Biological considerations in the treatment of cancer

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1. Changing concepts of the treatment of cancer

Until recent years the aim of surgeons and radiologists treating patients with cancer has been to remove or destroy all the cancer to the last cell. Gradually, however, it has become clear that in the common, metastasizing types of cancer, like those of the breast, this aim cannot often be accomplished. Usually cancer cells have entered the lymphatics and the veins, and are widely disseminated throughout the body before the diagnosis of cancer is made. All that surgery or irradiation can accomplish is to remove or destroy the primary tumor and its metastases in regional nodes. The fate of the widely distributed cancer cells, and the fate of the patient too, then depend on the resistance of the host.

Fortunately the host is often able to destroy the cancer cells that have been carried in blood or lymph to distant parts of the body. There is mounting evidence from both clinic and laboratory that much, if not all of this natural resistance is immunologic and depends on the ability of the immunocyte or killer lymphocyte to become

sensitized to a specific tumor antigen and to seek out and destroy a cancer cell that bears this antigen. Thus, in recent years the aims of the surgeon and radiologist have changed, so that instead of viewing their techniques solely as a means of destroying the last cancer cell, regardless of systemic effects induced by treatment, they have begun to evaluate the usefulness of their treatments also in terms of their effects on the defenses of the host.

If a radical operation or extensive irradiation destroys not only the primary tumor and any metastases that may be present in regional nodes, but also depresses the immunologic defenses of the host, the balance may be tipped in favor of the growth of the widely disseminated cells that, unopposed by immunocytes, can grow into metastases. For this reason, those of us who are involved in the treatment of cancer are now in a period of reappraisal of our methods and techniques. We have begun to question the value of the routine use of radical operations and of prophylactic irradiation. I will outline the evidence from both laboratory and clinic that points to the need for reevaluating many of the standard practices employed in the treatment of cancer.

2. Laboratory evidence indicating the importance of regional nodes in the defense against distant metastasis

a. Metastasis is increased by removing regional nodes

In 1954 Mitchison[1] showed that immunity to an allogeneic tumor could be transferred by transplanting the regional nodes that drained the tumor into another mouse of the same inbred strain. Transplantation of contralateral nodes or lymphocytes from blood or spleen failed to transfer immunity.

Exploring the other side of the coin, I have shown[2] that amputation of a mouse's tumor-bearing foot and removing the popliteal node early in the course of a tumor's growth results in abrogation of immunity to reimplantation of the tumor on the contralateral foot, whereas the immunity persisted if the tumor-bearing foot were removed and the node was left intact. Irradiation of the node resulted in a similar abrogation of immunity. Moreover, isogeneic tumors in two different strains of mice metastasized to the lungs two to three times as often when the tumors were removed by amputation of the tumor-bearing foot and the popliteal node than when only the foot was removed.

b. Loss of concomitant immunity after removing "primary" tumor

The term concomitant immunity refers to the immunity of a tumor-bearing animal to reimplantation of the same tumor elsewhere in its body. Although the "primary" tumor is so large and well established that it overrides immunity and continues to grow progressively, there is enough immunity elsewhere in the body to protect against small inocula of cells of the same tumor.

When the "primary" tumor is removed by simple amputation of the tumor-bearing foot, immunity to challenge by injecting tumor cells into the contralateral foot wanes rapidly. A perceptible diminution in immunity is evident by the 4th day after amputation, and by the end of a week the challenged mice show growth of tumor. If the tumor-bearing foot is irradiated by

a single, destructive dose of 4,000 R, however, the immunity of the mouse persists during the three weeks in which the tumor is regressing and dying. Apparently during this period the doomed, but not yet dead, tumor cells retain their antigenicity and maintain the immunity of the host. Finally, using an isogeneic tumor, it was demonstrated that simple amputation of the tumor-bearing foot resulted in a doubling of the incidence of pulmonary metastasis as compared with treating the foot with 4,000 R in a single dose.[3]

c. Tumor cells are present in the lungs of a tumor-bearing mouse long before they are able to implant themselves and give rise to metastasis

Sarcoma I, isogeneic and never rejected in Strain A mice, metastasizes early to regional nodes but rarely to the lungs no matter how long it is allowed to grow on the feet. Yet when the mice were killed on the 14th day after the tumor had been implanted on the feet, and their lungs were minced and injected into the thighs of other mice of the same strain, cancer was transferred to all of the injected mice. In many mice cancer could be similarly transferred by injecting blood of the tumor-bearing mice. By this technique it was shown that from the 7th day on enough cancer cells were present in blood or lungs of tumor-bearing mice to enable the tumor to be transferred. Yet control mice treated at the same time by simple amputation of the feet and allowed to survive until they died of their regional node metastases failed to develop pulmonary metastasis.[4] This experiment shows again that cancer cells are widely distributed in the body but do not necessarily grow unless there is an abrogation of the animals' immunologic defenses.

d. Summary of laboratory observations

There is mounting evidence that in mice, all carefully studied tumors are antigenic regardless of whether they occur spontaneously, are the result of infection by a virus, or are caused by treatment with a carcinogen. Since tumors that metastasize to lungs regularly in isogeneic hosts rarely do so in allogeneic hosts, it seems that the host's resistance to metastasis depends to a large extent on the antigenicity of the tumor and the integrity of the host's immunologic system. Many tumors that do not metastasize in hosts whose immunologic system is intact will do so when immunity is suppressed, as by antilymphocytic serum. Since removal or irradiation of regional nodes early in the course of a cancer's growth increase metastasis, since cancer cells can be shown to be present in blood and lungs even in animals who do not develop pulmonary metastasis, and since removal of cancers results in the rapid waning of concomitant immunity, it would seem that to perform a radical operation that removes the primary tumor and regional nodes would predispose to the establishment of distant metastases. Moreover, current experiments suggest that irradiation of uninvolved but immunized nodes releases an enhancing antibody, or in some other way abrogates immunity to the extent that an allogeneic tumor grows 30% faster when irradiated immune nodes are transplanted into the host's abdominal cavity than in control animals or in

animals injected with irradiated normal nodes. This transfer of enhancement by irradiated immunized nodes is the reverse of the Mitchison experiment in which immunity was transferred in nonirradiated immunized nodes. When radiation is given prophylactically to the regional nodes that drain a cancer, it is possible that similar enhancing or blocking antibodies are liberated.

In summary, if one relies on animal models, it would seem that in the absence of demonstrable nodal metastasis the treatment least likely to promote systemic spread of cancer is a single, destructive dose of radiation to the primary tumor, with the regional nodes carefully shielded. Later, if nodes become palpably involved they can be treated.

3. Clinical evidence of the importance of regional nodes in the defense against metastasis

a. Clinical experience

Until McWhirter showed that treatment by simple mastectomy and irradiation was as effective as radical mastectomy, the Halsted operation was standard treatment in both Europe and America. Since that time the conventional operation has been challenged on every side, not only by Urban and others who advocate extended radical mastectomy with removal of the nodes of the internal mammary chain but also by Peters,[5] and recently by Wise and his colleagues,[6] Atkins and his colleagues,[7] and Taylor and his colleagues,[8] who have recorded survival rates as high after local excision and irradiation as after radical mastectomy with or without irradiation. Local excision without irradiation has been reported to be as effective as total mastectomy in both the rate of survival and the incidence of local recurrence.[9]

b. Experience at the Cleveland Clinic

For the past 10 years I have been reporting that when axillary nodes are not involved the survival rate of patients appears to be higher when the nodes are not removed or irradiated.

In 1955 my associates and I initiated a prospective clinical trial in which they would continue to treat patients with breast cancer in the conventional way, usually by radical mastectomy with or without added irradiation, whereas I would simplify the treatment as much as possible, seldom using prophylactic postoperative irradiation, performing no radical mastectomies at all, using no skin grafts, cutting all skin flaps short and thick so that their blood supply would not be impaired, and using simple mastectomy without irradiation whenever there was no palpable involvement of nodes. When the tumor was small and located in the periphery of the breast, treatment was often by wide local excision (partial mastectomy), usually without irradiation. When the nodes showed slight to moderate involvement, as judged by palpation of the axilla during the operation (operative as compared to clinical staging), treatment was by modified radical mastectomy, in which the axillary fat pad from the vein down was removed without dividing or removing the muscles. No irradiation was added. But if nodal involvement was extensive and involved the apex of the axilla, the axillary dissection was abandoned and after removing the breast and sometimes the largest low and central

nodes, cobalt teletherapy was given. In this way no patient was subjected to the morbidity and risk of lymphedema of the arm that so often follows radical axillary dissection and irradiation.

The incisions used for mastectomies were the same regardless of whether or not the axillary contents were removed. They were made transversely and ended just below the hairline of the axilla.

The first clinical trial lasted only 3 years, for by then my colleagues had become convinced that in terms of recurrence, radical mastectomy gave no better results than simple operations. Moreover, the more radical forms of treatment increased the discomfort and disability of their patients. During the 3-year period, however, we had an opportunity to compare the survival of patients treated by radical or modified radical mastectomy with or without irradiation with that of an unrandomized but similarly staged group of patients treated by simple mastectomy or local excision with or without irradiation. The survival of the patients treated by simple operations, usually without irradiation, was a little higher at 5 years than that of the patients treated by radical operations, often supplemented by radiation. Yet in terms of survival no claim of superiority of one method of treatment over the other can be made because factors of selection were present and the study was not randomized. Its chief significance was to show that the difference in favor of the simple operations was even greater at 10 years than at 5, thus negating the contention that if radical operations are not done the short range survival is good but the long term results are inferior.

After 1957 fewer than 1% of the operations done for breast cancer at the Cleveland Clinic were radical mastectomies. The type of treatment given from 1957 through 1965 is listed in *Table 1* and the results are listed in *Table 2*. Moreover, the incidence of partial mastectomy has increased steadily until now it is used in nearly half of the operable patients.

Even more astonishing than the results obtained by simple mastectomy without irradiation are the extraordinary results after partial mastectomy (wide local excision) of breast cancers usually without irradiation. From 1957 through 1965, 53 patients with

Table 1.—Treatment 1957 through 1965; operable patients, Stages I and II

Treatment	Number	Percent
Radical mastectomy	4	1
Modified radical mastectomy	220	48
Simple mastectomy or local excision	231	51
Local excision	49	11
Cobalt postoperatively	96	21

Table 2.—Five-year survival; 1957 through 1965

	Number	Percent
Crude survival (all patients in all stages)	339/571	59
Operable Stages I and II	326/455	72
Inoperable Stages I and II	0/8	0
Stages III and IV	13/108	12
Local recurrence	27/455	6
Followed 5 years	568/571	99.5

Table 3.—Comparison of results of partial vs total mastectomy

Results	Partial mastectomy	Total mastectomy
Lived 5 years	41/53 77%	37/53 70%
Local recurrence	3/53 6%	4/53 8%

1. Patients were matched at random for size of tumors (average 2 cm) and involvement of nodes (40%) in both groups.
2. All had invasive cancer. Age and histologic types were the same.
3. Axilla was dissected or irradiated less frequently after partial mastectomy (40%) than after total (66%).

relatively small peripherally placed invasive cancers were treated in this way. Sixty percent of them had true Stage I* cancers and 40% had true Stage II. Seventy-seven percent of these patients survived for 5 years. Each of these patients was matched at random with a patient from the total mastectomy group who had a tumor of the same size and similar involvement or noninvolvement of axillary nodes. Seventy-seven percent of the patients treated by partial mastectomy were alive after 5 years compared with 70% of those treated by total mastectomy. The only local recurrence in a patient with Stage I cancer was in a woman who had a prophylactic axillary dissection and was found to have nine nodes involved. There were two local recurrences in the clinical Stage II patients. Thus there were three local recurrences (6%) in the patients treated by partial mastectomy compared to four (8%) in those treated by total mastectomy† (*Table 3*).

These results of our current studies of breast cancer give support to the laboratory studies that indicated the importance of uninvolved regional nodes in the host's defense against cancer. These results indicate that when nodes are involved there is no difference in survival regardless of whether the nodes are resected prophylactically, as in radical mastectomy, or if they are not treated until they become palpably involved and then are resected by delayed axillary dissection (*Table 4*). They also suggest that resection of uninvolved nodes may promote metastasis because the survival rate of patients who had no involvement of nodes was higher when the nodes were neither irradiated nor removed than when they were resected prophylactically (*Table 5*).

It is clear from the above results that no harm is done when axillary dissection is delayed until the nodes are palpable. This observation and the low incidence of local recurrence after partial mastectomy has encouraged us to treat a higher proportion of patients by partial mastectomy without irradiation. At present about 40% of the patients with operable breast cancer are being treated in this way.

4. Clinical results with conservative operations for cancers other than of the breast

The principles of cancer surgery have been so deeply and at times so

* *True Stage I means that if axilla was dissected no nodes were found to be involved or if it were not dissected involvement of nodes never occurred.*

† *Local recurrence is defined as any recurrence in the skin, scar, breast, chest wall, or axilla, with the provision that if the axilla was not dissected or irradiated the first appearance of cancer in axillary nodes is not counted as a local recurrence.*

Table 4.—Operative Stage I with occult carcinoma in nodes, 1955–1965

Treatment	Average number of nodes positive	Patients with only one node positive	Lived 5 years
Radical or modified radical mastectomy; 27 patients	3.8	8/27 30%	17/27 63%
Simple mastectomy; no radiation; axilla dissected later; average delay 22 months; 26 patients	3.4 to 4.3*	10/26 38%	17/26 65%

* Indefinite figure because when nodes became palpably involved three of the 26 patients were treated by irradiation instead of by axillary dissection. Lower figure assumes one node involved, upper figure assumes 10 nodes involved.

Table 5.—True Stage I; all invasive carcinoma 1.5 cm to 4.5 cm in diameter, 1955–1965

Treatment	Average size	Average age	Lived 5 years
Radical or modified radical mastectomy	2.75	55	52/73 73%
Simple mastectomy without radiation	2.7	58	101/120 84%

dogmatically imprinted on the minds of medical students that some surgeons find it impossible to believe that simple operations can often be as effective as radical ones. A century ago, when the first radical operations for cancer were being developed, almost all cancers were advanced and hopelessly incurable. All that could be hoped for was local control of the disease. Today this has changed, and the majority of cancers are so small that to treat them in the way they were treated at the turn of the century would be an anachronism.

Many cancers are internal, affecting organs such as those of the gastrointestinal or genitourinary tracts, and many of these are still advanced when first recognized. It is not simple to treat these cancers locally because they are so large and because there is no way of observing the lymph nodes so that involvement can be recognized early and treated appropriately. But there is growing evidence that cancers such as those of the breast, mouth, skin, and even rectum can be treated primarily by local excision, electrocoagulation, or intense local irradiation. If later on, nodes that do not seem to be involved become palpable, they can be dissected secondarily. The rate of survival appears to be just as high as if they had been removed at the same time the primary tumor was treated.

In our experience with rectal cancer, it is clear that small or medium sized low lying cancers can be treated more effectively, in terms of survival, by electrocoagulation than by radical surgery, unless the mortality rate of the radical operation is lower than 3%. Since only 30% of these cancers have nodes involved and only 20% of those with nodes involved are permanently cured by abdominoperineal

resection, radical operations result in only a 6% higher rate of cure than local treatment in which the nodes are disregarded. Moreover, if the patient dies of the operation his survival time is zero compared to 5 to 10 years in many of the patients who die ultimately of metastasis after electrocoagulation. It is clear that the mortality rate of the combined abdominoperineal resection must be much lower than the 10% national average before the radical operation can result in more man-years of survival than local treatment.[10]

Conclusion

Since it is now well established that in terms of survival, conservative, nonmutilating methods of treatment can compete successfully with conventional radical operations, it is time to reevaluate many of our standard methods of treating cancer. Fear of the treatment, whether it be radical mastectomy or colostomy, may be more compelling than the fear of the disease, and may result in fatal delay.

The ability to avoid the disfigurement of mastectomy or the embarrassment of colostomy may lead patients to accept conservative treatment earlier than they now do the radical operations.

If surgeons can simplify their treatments, it is likely that patients will accept them earlier, and that a higher proportion of patients with cancer will be cured.

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