# Surgical Resection and Adjunctive Immunotherapy for Selected Patients with Multiple Pulmonary Metastases

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LOGIC might suggest that the presence of pulmonary metastases would indicate disseminated malignancy uncontrollable by surgical treatment. However, many patients dying with pulmonary metastases have no other foci of disease detectable upon autopsy.[9,24] Furthermore, the 5-year survival rates in patients undergoing surgical resection of metastatic pulmonary lesions are often better than results obtained following surgical treatment of primary bronchogenic carcinoma.

Some controversy exists on the indications for resection of pulmonary metastatic disease. Many surgeons believe that pulmonary resection is indicated in patients with solitary metastatic lesions that appear after a prolonged interval following removal of the primary neoplasm in patients who have metastases limited to the lungs.[1,6,8–13,16,17,19,23] Most surgeons do not consider surgical treatment for patients who have multiple pulmonary metastases, especially if bilateral. However, as has been pointed out by others, the results of surgical resection for patients with multiple metastases rival those reported in patients with solitary lesions.[20,22] Furthermore, many patients who are subjected to thoracotomy for apparently solitary lesions are found to have multiple small subclinical metastases not detectable on radiological examination. Therefore, a re-evaluation of surgical treatment for multiple pulmonary metastases is indicated. Since approximately 30% of patients with malignant disease will have pulmonary metastases at some time during their clinical course, it is important to have some criteria for the selection of these patients who would most benefit from pulmonary resection.

In a preliminary report we previously suggested that measurement of the tumor doubling time appears to provide an accurate method for judging the biological aggressiveness of malignancy in a given patient.[14] This measurement may be an important indicator for those patients who might benefit from resection of the pulmonary metastases whether solitary or multiple.

The purpose of this report is to evaluate surgical treatment for multiple pulmonary metastatic lesions and to discuss adjuvant immunotherapy of selected patients undergoing resection of the pulmonary disease.

## Materials and Methods

The patients included in this study were those seen by the authors in the Surgery Branch of the National Cancer Institute and Thoracic Surgical Services of George Washington University Hospital, and the Center of Health Sciences of the University of California at Los Angeles. We have approached pulmonary metastatic disease aggressively, attempting to resect most lesions if technically operable.

This report concerns 60 consecutive patients who were subjected to thoracotomy and resection of metastatic lesions.

Nineteen patients were treated with adjunctive immunotherapy following resection of their pulmonary metastases during the past 3 years. Immunotherapy was ad-

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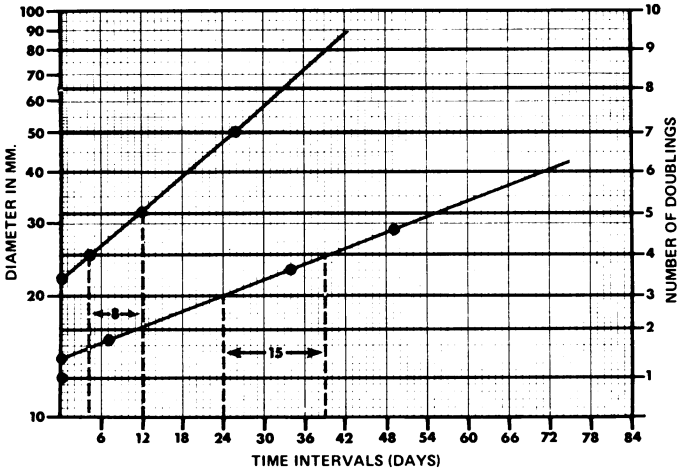


FIG. 1. Method of plotting tumor doubling time based upon the direct measurement of the changing diameters of metastatic pulmonary nodules. (Reprinted from Joseph, Morton, Adkins: J. Surg. Oncol. 3:143, 1971).

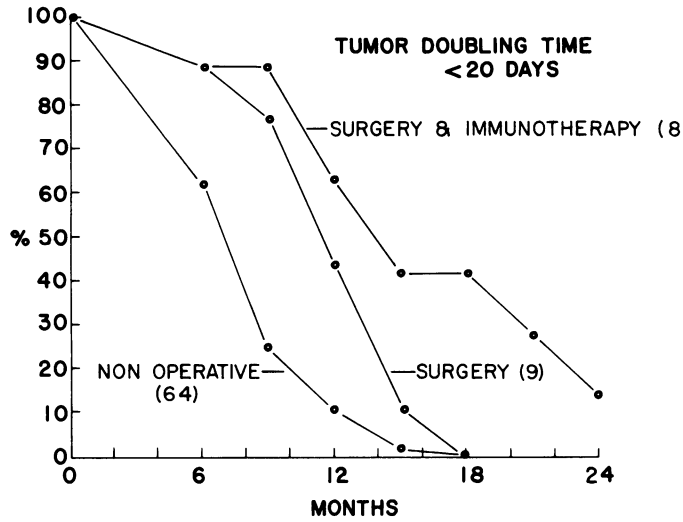


FIGURE 2.

ministered by methods previously described using a vaccine prepared from irradiated autologous tumor cells mixed with BCG.[18]

The methods used for measurement of the tumor doubling time (TDT) was reported previously.[2,3,14,15] Briefly, by using successive chest roentgenograms the changing diameters of each nodule are plotted on semilogarithmic paper against time and days between observations (Fig. 1). A line is drawn between the points; the slope of this line represents the rate of tumor growth. As this line crosses any two doubling lines, the horizontal distance in between represents the TDT in days. All patients had at least three serial measurements for each metastatic nodule. The TDT was calculated for those lesions that were clearly delineated on chest roentgenogram.

The survival rate of the 60 patients undergoing surgical resection of the metastatic disease was compared with a group of 89 patients who received no treatment or who received chemotherapy for the pulmonary metastases. Table 1 shows the range of tumor doubling times according to the pathologic diagnosis and the number of patients in each category. Of note was the considerable variation in tumor doubling time for each histologic type of neoplasm. Since the cell type of the primary neoplasm was not characterized by a particular tumor doubling time, these patients were reclassified into three groups on the basis of growth rates as measured by the tumor doubling time.

Our previous report showed that the growth rate and eventual prognosis correlated well when the TDTs were arbitrarily divided into three groups based upon a TDT of less than 20 days, 20-40 days, and greater than 41 days. Consequently, all patients with multiple metastatic foci were classified into three groups based upon their TDTs regardless of the histologic type of the neoplasms.

There were 10 patients with multiple pulmonary metastases in whom tumor growth rate varied extensively. Their calculated TDTs did not fall into a single category. These patients were grouped according to the growth rate of their fastest growing lesions, because as previously reported, prognosis appears to be determined by the fastest growing lesions rather than the slower growing lesions.[15]

The accumulative survival of patients in these three groups was plotted by the actuarial life table method.[5] The operative and non-operative groups are compared in Figures 2, 3, and 4. The three groups treated by surgical resection are compared in Figure 5.

TABLE 1. *Types of Neoplasms in Operative and Non-operative Treatment Groups*

| Type of Neoplasm | Surgical Resection | | | Non-Operative Treatment | | |
|---|---|---|---|---|---|---|
| | Patients | | Range TDT | Patients | | Range TDT |
| Carcinoma | 20 | 33% | 21–360 | 33 | 38% | 11–360 |
| Sarcoma | 34 | 57% | 13–360 | 50 | 55% | 5–360 |
| Miscellaneous | 6 | 10% | 11–55 | 6 | 7% | 13–80 |
| Total | 60 | 100% | | 89 | 100% | |

## Results

Twenty-seven patients had multiple lesions bilaterally whereas 33 had multiple nodules confined to one lung. Eighty-seven thoracotomies were performed in 60 patients. In most cases, the metastases were easily located beneath the pleura and were removed by wedge resection. Wedge resections only were performed in 71 thoracotomies. Twenty-six patients underwent staged bilateral thoracotomies and one patient had a simultaneous bilateral thoracotomy. Patients presenting with simultane-

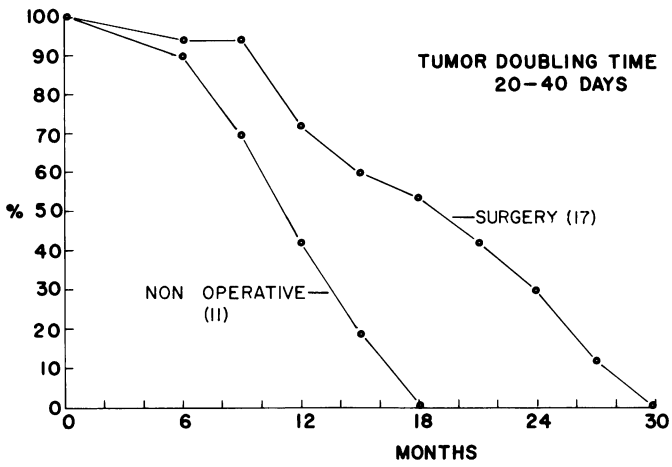


FIGURE 3.

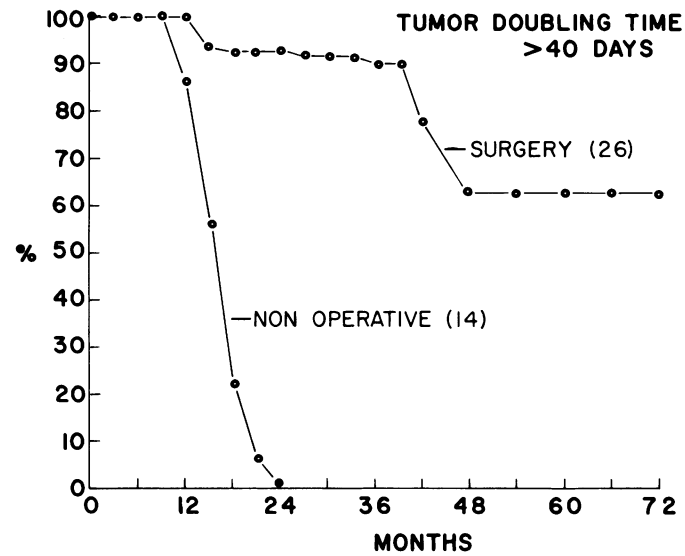


FIGURE 4.

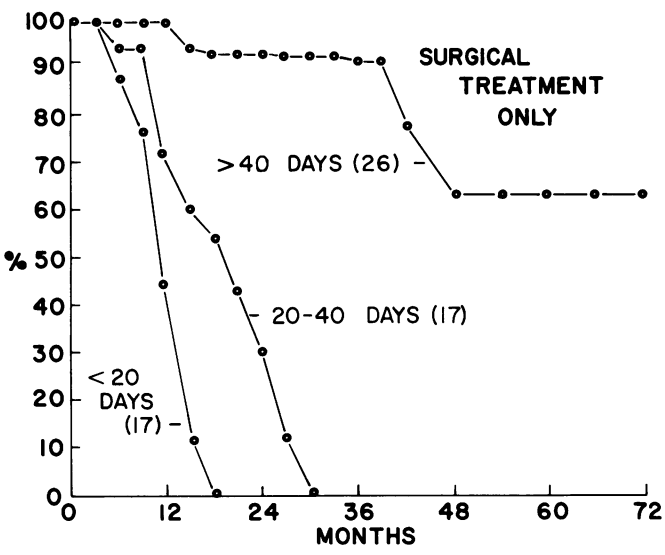


FIGURE 5.

ous bilateral pulmonary metastases usually underwent thoracotomies staged at 10-30 days between resections. Other patients had metastatic lesions in one lung which were resected, only to return, after several months or years, for resection of metastatic lesions in the opposite lung.

The number of wedge resections performed in one lung varied between three and 28. Because of their subpleural location, it was possible to detect lesions as small as 2 millimeters in diameter. Preoperative chest X-rays and tomograms accurately detected lesions upwards from 1 cm. in size. However, additional smaller subpleural metastases often were not radiographically apparent. Pulmonary tissue was preserved by resecting 85-90% of the subpleural lesions with a wedge resection of 2 cm. of normal surrounding lung. Major pulmonary resections were necessary in only 16 patients. Lobectomy was performed in 13 patients and three had pneumonectomy. There was one operative death in the 87 thoracotomies.

An extensive preoperative evaluation was carried out on all patients to exclude other sites of metastatic disease. This work-up included full chest tomograms to evaluate the multiplicity of metastatic nodules, metastatic bone series, radioisotope scans of the bone, brain, and liver, and liver function tests. Immunocompetence was tested by the DNCB skin test in those patients seen during the past 3 years.[7] Patients with equivocal liver function tests and liver scans underwent hepatic angiography. Exploratory laparotomy was performed in 10 patients as an added precaution to exclude hepatic metastases in patients with equivocal hepatic radioisotopic scans or angiograms. At the time of thoracotomy, four patients underwent transdiaphragmatic exploration of the peritoneal cavity and palpation of the liver, while six patients had transabdominal exploratory laparotomies prior to thoracotomy.

The accumulative survival of patients with tumor doubling times of less than 20 days is compared in Figure 2. In the group of 64 patients who received non-operative management, 63% were alive at 6 months, 11% at 1 year, and none beyond 18 months. Of the nine patients who had surgical resection alone, 89% were alive at 6 months, 44% at 1 year, but all were dead by 18 months. Of the eight patients who received adjuvant immunotherapy in addition to surgical resection, 88% were alive at 6 months, 63% at 1 year, 40% at 18 months, and 13% at 24 months.

Although the numbers of patients in the operative groups are small, there appears to be a modest prolongation of survival in this group. If the two groups receiving surgical therapy are combined, the 1 year survival rate is 53%, or nine of 17 patients, in those receiving surgical treatment compared to 11%, or seven of 64 patients, in the non-operative group. These differences are statistically significant ($p = <0.05$). The number of patients receiving immunotherapy is too small at this point to defi-

nitively evaluate the effectiveness of adjunctive immunotherapy in prolonging survival. However, at this time, the prolongation in survival appears to be relatively modest.

The accumulative survival of patients with tumor doubling times of 20-40 days is compared in Figure 3. Of the 11 patients receiving non-operative treatment, 90% were alive at 6 months and 45% survived 1 year. No patients were alive beyond 18 months in this group. Of the 17 patients treated by surgical resection of the pulmonary metastases, 94% were alive at 6 months, 72% at 1 year, 54% at 18 months, 30% at 24 months, but no patient survived beyond 30 months. Comparing the 50% survival point, there is a life prolongation from 11 months to 18 months by surgical treatment. Thus, patients undergoing surgical resection of the metastatic lesions survived an average of 7 months longer than the non-operative patients.

The accumulative survival of patients with a tumor doubling time greater than 40 days is summarized in Figure 4. All patients in the non-operative group survived at least 9 months after the onset of pulmonary metastases. Eighty-six per cent were alive at 1 year but none survived beyond 2 years. In contrast, survival of patients who underwent pulmonary resection was considerably increased. At 2 years following operation when all of the non-operative treated patients were dead, 97% of those undergoing surgical resection were still alive. The differences between these groups are significant at the $p = <0.01$ level. In fact, 63% of patients who have been followed for more than 5 years in the surgically treated group with TDT > 40 days are still alive. Most patients in this group are free of disease at 5 years after surgical resection. This was true despite the fact that 14 of these 26 patients had bilateral pulmonary metastases and underwent bilateral thoracotomies. The results of surgical treatment alone in this group are so good that it is difficult to evaluate the influence of adjunctive immunotherapy in the eight patients who received this treatment.

## Discussion

This study clearly indicates that selected patients with multiple pulmonary metastases can be significantly benefited by aggressive surgical treatment even with bilateral disease or multiple metastases in the same lung. Measurement of the tumor doubling time appears to be a remarkably accurate means of selecting those patients who will benefit most from aggressive surgical treatment. Those patients with a tumor doubling time of greater than 40 days may have a 63% 5-year survival rate following surgical resection whereas patients managed by non-operative treatment usually will not survive more than 2 years. Conversely, patients with a tumor doubling time of less than 40 days show only a 7-month increase in survival from surgical treatment beyond that expected from non-operative management. Adjunctive immunotherapy slightly increased survival beyond that obtained by operation alone in this group of patients. We anticipate new methods of immunotherapy that may improve these results.

Based upon the tumor doubling time, the striking differences in the results of surgical treatment in these patients appears to indicate a fundamental characteristic in the tumor-host relationship of each patient.[14,21] The growth rate of each patient's tumor was dependent upon the interrelationships of the immune defense mechanisms and the intrinsic growth potential of the neoplasm. The improved results in patients with a prolonged tumor doubling time appears to indicate a favorable host immune response to the neoplasm. Patients with a rapid tumor doubling time are more likely to have metastatic lesions at other sites such as the liver, brain, or bone, so that treatment of the pulmonary metastases results in relatively little improvement in survival. In contrast, patients with prolonged tumor doubling time are more likely to have metastases limited to the lungs and aggressive treatment of the pulmonary metastases results in greatly prolonged survival.

Evidence that the patient's immune response is a significant factor in determining the growth rate of the neoplasms comes from studies of complement fixing antibody titers in patients with metastatic sarcomas. In these cases, we found a good correlation between a high titer of antibody and a slowly growing sarcoma. Patients with pulmonary metastases who had titers of 256 or greater usually had tumor doubling times of greater than 40 days, whereas patients with tumor doubling times of less than 20 days had little or no detectable antisarcoma antibody in their serum. Thus, the time of tumor doubling is a measure of the biological aggressiveness of a neoplasm in a given patient which can account for both the intrinsic growth potential of the neoplasm and the inhibiting influence of the host's immune defenses. Therefore, the patient's tumor doubling time can be used as a criterion for pulmonary resection with assurance of a favorable prognosis. For this reason, we urge that patients in whom metastatic pulmonary lesions demonstrate a tumor doubling time greater than 40 days be considered for surgical resection even though the lesions are multiple and bilateral.

In patients with multiple metastases, it is very important to measure the tumor doubling time of all visible lesions. Approximately 16% of patients will have wide variations in the TDT of some of their metastatic lesions. Since prognosis depends upon the TDT of the fastest growing lesions, such measurements can be critical. A maximum delay of 1 month is necessary to determine the tumor doubling time of pulmonary metastases. In this time, three observations can be made. An initial X-ray, one at 2 weeks, and one at 1 month will show significant growth in lesions with a tumor doubling time of less than

40 days. Sometimes, these rapidly growing lesions, make a TDT calculation possible in a 2-week observation period.

It must be emphasized that no patient should be considered for resection of pulmonary metastases without extensive preoperative evaluations to exclude metastatic foci at other sites. We believe it is important to include a measurement of the patient's immune response to a new antigen such as DNCB in this work-up since our experience has shown that patients who are anergic to this chemical have metastases at other sites even when these lesions are not clinically detectable. In addition to liver function tests, metastatic bone series, and radioisotopic scans of the bone, brain, and liver, we advocate full chest tomograms to detect any additional lesions that might be missed on plain chest films.

Certain technical aspects of the operative procedure deserve emphasis. We believe that patients with bilateral metastases should have resection on the least involved lung first. In this way, the extent of disease on the minimally involved side is known at the time of thoracotomy on the opposite side when one may be faced with a major pulmonary resection such as bilobectomy or pneumonectomy. In addition, the patient has more adequate pulmonary function for the second procedure than if the pneumonectomy or bilobectomy was done first.

We have found the following operative technic to be useful. Upon entering the chest, a careful search is made for mediastinal or hilar lymph nodes which, if found, are removed for frozen section examination. Following this, a careful search is made for pulmonary metastatic lesions. Each metastases is marked with a suture to indicate its location. A majority of the metastatic lesions are subpleural in location for unknown reasons. It is of interest, however, that approximately 90% of pulmonary metastases in animal neoplasms are also subpleural in location. Whatever the explanation, this location greatly simplifies the surgical excision.

Extreme care is taken in examining the lung in both the inflated and deflated conditions. The exploration and search usually takes at least 15-20 minutes during which time the surgeon carefully marks each lesion he is able to palpate. Following this, he has his first and second assistants carefully examine the lungs for metastases. Not infrequently, the assistants find one or two additional metastatic lesions. All of the metastatic lesions should be detected and marked prior to resection of any one lesion because the resection inevitably results in artifacts at the suture line and atelectasis which may be mistaken for additional lesions.

After exploration is completed, and all metastatic lesions have been marked with sutures, it is easier to plan the extent of resection and make the decision between multiple wedge resections and a lobectomy. The subpleural location of the metastases makes a wedge resection feasible in most instances. We have found that the mechanical stapling device is an extremely useful instrument in patients who need multiple wedge resection. Its use is facilitated if the metastasis is outlined with clamps such as Bouie hemorrhoid clamps. The excision is performed with the mechanical stapling device beyond the clamps. This insures an adequate margin of normal lung parenchyma beyond the metastases. Using this technic, local recurrence of metastases at the suture line has been kept to a minimum. In fact, we have had only one incident of local recurrence and two incidences of missed metastatic lesions that required additional thoracotomies in the 26 patients with tumor doubling time greater than 40 days who have survived for long periods.

## Summary

Evaluation of the results of surgical treatment in 60 patients with multiple pulmonary metastases indicates that aggressive surgical resection is indicated when tumor doubling time is greater than 40 days. Approximately 60% of these patients will survive 5 years after operation; therefore, these patients should undergo pulmonary resection even when bilateral thoracotomy is necessary. Conversely, patients with tumor doubling time of less than 40 days were only slightly benefited by surgical resection and were dead of the disease within 2 years. The marked differences in surgically treated patients with tumor doubling time of less than 40 days when compared to those with a TDT of greater than 40 days is illustrated by the fact that only 6% of patients with tumor doubling time less than 40 days survived 2 years while 94% of those with tumor doubling times greater than 40 days survived beyond 2 years. Fifty-four per cent of patients in the greater than 40-day group required bilateral thoracotomy because of bilateral metastatic lesions.

These differences in the results of surgical treatment appear to be due to differences in the biological aggressiveness of the neoplasms in these two groups of patients. Patients with prolonged tumor doubling time are less likely to develop extra pulmonary metastatic lesions and, therefore, resection of the present pulmonary metastases greatly improves survival. In contrast, patients with tumor doubling times less than 40 days invariably have extra pulmonary metastatic lesions which are not detectable on clinical examination and eventually contribute to their death. Thus, pulmonary resection in this group of patients results in only a minor prolongation of survival. Although immunotherapy appears to prolong survival somewhat in these patients, they all eventually died of the disease. Hopefully new methods of immunotherapy may improve these results.

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### Discussion

Dr. Edward J. Beattie, Jr. (New York City): I think it is a major contribution that Dr. Morton has been able to segregate a group of multiple pulmonary metastases, and then get a 60% 5-year survival rate. The primary tumor must be under control for this to be done.

I thought you might like to hear a progress report on the studies that have been going on at our institution with osteogenic sarcoma of the extremities in children.

This is a tumor which is treated with amputation and thus has an advantage, that the primary lesion is under control. Dr. Ralph Marcove reviewed a series of 145 patients under 21 years with osteogenic sarcoma in the extremities, and found that one of six was cured by amputation. Fifty per cent of those not cured by amputation were dead in 12 months. Eighty-eight per cent were dead in 24 months, and 95% were dead in 36 months.

Dr. Marcove used autologous tumor vaccines made from the tumor at the time of amputation in a series of 15 patients. He had nine patients or 40% who remained free of disease at 36 months. That is a considerable improvement, but it is very small series which needs expansion.

Two years ago we reported a series of 29 patients with pulmonary metastases of osteogenic sarcoma. At operation, seven patients had showers of tumors and it was impossible to clear the lungs. In 22 patients, it was possible to remove all of these tumors. In those 22 patients, we have now done 61 thoracotomies, removed over 150 metastases, and six of 22 are well 5 years after amputation.

One of our best cases was a girl who had had a hip disarticulation with a negative chest X-ray. Four months later she had nine metastases. After four thoracotomies, and removal of 11 metastases, there is no evidence of disease 7 years after amputation, and she has graduated from college and married.

Many of our children have too many metastases to remove, and we have been using intensive chemotherapy. Dr. Jerry Rosen of our pediatric department, who treats disseminated osteogenic sarcoma patients, has had marked regression in nine of ten patients.

We have monitored the immune status of these children, and found that they have remained DNCB positive and maintained their skin reactivities until they were terminal. Even then some of them maintained a positive DNCB.

Presently, we are trying to see whether immunotherapy and chemotherapy with operation will improve our results. It is possible to cure one of six with amputation; perhaps another 20 to 25% with pulmonary surgery alone; and possibly with the addition of immunotherapy and chemotherapy this cure rate can be improved.

Dr. William S. Blakemore (Philadelphia): For some time we have been interested in immunotherapy. Following some disappointing results with tumor injection of preparations from the patients' tumor, particularly melanoma, in the middle 1950's, we