

**IS THE CURRENT TREATMENT OF CANCER SELF-LIMITING IN THE EXTENT OF ITS SUCCESS?**

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**Summary**

It can no longer be doubted that under certain conditions diagnostic or surgical procedures can result in metastases. Analysis of metastatic growth rates has shown that from 30% (in hypernephroma) to 90% (in sarcoma and seminoma) of the diagnosed metastases were provoked by such procedures. This has been established by numerous animal experiments and clinical observations and necessitates a change in the currently held concept of cancer therapy. The previously applied and proven treatments by surgery and radiation must be preceded by metastasis prophylaxis. Three different ways to achieve such a prophylaxis are proposed.

**Introduction**

It is clear that there have been remarkable successes in cancer therapy in the recent years: remission and survival times were substantially prolonged in many cancer patients, and much relief was achieved by means of improved surgical techniques, modern high voltage irradiation methods, and cytostatic treatment programs. However, the balance looks different when the quota of actual cures is considered. Before we proceed with details the following remarks must be made:

- Statements made in this paper about cancer diseases concern solid tumors such as carcinomas, seminomas and melanomas, but not systemic diseases nor the malignant diseases of the blood and lymph system.
- The concept "cure" is rather difficult to define, particularly in the case of cancer. In this paper "cure" shall be understood as survival for at least 10 years. This definition neglects the occurrence of late metastases, a rare event seen in at most two percent of the cases (1-5).
- The quota of cures has slightly increased in recent years. This increase is not due to the improved or more elaborate treatment methods but to the fact that as a consequence of wider public education and better diagnostic methods, more patients than previously are now being treated at an early and responsive stage of their disease.
- Comparative evaluations of success rates after different treatment methods have certainly given some substantially different results; however, the reported towering success rates shrink when they are analyzed according to the probability screening method after Boag (6). Inflated success rates are the result of either selective composition of the groups of patients studied or of correspondingly adapted, i.e., corrected, statistics.

**Cytostatic Therapy?**

The omission of cytostatic therapy in this paper must not be misunderstood as showing a lack of appreciation. With regard to the tumors discussed here the cytostatic therapy may give relief and prolong remission in advanced cases, and thus, it may achieve palliative success. However, this report is concerned with clinical cancer cases at an early stage for which a cure in the above-mentioned sense can still be expected.

After these introductory remarks, four observations are presented which make the current concept of cancer therapy questionable:

**Do Current Approaches Program Failure?**

1. A comparison of success rates of curative cancer therapy at the present time with earlier results, e.g., according to Oeser (7), shows that the quota of cures achieved by therapeutic procedures and related to the same stage, respective size of tumor, has not definitely increased in the last 20 to 25 years.
2. The studies of Benninghoff and Tsien (8) on approximately 26,000 patients with mammary carcinoma, treated in 15 different clinics according to different treatment procedures, show that neither the kind nor extent of the treatment but only the proportion of early-stage cases in the whole patient group determined the success rate.
3. Gregl (9) found in his extensive studies of patients with mammary carcinoma that elderly women with an untreated mammary carcinoma live longer than women of the same age after palliative or radical therapy. His co-worker, Mueller, concludes from these studies that elderly women with

mammary carcinoma should not be treated at all (10).

4. The following observation is widely known and has been repeatedly described (11-13) but not further analyzed: in very many patients whose tumor had been removed by surgery and radiation and who are, therefore, believed to be free of cancer, metastases occur frequently at a certain time after the operation. It is remarkable that the time interval from operation to diagnosed metastasis is shorter in the fast-growing tumors (seminoma, sarcoma, melanoma) than in the slow-growing tumors (hypernephroma, bronchial or mammary carcinoma) (Figure 1). This observation suggests that in these instances the metastases of the slow-growing and of the fast-growing tumors begin their development at the same time.

These four observations make it necessary to rethink the current therapeutic concept of the treatment of cancer. Obviously, the current treatment program with the fully developed techniques of surgery and radiation has achieved what it can achieve. Are now the limits of therapeutic success inherent in the disease or are they set by our therapeutic concept? In other words, is the failure of our therapeutic efforts possibly also programmed by our therapy? This would mean that there is a second Semmelweis phenomenon!

Figure

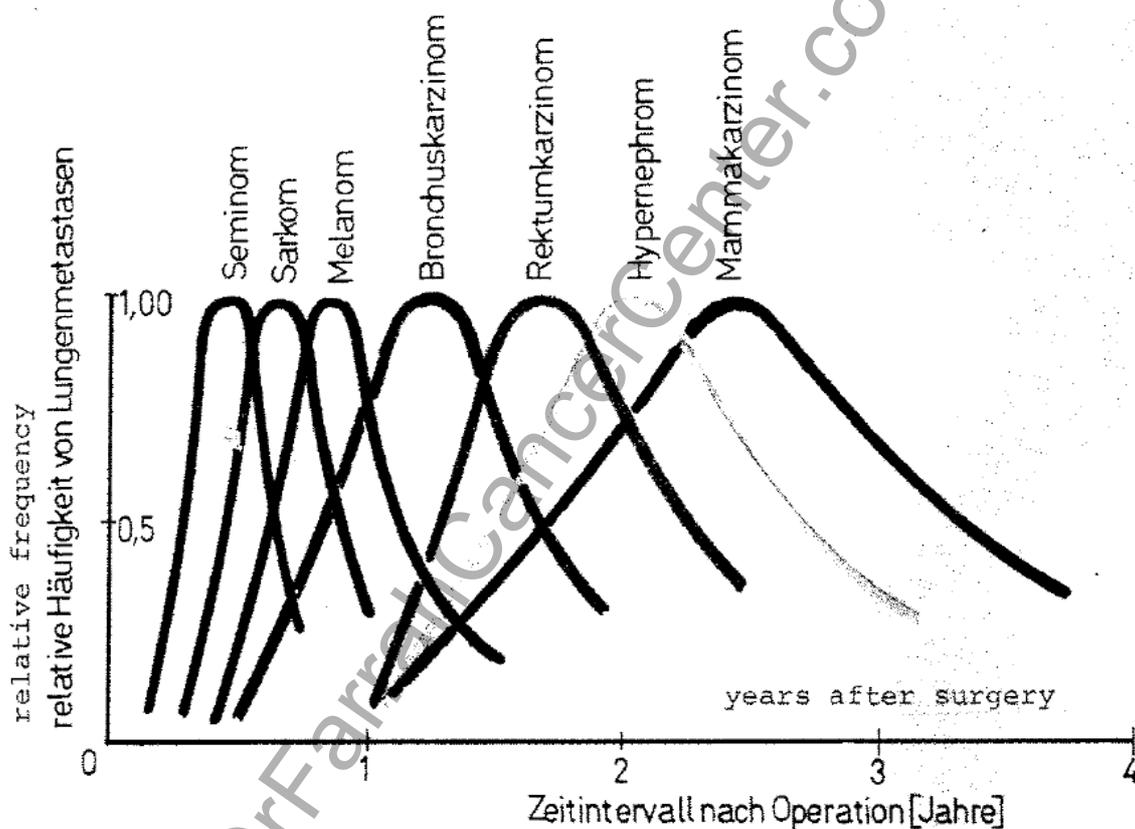


Figure 1: Time interval from surgery to the time when lung metastases are radiologically diagnosed. This basic question has been studied in a series of investigations spanning 16 years. The results of these studies were presented at the 58th German Roentgen Congress at Muenster in 1977 (13-14). It should be noted, first of all, that the clinical course of a cancerous disease is generally not determined by the primary tumor but almost always by the presence, number and localization of metastases. The primary tumor causes death in exceptional cases only, such as, for instance, due to vascular erosion, obstruction or perforation of the esophagus, etc. On the other hand, there is a firm relationship between the frequency of metastasis formation and the survival rate. Exceptions, such as, for instance, the radioiodine-accumulating thyroid carcinoma which remains curable even after metastasis formation, occur in comparatively very small numbers.

### Metastatic Invasiveness

The following discussion will, therefore, focus on the formation of metastases. The growth of metastases, for instance, in the lung, can be determined from a sequence of thorax radiograms (Figure 2). The change in size of the lung metastases during the study also permits determination of the growth rate as shown in Figure 3. This can be done much more easily with metastases than with

primary tumors since lung metastases appear round and sharply delineated in good contrast to the air-containing lung tissue. The metastases grow faster than their primary tumors and are, therefore, less subject to growth-affecting interferences. However, it is more difficult to extrapolate from this growth curve to the preclinical period. To be able to obtain sufficiently reliable data in this respect, the following two conditions must be fulfilled: (1) the growth curve must be studied as long as possible in single cases, and (2) many courses of metastatic growth must be analyzed.

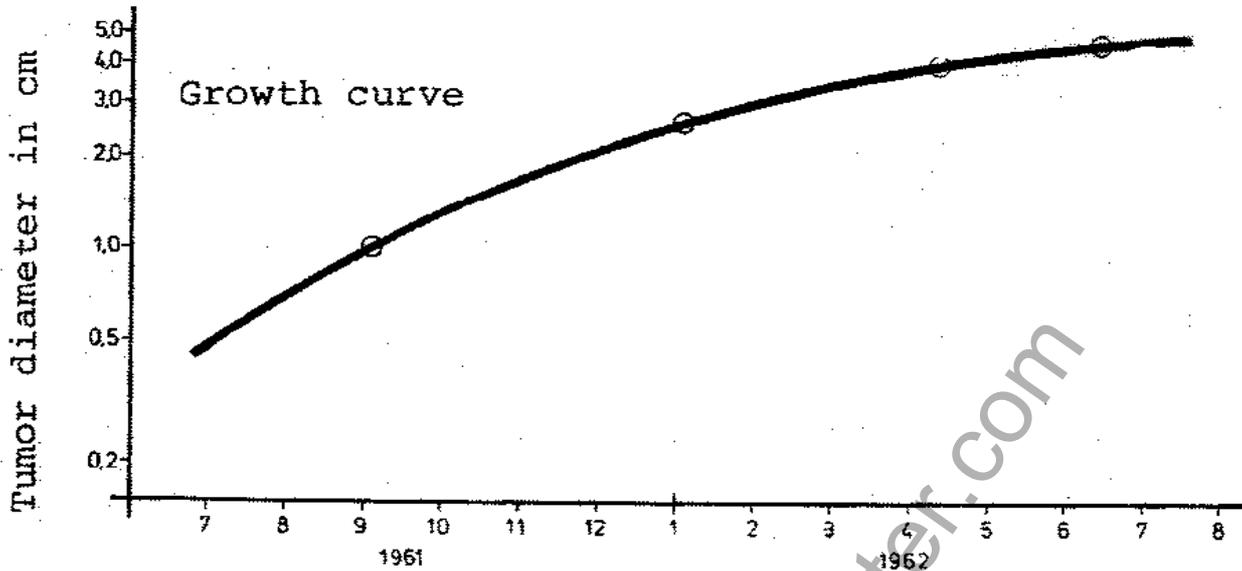


Figure 2: Growth curve of lung metastasis

The present analysis is based on 2,893 courses of metastatic growth in a total of 568 patients with different tumors. It is further supported by controlled growth curves of tumors in animals and from observations made in humans (unintended) through kidney transplantation, or intended (15) transplantations of tumor cells.

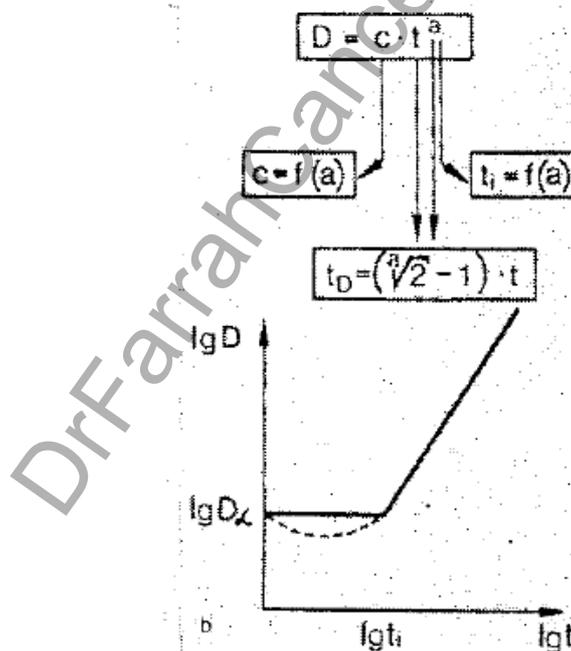


Figure 3: Growth Formula

$D$  = metastasis diameter,  $t$  = time,  $a$  + approx. 2,  $t_D$  + tumor doubling time,  $c$  = proportionality factor,  $t_i$  + implantation time

Two examples among the large number of metastatic growth courses that were analyzed will demonstrate the essential features.

Figure 4 shows the growth courses of six lung metastases after surgery of a bronchial carcinoma and, the growth of four intrapulmonary metastases of a synovioma. In the latter case the metastases were triggered by injection of cortisone into the primary tumor subsequent to an erroneous interpretation of a finding.

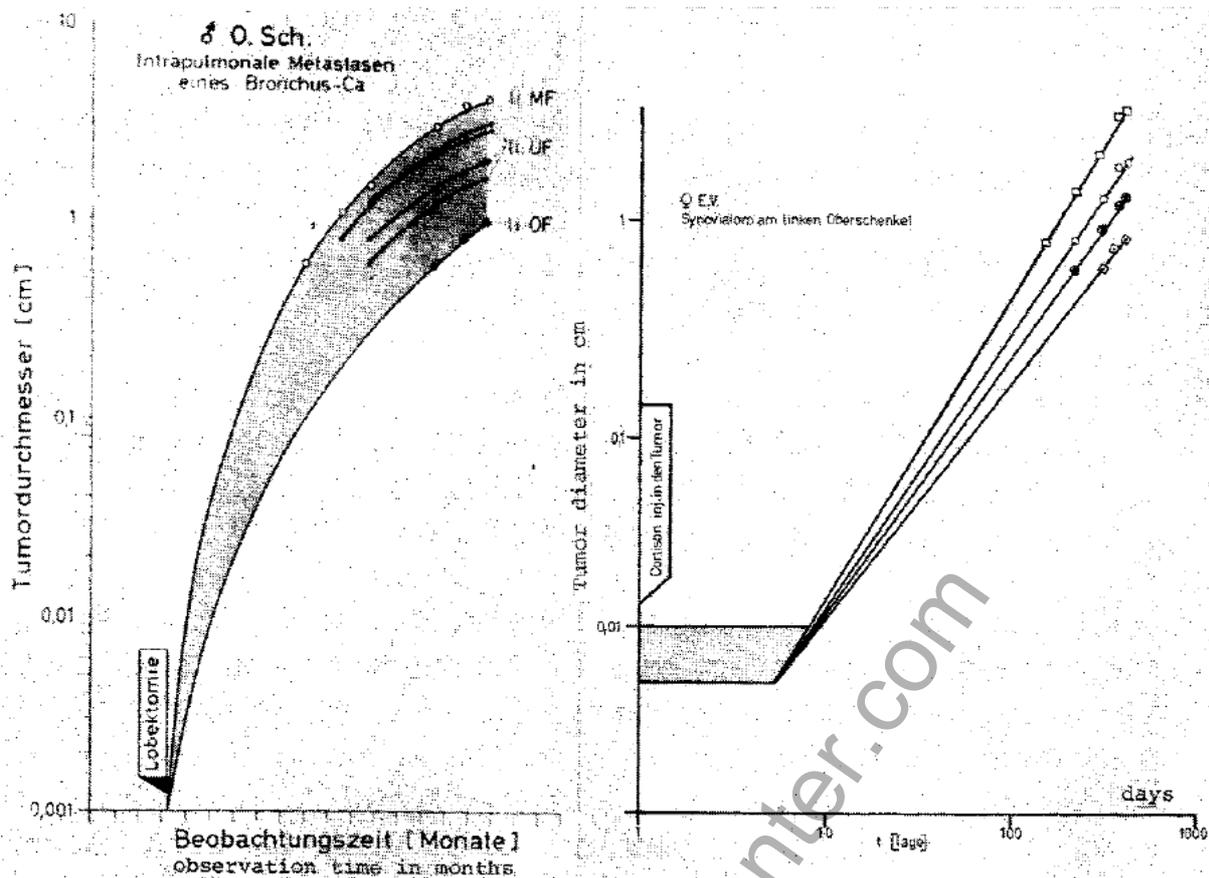


Figure 4: Growth courses of six lung metastases after surgery of a bronchial carcinoma and growth of four intrapulmonary metastases of a synovioma

As a result of the present growth analysis the following points should be noted:

1. Metastases arise only from primary tumors or from their local recurrences; they disseminate at one time or only in a few shoves.
2. Lymph node metastases behave biologically differently from organ metastases.
3. The more than 3,000 growth curves (including experimental data from animals) can be described by a growth formula. The growth curves of a very large number of metastases, from 30 to 90 percent depending on the type of tumor, can be traced back to the time of the first treatment, considering that a certain critical number of tumor cells must be present for a metastasis to be viable and that growth into a metastasis begins only after a certain time interval, the so-called implantation time.

It can be concluded from these points that in many cases our therapy provokes metastasis formation!

### Is There Any Supporting Evidence For This Shocking Statement?

⊕ First of all, it should be noted that this statement has been made earlier by many authors(16-22) without having resulted in any far-reaching consequences for the treatment of cancer. In addition, it has long been taught in medicine that a melanoma should not be injured since lesions would cause an almost explosion-like growth of metastases. Re-examination of the current concept in cancer therapy seems to become more evident only after the urging of this author at the German Roentgen Congress at Muenster.

⊕ The various above-mentioned observations, concerning: 1. No increase of the cure rate for the past 25 years; 2. Independence of the success rate from type of treatment given, and 3. Occurrence of metastases in certain tumor-specific time intervals after surgery can easily be explained from the results of the investigations presented here.

⊕ The connection between surgery and formation of metastases was particularly impressive and evident in single observed cases: in a patient with a sarcoma, formation of metastases occurred after surgery of the primary tumor and each time after four further surgeries of locally recurrent tumors (Figure 5).

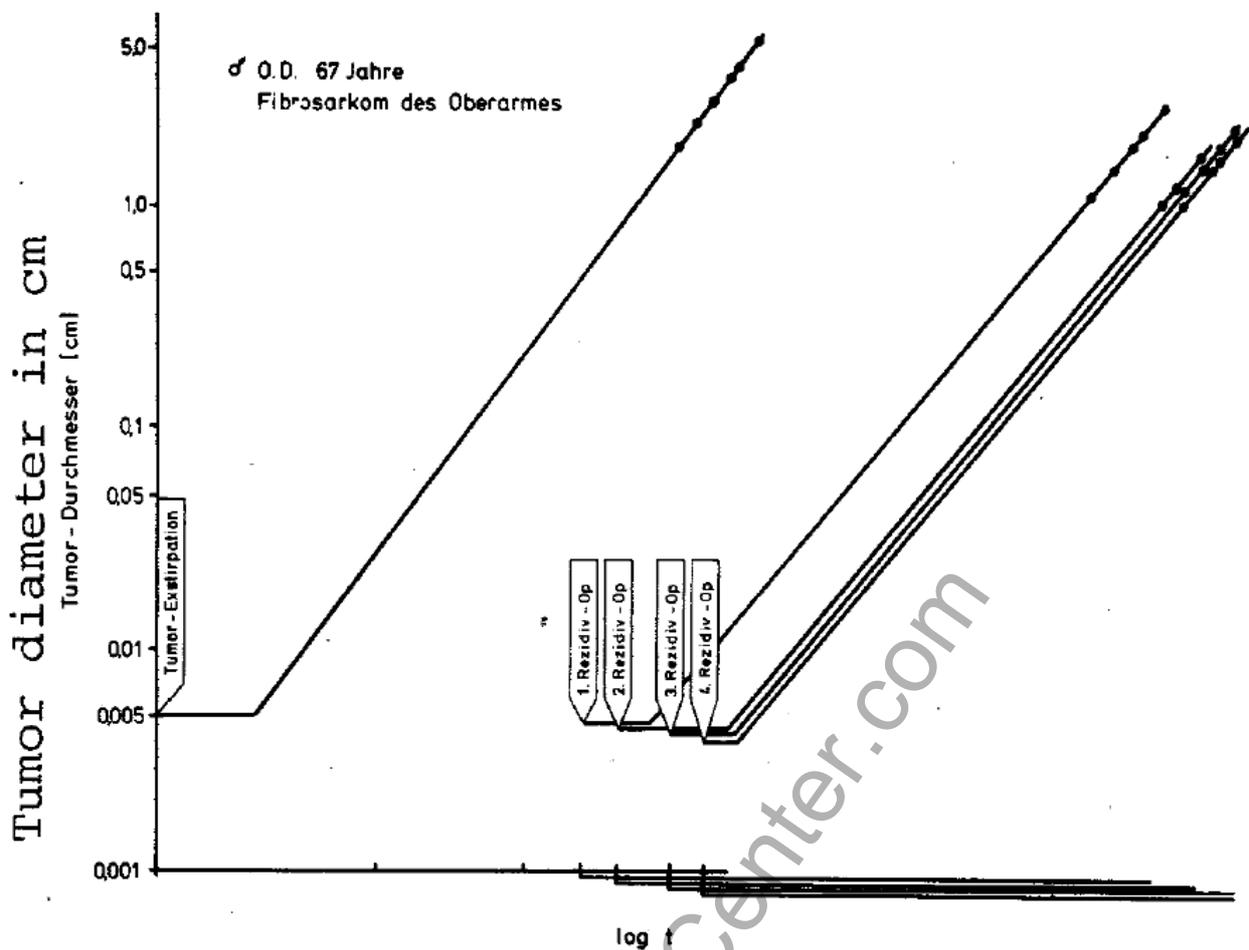


Figure 5: Induction of lung metastases in a patient with a sarcoma after surgery of the primary tumor and each time after four further surgeries of locally recurrent tumors

- ⌚ Direct proof for the metastasis-promoting action of surgery is given by the animal studies of Fisher and Fisher (23) after intraportal injection of tumor cells, disseminated tumors appeared only after surgical inspections.
- ⌚ Observations on tumor growth which have been published by other authors (24-26) can only, or at least better, be explained with the above growth curves.
- ⌚ The points in time at which, according to the growth curves, the metastases become detectable agree very well with the actual observations of the time intervals between surgery and metastasis diagnosis.
- ⌚ The shape of the growth curve agrees with observations made in animals that growth slows down with increasing lifespan of the tumor: that is, the tumor doubling time increases steadily.
- ⌚ The occurrence of late metastases which selectively effects certain types of tumors can now, for the first time, be interpreted formally, qualitatively as well as quantitatively, with the present growth analysis.

The above discussed growth analyses and the supportive evidence no longer permit us to ignore the conclusion that metastases can be provoked by a surgical procedure!

### Discussion

The induction of metastases by a surgical procedure at the primary tumor can be suspected on the basis of previously known and reported observations. It is known that tumor cells circulate in the blood of most tumor patients, though this finding alone is insufficient for the prognosis. It has furthermore been shown that manipulation of the tumor, such as severe palpation, biopsy or surgery, results in a sudden increase of the number of tumor cells released into the blood circulation. It has been established that the probability of metastasis development clearly increases with an increasing number of circulating tumor cells as shown in Figure 6 (27).

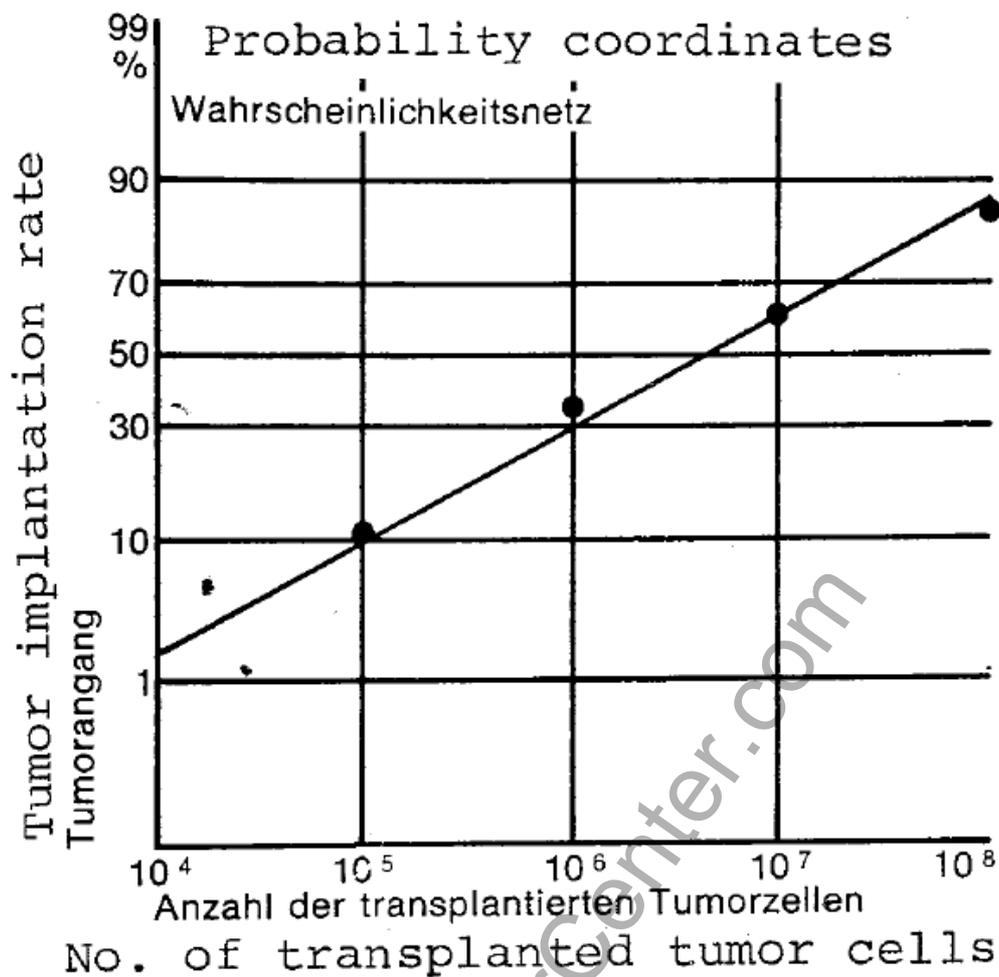


Figure 6: Implantation rate of metastases plotted against the number of transplanted cells

It is understandable from these findings that a medical procedure can induce metastases under certain conditions. In one of the observed cases metastases were also induced by a surgical operation, not at the tumor but far from the tumor site at the gallbladder. It can be concluded from this that it is probably not only the event at the primary tumor per se (excision or puncture) which is necessary and decisive for the induction of metastases, but that a transitory drastic reduction of the body's defense mechanism can also favor the induction of metastases.

Temporary breakdowns of the defense mechanism could be the reason for the so-called spontaneous metastases. Certain indications from our own observations support this interpretation. It follows from this that the development of metastases results not only from the inducing factor, namely the surgical procedure, but from other predisposing and actualizing factors, such as size and transplantability of the primary tumor, and systemic as well as local tissue defense factors.

At this point we may ask if metastases provoked by a surgical procedure, i.e., new metastases at the beginning of their growth, can be made to regress. To achieve this goal, or at least to devitalize or temporarily impair the tumor cells released from the primary tumor, various measures have been previously suggested. Such measures include the recommended radiation of the tumor immediately before surgery (28-33) and circumoperative chemotherapy. However, both of these measures failed to be successful. Retrospectively, we may assume that with both measures the success in the devitalization or destruction of tumor cells was nullified by the simultaneously effective immunosuppressive action.

We must ask again what possibilities are presently known for metastasis prophylaxis preceding a diagnostic or surgical procedure. The following possibilities can be mentioned:

1. Administration of immune stimulants: BeG, levamisole.
2. Administration of aggregation inhibitors.
3. Application of the radiogenic protective effect (34) described in 1966 by this author and Taenzer (35-36). This effect may have an immunological action and applies not only to the second radiation following the whole body radiation after a certain time interval but also to other biologic effects, e.g., the tumor implantation rate (37), see Figure 7.

## Zeitintervall zwischen Vor- und Massivbestrahlung

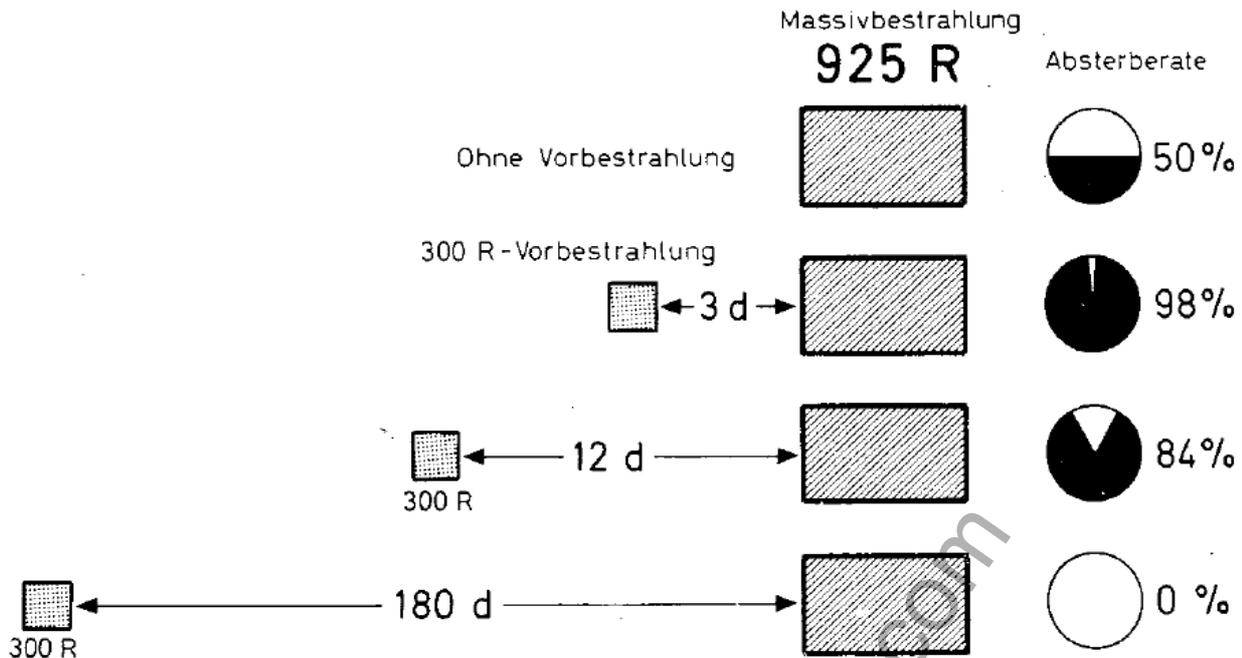


Figure 7: Radiogenic protective effect. 35-36 LD<sub>50</sub> after whole body radiation is 925-R for white Wistar rats. Note the decreasing mortality with increasing time interval from 300-R protective radiation dose to full radiation.

So far, the author has tested and recognized only the effectiveness of the third possibility. Further studies are required but we may be certain that metastasis prophylaxis is necessary before every medical procedure. It remains to be determined which one of the above possibilities will be most effective.

### Conclusion

The essential conclusion to be drawn from this investigation is that the current generally held therapeutic concept of tumor therapy must be changed! This requires a close cooperative collaboration between the different medical disciplines, particularly between surgery and radiology. Metastasis prophylaxis must precede the first operative treatment since implantation of just arrived tumor cells is a labile phase which decides whether or not the invading cells will succeed in expanding their 'bridgehead'. If they succeed then further invasion is irresistible, and the fate of the patient is thus decided. On the other hand, if it is possible to reduce during this labile implantation phase the still very small number of invading tumor cells so that less than the critical quantity remain viable, then the new metastases gradually regress. It is not even necessary that all tumor cells of the newly developing metastases be killed. Animal experiments have clearly shown that this strategy can be successful (38). Thus, if the provoked metastases can be forced to regress during the implantation phase, the success rates of cancer treatment would leap upwards (14)!

Metastases, which have already grown, comprise so many tumor cells that they can no longer be forced to regress. This makes it clear that the chance to decisively improve the cure quota occurs only once during the course of cancer, namely at the time of the first treatment.

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