ABSTRACT
Peripheral pulmonary tumours are often quite difficult to diagnose and treat. Their detection brings immediately the problem of whether clinicians should just wait and observe or operate the patients.
The aim of this study was to determine if there is a direct correlation between tumour size and the risk for malignancy and whether the tumor size should be considered a risk factor for malignancy.

PATIENTS AND METHODS: Between 1997 and 2009, 145 patients with peripheral pulmonary tumours of less than 3 cm in diameter underwent video-assisted thoracoscopic (VATS) resection for the purpose of histologic examination of the tumor.

RESULTS: The mean age of the patients was 62.60 ± 0.95 years. The youngest patient was 17 years old and the oldest – 82. The study sample included 61 women and 84 men; the men were statistically significantly more than the women (57.3% and 42.07%, respectively) (t = 2.74, P < 0.01). The total number of patients we operated were 145 with 198 resected tumours. The diameter of the lesions ranged between 0.30 cm and 3 cm (mean 1.41 ± 0.06 cm). We found that 108 (54.55%) of the tumours were malignant, and 90 (45.45%) were benign, the difference between them failing to reach statistical significance (t = 1.82, P > 0.05).
The mean size of malignant lesions was statistically significantly greater than that of benign tumours (1.62 ± 0.08 cm vs 1.15 ± 0.06 cm).

CONCLUSION: The results of this study suggest that the bigger the diameter of the nodule, the greater the percentage share of malignant tumours, which means that the size of the tumour is an important risk factor for malignancy.

Key words: peripheral lung nodules, size, malignancy

INTRODUCTION
The peripheral pulmonary nodules can be either solitary or multiple, the solitary nodules occurring much more frequently.
The solitary pulmonary nodule is a single mass lesion of unclear etiology which is seen on X-rays as a well-margined rounded opacity less than or equal to 3 cm in diameter, surrounded by normal lung parenchyma and unassociated with atelectasis or lymphadenopathy.1,2 There are more than 80 nosological entities that present radiologically as peripheral rounded opacities. They can be benign lesions, primary bronchial carcinomas or pulmonary metastases.1-3
The newly found solitary pulmonary nodules have recently been found to increase in incidence.2,4 According to literature estimates, 30% to 68% of these lesions are malignant.2 Among these the bronchial carcinoma has the greatest incidence; the only therapeutic modality that is known currently to be efficient in treating these tumours is immediate surgical resection. It is therefore important that a prompt and definitive histologic diagnosis be made.2,5,6
With the advent of such imaging techniques as HR-CT and PET in the last 20 years the diagnostic accuracy in this respect has been considerably improved without however solving definitively the problem with the histologic identification of the solitary pulmonary nodules which still present a serious diagnostic and therapeutic challenge.

The moment these nodules are detected clinicians are faced with the dilemma of whether they should simply wait and observe or operate them immediately. This problem is often hard to solve depending, as it does, on many other factors.\textsuperscript{11,12}

In the present study we set to find if there is a correlation between the size of the tumour and its malignancy and if the answer is positive whether we can use it as a prognostic factor so that a timely and accurate diagnosis can be made.

**MATERIALS AND METHODS**

We recruited in the present study 145 patients (aged 17 through 82 years) with peripheral pulmonary nodules of unknown histological nature measuring 3 cm in diameter and less, located in the lateral third of the lung and in the interlobar fissures. All patients underwent video-assisted thoracoscopic surgery (VATS), 5 of the patients bilaterally, i.e. a total of 150 surgical procedures that were performed in the following clinics:

- the Clinic of Thoracoabdominal Surgery in Plovdiv Medical University, Bulgaria - 21 patients operated between 01.01.1998 and 30.06.2002.
- the Clinic of Visceral, Vascular and Thoracic Surgery in the University Hospital of Aschersleben, Germany – 57 patients operated in the period from 01.06.2005 to 31.07.2009.
- the Clinic of Thoracic Surgery, University Hospital, Bremen-East, Germany – 67 patients between 01.05.2008 and 31.07.2009.

All patients were administered a standardised preoperative surgical procedure which included conventional X-ray study, lung CAT, and bronchoscopy. A transthoracic biopsy in operable patients for the purpose of presurgical diagnostics was considered redundant.

All patients received at first an atypical lung resection in which we removed the tumor and made an intraoperative cryosection histologic test. In case the histology study found malignant tissue the surgical procedure was adjusted accordingly as required by oncological criteria for management of neoplasms.

The statistical analysis used parametric, non-parametric and graphic methods to present the results and calculate them using SPSS v. 17.

**RESULTS**

The youngest patient was 17 years old, the oldest - 82 years. The mean age of the patients was 62.60 ± 0.95 years. A total of 145 patients were included in the study sample (61 women, 84 men); the number of operated men was statistically significantly more than that of women (57.3% and 42.07%, respectively) (t = 2.74, P < 0.01). There was no significant difference between men and women in their age distribution (\(\chi^2 = 3.68, \text{df} = 7, P > 0.05\)).

Seventy patients (48.28%) had a history of malignancy; the remaining 75 patients (51.72%) had no previous history of tumours. The statistical difference between these two groups failed to reach significance (t = 0.59, P > 0.05).

A total of 198 nodules were resected in 145 patients. Single solitary nodules were removed from 97 patients (66.90%), two tumours – in 26 patients (17.93%); 22 patients (15.17%) presented with more than two nodules.

Out of the 198 nodules we investigated, 108 (54.55%) were malignant, and 90 (45.45%) – benign; we found no significant difference between the percentage shares of these two groups of patients (t = 1.82, P > 0.05) (Fig. 1).

The malignant tumours with histological confirmation were 108 in 76 patients. Forty one (53.95%) of these patients had a primary lung carcinoma, and 35 (46.05%) – lung metastases.

Sixteen tumours were excluded from the study results as their size measurements were not entirely accurate.

The nodules ranged between 0.30 cm and 3 cm, but the lesions of 0.5 to 1 cm were the most frequent. Their mean diameter was 1.41 ± 0.06 cm. The distribution of these tumours by their size is presented in Fig. 2.

We also studied the tumours in terms of their size and malignancy.
mean size in the patients with malignant and in the patients with benign nodules. The mean size of the malignant lesions (1.62 ± 0.08 cm) was statistically significantly greater than that of benign tumours (1.15 ± 0.06 cm) (Fig. 3). This finding was confirmed and reached statistical significance when we analysed the bidimensional distribution of the nodules by size ($\chi^2 = 19.14, df = 5, P = 0.002$) (Table 1): the bigger the nodule, the higher the percentage of malignant tumours. Of up to 0.5-cm lesions 14 (46.66%) were malignant, 13 being metastases and one being a primary lung carcinoma. Twenty-four (40.67%) of the lesions ranging in size from 0.5 to 1 cm were malignant: eight lesions were primary lung carcinomas and 16 had metastases. The percentage share of the benign tumours in these two groups was greater than that of the malignant tumours (53.34% for lesions 0.5 cm in size and 59.33% for the lesions 0.5 cm to 1 cm in size, respectively). In the lesions between 1 cm and 1.5 cm, the malignant tumours were predominant (54.28%). The ratio of malignant to benign tumours was 2:1 for those measuring between 1.5 cm to 2 cm, while for the lesion 2.5-3 cm this ratio was 10:1.

We performed a one-factor regression analysis with the histological characteristic of the tumour as a variable coded as a binary parameter (zero for benign tumours and 1 for malignant tumours). The tumour size was analysed as a dependent variable in a binary code with 0 designating tumours smaller than or as large as 1.5 cm, and 1 – for tumours bigger than 1.5 cm; tumours with a diameter less than or equal to 1.5 cm were used as a reference parameter.

We found that if the tumour is bigger than 1.5 cm the malignancy risk is twice as high (Table 2).

### Table 1. Tumour distribution by size and type

<table>
<thead>
<tr>
<th>Size of tumour</th>
<th>Malignant</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>0.5 cm</td>
<td>14</td>
<td>46.66</td>
</tr>
<tr>
<td>0.5 to 1 cm</td>
<td>24</td>
<td>40.67</td>
</tr>
<tr>
<td>1 cm to 1.5 cm</td>
<td>19</td>
<td>54.28</td>
</tr>
<tr>
<td>1.5 cm to 2 cm</td>
<td>19</td>
<td>67.85</td>
</tr>
<tr>
<td>2 cm to 2.5 cm</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>2.5 cm to 3 cm</td>
<td>20</td>
<td>90.9</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>82</td>
</tr>
</tbody>
</table>

### Table 2. Relative risk assessment using one-factor regression analysis

<table>
<thead>
<tr>
<th>Size of tumour</th>
<th>Relative risk (Exp(B))</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 cm</td>
<td>1</td>
<td>1.34; 2.27</td>
<td>0.0001</td>
</tr>
<tr>
<td>1.5 cm</td>
<td>1.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>const</td>
<td>0.204</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### DISCUSSION

The incidence of malignant cancer in patients with solitary nodules, as given in literature, ranges from 30 to 68%.

Passlick et al. have found that benign tumours in such cases are as frequent as 60%.

Roke13 reports that incidence of malignancy in solitary nodules is as high as 62%, while benign tumours occur in 38% of all cases. Onregado et al. found that 68% of the 182 solitary lung lesions they studied were malignant.14 In 2008 aroli F et al.
reported of 276 solitary lung nodules they removed and found 138 of them (50%) to be malignant.\textsuperscript{15}

Our results are consistent with the findings in these studies - we found 54.55% malignant nodules and 45.45% benign tumours.

The difference in the results reported in literature can probably be accounted for by the preselection of the patient sample – some of these studies did not include patients with history of cancer.

Cardilo G et al. reported of 429 patients who underwent thoracoscopic surgery: the mean nodules size in their study was 2.3 cm and the conclusion made was that a size of the nodule bigger than 2 cm can be considerate a statistically significant factor for malignancy.\textsuperscript{16} Varoli F et al. reported of 276 patients with solitary pulmonary lesions operated thoracoscopically and made the same conclusion.\textsuperscript{15}

The reports in the relevant literature about the malignancy of small subcentimeter lung lesions are rather contradictory. Midthun et al. for example report in a study that nodules measuring less than 4 mm in diameter are not malignant and only 0.8% of the nodules between 4 and 7 mm are malignant.\textsuperscript{17} Henschke et al hold a similar view – they found that that nodules measuring less than 5 mm in diameter are always benign while 5.9% of the lesions 5-9 mm in size are malignant.\textsuperscript{18} Klein et al., however, found that studies in which lung lesions were removed surgically tended to show a greater incidence of malignancy in subcentimeter nodules (58%).\textsuperscript{19}

Our results are similar to the results in literature as described here. The mean diameter of the lesions we operated was considerably smaller than the lesion diameter reported by Varoli\textsuperscript{15} and Cardio\textsuperscript{16} (1.41 cm and 2.3 cm, respectively) indicating that the surgery our patients received was performed at a considerably earlier time. The frequency of malignant lesions in the category of subcentimeter nodules in our study is higher than that reported in most of the research, especially in cases of nodules less than 0.5 cm in diameter (46%). These differences are most likely due to the different preoperative selection of patients. The percentage of patients with a history of cancer in the present study is relatively high (48.28%). The pulmonary nodules discovered while following up these patients with a previous cancer disease were surgically removed using VATS relatively early, after their identification as suspicious for lung metastases.

On the basis of the results reported herein we can make the following conclusions:

CONCLUSIONS

The nodule size is a statistically significant risk factor for malignancy. For nodules greater than 1.5 cm in diameter the risk for malignancy is twice as great. For this reason all indeterminate peripheral pulmonary lesions measuring 1 cm and larger should be examined histologically.

REFERENCES

РАЗМЕР ОПУХОЛИ КАК ФАКТОР РИСКА ЗЛОКАЧЕСТВЕННОСТИ У ПАЦИЕНТОВ С ПЕРИФЕРИЧЕСКИМИ ЛЕГОЧНЫМИ ОПУХОЛЯМИ
Г. Присадов, А. Учиков, Kathrin Welcker, Herbert Wal- limann, К. Мурджев, В. Узунова
РЕЗУМЕ
ВВЕДЕНИЕ: Пациенты с периферическими легочными опухолями часто представляют серьезную диагности-ко-терапевтическую проблему. Вместе с диагностицированием возникает и дилемма: „выжидать и контролировать или оперировать“.
ЦЕЛЬ: Работа ставит себе целью ответить на вопрос – существует ли зависимость между размером опухоли и его злокачественностью и можно ли считать размер опухоли фактором риска злокачественности.
РЕЗУЛЬТАТЫ: Средний возраст пациентов - 62.60 ± 0.95 г. Самому младшему пациенту 17 лет, а самому взрослому – 82 года. В обследованную группу включено 61 женщина и 84 мужчины, при чем процент оперированных мужчин – 57.3% - статистически более высок, чем процент женщин – 42.07% (t = 2.74, P < 0.01). Резецировано 198 опухолей (145 оперированных). Диаметр поражений от 0.30 до 3.00 см (средний диаметр 1.41 ± 0.06 см). Мalignены 108 (54.55%) опухолей, а 90 (45.45%) бенигнены, без статистически значимой разницы (t = 1.82, p > 0.05). Установлен статистически значимый более большой средний размер злокачественных опухолей (1.62 ± 0.08 см) по сравнению с доброкачественными (1.15 ± 0.06 см).
ЗАКЛЮЧЕНИЕ: Полученные результаты показывают, что с нарастанием диаметра поражения статистически значительно нарастает и процент злокачественных опухолей, т.е. размер опухоли является важным фактором риска злокачественности.