.24)
Negative predictors	7.4% (2.9–17.6)	65.4% (46.2–80.6)	30.8% (12.7–57.6)	25.4% (16.5–36.9)	26.3% (17.9–36.8)	0.214 (0–121.6)	1.416 (1.28–1.57)	0.151 (0.04–0.55)
Combined model	92.6% (82.5–97.1)	23.8% (11–42.1)	71.4% (60–80.7)	60% (31.3–83.2)	70% (59.2–78.9)	1.204 (1.09–1.33)	0.321 (0.07–1.56)	3.75 (0.96–14.7)

Legend: ND – non-defined, PPV – positive predictive value, NPV – negative predictive value, DA – diagnostic accuracy, +LR – likelihood ratio for a positive test, –LR – likelihood value for a negative test, DO – diagnostic odds

TABLE 7
PRESENCE OF A SINGLE RADIOLOGIC SIGN ON CT IMAGES DEPENDING ON THE PATHOHISTOLOGIC DIAGNOSIS

Characteristic finding	Total (N=80)	Mesothelioma (N=54)	Other diagnoses (N=26)	*p*-value*
CT-finding, number (%)				
Effusion	76 (95.0)	52 (96.3)	24 (92.3)	0.4433
Pleural thickening	44 (55.0)	36 (66.7)	8 (30.8)	0.0025
Plaque	11 (13.8)	11 (20.4)	0	0.0132
Calcification	6 (7.5)	6 (11.1)	0	0.0772
Osteolysis	0	0	0	0.9999
Tumors mass or node	14 (17.5)	6 (11.1)	8 (30.8)	0.0302
Pneumothorax	4 (5.0)	0	4 (15.4)	0.0031
Atelectasis	5 (6.3)	4 (7.4)	1 (3.9)	0.5377
Inflammatory infiltrate	6 (7.5)	1 (1.9)	5 (19.2)	0.0057
Scar lesions	1 (1.3)	0	1 (3.9)	0.1470

*p-value for the difference between diagnoses

TABLE 8
DIAGNOSTIC VALUES OF CHARACTERISTIC CT FINDINGS WITH 95% INTERVALS OF RELIABILITY

Characteristic finding	Sensitivity	Specificity	PPV	NPV	DA	+LR	–LR	DO
Effusion	96.3% (87.5–98.9)	7.7% (2.1–24.1)	68.4% (57.3–77.8)	50% (15–85)	67.5% (56.6–76.8)	1.043 (0.96–1.13)	0.482 (0–164200)	2.167 (0.29–16.3)
Pleural thickening	66.7% (53.4–77.8)	69.2% (50–83.5)	81.8% (68–90.5)	50% (34.5–65.5)	67.5% (56.6–76.8)	2.167 (1.65–2.85)	0.482 (0.41–0.56)	4.5 (1.64–12.3)
Plaque	20.4% (11.8–32.9)	100% (87.1–100)	100% (74.1–100)	37.7% (27.2–49.5)	46.3% (35.8–57.1)	1.524 (1.22–1.9)	0.796 (0.76–0.83)	9.845 (1.25–290)
Calcification	11.1% (5.2–22.2)	100% (87.1–100)	100% (61–100)	35.1% (25.2–46.5)	40% (30–51)	1.413 (1.07–1.87)	0.889 (0.85–0.93)	4.869 (0.55–151)
Tumor mass or node	11.1% (5.2–22.2)	69.2% (50–83.5)	42.9% (21.4–67.4)	27.3% (18–39)	30% (21.1–40.8)	0.361 (0.02–6.3)	1.284 (1.17–1.4)	0.281 (0.09–0.92)
Pneumothorax	0% (0–6.6)	84.6% (66.5–93.9)	0% (0–49)	29% (20–40)	27.5% (18.9–38.1)	0 (ND)	1.182 (ND)	0 (ND)
Atelectasis	7.4% (2.9–17.6)	96.2% (81.1–99.3)	80% (37.6–96.4)	33.3% (23.7–44.6)	36.3% (26.6–47.2)	1.926 (0–6250)	0.963 (0.92–1)	2 (0.21–18.9)
Inflammatory infiltrate	1.9% (0.3–9.8)	80.8% (62.1–91.5)	16.7% (3–56.4)	28.4% (19.4–39.5)	27.5% (18.9–38.1)	0.096 (0–?)	1.215 (1.15–1.29)	0.08 (0.01–0.72)
Scar lesions	0% (0–6.6)	96.2% (81.1–99.3)	0% (0–79.4)	31.7% (22.5–42.6)	31.3% (22.2–42.1)	0 (ND)	1,04 (ND)	0 (ND)

Legend: ND – non-defined, PPV – positive predictive value, NPV – negative predictive value, DA – diagnostic accuracy, +LR – likelihood ratio for a positive test, –LR – likelihood ratio for a negative test, DO – diagnostic odds

TABLE 9
MODELS OF CT IMAGING WITH 95% INTERVALS OF RELIABILITY

Model	Sensitivity	Specificity	PPV	NPV	DA	+LR	–LR	DO
Positive predictors	72.2% (59.1–82.4)	69.2% (50–83.5)	83% (69.9–91.1)	54.6% (38–70.2)	71.3% (60.5–80)	2.347 (1.8–3.06)	0.401 (0.34–0.48)	5.85 (2.1–16.3)
Negative predictors	13% (6.4–24.4)	42.3% (25.5–61.1)	31.8% (16.4–52.7)	19% (10.9–31)	22.5% (14.7–32.8)	0.225 (0.03–1.68)	2.057 (1.55–2.74)	0.109 (0.04–0.33)
Combined model	94.4% (84.9–98.1)	38.5% (22.4–57.5)	76.1% (64.7–84.7)	76.9% (49.7–91.8)	76.3% (65.9–84.2)	1.535 (1.36–1.74)	0.144 (0.05–0.38)	10.63 (2.6–43.4)

Legend: ND – non-defined, PPV – positive predictive value, NPV – negative predictive value, DA – diagnostic accuracy, +LR – likelihood of reliability for a positive test, –LR – likelihood of reliability for a negative test, DO – diagnostic odds

Computed tomography: has the highest sensitivity 94.4% with 35.5% specificity.

Direct digital radiography: has a sensitivity of 90.7% and specificity 46.2%. The diagnostic accuracy of DDR in relation to CT is 90%,when the two methods are compared. The results indicate that DDR is a less sensitive method in detecting primarily positive predictors.

Ultrasound: has a diagnostic accuracy of 80% in relation to CT. The results for US have revealed its markedly low specificity of 23.8% for mesothelioma, with diagnostic odds of 3.75 (95% CI, 0.96–14.7) that is without statistical significance. However, the results for US, when compared to the results for CT, are only slightly less sensitive in detecting positive predictors, primarily because of inferior contrast resolution (sensitivity 90.7%, specificity 46.2%, PPV 77.8%, NPV 70.6% for mesothelioma) with diagnostic odds of 8.4.

This study demonstrated that all three methods are mutually complementary in detecting particular radiologic signs of mesothelioma. No method among the studied ones yielded a pathognomonic radiologic sign for the diagnosis of mesothelioma.

Comparision with literature data for average age and sex

The comparison of the results obtained for the average age of examinees with a confirmed diagnosis of mesothelioma showed that they conform with data in the literature regarding the average age of patients with mesothelioma. According to data from the literature[4,5], the average age of patients with mesothelioma is about 48,5± 16,1SD.The ratio of men and women with mesothelioma in this study also corresponds to the data in the literature[3,5].

Comparision with literature data for radiological signs

Plaques: In the literature various ranges of sensitivity for DDR in detecting plaques[6] are stated, from 30% to 80%; in these data the proportion of false positive findings is 20%, considerably improved by 18% with the addition of a lateral view radiogram[6]. The same authors specify negative DDR findings in as many as 20% of patients with mesothelioma[6]. Atelectasis or parenchima consolidation: contrary to data in the literature, as is stated in some publications by Lynch and Benamore[7,8], in this study we didn't confirm either atelectasis or parenchyma consolidation as a negative predictor.

Effusions: Benamore, Odoherty and Entwisle[8], as well as Lichtenstein[9–11], also found no characteristic US sign pathognomonic for mesothelioma, which corresponds with the results of this study. In their results homogenous echogenic and incapsulated pleural effusions were also found to be negative predictors for the diagnosis of mesothelioma, although with less statistical significance than in the case of thoracic wall penetration, but with high specificity.

Pleural thickening: according to Peacock[12], the specificity of CT for pleural thickening, but also for nodes, is 94%, for mediastinal thickening it is 98%, and for circular thickening it is 100%. Scott and associates[13] asserted that a combination of CT and biopsy raises the sensitivity for differentiating malignant from benign pleural diseases from 83% to 100%.

Pneumothorax: Pneumothorax is stated in the literature as a negative predictor for the diagnosis of mesothelioma[14], but for the other negative predictors there are no reliability data.

Remy-Jardin, Staples and Leung[15] state 98 to 100% sensitivity, and 87 to 92% specificity of CT in diagnosing malignant pleural thickening. Remy-Jardin [15] accentuates the higher sensitivity and specificity of multislice CT.

According to the literature up to now[16], CT is more sensitive than other methods, particularly in the assessment of plaque extent[17], most probably due to better differentiation of extrapleural fat and surrounding opacities. This method exhibits higher image sensitivity in relation to DDR and US[17], but it hasn't the expected significance that is generally presumed in clinical practice. It has a distinctly higher sensitivity only in detecting pleural thickening. In the works[18] of Hierholzer, CT and MR have comparable sensitivity in diagnosing malignant mesothelioma.

More recent studies[19,20] have shown a high sensitivity of PET CT.

Pleurocentesis under us

In as many as 69 patients the final diagnosis was established from material obtained under US supervision. It must be stressed that an adequate sample was obtained from all patients, in the sense that the quantity of effusion was sufficient (>50 ccm) for microbiological, biochemical and cytologic analysis. This result corresponds with those from other authors[21] who had a percentage of adequate samples in the range of 97–100%. The percentage of negative pleurocenteses is stated[21] as 10%, when it is not guided by US. It is particularly important to emphasize the importance of the non-invasive feature of the ultrasonic method obtaining material for PHD analysis, that does not use ionizing radiation.

The results have opened the question concerning the need for a consensus about the use of particular methods (having in view their diagnostic properties) in the detection, and notably in the follow up of these patients. The multivariant models formed in this study indicate that CT best satisfies the criteria for diagnosing mesothelioma, when it is used as an independent method. CT is also the best method for staging and preoperative evaluation of tumor spread.

In the final analysis of this investigation, DDR exhibited statistical characteristics of the »first looking« method in diagnosing mesothelioma. The above mentioned characteristics make it also the method of choice in the follow up of patients with mesothelioma, According to the results, US is a satisfactory follow up method for monitoring the course of disease in these patients. For a more accurate assessment of the stage of disease, judging from these results it would be necessary to perform CT in these patients.

Advantages of the CT and MR

Acoording to the literature[5] CT usually provides precise localization and extent of the disease and may be of value in assessing chest wall and mediastinal involvment. In specific situations, magnetic resonance imaging (MR) may be useful as problem-solving tool when CT findings of the chest wall and diaphragmatic invasion are equivocal. CT and MR imaging are of nearly equivalent diagnostic accuracy in staging malignant pleural mesothelioma[22]. MR is superior to CT in revealing solitary foci of chest wall invasion and endothoracic fascia involvment and in showing diaphragmatic muscle invasion; however, this advantage does not affect surgical tretmant. For cost reasons, CT should be considered the standard diagnostic study before therapy[22], although CT and MR have comparable sensitivity in diagnosing mesothelioma[18]. Unfortunately, we did not have MR in our Clinic, and surgeons still operate based on CT studies[23]. Today, also CT-PET is indicated for diagnosis and staging of malignant pleural mesothelioma in the selection of patients who might benefit from surgery after neoadjuvant therapy. CT- PET is highly specific in identifying small recurrences and/or remote methastases[23].

Using spiral CT instead of widely accepted MDCT technology may be potential drawback of this study. According to the literature MDCT of the chest is superior in comparision with single-slice CT of the chest in detecting some small size lesions[24]. Unfortunatly, we had only single slice CT in our Clinic. But, also, in future maybe we should think abouth the potential doses delivered by newer CT tehnologies that can be quite higer[25].

It was necessary to perform CT despite the fact that the tumor had previously been proven by DDR and US because of the disease staging process; the clinicians could only decide on further therapy after the staging process was completed.

Another disadvantage of this investigation was not analyzing accuracy of each method based on different features of the tumor (size, location). Statistical analysis included only data on their number (Table 1, 4, 7). These variations of the tumor were not analysed since the aim has been to establish the presence of characteristic radiologic signs, in each diagnostic method. More important, it was to determine whether a pathognomonic radiologic sign for the diagnosis of mesothelioma exists.

However, the results listed in Tables 1, 4, and 7 indicate the presence of 14 nodal lesions and tumor masses on CT examination, 13 on DDR and only one on the US exam. Obviously, the size of the lesion affects the sensitivity[24] of the method, as well as their location. We found only one peripheral nodal lesions on US exam. After the literature[,9,10], use of the chest US is limited by the location of the lesion. The difference between the methods is probably lesser, since mesothelioma affects primary peripheral zone of the lungs (mostly pleura)[8,10].

The choice of the algorithm at the first visit of such a patient would be: DDR, US, CT.

For regular follow up DDR and US would be mandatory, while in case of progression of disease or new clinical signs CT should be used[24].

Conclusion

The results of this investigation indicate that CT best satisfies the criteria for individually diagnosing mesothelioma.

DDR demonstrated statistical characteristics of the method of choice, at the first visit of the patient, and US had a surprisingly high sensitivity. The methods emerged as mutually complementary in the detection of radiologic signs of mesothelioma.

None of the examinations that were used succeeded in revealing a pathognomonic radiologic sign for the diagnosis of mesothelioma, which is of particular importance in order to avoid the overestimation of newer methods (CT) in diagnosing this disease. In view of its statistical characteristics, CT is the method of choice for determining the stage of extent of mesothelioma.

Based on the results that are presented, the proposed choice of algorhythm at the first visit of a patient with

suspected mesothelioma would therefore be: DDR, US, CT.

In the course of regular follow ups, DDR and US should be used, and in case of progression or appearance of new clinical signs, CT should be added. Each imaging modality, even the latiest (PET-CT and MR) has its advantages and limitations, but their combined use is crucial in determining the most appropriate treatment options in patients with malignant pleural mesothelioma.

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J. Popić Ramač

University of Zagreb, »Merkur« University Hospital, Departmet of Diagnostic and Interventional Radiology, Zajčeva 19, 10000 Zagreb, Croatia
e-mail: jpopic@inet.hr

MOGUĆNOSTI I OGRANIČENJA DIREKTNE DIGITALNE RADIOGRAFIJE, ULTRAZVUKA I KOMPJUTORIZIRANE TOMOGRAFIJE U DIJAGNOSTICI MEZOTELIOMA PLEURE

SAŽETAK

Cilj istraživanja je bio usporediti mogućnosti i ograničenja direktne digitalne radiografije prsišta (DDR), ultrazvuka prsišta (UZV) i kompjutorizirane tomografije prsišta (CT) u otkrivanju mezotelioma pleure. Istraživanje je provedeno tijekom godine dana, na 80 bolesnika, uzastopno upućenih u specijaliziranu ustanovu, s kliničkom sumnjom na mezoteliom. Metoda istraživanja bila je usporedba nalaza dobivenih ispitivanim metodama sa patohistološkim nalazom biopsije za svakog bolesnika. Nalazi dobiveni navedenim metodama klasificirani su prema pronađenim radiološkim znacima, za svakog pacijenta posebno. Svakom od korištenih metoda analizirani su sljedeći radiološki znakovi: pleuralni izljev, zadebljanja pleure, plakovi,kalcifikati, tumorske mase ili nodusi, pneumotoraks, atelektaza, upalni infiltrate, ožiljne lezije, elevacija ošita i osteoliza. Dobiveni rezultati uspoređeni su s patohistološkim nalazom i obrađeni standardnim statističkim metodama. Najveću osjetljivost pokazao je CT (94,4%). Slijedi UZV (92,6%), te DDR (90,7%). Najveća je specifičnost DDR (46,2%), slijedi CT (35, 5%) i UZV (23, 8%). Usporedba metoda pokazala je 90% dijagnostičku točnost DDR-e u odnosu na CT. UZV je pokazao točnost od 80% u odnosu na CT. CT, kao pojedinačna metoda, najbolje zadovoljava većinu kriterija za dijagnostiku mezotelioma. Nije nađen patognomoničan radiološki znak za dijagnozu mezotelioma.