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TREATMENT OF MALIGNANCY

GEORGE W. CRILE, M.D.

No one can write adequately of any phase of the problems presented by malignant disease without acknowledging his debt to James Ewing. While the surgeon is primarily concerned with the possibilities of the removal of an invaded tissue, in the matter of the extent of operation in each case he must be guided by his decision as to whether the growth is truly benign, premalignant or frankly malignant. Doctor Ewing's purpose, as expressed in his preface, is to contribute something toward the reduction of mortality from cancer. Since it is only by increasing knowledge of the nature of cancer that mortality from this disease can be reduced, he has certainly made a great contribution toward the attainment of this purpose. Ever since the appearance of the first edition of "Neoplastic Diseases" in 1919, my associates and I have constantly made use of the wealth of information contained in that and in the succeeding editions.

While neither the cause of malignant disease nor its cure has yet been found, despite world-wide researches and vastly extending clinical experience, nevertheless great progress toward the conquering of this scourge of the human race has been made by the disproof of many false theories, by the discrediting of many so-called "cures," the studies of the incidence of malignancy in relation to age, race, climate, and the different bodily tissues, by investigations of its method of growth, and by the observation of the effects upon it of various physical and chemical agents. From all of these studies the practical results have been meager. We have learned, however, that cancer, whether of the external and visible parts or of the internal, invisible organs, obeys one general law of growth, and the old

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dictum based entirely upon clinical experience is established more uniformly than ever — namely, that the one and only cure for cancer is its early and complete removal. It is probable that with extending knowledge of the operation of physical laws in biological processes, new light may be thrown upon the causation of malignant growths, and that from this knowledge new methods of cure may be evolved. Already, investigations have shown that the electric capacity and conductivity of cancer of any part far exceeds the capacity and conductivity of the normal tissue, while the potential in cancer is opposite to that in normal tissue. The histologic appearance of a cancer offers a static picture of the cells. The capacity and potential measurements present the dynamic status of the cells, and it is with the dynamic status of the cells that we are primarily concerned in interpreting the status of any malignant or pre-malignant condition.

Whatever these and other researches may disclose to us in the future, at present the one sure method of approach to the cancer problem is that based upon clinical experience. I propose, therefore, to offer in this paper a review of the methods employed by my associates and myself in dealing with cancer of the various tissues, these methods being based upon our experience in 7,390 cases of malignancy.

It is of interest to note, in regard to cancer of the external parts, that, to my knowledge, no case of cancer has been observed on the normal, uninjured skin. The skin of the face, in particular, offers an opportunity for the study of the natural development of cancer which is of greater value than that of any condition induced in the laboratory. I have never seen a cancer develop upon the healthy skin of the face. It is always preceded by a pre-cancerous stage, a keratosis, a mole or wart, a benign tumor or ulcer. The pre-cancerous history is often a long one — of little scales picked off as frequently as they recurred, of a wart goaded by constant picking. In the case of a cancer on the buccal surfaces also there is usually a history of trauma from a rough tooth, from leucoplakia, or a fissure.

If in the cancer period of life every unhealthy scar were excised and the surface covered by skin grafting, if every chronic irritation were removed, if every ulcer were healed soundly, or excised and the surface covered by skin grafting, if every wart and mole were excised, if the mouth were kept wholesome, the teeth smooth and even, it would be found that the problem presented by cancer of the outer surfaces of the body would be well-nigh solved.

Since cancers obey one general law of growth, we may be sure that cancers of the inner, hidden parts follow the same course as do

cancers of the skin. We must conclude, therefore, that internal cancers have their pre-cancer stages — chronic irritation, ulcerative benign growths, etc. Thus in the larynx the pre-cancerous state may be a syphilitic ulcer or a papilloma; in the stomach it may be a chronic ulcer; in the gall-bladder, irritating gallstones and chronic inflammation; in the large intestine and rectum, ulcers and irritation from various sources; in the breast, chronic inflammation, benign tumors of certain types and senile changes; in the uterus, the irritations of pregnancy and senile changes, and benign growths; in the kidney and bladder, stones and benign growths.

Unfortunately, not all pre-cancerous conditions of the internal organs are amenable to treatment, but to the extent that these pre-cancerous states may be corrected, to that extent will the problem presented by cancer of these parts be solved.

Once the pre-cancer stage has passed, then complete removal of the growth — whether by excision, or by the X-ray or radium — becomes the only safe procedure. It is interesting and encouraging to note that increasing numbers of patients consult the surgeon as soon as any symptoms are presented which indicate an abnormal condition of any organ or tissue; in consequence, the percentage of cases of cancer which are caught in the early stages is increasing. Unfortunately, however, some of these internal cancers are symptomless in their earliest stages, so that when they come to operation they are so far advanced that even if removal of the local growth is still possible, there is danger that distant metastases are present.

It remains to discuss the treatment most preferred by my associates and myself for cancer of the various organs and tissues.

The Skin — In our experience in the treatment of 629 cases of carcinoma of the skin and subcutaneous tissues, we have found that radium is the most efficient treatment, except in the case of a pigmented mole, which should always be excised.

The Jaws and Buccal Surfaces — Our records include 549 cases of carcinoma of the buccal surfaces and jaw. Among these, 21.3 per cent were cases of carcinoma of the tongue, 43.3 per cent were carcinomata of the lip, and 13.3 per cent were carcinoma of the jaw. Among the cases on which we have follow-up data, 25.37 per cent have lived for five years or more.

Some years ago a study of 4,500 reported cases of cancer of the head and neck was made for me by Dr. F. W. Hitchings, who found that in less than 1 per cent of these cases secondary cancer foci were found in distant organs and tissues. In cases of cancer of the head and neck, therefore, death, when it occurs, is almost invariably

the result of the local development of the disease, the reason for this localization being the extraordinary barrier formed by the collar of lymphatics in the neck, every portion of which is readily accessible to the surgeon. Above this lymphatic collar, however, metastases are rapidly disseminated. In contradistinction to cancer of the skin and superficial parts which metastasize late, and are effectively treated by the local application of radium and the X-ray, cancer of the buccal surfaces demands the complete removal of the glands of the neck on both sides. In early cases of cancer of the jaws, on the other hand, since this condition metastasizes slowly, and usually on the side of the lesion, a less radical operation is indicated, but in the advanced cases of cancer of the jaws, a wide regional block dissection is indicated.

As for the removal of the primary focus, an early cancer of the lip is usually successfully treated by radium; early cancer of the tongue or of the buccal cavity may be treated by radiation, or perhaps better by electrocoagulation. Every case of advanced cancer of the lip or tongue should be excised, and as stated above, the lymphatic glands of the neck should also be removed by wide block dissection. In cases of carcinoma of the jaws a "platter" of underlying bone should be removed together with the intact growth.

It should be emphasized that while radiation of the local lesion may be indicated, radiation of the involved lymphatic glands of the neck should never be done, as this treatment cannot be depended upon. If the glands of the neck have been irradiated and the patient has recovered, we must conclude that the glands of the neck probably were not involved. After operation on any part of this field, post-operative treatment with deep, accurately measured X-ray or radium radiation is of advantage. Always in these cases should be borne in mind the prime importance of the minimum handling of the carcinomatous tissue and the avoidance of the implantation of cancer cells in the operative field.

The Larynx — Our series includes 134 cases of carcinoma of the larynx, in fifty-seven of which operation was performed. Among those patients on whom we have follow-up data, 63.2 per cent have survived for more than five years.

Cancer of the larynx calls for laryngectomy, which is one of the most successful operations for the permanent cure of cancer. Here, as nowhere else in the body, except in visible parts, the presence of cancer is evident in its earliest stages, for it is announced by every spoken word of the patient. Moreover, in cases of intrinsic cancer of the larynx there is practically no lymphatic involvement, for the reason that intrinsic cancer of the larynx is, as it were, confined in a

box through whose walls the cancer cannot penetrate, for cancer cannot penetrate through hyaline cartilage. There is no other situation in the body in which cancer declares itself immediately and from which it cannot be disseminated into the lymphatic glands. If a cancer of the larynx is extrinsic, then because of the abundance of lymphatic connections, it will extend rapidly, and generally operation is, at best, only a palliative remedy. In such cases the only hope lies in the local removal of the growth and block dissection of the gland-bearing area. In operable cases in which only tracheotomy can be attempted, radium is of value as a palliative measure.

For intrinsic cancer of the larynx, as stated above, laryngectomy is indicated, the general trend of opinion being against the use of radium, for laryngectomy offers a practical certainty of cure, provided the cancer is entirely intrinsic. The post-operative application of the X-ray, however, may be of value, as it may check any extension of the growth provided some undiscovered extrinsic focus exists, or provided some cancer cells have become implanted.

The Thyroid Gland — In our total series of thyroidectomies, there has been a carcinoma of the thyroid gland in 268 cases. In about 90 per cent of these cases the carcinoma was due to the degeneration of an adenoma. For this reason I believe that all adenomata should be removed. Thus the treatment of carcinoma of the thyroid gland, like the treatment of goitre, is mainly a problem of prevention. If the case is operable, there is no question as to the treatment; the only difficulties are presented by the inoperable cases in which the patient is suffering from obstruction and partial asphyxiation. In such a case the implantation of radium is indicated, together with a decompression operation if the distress of the patient demands immediate relief. In this operation the preglandular muscles are divided, thus relieving the back pressure of the gland upon the trachea.

Sometimes as the result of radiation the carcinoma will disappear; in other cases radiation seems to be of no avail. Radiation may produce myxœdema, but this is readily overcome by the administration of thyroid extract. What the end-result of decompression and radiation may be in any given case cannot be foretold, but the patient is certain to have a period of relief. It must be borne in mind that involvement of the neighboring tissues is almost sure to be present, and that if the cancer involves the trachea there is practically no hope of cure.

The Œsophagus — Our total series includes 111 cases of cancer of the œsophagus, in the majority of which the symptoms had been present for less than six months. This is one of the most hopeless

of malignant conditions, for when the patient presents himself it is usually too late for surgical treatment to be of any value. The emaciation and weakness due to the dysphagia, which is the prominent symptom, in itself makes every case a poor surgical risk. In most of our cases dysphagia was already so marked as to have produced extreme emaciation and exhaustion.

None of the cases of cancer of the œsophagus in our series have survived more than thirty-four months.

The Breast — Our total series includes 1,350 cases of cancer of the breast, fourteen in males. In 789 cases the patients have been treated by surgery alone; in 398 by surgery and radiation. Of the patients regarding whom we have follow-up data, 25.70 per cent have survived for five years or more.

According to Ewing, the United States Census for 1914 reported 5,423 deaths from cancer of the breast among 52,420 total cancer deaths, an incidence of over 10 per cent.¹ I am inclined to believe that the 1930 census will present a lower incidence, since, as the result of increasing knowledge on the part of the laity of the symptoms of the early stages of cancer, especially of cancer of the breast, the number of patients who present themselves with inoperable cancer of the breast is constantly diminishing. The majority of women are now ready to consult their physician upon the first appearance of any abnormality in the breast.

The problem for the surgeon, therefore, has become one of accurate differentiation between benign and malignant tumors. Frank cancer is easily diagnosed, but the diagnosis of border-line cases is by no means a simple problem. Bloodgood at one time submitted specimens from over sixty border-line cases to a number of pathologists. These pathologists were divided into two groups, one of which favored a diagnosis of cancer, the other believed the growth to be a benign lesion. "In not a single case has there been a uniform agreement as to whether the lesion was benign or malignant."²

Ewing states that "the great majority of mammary cancers are rather easily recognizable by inspection and palpation."³ In cases in which the clinical symptoms and the frozen section cannot give absolute proof of the character of the tumor, the utmost safety of the patient demands the complete excision of the breast and of the regional lymphatics, for unlike cancer of the head and neck or the imprisoned, intrinsic cancer of the larynx, the abundant, lymphatic channels from the breast may readily and easily produce thoracic and abdominal metastases.

Among the so-called benign breast lesions which are possibly

precancerous are diffuse hypertrophy, traumata, chronic mastitis, and cysts, as well as the so-called benign tumors.

In regard to the so-called benign tumors, Deaver has stated, "Tumors of certain types having certain structure are constantly harmless; those of other types, having another structure, are persistently invasive, destructive and constantly fatal. Unfortunately these are the extremes of a series between which lie many tumors that may or may not be harmful, or whose structures may fail to give a clue to their true disposition."⁴ I am far from recommending the radical operation in every case of tumor of the breast, but I do wish to emphasize the importance of frequent examination of the breast after the local excision of what appears to be a benign tumor, so that the radical operation may be performed immediately if the lesion shows any suspicion of malignancy. A biopsy should never be performed, for if the growth should prove to be malignant there is danger of its dissemination, and whatever its character, in any case it should be removed entirely and then sectioned.

As for the role of radiation — from a study of the end-results in our series, Portmann draws the following conclusions:⁵

"1. Intensive X-ray therapy, especially by the cross-fire method, is not the preferred procedure or the post-operative treatment of carcinoma of the breast.

"2. Post-operative X-ray therapy by moderate repeated dosage decreases the number of recurrences and metastases, and prolongs the life of many patients suffering from carcinoma of the breast."

We, therefore, give radiation therapy as soon as possible after operation, not waiting until the wound is healed. Only if a case is entirely inoperable is radiation employed as a palliative measure instead of surgery.

The Stomach — A study of the records of our 648 cases of cancer of the stomach shows that the history is commonly a history of indigestion or of ulcer; that ulcer of the stomach has a distinct potentiality as a precancerous condition; that the history and the X-ray findings are the most valuable means of diagnosis; that a differential diagnosis between an old ulcer and early cancer cannot be made with certainty; that when the probability of cancer is suspected an exploration should be made at once. In late cases, as in late cases of cancer elsewhere, even though the operation is survived and the local lesion removed, there is great danger of metastases, especially in the liver or retroperitoneal glands.

A cancer of the stomach is characterized by such a rapidity of growth and such an extent of lymphatic involvement that an inoperable stage is reached very early in its progress. Since the earliest

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stages are practically symptomless, and the earliest symptoms are those of more or less mild indigestion, in the majority of cases the patients come too late for possible cure.

The operation indicated is the widest possible excision of the growth and the patient should be offered every safeguard and aid that surgery has to offer. By the use of blood transfusion, saline injections, diathermy during and after the operation, the application of hot packs, and a divided operation in many cases in which the prognosis appears to be hopeless, the patient may be carried through to cure or to a comparatively comfortable prolongation of life. In regard to the divided operation, it may be added that in certain cases in which the diagnosis of cancer has been made, the supposedly cancerous mass has disappeared in the interval between the two stages so that the second stage has not been required.

Among our cases of cancer of the stomach, of those patients on whom follow-up data are available, 4.44 per cent have passed the five-year period. Resections have been made in ninety-five cases with five-year survivals in 6.94 per cent; gastroenterostomy in 168, with five-year survivals in 5.21 per cent; and radiation therapy alone in twenty with no five-year survivals. In the last two instances, perhaps our diagnosis may be questioned, but in each of these cases the clinical signs, the X-ray picture and the exploratory operation gave every evidence of an inoperable carcinoma.

Gall-bladder — Our records include sixty-four cases of carcinoma of the gall-bladder and bile-ducts among which operations were performed in twelve cases. We have a record of two five-year survivals.

If a patient presents symptoms referable to the gall-bladder of more than one year's duration, the possibility of malignancy of the gall-bladder should be considered. Cancer of the gall-bladder is usually associated with cholecystitis, and consequently in many cases the patient is treated for the latter condition until the disease has extended into the liver and deep structures. Then when its malignant character is recognized, it is too late for operation to be of any avail. If the presence of the malignant condition is recognized before extension to the liver has occurred, then an immediate cholecystectomy is indicated.

The Liver — Of cancer of the liver it is necessary to state only that it is rarely primary and is always incurable. Only palliative efforts can be made and their effect at best is but temporary. Our records include 103 cases of cancer of the liver, among which three were shown at autopsy to be primary.

The Intestines and Rectum — Our total series of cases of carcinoma of the large intestine and rectum includes 685 cases. Of the cases in regard to which we have follow-up data, 8.45 per cent have survived for five years or more.

The diagnosis of carcinoma of the small intestine is made from the history and clinical signs and the X-ray picture. If the presence of a cancer is indicated then an exploratory operation should be performed to determine operability, with immediate removal of the growth if possible. As in the case of carcinoma of the stomach, every available method for the conservation and restoration of the patient should be employed. Our records include twenty-one cases of carcinoma of the small intestine.

In cases of carcinoma of the large intestine and rectum, a colostomy should be performed, followed by radical operation, X-ray radiation being employed after the operation. In cases in which the growth is so low in the rectum as to be readily accessible, the implantation of radium needles and the application of radium packs may be sufficient. In inoperable cases a colostomy should be done, followed by radiation. There should be a period of about ten days between the colostomy and the final operation, or rather, between the colostomy and the decision as to the method of treatment, as a period of that length is necessary to allow the inflammatory reactions of the disease to subside sufficiently to make it possible to determine what operation shall be performed. This decision depends, of course, upon the findings of an exploratory operation. The entire picture may change during this period.

While the application of deep X-ray radiation is beneficial after operation or after radium treatment, it is of little, if any, value in the treatment of recurrences.

A statistical study of cases treated at the Cleveland Clinic since 1921 shows the following survival percentages:

CANCER OF THE RECTUM AND SIGMOID

Treatment	Total cases	Traced cases	Survival more than five years
Resection.....	145	125	7.2 per cent
Resection and radiation.....	39	34	20.6 per cent
Colostomy only.....	108	63	0 per cent
Colostomy and radiation.....	76	70	10 per cent
Radiation only.....	36	27	7.4 per cent

These figures show, as Jones⁶ has reported, that although operation by the abdomino-perineal route, combined with radiation, is the treatment of choice, if operation is refused or if the condition is

inoperable, there is sufficient evidence that a cure can be obtained in certain cases and marked palliation in others by the use of radium and Röntgen-ray.

The Genito-urinary Organs — The records of Doctor Lower and his associates at the Cleveland Clinic include 805 cases of malignant disease of the genito-urinary organs — 335 of the bladder, 124 of the kidney, 16 of the urethra, two of the ureter, 268 of the prostate, and 60 of the testicle.

Among these cases in which the results are known, there have survived for five years or more 9.84 per cent of the cases of malignant disease of the bladder, 8.74 per cent of the cases of malignant disease of the kidneys, 3.75 per cent of the cases of carcinoma of the prostate.

In general, malignant tumors of the genito-urinary organs are best treated by surgery with the addition of radiation in certain cases. In inoperable cases, radiation may be the only available method of treatment.

In some cases, tumors of the kidney in children may be reduced by deep X-ray therapy, but the radiation must be followed later by surgery.

For malignant tumors of the kidney in adults, the indicated treatment is surgery with radiation both before and after operation. In many cases radiation will so reduce the size of the tumor that cases which have seemed to be inoperable become operable. Tumors of the kidney should be irradiated no matter how hopeless the outlook. In the case of deep-seated bladder tumors, radium has seemed to prevail in certain cases, but the results are too uncertain for radiation to be used routinely. Post-operative radiation is employed in many cases, but principally because of the hope that it may be of avail rather than because of any definite results that have been secured up to the present time.

Malignant tumors of the testes are treated by surgery with radiation both before and after operation.

Whether or not prostatectomy or radiation is the preferred treatment for carcinoma of the prostate remains to be decided. We believe that prostatectomy is to be preferred in uncomplicated cases, but we know that in cases in which a high blood urea cannot be reduced, radiation may provide the only possible method of treatment, or it may tide the patient over until prostatectomy can be performed.

The Uterus — Our records include 783 cases of carcinoma of the uterus. Of the 211 cases of carcinoma of the fundus, 14.84 per cent of those patients on whose cases we have follow-up data have survived for five years or more.

Of the 572 cases of carcinoma of the cervix we have follow-up data in 208 cases treated by radiation, and in 129 cases treated by surgery, before we adopted our present policy — 9.13 per cent of the former and 17.05 per cent of the latter have survived for five years or more.

The preferred treatment of carcinoma of the fundus still seems to be *sub judice* — both as to whether surgery or radiation is the treatment of choice, and as to the type of operation to be performed.

As to carcinoma of the cervix, on the other hand, the pre-eminent value of radiation appears to be established. At the Cleveland Clinic we now use radiation rather than surgery in the treatment of carcinoma of the cervix, reserving our final judgment until sufficient time has elapsed for a definite comparative study of the end-results.

As the presence of any but a frankly benign tumor of the breast demands the removal of that organ, especially in a patient past middle age, so when an intermittent or continuous uterine discharge occurs in a patient who has passed the menopause, we believe that a complete hysterectomy should be performed at once. Even if the character of the discharge does not appear to indicate the presence of a malignant condition, this operation should be performed without delay. In such cases curettage is contra-indicated, as if cancer is present, the cancer cells will be disseminated.

In inoperable cases of carcinoma of the fundus, deep X-ray therapy is of value as a palliative agent and for the prolongation of life.

In the treatment of carcinoma of the cervix, both radium and deep X-ray therapy are used, the former being applied in needles and by radium packs.

Ovary — We have seen 128 cases of carcinoma of the ovary. This growth is rarely primary, and in cases in which it is primary the removal of both ovaries is indicated. If the peritoneum is extensively involved, deep X-ray therapy may retard the progress of the disease.

There have survived, for five years or more, 7.57 per cent of our cases.

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Bone — Exclusive of carcinoma of the jaw, we have seen 161 cases of malignant disease of bone. It is still uncertain whether a primary malignancy of bone should be treated by X-ray or by surgery, but two things are certain: first, if an operation is performed, it should be preceded and followed by X-ray radiation, and second, if the condition is in a limb, amputation should immediately follow radiation, provided the condition is not inoperable. As for metastatic tumors, palliative treatment by the X-ray is the only therapeutic measure. Radium is contra-indicated as it would destroy the periosteum, and necrosis would follow.

The data which are being accumulated by the Registry of Bone Sarcoma of the American College of Surgeons may finally lead to a decision as to the relative merits of surgery and of radiation in the treatment of malignant diseases of bone.

Malignant tumors of other tissues might be included in this discussion, but in some instances they are exceedingly rare; in others they are practically never primary; in some they belong in the domain of the specialist. We shall only add here that in these cases the same rule applies as in those we have discussed above, that is removal of the tumor by the most effective method if the site and extension of the tumor and the condition of the patient permit.

Finally, it may be emphasized that, whatever his present point of view regarding the method of choice in the treatment of a malignant tumor of any organ or tissue, the surgeon must hold himself in readiness to alter that view if accumulating experience indicates that other methods are to be preferred or are at least worthy of trial. It may be that as the result of the researches — clinical and experimental — which are in progress in many clinics and laboratories, some new and effective measure may be developed of which we should be ready to avail ourselves.

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