Infra-red thermography and breast cancer doubling time

by V.D. FOURNIER, F. KUBLI, J. KLAPP, E. WEBER, F. SCHNEIDER-AFFELD

Obstetrics and Gynaecological Clinic, Heidelberg (West Germany)

SUMMARY. **In 100 cancers 2 to 11 serial mammographies were performed before final diagnoses. The average number per tumour was 2,8 with a range of 2 - 11, the retrospective observation time was 2 month to 11 years, the observed doubling times ranged between 44 and 1.369 days, the geometric mean of the doubling time is 202 days with 95% - confidence limits of 179 and 227 days. The distribution of frequency of tumour diameters, volume doubling times and age of patient were log-normal. The theoretically calculated time span of growth from a first tumour cell to a 10 mm tumour (30 doubling times) takes about 16 years, from a tumour size of 2 mm to 10 mm it would take about 4 years on the average (7 doubling times). No significant correlations between doubling times, metastasizing rate and histological differentiation could be found. The shorter doubling time occurred, more often thermographic pathological signs where evident. Rapidly growing tumours with doubling times of less than 150 days were thermographically suspicious in 70%, but moderate and slowly growing tumours (doubling times of more than 150 days) in 41% only.**

Key words: thermography, mammography, tumour volume doubling time, breast cancer.

On the assumption that malignant growth is starting within one single cell or small cell cluster the number of volume doubling necessary for one given size of a tumor can be calculated (Schwartz, 1961). With known volume doubling time growth rates and - assuming constant volume doubling ,times - life spans of tumors are projectable. Information on growth rates of malignant tumour is important in many respects, especially however in view of the problems related to mass-screening for early cancer detection.

In regard to mammary carcinoma according to Spratt jr. (1977) the most important factor for prognosis and success of therapy is probably the individual growth of each tumour. Gros (1976, 1977) and Amalric (1977) showed that there are some connections between thermographic alterations and prognosis for mammary carcinoma: the more significant the alterations in thermography the less the 5-years-surviving chance.

In this paper information on the growth rate of carcinoma of the breast is given on the basis of 276 mammographies in 100 mammary carcinomas with observation times of 0,2 - 11 years. In 32 of these cases the thermographic observation are compared with the speed of growth and the metastasizing rate.

PATIENTS AND MATERIAL

In 21000 women 70% of which were asymptomatic, 582 cancers were found. In 100 cancers, 4 of which were secondary tumours in the same breast, several mammographies were performed before final treatment.

In 53 of these cases therapy was carried through in our Institute, whereas about half of the preceeding mammographies had been made at other institutes. The other 47 were X-rayed at 16 various institutes and therapeutic centers.

The average number of mammographies per tumour was 2.S with a range of 2-l 1. The average observation time was 46 months with a range of 2 months to 11 years (Table I, Table II). Serial mammographies were done in this population due to delay of the final diagnosis to refusal of treatment and to other reasons.

METHODS

Measurement of tumour diameter

Each mammography with tumour specific density (tumour nucleus shadow) was identi-

Tab. I. **Patients and material.**

Patients screened, total	21000
Breast cancers with serial mammographies	100
Number of contributing Hospitals/Institutions	17
Number of serial mammographies, total	276
Range of series per case	2-l 1
Average number of series	3
Range of observation times	0,2-l 1 years
Margin of error in doubling times (in cases with tumour diameter of 20-30 mm)	11,3%

fied and its diameter was measured in three planes perpendicular to each other.

Calculation of tumour volume doubling times

The doubling time, i.e. the time needed by the tumour to double in volume (Tv) was calculated on the basis of the the tumour diameters » and the time intervall between two measurements according to Schwartz (1961) using this equation:

$$T_v = \frac{t_2 - t_1}{\log_2 V_2 - \log_2 V_1}$$

t = time (days) v = volume (mm^3)

The inaccuracy in measurement increased the smaller the tumour becomes: when the inaccuracy in measurement is + 0,75 mm, the margin of error was 11,3% in tumours of between 20 and 30 mm (Wolff, 1967).

Construction of growth curves by geometric approximation

Individual growth curves were plotted for all tumours, using the individual observations.

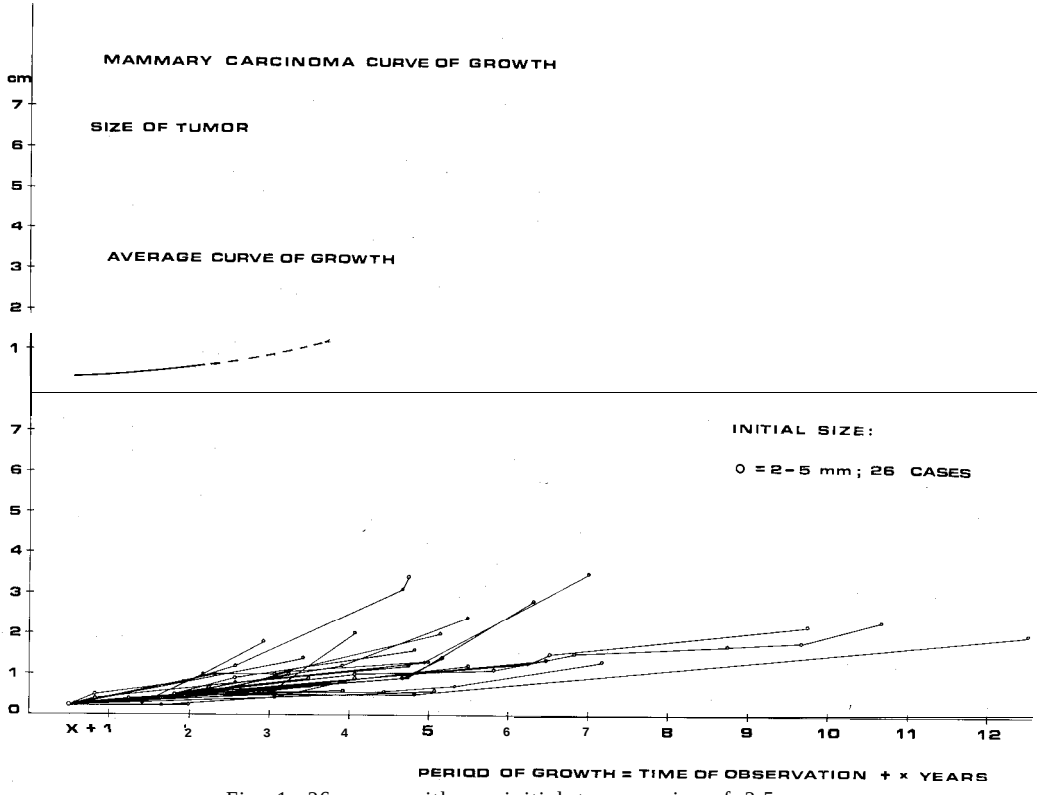

Fig. 1. 26 cases with an initial tumour size of 2-5 mm.

The main problem consists in the fact that the position of the individual initial tumour diameters is not defined on the overall time axis (x-axis).

For the construction of an average growth curve by geometrical approximation all individual curves with initial tumour diameter of 2 mm (9 cases) started at the O-point of the time axis. An average growth curve was empirically established and the next group with initial diameters of 3-5 mm (17 cases) were started on the average growth curve of the smaller tumours (Fig. 1). The same method was used to plot initial tumour diameters of the other cases between 6-30 mm (27 cases) on the average growth curve of the forgoing smaller tumours. The final composite overall growth curves is based here on 163 single tumour measurements in 53 cases and ranges between an initial size of 2 mm and a final size of 60 mm (Fig. 2).

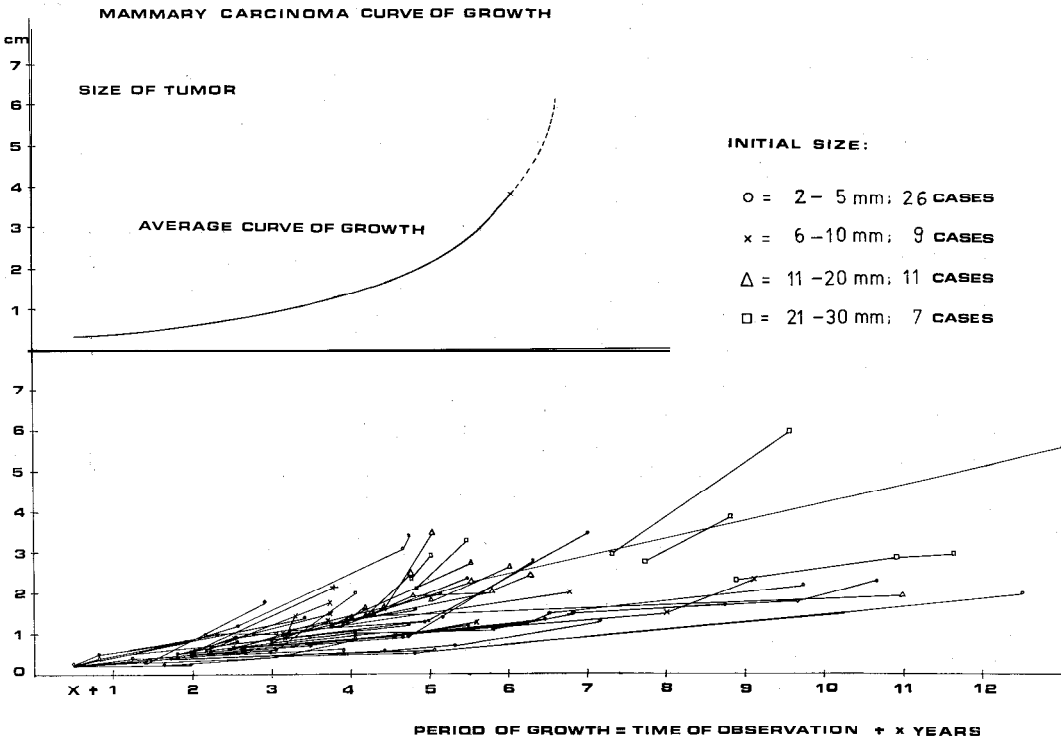

Fig. 2. 53 cases, individual and average curves of growth, geometrical approximation.

Biometrical evaluation of data

The model of the Gompertz-function frequently used is not applicable for the growth phase of the mammary carcinomas observed here. The knowledge of tumour diameter gained through mammography originates only from one part of the very short time period M shown in Fig. 6 of the whole assumed tumour life. However, this extremely small region gives too little information for estimating the parameters of the Gompertz-function.

The growth in the time period M (Fig. 6) may be fitted by an exponential growth model (logarithmic transformation)

$$\log Y = \log A + x \log B$$

The volume doubling time Tv with the upper and lower confidence limits is being estimated with the linear regression

$$Y_1 = a + b\,x_i + e_i \qquad (i = 1,2, \ldots, n)$$

Symbols:

n = number of measurements, i.e. mammographies per patient
Y_i = log, of the volume V_i in mm^3
x_i = time in days
b = regression coefficient
a = additive constant
e_i = error terms, i.e. the deviation of observation Y_i of the estimated values $y_i = a + b X_i$, $e = y_i - y_i$
s_b = standard deviation of b
significance level, in this study we used = 0,05

The parameters a and b are estimated by the least square method so that the sume of squares of the residuals

$$\sum_{1=i}^{n} \cdot e_1^2$$

is minimized.

For the estimation of b and s_b the equation is:

$$b = \frac{S_{xy}}{Sx} \text{ and } S_b = \sqrt{\frac{S_y}{Sx} \cdot \frac{1 - r^2}{n - 2}}$$

Thermographic examination

Thermographic examination with Bofors-Camera MARK 2 was performed as follows:

After cooling for 10 minutes the patient is sitting with raised arms. One frontal and two left and right oblique views are taken in order to have the lateral skin well drawn.

6 parameters or pathological signs are considered which are:

1. « Hot spot » of more than 0,8 °C
2. << Whole breast hyperthermia >) of more than 0,8 °C
3. Correspondence in projection of clinics-, roentgenography and thermography
4. Asymmetrical hypervascularization
5. Difference in thermographic types A, B, C, D, E from right to left
6. Edge sign positive

4 outstanding pathological signs were considered as ((malignancy sign P according to Amalric et al. (1976):

1. <(Hot spot >> of more than 1,5 “C
2. Total breast hyperthermia of more than 1,5 °C
3. « Anarchic hypervascularization »
4. « Extended positive edge sign »

RESULTS

Individual volume doubling times

Doubling times between 44 and 1869 days (Table II) were observed, in 9 cases - not registered in the table - even a standstill of growth was observed for some time.

Variability of doubling times within individual tumours

The variability of observed doubling times within one and the same tumour is striking. Thus one case (No. 33) showed a doubling time of 63 days, just before a T, of 384 days and later on one of 174 days.

In semilogarithmic presentation of the geometrically constructed average growth curve (of 53 cases) this curve shows a deflection to the time-axis (Fig. 3). This means, that with increasing size and age of the tumour there is an increase of volume doubling time also. But a certain selection of slower tumours with increasing observation times cannot be excluded. This deceleration of growth with increasing size and age of the tumour as shown in the semilogarithmical presentation, could follow a special exponential function known as power-function (Archambeau, 1971).

Following the geometrically constructed average growth curve (Figs. 2 and 3) it would take on the average 6 years of growth from a tumour of 2 mm in size to 10 mm in size (7 doubling times).

Rapid, slow and moderate growth

It seems reasonable to distinguish subjectively in speed of growth (Table III). Very rapid growing tumours with T_v, of less than 100 days we saw in 13%, fast growing tumours with T,. of less than 150 days in 30%, moderate growing tumours (T, = 151-300 days) in 46%, and slow growing tumours (T_v>300 days) in 24%.

Growth rate and histological diagnosis

In the 100 cases no correlations of histological diagnosis to speed of growth could be found.

Biometrical evaluations of data:

Fig. 4 indicates the frequency distribution of measurements in Table II. The distribution

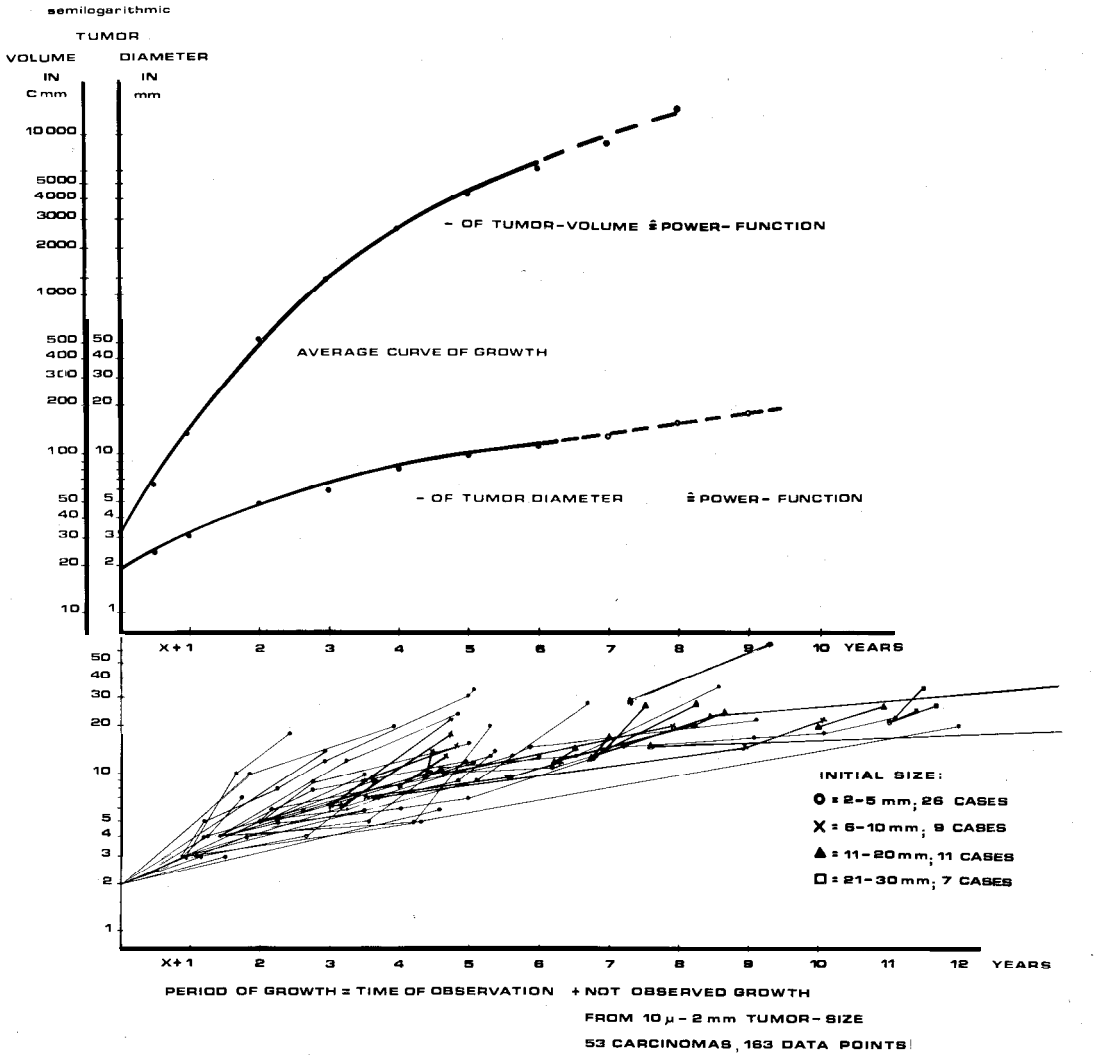

Fig. 3. Mammary carcinoma curve of growth.

of the tumour diameter (Fig. 4 A) the tumour volume (Fig. 4 B) and the volume doubling time (Fig. 4 D) show a positive skewness, their logarithms do not differ significantly from normal distribution.

The distribution of ages (Fig. 4 C) do not differ significantly from normal distribution (skewness and excess were examined).

95% of the observed volume doubling times lies between 65 and 627 days. Beyond these limits lie the 4 cases No. 8 and No. 55 with 62 und 44 days as well as No. 40 and 95 with 693 and 675 days. The cases No. 41 and 46 with extreme slow growing tumours (T_v = 1869 and 1092 days) were not considered.

Since the volume doubling time has a log-normal distribution the geometrical mean was calculated, because taking the arithmetical mean, the relatively small number of cases with slowly growing tumours would contribute too much. After retransformation the geometric mean is 202 days. Its 95% confidence limits are 179 and 227 days.

Tab. II. Basic data of 100 mammary-carcinomas at diagnosis: age at diagnosis, turnour size volume doubling time Tv: (geometric mean), stage (TNM), histological findings in axillary limph nodes.

case No	age in years at diagnosis	diameter mm	volume cm³	doubling time, Tv: days (geometr. mean)	stage (TNM)	axill. lymphnodes Met
1	53	34	20.508	169	2	—
2	54	20	4.147	200	1	
3	56	13	1.048	284	1	+
4	52	34	21.020	66	2	+
5	65	18	2.875	90	1	
6	44	25	8.454	87	2	+
7	48	32	17.538	104	2	+
8	58	29	12.299	62	2	?
9	61	14	1.539	106	1	?
10	58	18	2.969	88	1	
11	50	24	6.912	166	2	?
12	46	7	.205	119	1	+
13	77	13	1.123	297	1	—
14	65	12	.980	265	1	
15	47	14	1.290	129	1	
16	47	16	2.279	217	1	+
17	68	22	5.253	114	2	—
18	43	13	1.239	107	1	+
19	68	18	3.204	120	1	
20	50	15	1.869	180	1	—
21	66	28	11.817	164	2	+
22	64	15	1.696	172	1	
23	48	10	.565	180	1	?
24	52	10	.467	185	1	
25	42	19	3.854	249	1	—
26	79	6	.110	359	1	
27	54	12	.980	293	1	?
28	55	15	1.736	270	1	—
29	54	28	11.817	237	2	+
30	60	20	4.147	564	1	—
31	48	3	.019	252	1	+
32	61	9	.377	188	1	+
33	46	6	.110	426	1	—
34	69	23	6.624	521	2	+
35	69	35	22.981	262	2	+
36	67	13	1.123	377	1	+
37	60	22	5.529	504	2	+
38	33	12	.968	463	1	+
39	70	20	4.398	411	2	
40	51	51	70.284	693	3	-
41	55	20	4.377	1869	2	
42	40	26	9.529	270	2	—
43	66	18	2.875	277	1	+
44	49	26	8.836	277	2	+
45	68	60	114.040	272	3	
46	43	30	13.651	1092	2	+
47	46	13	1.225	383	1	—
48	43	9	.424	305	1	+
49	45	39	31.611	261	2	?
50	46	25	8.063	293	2	
51	63	24	7.540	235	2	+
52	76	22	5.564	357	2	?
53	44	18	3.204	277	1	+
54	65	27	10.249	82	2	+
55	41	31	16.069	44	2	—
56	63	6	.110	102	1	—
57	55	50	66.235	83	3	—
58	46	15	1.838	151	1	—
59	52	13	1.225	150	1	—
60	43	16	2.069	105	1	—
61	64	9	.377	96	1	—
62	51	60	114.040	178	3	+
63	46	12	.980	102	1	—
64	47	20	4.377	126	2	—
65	77	27	9.896	147	2	—
66	45	40	33.929	157	2	—
67	55	17	2.403	144	1	—
68	49	21	5.184	67	2	—
69	45	50	63.827	97	2	+
70	66	15	1.869	83	1	+
71	64	11	.691	108	1	+
72	40	41	36.838	196	2	—
73	70	13	1.239	239	1	—
74	51	26	9.189	197	2	—
75	50	5	.079	209	1	—
76	54	6	.132	322	1	—
77	62	9	.424	87	1	—
78	47	11	.760	153	1	+
79	57	28	11.479	299	2	—
80	61	11	.622	308	1	—
81	51	44	43.354	187	2	—
82	63	12	.980	204	1	—
83	47	11	.760	142	1	—
84	62	12	.898	232	1	+
85	65	8	.302	145	1	—
86	52	10	.576	239	1	—
87	72	19	3.760	190	1	—
88	56	12	.824	254	1	—
89	63	19	3.552	350	1	+
90	43	11	.691	522	1	—
91	47	17	2.413	284	1	—
92	48	8	.264	345	1	—
93	58	22	5.529	236	2	+
94	70	28	11.905	409	2	—
95	22	50	64.507	675	2	—
96	44	10	.576	561	1	—
97	71	23	6.359	297	2	—
98	68	6	.110	326	1	—
99	67	15	1.847	358	1	—
100	43	16	2.111	251	1	—

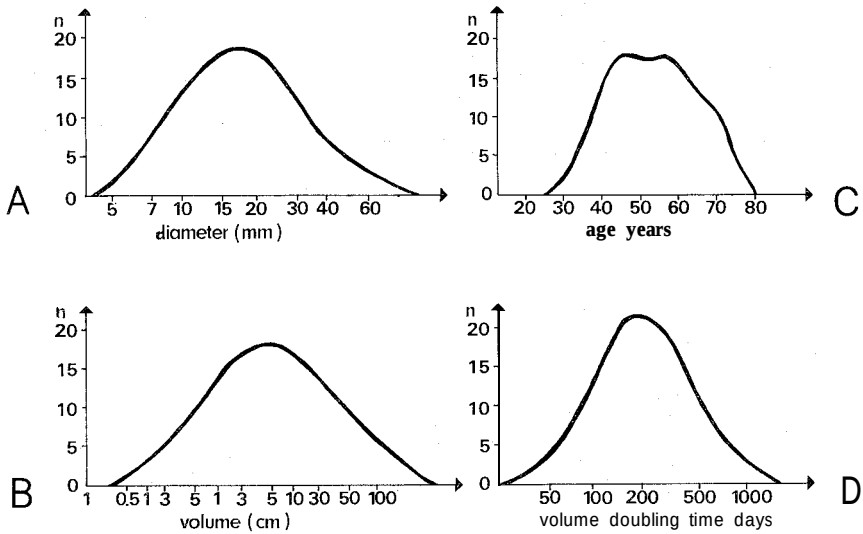

Fig. 4. Frequency distribution in: (A) tumour diameter, (B) tumour volume, (C) age of patient, (D) volume doubling time.

Tab. III. **Rapid, moderate and slow growing tumours.**

Speed of growth		*Frequency*	
		No.:	*%*
very rapid:	TV 5 100 days	13	13%
rapid:	TV 5 150 days	30	30%
moderate:	TV 150-300 days	46	46%
slow:	TV > 300 days	24	24%
		100	100%

Discussion of 12 cases with 5 and more mammographies per case

Fig. 5 contains these 12 cases. All cases show exponential growth in this relatively short phase of growth. The solid straight corresponds to the estimator

$$I', = a + bx_i$$

The deviation parallel to the ordinates of the observed volumen y_i (=points) from the estimated value y_i corresponds with the previous mentioned residuals e_i. The fitness of the observation y_i and the estimation y_i is the previous mentioned r^2, - it is good in all cases, except case No. 13, 25 and 28.

Growth rate and thermographic findings:

In 32 carcinoma cases the more conspicious then were shown by thermography the shorter their volume doubling time (Table IV). The 8 pathological thermographic signs occured more frequently the faster the growth rate of individual tumours, see Table V.

The left « column » shows rapid growing tumours with a relative frequent occurrence of pathological signs in thermography.

The right « column » shows the slower growing tumours, where thermographic signs were not so frequent.

The fast growing tumours with doubling times of less than 150 days were « suspicious » in 70% (7/10), « in need of control » in 10% (1/10) and G unsuspicious >> in 20% (2/10), (Table IV).

The medium-fast and slow growing tumours together were << suspicious >> in only 41% (9/22), « need of control » in 27% (6/22) and « unsuspicious » in 32% (7/22).

These differences, however, were not significant statistically.

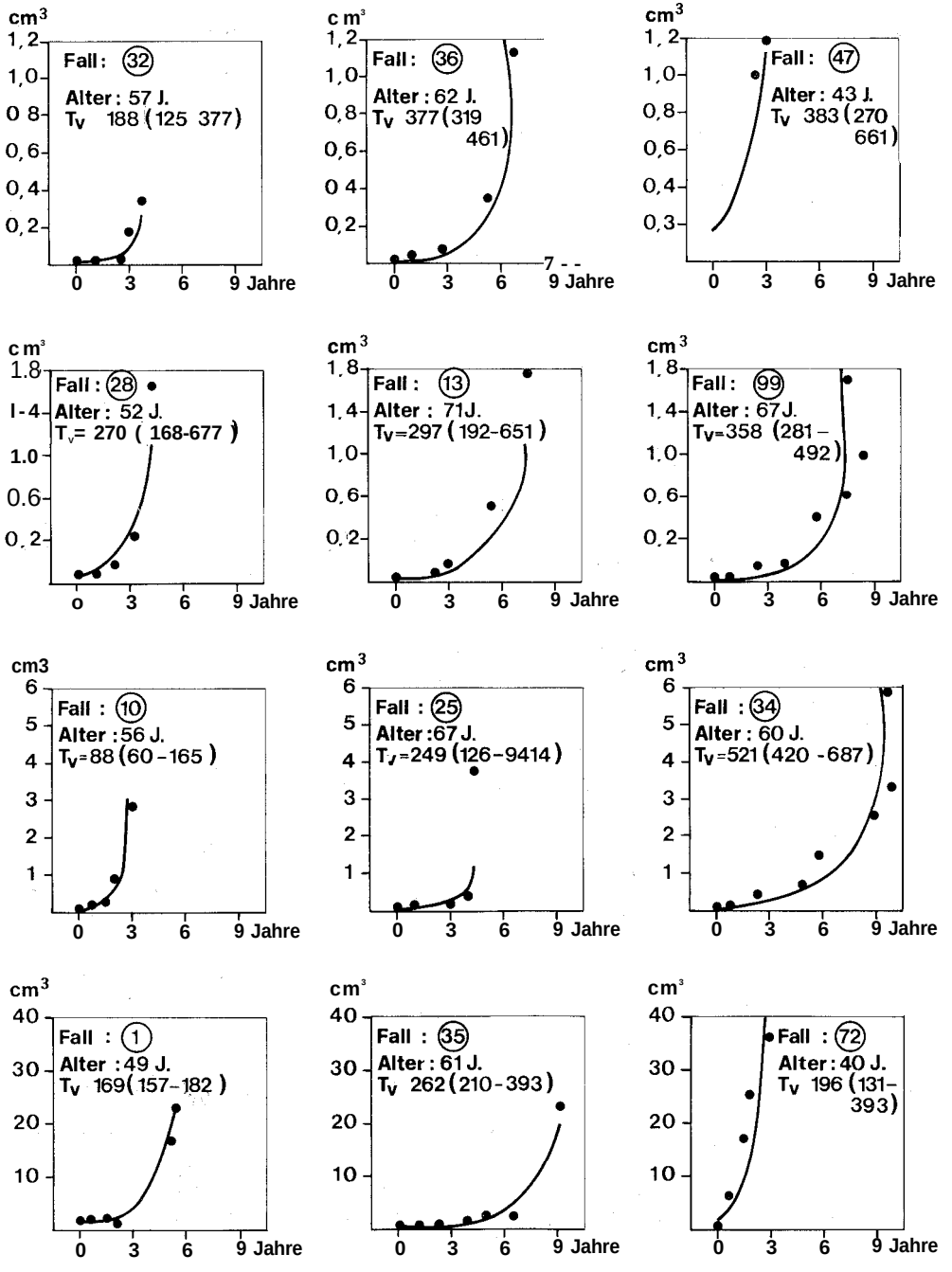

Fig. 5. Growth curves in 12 cases with 5 and more mammographies per case.

Tab. IV. **Thermographic diagnosis depending on growth rate; 32 cases of mammary carcinomas.**

Growth rate *Volume doubling time* *Tv per days*	*Thermographic diagnoses*		
	suspicious	*need of control*	*unsuspicious*
rapid growth: T_v < 150 days N = 10	7 = 70%	1 = 10%	2 = 20%
medium/slow growth: T_v more than > 150 days N = 22	9 = 41%	6 = 27%	7 = 32%

Tab. V. **Pathological and thermographic signs and speed of growth in 32 cases of mammary carcinomas.**

Pathological signs	*N = 10 rapid growth Tv < 150 days*	N = 22 *slow and* moderate *growth Tv > 150 days*
1. « hot spot » dt > 0,8 °C	90%	68%
2. correspondence: clinics-roentgenography - thermography	70%	41%
3. « hot spot » dt > 1,5 °C	70%	50%
4. type C	60%	45%
5. difference in type A-E	60%	45%
6. dt > 0,8 °C total breast hyperthermia	50%	27%
7. hypervascularization	80%	45%
8. edge sign	50%	27%

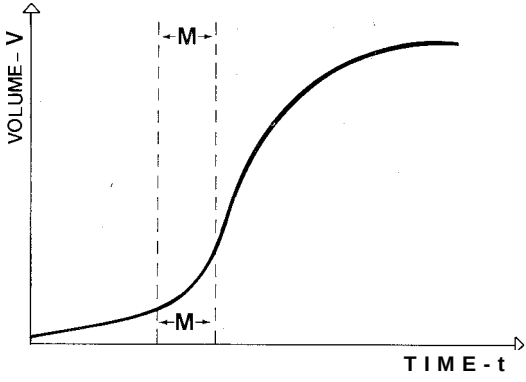

Fig. 6. Gompertz-function, a model for describing tumour growth

$$V = k_0 \times \exp. \left[\frac{k_1}{k_2} \times \left(1 - \exp. \left(- k_2 t \right) \right) \right]$$

k_0 = size at beginning
k_1 = « accelerating factor »
k_2 = « inhibiting factor »
M = time interval in which tumour measurements in mammographies were performed

Growth rate and lymph node metastases

In 32 cases the rate of axillary lymph node metastases was higher on average, the faster the tumor grew. This, however, was not significant statistically due to the small number of cases.

DISCUSSION

The construction of an average growth curve:

Geometrical approximation of all individual curves results in a curve which follows a special exponential function which corresponds to a « power-function ». This means that in semilogarithmic presentation (Fig. 3) the speed of further growth decreases with increasing age and size of tumours. On the other hand the biometrical evaluation of 12 cases with 5 and more mammographies per case demonstrates that all (within the relatively short phase of

growth we observed), show exponential growth. This short phase of observed growth also gives too little information for estimating the parameters of the « Gompertz » - function (a frequently used model for describing tumour growth Fig. 6).

The observed doubling time showed a positive log-normal distribution with a range between 44 and 1869 days. The geometric mean of the volume doubling time is 202 days. Its 95% - confidence limits are 179 and 227 days. The variability of observed doubling times within one tumor may be significant (see case No.: 33), the 12 cases with 4 and more doubling times per case, however, showed exponential growth when observation time was long enough.

Discouting failures in measurement, a certain selection of slower growing tumours during increased observation times cannot be excluded.

These results correspond with observations of Gershon-Cohen (1963) who found doubling times varying between 23 and 209 days in 18 cases.

A log-normal distribution of frequency in the doubling times was described by Kusama (1972) and Spratt (1977). Kusama found that the doubling times observed in patients under 30 years of age were shorter than those observed in patients older than 60 years. We - as well as Philippe and Le Gall (1968) and Kusama (1972) -- could only assume a connection between doubling time and rate of metastasizing into the axillary nodes but not maintained definitely.

In 12 cases with 4 or more individual doubling times the growth curves corresponded with exponential functions.

Where the average curve of growth was gained by geometrical approximation (see Figs. l-3) this corresponded to a power-function as theoretically discussed by Archambeau (1970).

Possibly this average growth curve also corresponds to a Gompertz-function, a fact, that can be established as << mathematically reliable » only when the growth of tumours will be observed in cases where the weight is considerable.

At the present time only speculation can be made with regard to the behaviour of tumour growth or even the cause of its behaviour. It seems that the effective growth of breast cancer is the net result of the predisposing cell dividing rate and also of growth inhibiting factors. The importance of these factors will probably increase the bigger the tumour becomes.

1. There may be an immunological destruction of the cells on the tumour surface.
2. It can be suggested that the bigger a tumor becomes, the more the cells are destroyed by increasing hypoxia.

Few observations are to be found in literature with regard to growth rate of mammary cancer and thermographic parameters. We showed that shorter doubling times took place more often when thermographic pathological signs were observed. Rapidly growing tumours were more often thermographically suspicious (70%) than average or even slowly growing tumours (41%). Conforming with our observation Amalric and Spitalier (1977) and Gros (1977) proposed that prognosis will be worse as the frequency of thermographic pathological signs increas. We also arrived at this result with very rapidly growing tumours with doubling times of less than 100 days in 13% (13/100) of our observed patients. These results again confirmed the observations of Spitalier (1977) who - on the basis of clinical and thermographical parameters - gave a very bad prognosis in 11% of cases.

The growth speed of metastases in mammary cancer is on average more rapid than that of the primary tumour (Kusama, 1972, Philippe and Le Gall, 1968, Lee, 1972, Spratt, 1977), especially when the epithelial surface is interrupted (Cutler, 1970).

As proof for the growth speed we examined the new thoracic wall metastases in cases with positive axillary lymph nodes (bad prognosis!), i.e. in cases where no irradiation of the thoratic wall had been performed, with the following results (N = 510): After 1 year: 4,7%, after 3 years: 8,5%, after 5 years: 14,7% thoracic wall metastases.

Practical problems should include:

1. The rate of very fast growing breast cancers with doubling times of less than 100 days (13%), the geometric mean of all observed doubling times being 202 days.
2. When (theoretically), more than 16 years

pass before a first tumour cell of 10, grows to a 10 mm tumour (30 doubling times). The time span then between a tumour size of 2 mm and a size of 10 mm is about 4 years on the average (7 doubling times).

Therefore the time interval between two mammographies in screening should be 1,5 years, when the x-ray is easily interpreted.

3. Therapeutic results should only be judged after 10 years when primary spread tumour cells even in a slowly growing tumour have had enough time to grow to a detectable size.
4. The more pathological signs shown by thermography the faster the speed of the growth will be.

Thus pathological findings in thermography are related to prognosis and therapeutical judgements.