ACTA STEREOL 1985; 4/2: 261—266
PROC ESS IV-1 GÖTEBORG 1985
ORIGINAL SCIENTIFIC PAPER

THE STEREOLOGY OF PROJECTION PROVIDES REASONABLE PARAMETERS FOR THE CONTROL OF TUMOUR THERAPY

Helmut Röhrer* and Ortwin Leder**

* Rosmann-Krankenhaus, D 7814 Breisach am Rhein, Deutschland.

** Anatomisches Institut der Universität, D 7800 Freiburg i.Br. Deutschland.

ABSTRACT

Methods of stereology were applied to X-ray films of patients with malignant chest disease for therapy control. In clinical medicine measurements with a digitizer table do not work within a reasonable time. A point count with an isometric point grid is better suited and trends may be followed up in a simple way.

Keywords: Stereology of projection, malignant disease, therapy control.

INTRODUCTION

The assessment of therapeutic success in malignant disease is largely qualitative. Therefore,the correct interpretation of X-ray films may remain vague. Moreover, the results are difficult for others apart from the physician in charge to realize. Occasionally,diameters of lung metastases are measured. Furthermore, as a measure of size a rectangle circumscribed around the focus is recommended (Wander and Nagel,1984). In such a way all or only one of the foci may be examined. Some questions arise with these methods as how to record and condense the values or to find the appropriate focus. Therefore,we have attempted to use simple methods of stereology of projection for therapy control of malignant chest disease.

MATERIALS AND METHODS

X-ray films from patients with malignant disease incurable with standard therapy and treated with a special xenogeneic peptide fraction (Factor AF 2 of biosyn Arzneimittel GmbH,Ludwigsburg) in combination with mitomycin C,doxorubicin,bacterial extracts and key hole limpet hemocyanine were used.The following methods were applied for the estimation of the tumor tissue:

1) The malignant foci were traced on overhead leafs. Then,the area of the foci was measured with the digitizer table of the semiautomatic device MOP AM 02 (Kontron Bildanalyse GmbH,Eching bei München). The tracings were delineated and measured by one of us only (O.L.).Two copies were produced in such an interval that the second can to be assumed to be independent from the first (needless to say that personal mistakes and bias are not excluded).

2) An isometric point grid with spacings of 3 cm was drawn onto a circular plexiglas plate (cf.Figure 1). The grid was not centred but placed at random onto the plate. This plate could be tossed at random onto the X-

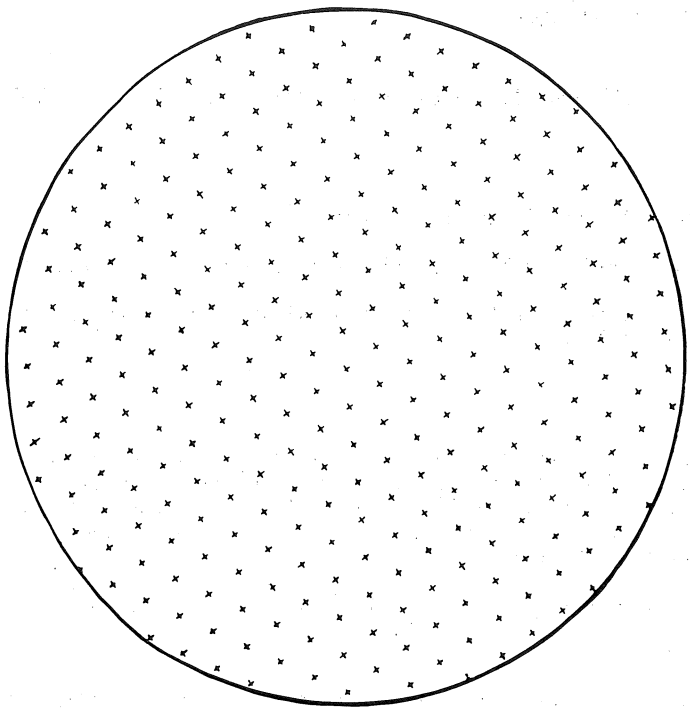

Fig. 1. Isometric point grid. Diameter of the plate 55 cm. The points are arranged at the corners of isometric triangles. Length of the edges of the triangles 3 cm. Area of test point 7.8 cm^2. A 'hit' of a test point is defined as the coincidence of a focus with the intersection of those edges of the crosses that form open angles to right or upward.

ray films, lying horizontally upon and illuminated by a light box. The plate was tossed three times a run and the points within the foci were counted. The design of the grid and its use are not the only possible way, but first of all a compromise between statistical requirements and the demands of the interpretation and evaluation of the X-ray films. The estimations were repeated after weeks or some days at least. Altogether, 2 x 3 counts were carried out by us (O.L.) on each X-ray film.

RESULTS

Patient 1: Lung metastases of a cervical carcinoma of the uterus. In Figures 2 and 3 the X-ray films from the beginning of therapy and the end of the third course are reproduced. Generally, there is a remarkable reduction of tumour metastases. The malignant process as it was evaluated with the digitizer table and with the point grid is shown in Figures 4 and 5. All diagrams show a trend of the areas of projection of the lung metastases. However, there are some differences between the means as measured with the digitizer table and the means estimated with the point grid especially within the first therapy course. Point counts on the tracings

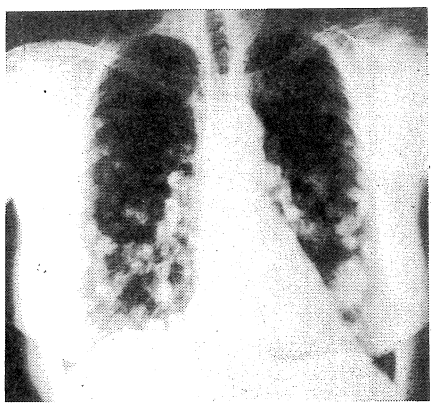

Fig. 2. Lung metastases before the beginning of therapy, June 20th 1984
The areas of projection for the right and the left lung as measured with the MOP were
280.6 + 2.2 cm^2
213.3 $\pm$ 3.2 cm^2

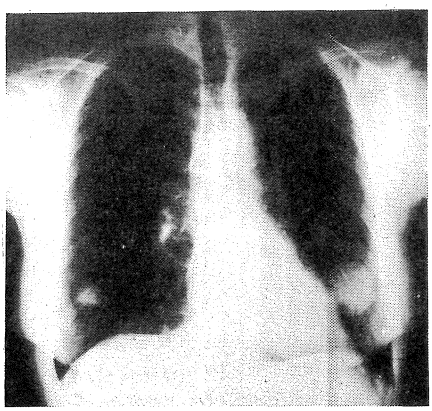

Fig. 3. Lung metastases at the end of the 3rd course, March 7th 1985
Areas of projection of the right and the left lung as obtained with the MOP
270.8 + 0.1 cm^2
200.4 $\pm$ 1.7 cm^2

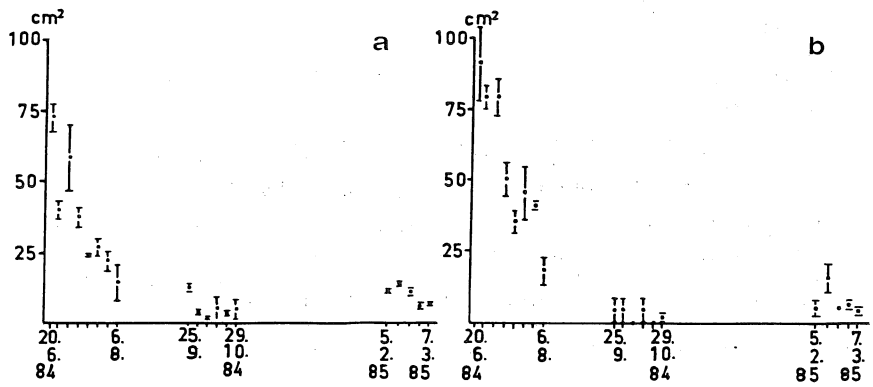

Fig. 4. Right lung. Area of projection of lung metastases as evaluated with the digitizer table (a) and the point grid (b) during three courses of therapy.
Differences between the results of the two methods are observed at high density of metastases during the first course.

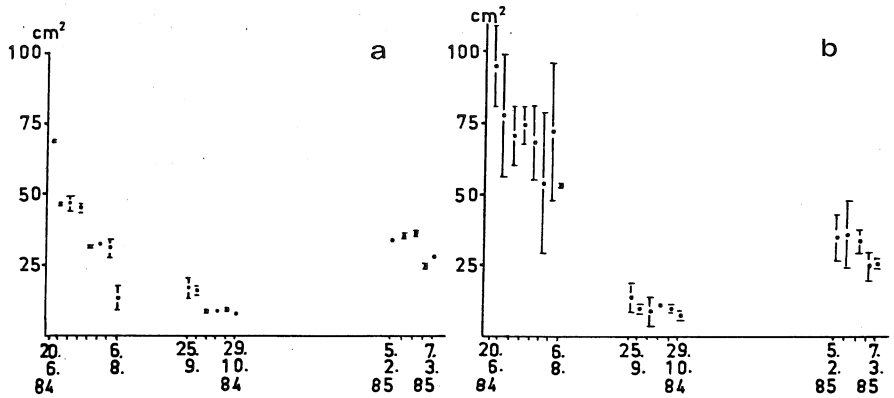

Fig. 5. Left lung. Area of projection of lung metastases as measured with the digitizer table (a) or estimated with the point grid (b) during the three courses of therapy.
Values obtained with the point grid are above those measured with the MOP during the first course.

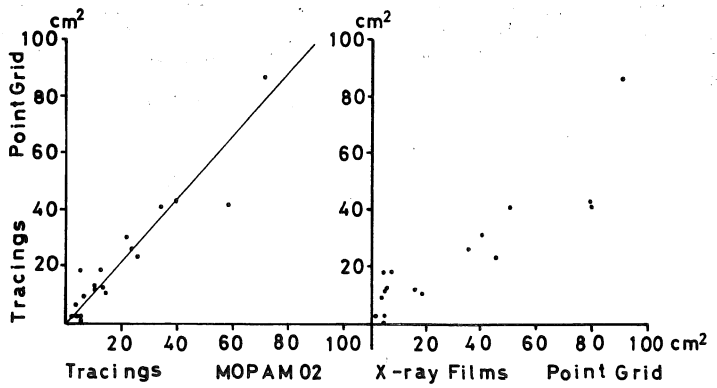

Fig. 6. Scatter diagram between the evaluations of the area of projection of the metastases of the right lung with the MOP and with the point grid on tracings and between the areas on the X-ray films and the latter,if the point grid is used only.
Regression line of the scatter diagram on the left:y=0.63 + 1.07 x (y counts on tracings, x measurements with the MOP).

practically show the same result as the use of the digitizer table. Moreover,a scatter diagram of the values of point counts on tracings vs. MOP measurements on tracings shows the points lying around a regression line with slope 1.1, whereas the point count on X-ray films as compared with the count on tracings seems to overestimate the area of projection of the metastases at the higher values (cf. Figure 6 right). Probably the interpretation of the X-ray films introduced some mistakes into both procedures. Such an inequacy of interpretation was detected,when it has been noticed that the difference between the counts of the number of foci was considerble within the first course (cf. Figure 7).

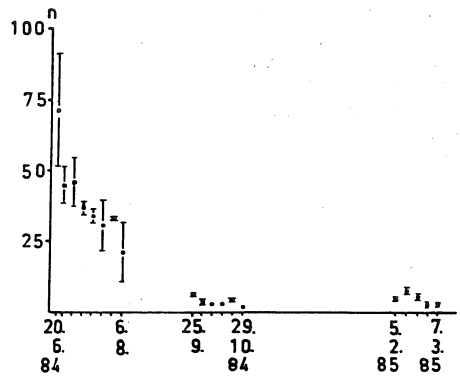

Fig. 7. Number of lung metastases of the right lung. Means with standard error of both the tracings.

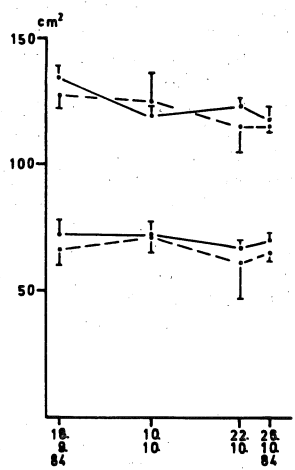

Fig. 8. Area of projection of lung metastases of an uterine leiomyosarcoma —— point grid, ---- MOP. Right lung above, left lung beneath. n=3.

Patient 2: Lung metastases of an uterine leiomyosarcoma. State after surgical and radiation therapy. Again the metastatic disease was followed up with the digitizer table and with the point grid (cf. Figure 8). Both the methods gave the same result. The disease did not respond to the treatment.

Patient 3 suffered from a malign pleural mesothelioma. Typical foci were observed within the right chest cavity one year after a malignant effusion. The patient was treated with palliative pleurectomy and chemotherapy and suffered from effusion again one month after the end of the chemotherapy. The xenogeneic peptide and a bacterial extract were injected besides mitomycin C (altogether 10 mg) into the right intrapleural space till no effusion could be gained. A second course of therapy with the peptide and

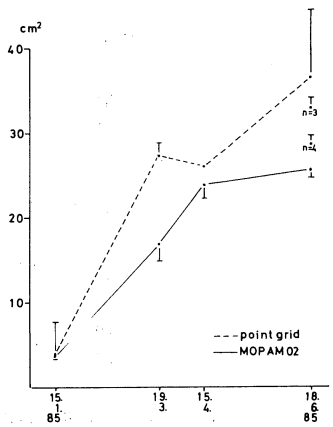

Fig. 9. Area of projection of a malign pleural mesothelioma of the right chest cavity. The two additional means (June,18th 1985) are calculated after two further repetitions of the counts.

key hole limpet hemocyanine has been started when progression of the foci was observed this year. It would be essential to know, if there is some response to this experimental therapy. Figure 9 shows the process as estimated with both the methods and hints at the difficulties with the interpretation of X-ray films. After the beginning of the second course in the middle of april 1985 the measurements with the digitizer table seem to indicate no progression,whilst an outlyer of the point count reveals the contrary. However,the standard error of the point count is so extremely high that it warns against this estimation. Certainly, the outlyer should not be removed,but it should be allowed to repeat the point count until the standard error is reduced to values comparable to the others. One condition is to fulfil in order to receive a reliable estimate. The counts should be repeated without an influence from previous knowledge and this is difficult to achieve.At the moment a decision is impossible and further development of the disease must be waited for.

DISCUSSION

The three examples of a stereological evaluation of tumour disease are presented with descriptive statistics only. Undoubtedly,some subjectivity is inherent to both the methods and in the long run totally automated procedures may be preferable. At present the semiautomatic device and the point grid may be a support to a more critical interpretation of X-ray films. The point grid allows to estimate the area of malignant foci within a reasonable time,so that it may have some chance for application in hospitals.

REFERENCES

Wander H-E,Nagel GA . Mammakarzinome.
München,Bern,Wien: W.Zuckschwerdt Verlag, 1984, 105.