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The Possible role of irradiation therapy to the internal mammary lymph node chain following radical mastectomy for stage I and stage II carcinoma of the breast

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THE POSSIBLE ROLE OF IRRADIATION THERAPY TO THE INTERNAL MAMMARY LYMPH NODE CHAIN FOLLOWING RADICAL MASTECTOMY FOR STAGE I AND STAGE II CARCINOMA OF THE BREAST

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INTRODUCTION

Carcinoma of the breast is responsible for the death of 17,000 women annually.(1) In spite of the many advances in surgical technique, adjuncts to surgery, and education of the lay public concerning the cancer problem and its early diagnosis, there has been very little improvement in the cure rate in the past thirty years.

Historically, many contributions have been made in an effort to increase the cure rate. Some of these have been excisional biopsy, frozen section technique, redraping, repreping, the use of new instruments after the biopsy and many more, all of which have cut down the incidence of local recurrence and consequently have saved more lives. Extended operations, such as the supra-radical mastectomy of Urban (2), have been designed in an effort to salvage those people with internal mammary node metastases. The use of irradiation therapy in combination with surgery has been tried, again slightly improving the cure rate. More recently the use of biologicals, such as nitrogen mustard, thiotepa, and others, have been tried. Hormone therapy, oophorectomy, and adrenalectomy have been proven to be useful palliative agents. None of these forms of therapy, with their added positive results, would have been developed if a fatalistic viewpoint had been accepted in the past.

If the cure rates are to continue to improve, even if by only a few percentage points, results of treatments must continually be reviewed and other adjuncts to therapy contemplated and tried. Also, more extensive studies of breast cancer and its mode of spread must continually be made.

We know that breast carcinoma usually arises as a single focus in a duct, that it spreads locally along the ducts, fascial strands, and into the less resistant mammary fat, and that it metastasizes by lymphatics and the blood stream. The primary focus is quite radioresistant (3), but the metastases are much more radiosensitive and capable of sterilization.(4) The tumor is most likely under hormonal influences as it never occurs prior to puberty.(5)

Some stage I and about one-half of stage II carcinoma patients will develop metastases or die of the disease within five years of surgery. If the operation had removed all the tumor and its lymphatic metastases this should not occur. This, therefore, indicates that the original staging was incorrect and that some patients already had blood borne metastases, while others had internal mammary and/or supraclavicular nodal involvement. Handley (6) reported that 46 per cent of patients with axillary nodal involvement will have deposits in the internal mammary chain; 33 per cent will metastasize only to the internal mammary

chain; and 60 per cent of inner quadrant lesions (20 per cent for lesions in the outer quadrant) have spread to the anterior mediastinum when treatment is begun.

Treatment of the internal mammary chain has been by two methods:

1. The Urban supra-radical mastectomy removing these lymph nodes.
2. Post-operative irradiation to the internal mammary lymph node chain.

It is, therefore, proposed that the internal mammary chain of lymphatics is a primary lymphatic drainage of the breast and must be eradicated either surgically or by irradiation if the cure rate for breast cancer treated by radical mastectomy is to be increased. The purpose of this paper, therefore, is to review the effects of irradiation on the breast cancer cells and postulate expected results of irradiation to the internal mammary chain of lymph nodes.

The conclusions drawn will be applied solely to potentially curable carcinoma of the breast and not to inoperable or widely disseminated disease.

ANATOMY OF THE INTERNAL MAMMARY LYMPH NODE CHAIN

The internal mammary chain of lymph nodes lies deep to the plane of the costal cartilages and is plexiform

around the internal mammary blood vessels. Lymph glands are usually present opposite the first, second, third, and sixth intercostal spaces; the second intercostal space gland is usually the most constant. The chain drains the anterior chest wall, breast, and anterior mediastinum, and, it is presumed, the upper abdominal wall and periphery of the diaphragm. It commonly empties itself into a gland situated just above the medial end of the clavicle and from there into the great veins; however, this gland is not always present. In addition to macroscopic nodes, there are in the internal mammary lymphatic network many small nodes, and each composed of only a few lymphoid follicles.(6,7)

HISTOLOGIC EFFECT OF IRRADIATION ON NORMAL TISSUE

Irradiation in excessive amounts when applied to living tissue produces damage to the various components of cells. This damage is greater the nearer the source of irradiation is to the tissue, but it affects indiscriminately all living cells in the field with what has been termed a "cytocaustic" effect. This effect is similar to that which is due to an excessive application of any heat, cold or caustic substance. On the contrary, appropriate amounts of irradiation of the proper quality may pass

through the superficial layers of tissues without any adverse effects and have an effect only on cells more deeply situated. This is referred to as the selective cytolethal effect and is utilized in the treatment of malignant tumors by radiotherapy.(8)

The lethal effect of irradiation on living cells is the final result of the ionizations produced in their collision with the components of living cells. Although the immediate effect in some instances may be the death of the cell, the damage done may become manifest only after the cell undergoes mitosis, and still in other instances it is only appreciable in the cell's descendants. The expression "lethal dose" has no significance in radiobiology. Cells of the same species simultaneously irradiated die after receiving extremely variable amounts of irradiation. Working with different unicellular organisms, it was noted that irradiation induced several types of lesions and that the relative proportions of these lesions varied with the dose. Interpreting these facts according to the quantum theory (corpuscular nature of irradiation), these lesions were attributed to different qualitative and quantitative actions of irradiation on the individual cells. These were:

1. The immediate death of the cell due to the absorption simultaneously of large numbers of particles in the cell producing the destruction of the different cellular components.

2. Delayed growth due to partial destruction of protoplasm.

3. Suppression of motility due to its actions on the motor center of the cell.

4. Suppression of reproduction due to destruction of the centriole.

5. Abortive anomalies of cellular division due to destruction of varying quantities of nuclear chromatin.

6. Hereditary malformation due to a lesion of a particular segment of chromosomic substance (gene).

The effects so far mentioned can be attributed to the ionization of molecules in the path of the ionizing particles, but it has been shown that the biologic effect is not solely determined by the total number of ions but that it is also conditioned by the spatial distribution of the ions.

The effects of irradiation on living cells cannot be explained, however, on the basis of physical trauma alone, nor can the complicated organization of normal tissues be considered, for the understanding of radiobiology as the equivalent of an aggregate of unicellular organisms. The chemical effects of ionization of cellular components, the possible changes of the permeability of the cellular membrane, the ionization of circulating minerals and their effect on the interchange of fluids, and the effects of irradiation on the connective tissue and on blood supply contribute, in all probability, in a lesser or greater extent to the final result.(9)

Living tissues react very differently to irradiation.

Those tissues formed by uniform cells, not usually arranged in layers, generally show very little radiosensitivity; their injuries due to irradiation are usually an indirect consequence from the resulting fibrosis or impaired vascularity. Tissues composed of multiform cells in continuous transformation, usually arranged in several layers (epidermis, seminiferous tubules, etc.), present marked radiosensitivity. But the individual cells of these complex tissues show a very variable degree of response to irradiation, the germ cells (spermatogonia, lymphoblasts, etc.) being considerably more affected than their somatic descendants; this results in an apparent latency of the effects which may not make themselves evident for several weeks.

The intensity of the effects of irradiation and their permanency depends upon various intrinsic or extrinsic factors. The quality and quantity of irradiation has an obvious bearing on the results; the greater the dose and the lesser the quality of the radiations, the less selective is its action and the more marked and diffuse is its effects and the less reversible are these effects. The elongation (fractionation) of irradiation results in exactly the opposite effects.

The immediate reaction and the ultimate effects of radiation on the different tissues and organs greatly

depends upon the quantity and character of the radiations and the circumstances of their application.(5)

HISTOLOGIC EFFECTS OF X-RAY ON MALIGNANT TUMORS

Irradiation of neoplastic cancer cells may produce almost immediate destruction of those cells in mitosis, and shortly after, an abnormally large number of degenerative mitoses followed by death of the cells from accelerated maturation. Whenever this result can be accomplished repeatedly by new irradiation, complete destruction of the tumor can be accomplished. However, a large number of malignant tumors even under intense irradiation may not respond in such a manner and may continue to grow. This difference in response to irradiation is primarily an attribute of their cell of origin.

Individual cells within a tumor may present a widely different susceptibility to irradiations. In tumors composed mainly of radiovulnerable cells (lymphosarcomas, myelomas, etc.), the administration of a small dose of irradiation results in immediate destruction of a great proportion of these cells and in grossly evident reduction in size of the tumor, although a recurrence of growth may rapidly follow. In tumors composed of a variety of cells in different stages of differentiation (epidermal carcinoma), even a large dose of irradiation may not affect the

most differentiated cells (horny layer). There may be no grossly noticeable effects for days or even weeks, yet the destruction of the germinal cells eventually results in complete disappearance of the malignant tumor. In tumors composed mostly of cells which are not radiolabile (malignant melanoma), the most intensive irradiation may not produce any immediate or delayed effect. These examples illustrate that the radiosensitivity of a tumor depends primarily on the radiosensitivity of the cell of origin; that the gross reduction in size of a tumor depends on the proportion of cells that are immediately affected by the irradiation; that the lack of immediate response does not necessarily indicate radioresistance; and that radiosensitivity is not synonymous with radiocurability although the radiocurability of a tumor depends, above all, on its radiosensitivity.(10)

The number of mitotic figures or the proportion of undifferentiated cells may be indicative of the immediate response of a so-called radiosensitive malignant tumor, but anaplasia and reproductive activity are not in themselves signs of radiosensitivity in any or all malignant tumors.

The main requisite of radiocurability is radiosensitivity. Radioresistant or fairly radiosensitive malignant tumors are not radiocurable since their destruction by means of irradiation requires a dose so intense that it

produces a diffuse cytocaustic effect which implies necrosis of surrounding structures. A relatively small dose of irradiation may result in a rapidly noticeable effect in a lymphosarcoma of the tonsil, while it may not appreciably affect an epidermoid carcinoma in the same area. Yet all other conditions being equal, the total dose required for the sterilization of either tumor does not differ greatly. Moreover, one type of tumor may be cured by administration of rather different amounts of irradiation, depending on several variable factors, including the period of time over which the therapy is given. Thus, the total dose necessary to sterilize different tumors is not necessarily an index of their radiosensitivity.(10)

The total sterilization of a tumor requires a minimum total dose of irradiation capable of destroying all germinal cells within a tumor and consequently discontinuing reproductivity of malignant cells. Radiocurable tumors are those in which the administration of such minimum doses is compatible with sufficient recovery of surrounding normal tissues to assure the integrity of the tissues. This margin between the destruction of the tumor and the untoward effect on neighboring normal tissues decreases as the tumor becomes less radiosensitive; it becomes a negative quantity in non-radiocurable tumors, for the quantity of x-ray necessary for the tumor destruction

is incompatible with the life of the surrounding tissues and implies irreparable injury or death. If the required amounts of irradiation are delivered in a single dose, the margin of safety is narrow.(11)

Effect of X-ray on Breast Carcinoma Cells, Both Primary and Metastatic

The histologic findings reported following serial section of breast and nodes removed for carcinoma and which had previously been treated with high voltage irradiation (between 2000 r and 4000 r) are as follows:

The most striking change noticed was the actual disappearance of malignant cells following irradiation, which seemed to take place in one of the following ways: (a) Acute cells dissolution, immediate or delayed; (b) Alteration of cell structure followed by death.

Cell dissolution

In different tumors varying numbers of malignant cells die and disappear from the tissues according to the sensitivity of the individual neoplasm. A certain number of cells are killed and removed, while others remain without showing any specific microscopic changes until at a higher dosage or after a longer period of time they also undergo necrosis. These changes were noted by studying multiple biopsies taken from the same tumors after varying dosages.

An important point which may be stressed is that some malignant cells seen remaining in a biopsy specimen taken soon after irradiation therapy has finished may disappear after a time interval even though no further irradiation has been given. Clearly such cells must be fully differentiated and incapable of further reproduction.

It would appear to be significant that in all the cases studied receiving a dosage higher than 3500 r very considerable tumor destruction occurred. In 4 out of 11 cases there was complete disappearance of malignant cells, and in the 7 remaining cases only grossly altered cells, of a type which will be considered later, were demonstrated histologically after careful search.(12)

The actual mechanism of acute cell dissolution seems to be principally by lysis of both nucleus and cytoplasm, although some examples of pyknosis and karyorrhexis of the nucleus were seen.

Alteration of cell structure

(a) Degenerative changes which are felt to be a mutation-like alteration.

(b) Nuclear changes include a tendency to pyknosis on the one hand and enlargement with or without vacuolation on the other. A type of nuclear enlargement seen where there is a conglomeration of chromatin to produce an intense hyperchromatic appearance with loss of normal

pattern. Vacuolation of the nucleus is occasionally seen.

(c) Cytoplasmic and cell membrane changes. Vacuolation in the cytoplasm together with a foamy transformation of the cytoplasmic substance. The permeability of the cell membrane is altered and there is a constant tendency for the cells to run together to form a syncytium, a further evidence of cell membrane damage.

(d) Giant cells were seen commonly, either as large cells with a single dense hyperchromatic nucleus, usually without a clear-cut chromatin network, or as multinucleated cells.(12)

Lumb disagrees with Melnick (13) who stated that nuclear calcification was the most significant mechanism of post-irradiation death other than acute dissolution because they found areas of calcification in only 50 per cent of the cases and in those it was not constant throughout the tumor.

The connective tissue change noted was that the fibrous stroma is laid bare and small capillaries dilate following the disappearance of the malignant cells. The ensuing stromal changes closely followed the normal course of repair, in that a gradual increase in fibroblastic activity occurred with the appearance of collagen strands, and gradual obliteration of small vessels. Of the remaining blood vessels it was common to find evidence of some

intimal proliferation, but only occasionally did this produce lumen obstruction and only in two cases was vascular thrombosis found.(3)

SUMMARY

The fact that some Stage I and one-half of Stage II carcinoma of the breast patients die of the disease or its metastases is noted. This is in spite of radical mastectomy which is intended to remove the primary focus and its lymphatic drainage. Therefore, it is felt that the original staging was wrong and that many of the patients have blood borne or internal mammary nodal involvement. The internal mammary chain as a primary lymphatic drainage of the breast may be eradicated in two ways, thereby saving patients with involvement limited to these nodes. The methods are (a) the Urban supra-radical operation and (b) post-operative irradiation to the area of the internal mammary chain.

The effects, histologically, of irradiation in normal tissue and malignant tissue is discussed with particular reference to breast cancer cells.

CONCLUSION

The previous statements made are the facts as known to date. The problem arises because of:

(a) The many conflicting reports by various authors concerning the degree of regression and sterilization of the primary focus and metastatic involvements of breast cancer when treated by irradiation.

(b) The varying dosages of irradiation given both pre-operative and post-operative to metastatic lesions in the past, thus making evaluation of their results very difficult.

(c) The lack of series of sufficient duration in which post-operative irradiation of adequate quantity was given to the internal mammary nodal chain so that an evaluation of its effects might be noted.

Although irradiation treatment both pre-operative and post-operative has been used for years, most series reported used what today is considered to be a very inadequate dose. The present day concept is that at least 4500 r or more is necessary if any real attempt at sterilization of metastatic lesions is to be made.

Because of this lack of controlled studies of the effect of post-operative irradiation to the internal mammary chain, it is not justified to draw a conclusion as such. However, a premise may be proposed, on the basis of the known facts, which may be proven or disproven in the future but which may serve as a basis for experimental work at the present.

The histologic changes noted in mammary cancer cells following irradiation, as reported by the various authors, would suggest that in general mammary cancer cells are radiosensitive in themselves and are able to be destroyed. However, it has also been shown that in the primary focus of tumors even when irradiated by adequate doses of x-ray, viable tumor cells remain. This, however, is not the case with all metastatic lesions. They have been shown to be more susceptible to sterilization by irradiation. The reason for this is not known.

Because of these facts it therefore seems quite reasonable to assume that metastatic involvement of the internal mammary lymph node chain if treated by adequate amounts of irradiation could be destroyed. If, therefore, this treatment were used in conjunction with radical mastectomy we would be eradicating the primary focus of tumor along with the two primary lymphatic pathways, i.e., axillary and internal mammary. In those patients with tumor limited to those areas and treated in this way a cure should be effected. This then should add to the cure rate those patients who up to now have been considered to have either no lymphatic involvement or only axillary involvement, while in reality they had involvement of the internal mammary chain.

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BIBLIOGRAPHY

1. Haagensen, C. K., Diseases of the Breast, 2nd ed., Philadelphia, W. B. Saunders Co., 1956.

2. Urban, J. A. and Baker, H. W., Radical Mastectomy in Continuity with EN Block Resection of the Internal Mammary Lymph Node Chain, Cancer, 5:999, 1952.

3. Williams, I. G. and Cunningham, G. H., Histologic Changes in Irradiated Cancer of the Breast, Brit. J. Radiol., 24:123, 1951.

4. Richards, G. E., Mammary Cancer; The Place of Surgery and Radiotherapy in its Management: Part I, A Study of Some Factors Which Determine Success or Failure in Treatment, Brit. J. Radiol., 21:109, 1948.

5. Haagensen, C. K., Diseases of the Breast, 2nd ed., Philadelphia, W. B. Saunders Co., 1956.

6. Handley, R. S. and Thackray, A. C., The Internal Mammary Lymph Node Chain in Cancer of the Breast, Lancet, 276-78, (Aug. 13) 1949.

7. Handley, R. S. and Thackray, A. C., The Internal Mammary Lymph Node Chain in Cancer of the Breast, A Study of Fifty Cases, Lancet, 2:276, 1949.

8. Bloom, W., Histopathology of Irradiation, From External and Internal Sources, Nuclear Energy Series, Division iv, Vol. 22, I, New York, McGraw Hill Book Co., 1948.

9. Ackerman, L. V. and del Regato, J. A., Cancer, Diagnosis, Treatment and Prognosis, St. Louis, C. V. Mosby Co., 1954.

10. Warren, S., The Radiosensitivity of Tumors, Am. J. Roentgenol., 45:641-50, 1941.

11. Lenz, M., Tumor Dosage and Results in Roentgen Therapy of Carcinoma of the Breast, Am. J. Roentgenol., 56:67, 1946.

12. Lumb, G., Changes in Carcinoma of Breast Following Irradiation, B. J. Surgery, 38:182, 1950.

13. Halley, E. P. and Melnick, P. J., Pre-operative Irradiation in Carcinoma of the Breast: Histologic Study, Radiology, 35:430-38, 1940.