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The role of radiation in the treatment of childhood malignancies

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Improvement in the cure of childhood malignancies in the last decades has mostly been due to chemotherapy, however, this modalitity alone is unable to cure solid tumors; there, radiation treatment is an essential part of therapy, especially when surgery is not feasible.
The treatment of malignant tumors in children is therefore often combined: surgery, radiation and chemotherapy may be used sequentially or simultaneously.
At present we are still gathering new information about the timing of radiation, the curative tumor doses, the tolerance of normal tissue when radiation is combined with chemotherapy. The late effects of combined treatment remain a major problem, increasing with the time of observation. These considerations are crucial in children who are more susceptible to radiation damage and have a longer time to develop sequelae and live with them.
Regular follow-up with psychosociaal, endocrinological and cytogenetic aspectst have to be evaluated in detail in children treated for malignancies.

Key words: neoplasms-radiotherapy; child

Introduction

Ionizing radiation has been a part of cancer treatment virtually since its discovery by the Curies and W. C. Roentgen about 90 years ago. In sufficient doses it will kill normal as well as malignant cells and its clinical effect is based on the generally greater sensitivity of the latter. While it is used in some benign conditions, its beneficial effect in patients with malignant tumors has been well recognized.

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The treatment of malignant tumors in children is often combined: surgery, radiation and chemotherapy may be used sequentially or simultaneously.

Although the dramatic improvement in the cure of childhood malignancies in the last decades has mostly been due to chemotherapy, this modality alone is unable to cure solid tumors. Radiaton treatment is an essential part of treatment of these, especially when surgery is not feasible (Figure 1).[1]

If the choice is radiation treatment with attempt to cure, this goal should be pursued vigorously, taking into account some degree of complications, since the issue here is life. After deciding whether curative or palliative radiation therapy is indicated, the dose, volume, and

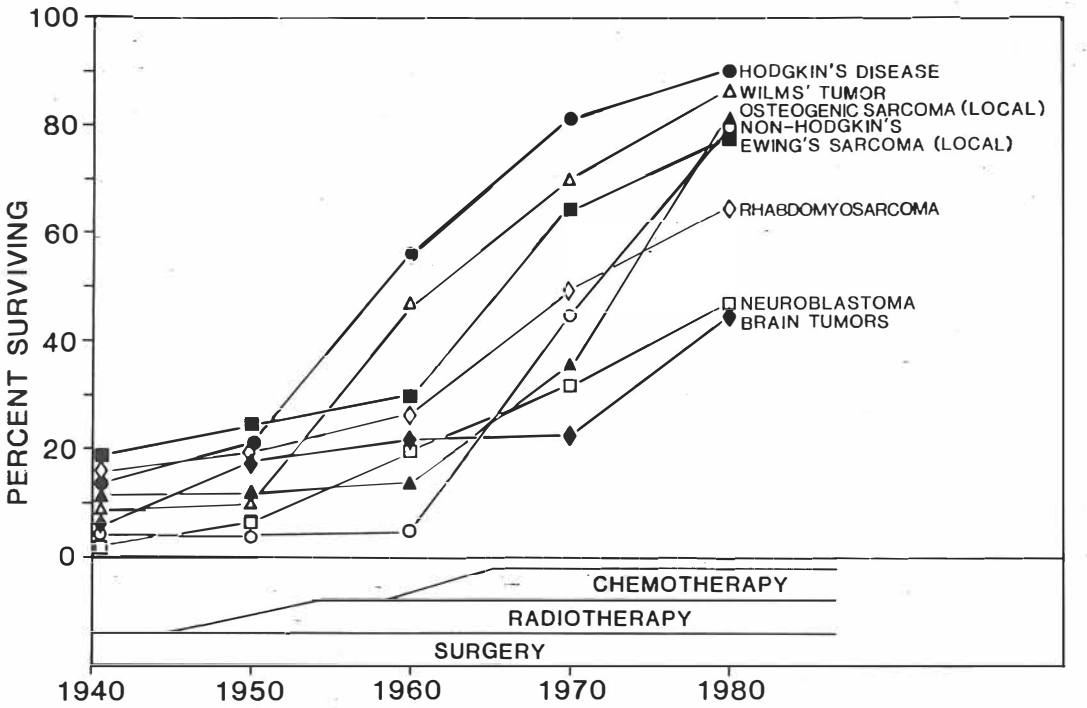

Figure 1. Improvement of 2-year survival of children with malignant tumors during the decades when surgery, radiation therapy, and chemotherapy were developed as a combined modality therapy (1940–1980) – Hammond 1986.

time during which it is delivered are determined.

Some radiobiological and technical aspects

Although radiation affects all parts of the cell, the inhibition of mitotic activity is its most important feature. Rupture of chemical bonds within the DNA molecule strands occurs either by direct absorption of radiation, or indirectly, by ionization of H_20 producing active radicales and electrons.

Microscopical changes are essentially the same, whether the irradiated cell is normal or malignant. The radiosensitivity of a malignant tumor tends to be in the same range, though usually at least somewhat higher, than that of the tissue from which it arose. Thus, tumors, arising from bone marrow, lymphatic tumors, and seminomas, tend to be very radiosensitive, while those arising from cartilage, bone, connective and neural tissues are much more resistant to radiotherapy. The radiocurability will depend, among other factors, on the radiosensitivity of a tumor and the tumor site, limiting the dose of radiation tolerated, as well as on the tumor size.

In order to increase the selectivity of radiation we can:

1) plan such a dose distribution that will result in a low dose (below the tolerance level) for normal tissue and a higher dose (tumoricidal) to the tumor. An adequate image of the treated area, often at several angles, is necessary for planning. A CT scan is usually helpful (Figure 2).

2) increase the gap between the effect on tumor cells and normal cells by fractionation (Figures 3a, 3b, and 3c).[2, 3]

In general, protracted fractionation is used over several weeks, with about 1000 cGy delivered each week. Recently, attempts were

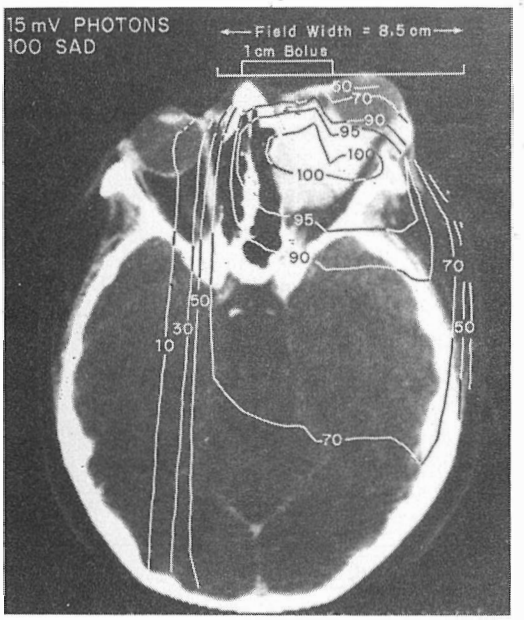

Figure 2. Treatment plan (isodose distribution) for a patient with embryonal rhabdomyosarcoma of the orbit.

made to base the fractionation scheme on modern radiobiologic research, using 2 or 3 daily fractions. Ideally, the dose and its distribution should be timed with the individual tumor growth, but we still lack the knowledge to achieve this (Figures 4, 5).[2]

3) moodify the effect of radiation with radiosenzitizers and radioprotectors (Figure 6).

Various physical, chemical, and biologic agents can modify the radiation response of the cells. Antimetabolites, such as Methotrexate, 5-fluorouracil, and 6-mercaptopurine, also interfere with the DNA synthesis. Cells exposed to these agents become more sensitive to radiation.

Clinical aspects of radiotherapy

Radiation therapy can be given:

locally:
- directly to the tumor (radiosensitive), to inoperable tumors: e. g. ERMS of the epihparynx,
- postooperatively to the tumor bed e.g. Wilms' tumor, Ewing's sarcoma)
- preoperatively, although it has been mostly replaced by chemotherapy it is still used when the response to chemotherapy is poor e.g. neuroblastoma)

or sistemically:
- TBI (total body irradiation) and
- HBI (hemibody irradiation).

It can be given after, before or sandwiched between chemotherapy (e.g. Hodgkin's lymphoma).

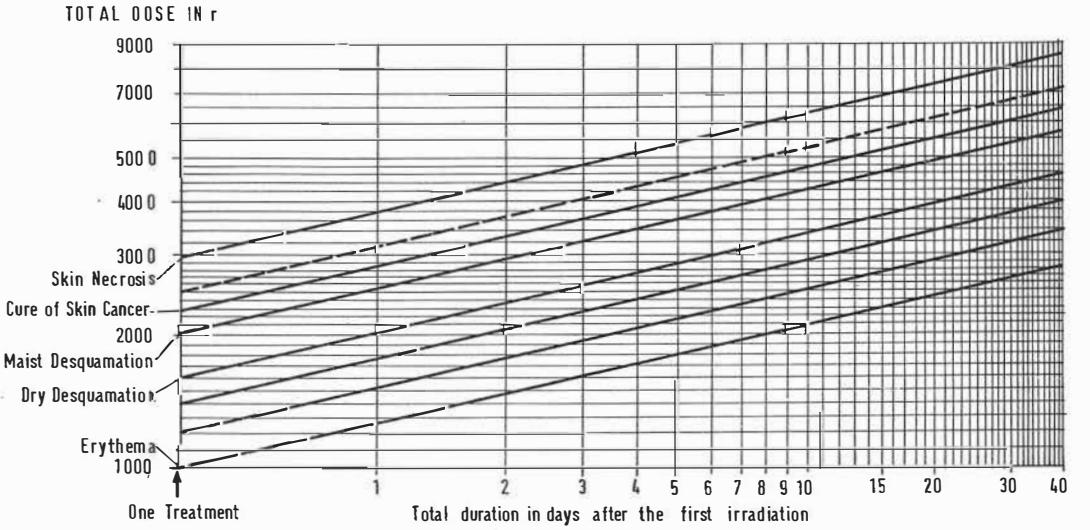

Figure 3a. Effect of fractionated radiation on tumor and normal cells – shematic presentation.

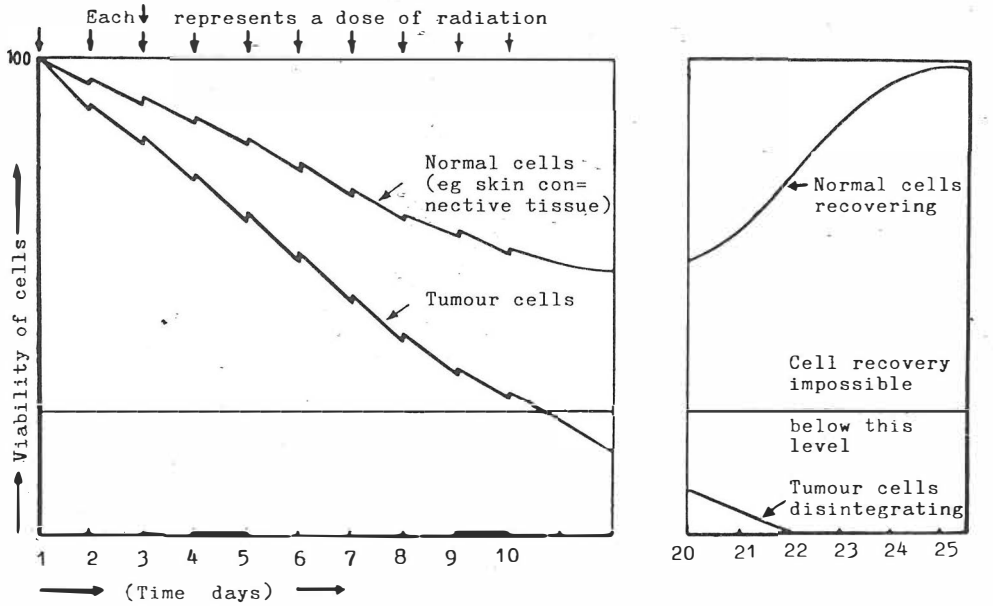

Figure 3b. Effect of fractionated radiation on tumor and normal cells – shematic presentation.

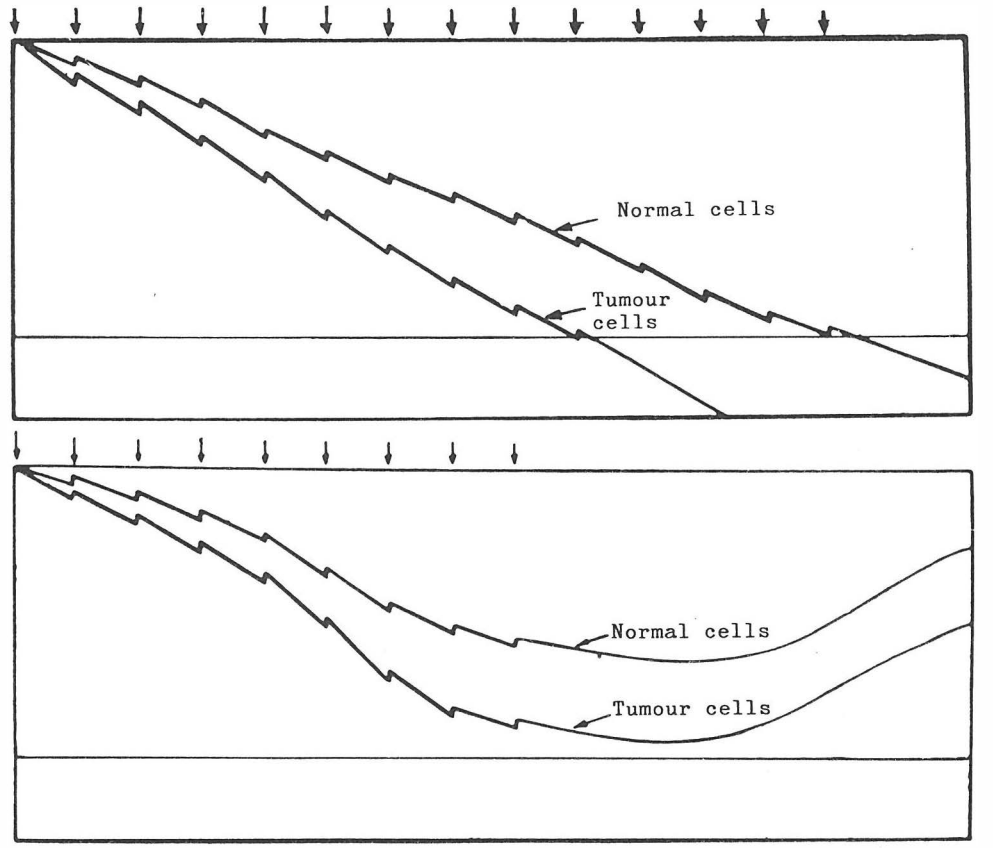

Figure 3c. Effect of fractionated radiation on tumor and normal cells – shematic presentation.

The main sources of radiation used in clinical practice are either external beam machines or sealed radioactive sources. External beam machines emanate:

photons (X-ray machines, betatrons, linear accelerators),

gamma-rays, (Co60 machine, teratron, gammatron, etc.)

electrons: betatrons, linear accelerators protons, neutrons are still only seldom used.

The advantages and disadvantages of different sources can be understood by comparison of the absorbtion of radiation in tissue presented by the isodose distribution courves (Figure 7).

The amount of irradiation prescribed is expressed in units, i.e., the quantity of energy absorbed by unit of mass (ergs/per gram). Rad is the unit absorbed dose where:

1 rad = 100 ergs/gram

A special name for the unit of absorbed dose

is Gy where

1 Gy = 100 rad.

Radiotherapy treatment planning is a routine procedure, and significant improvements are unlikely to occur in the near future. The difficulties, however, are still on the medico-clinical side, e.g. how to specify the targer volume occupied by the tumor bearing tissue more accurately.

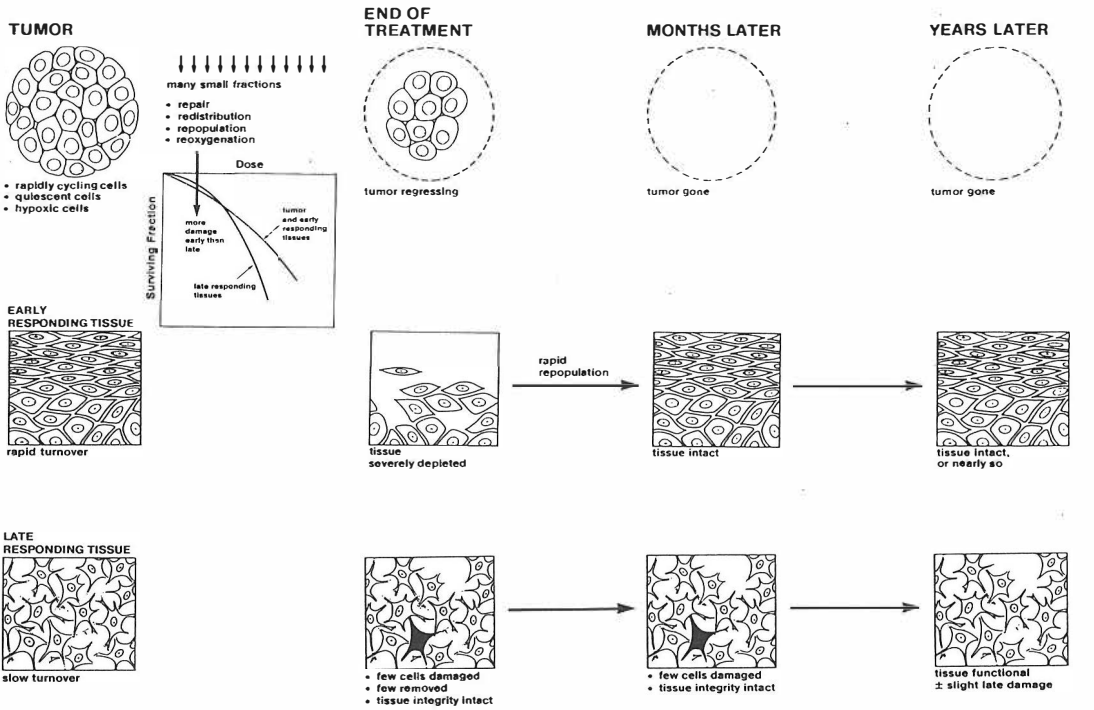

Figure 4. The kinetic pattern following irradiation with many small dose fractions. A small dose fraction produces relatively less damage to late-responding that to early--responding tissues because of their curvy dose-response relationship. The tumor regresses and disappears. The early-responding tissues show a reaction but repopulate by rapid cell division. The late responding tissues show little damage.

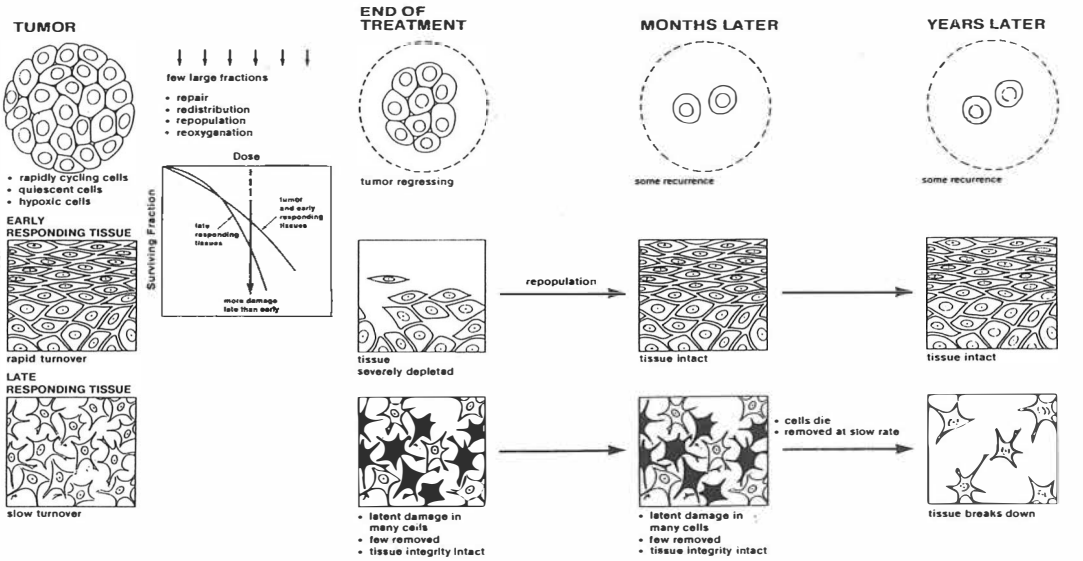

Figure 5. The kinetic pattern following irradiation with a few large dose fractions. A large dose fraction produces relatively more damage to late-responding than to early-responding tissues because of the difference in curviness of the dose-response relationship. The tumor regresses and disappears, though there is evidence of a higher recurrence rate after radiotherapy regimens involving a small number of fractions, perhaps because there is less opportunity for reoxygenation. The early-responding tissues show a reaction but repopulate by cell division; this is the same as in Figure 4 and 5. However, the late responding tissues carry a large amount of latent damage which is expressed months or years later when the cells in these tissues begin to turn over.

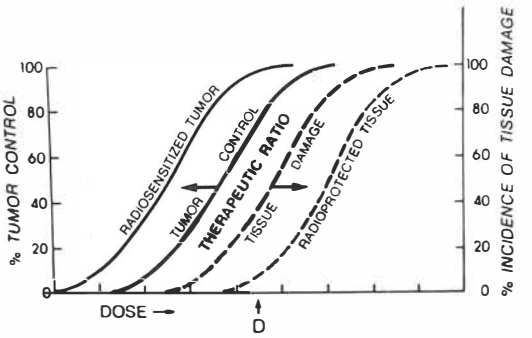

Figure 6. Scheme of therapeutic ratio modification.

Rather than in radiotherapy treatment planning, advances are likely to occur in areas such as combination regimens and modification of dose fractionation schemes. Also, as the prognosis is related to the extent of disease at the beginning of treatment, an earlier diagnosis is essential together with a better knowledge of the spread, and patterns of failure of different tumors. Chemotherapy is an integral part of treatment in the great majority of tumors in children (Figure 8).[4]

Knowledge on the effects of such combined treatment has accumulated very rapidly in the last decades; it is likely, however, that in the near future, we shall still be gathering new information about the timing of radiation, the curative tumor doses, and the tolerance of normal tissue when radiation is combined with chemotherapy.

Although the acute radiation effects (even severe when ChT is given concomitantly) on normal tissue may resolve rapidly, the late effects of radiation remain a major problem, increasing with the time of observation. These considerations are crucial in children who are more susceptible to radiation damage and have a longer time to develop sequelae and live with them (Figure 9).[5]

Some late sequelae have not been recognized until recently and some may be more common

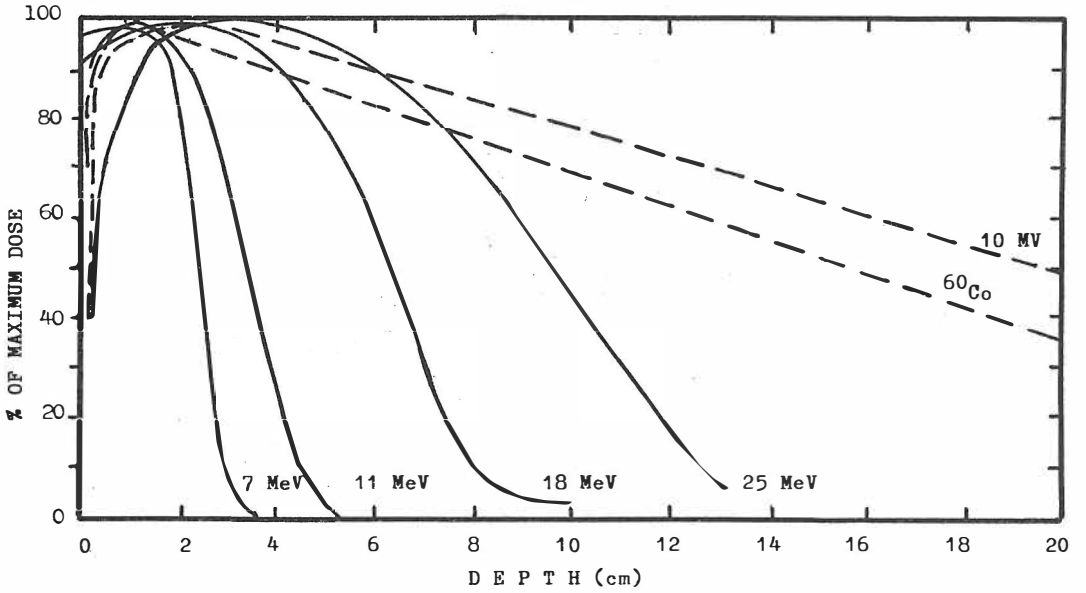

Figure 7. Central-axis-depth dose curves for electron and X-ray therapy beam.

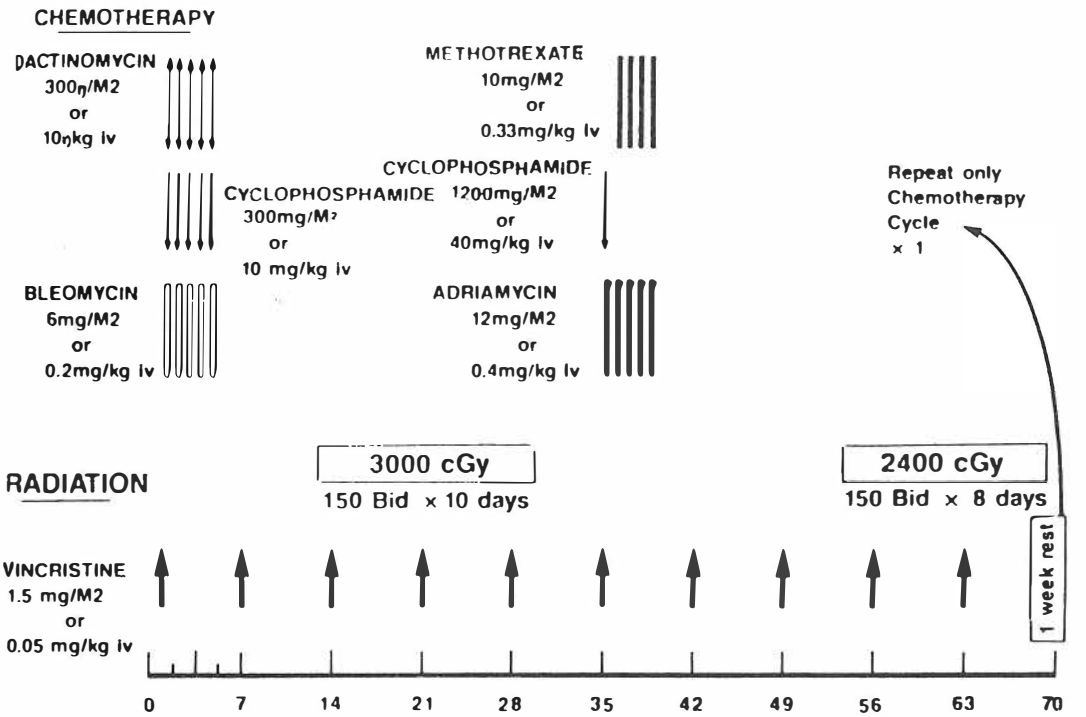

Figure 8. Multidiscipline protocol for solid tumors (Memorial Sloan-Kettering Cancer Center).

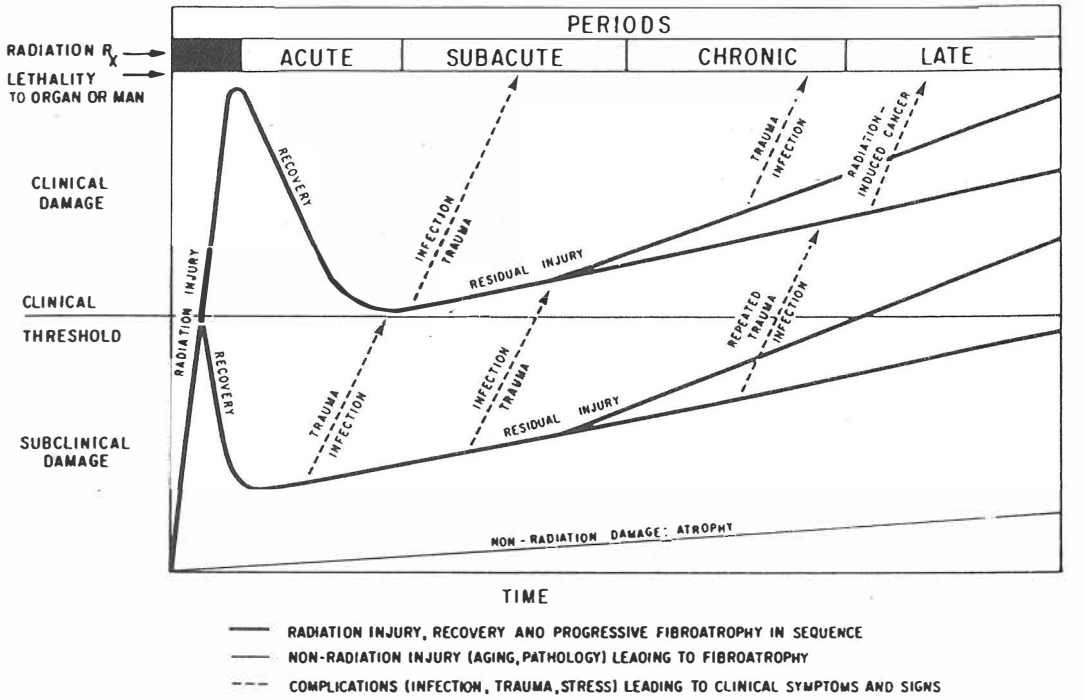

Figure 9. Clinicopathological course of radiation effects: general scheme (Rubin 1968).

than appreciated in the past. While our predominant concern some decades ago was to save the life of the afflicted child, it is now becomming equaly important to minimize the treatment sequelae.[6] Regular follow-up including detailed psychosocial, endocrinological and cytogenetic investigations is required in children treated for malignancies.[7] It has been recognized also that some sequelae can be effectively treated or compensated for. Even secondary tumors, the most serious of the consequences, can be successfully treated if recognized in time.

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