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# Complications of Radiation Therapy and Factors in Their Prevention

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**Radiation therapy of most malignant tumors requires dose-fractionation regimens near the tolerance of the surrounding normal tissues. With the exception of the bone marrow and the lung in which the morbidity may be minimized by reducing the volume irradiated, other structures require limitations of total doses to minimize adverse effects. In thoracic irradiation, the most sensitive normal structure is the lung, while the heart and esophagus do not frequently have serious late effects. Pelvic irradiation carries a much greater risk of morbidity, primarily to the fixed segments of small bowel and less frequently to the large bowel and bladder. Irradiation of the upper aerodigestive tract may be complicated by necrosis of soft tissues and bone, especially the mandible. Dental management greatly affects the risk of complications. Bones and soft tissues elsewhere in the body are rarely affected except in the growing child. The normal pituitary may be irradiated when tumors near the base of the skull are treated. The production of growth hormone may especially be compromised in children. Acute, subacute, and late effects of irradiation of the brain are well recognized. While transient radiation myelopathy is frequent and not serious, progressive radiation myelopathy is rare but extremely grave. Host factors, other diseases, and technical aspects of radiation therapy affect the risks and severity of adverse effects on normal tissues. Surgical procedures may be important in preventing complications as well as in managing them.**

Every treatment for cancer is associated with a certain risk of adverse effects. There are few forms of cancer in which the results are so excellent that clinical investigators would not consider accepting a somewhat higher complication rate if a new therapy offered unequivocally superior results. A few malignant tumors are so exquisitely sensitive to ionizing radiations that they can be eradicated consistently with little risk of morbidity. To eliminate most tumors, however, requires doses of radiations near the tolerance of the surrounding normal tissues.

The most radiosensitive normal tissues, such as the lens, the gonads, and the hematopoietic stem cells, can be altered profoundly by doses of 1.0 gray (1.0 Gy = 100 rad) or less. The least sensitive normal tissues may be injured only when doses reach levels nearly 100 times greater. Table 1 lists normal tissues in the approximate order of decreasing sensitivity to ionizing radiations. In the clinical setting, certain structures are avoided entirely unless adequate treatment of the malignant tumor makes it impossible to do so; these structures include the gonads and the lens. Two other normal tissues, the bone marrow and the lung, are often unavoidable, and the doses administered to them are well above their tolerance. Clinically apparent adverse effects are prevented by limiting the volume of normal tissue irradiated rather than making any attempt to limit the dose received. For the remainder of the normal tissues listed in Table 1, it is usually possible to limit the total doses received within the structures to levels that assure a minimal risk of complications of radiation therapy.

It is beyond the scope of the current discussion to review in detail the radiopathophysiology of each of the normal tissues listed. In order to complement the other presentations in this symposium, 5 separate clinical groupings will be explored briefly: thoracic irradiation (lung, heart, esophagus), pelvic irradiation (small bowel, large bowel, bladder), irradiation of upper aerodigestive tract (oral and pharyngeal mucosa, pituitary gland, mandible), soft

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**Table 1.** Relative sensitivity (decreasing) of mature tissues to ionizing radiations.

| | |
|---|---|
| 1. Bone marrow | 16. Pituitary |
| 2. Ovary | 17. Thyroid |
| 3. Lens | 18. Larynx |
| 4. Testis | 19. Oral mucosa |
| 5. Lung | 20. Esophagus |
| 6. Kidney | 21. Arterioles |
| 7. Lymph nodes | 22. Skin |
| 8. Liver | 23. Bladder |
| 9. Salivary gland | 24. Breast |
| 10. Small bowel | 25. Pancreas |
| 11. Stomach | 26. Capillaries |
| 12. Colon | 27. Bone |
| 13. Spinal cord | 28. Cartilage |
| 14. Brain | 29. Vagina |
| 15. Heart | 30. Uterus |

tissues, bone and cartilage, and nervous system (brain, spinal cord, peripheral nerves). For more detailed discussions of radiation effects, standard texts may be consulted [1, 2].

## Thoracic Irradiation

### *Pulmonary Effects of Irradiation*

The lung is one of the most sensitive structures to irradiation. The pulmonary effects of irradiation are dependent on an interplay of host and treatment factors. Both early and late changes can be seen [3]. The total dose, fractionation scheme, and volume treated are critical elements.

Whole lung dose response data for single fraction treatments, as in half or total body irradiation (Fig. 1) [4], show a steep upward curve with a threshold of 7.0 Gy and a rapid rise to an 80% lethality at 11.0 Gy, with a frequency of 50% at 9.3 Gy, corrected for lung transmission [5, 6]. High dose rates (above 0.05 Gy/min) may increase the frequency [7]. Common fractionation with 1.5 to 1.8 Gy/day improves lung tolerance, presumably by allowing the lung to repair sublethal radiation damage, and results in a frequency of pneumonitis below 5% at total doses of 18–22 Gy [8].

The morphologic changes resulting from irradiation are well described, from both animal work and clinical studies [9, 10], but the dynamic mechanisms of radiation injury are less well understood [11, 12]. The immediate radiation injury is to the type II pneumocyte with early release of surfactant. There is no clinical or radiographic manifestation of this [13, 14]. After a latent period of 1–3 months, injury to the type II alveolar cell may result in its eventual loss, with a compensatory hypertrophic response [15]. During this phase, there may be an infiltrate evident on chest x-ray conforming to the radiation

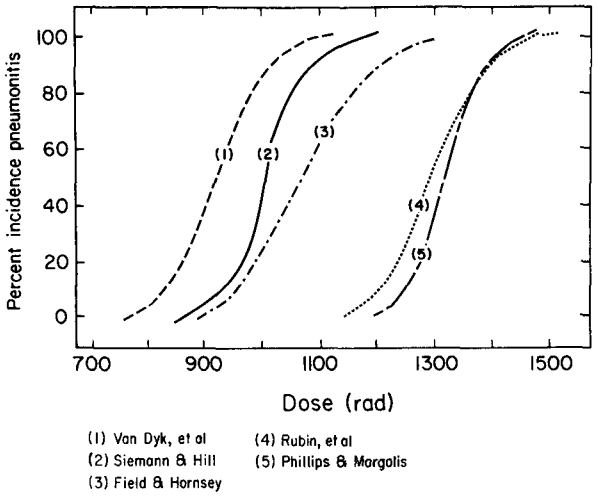


**Fig. 1.** Dose response curves from several studies for pulmonary effects of radiations. From Rubin, P., Int. J. Radiat. Oncol. Biol. Phys. *10*:5, 1984 [4], reproduced by permission of the author.

portal. Clinical symptoms of cough, dyspnea, or low-grade fever may range from none to mild or moderate, depending on the volume of irradiated lung and dose given. Opportunistic infections may worsen the picture.

The late or fibrotic phase may begin at 3 to 6 months and is characterized by sclerosis of the alveolar wall, endothelial damage to small vessels, replacement of alveolar spaces by fibrosis, and functional loss. Interstitial fibrosis, pleural thickening, and increased lung density are seen radiographically with gradual volume loss [9, 16, 17].

Partial lung irradiation is given much more commonly, as in the treatment of pulmonary or esophageal tumors. Portions of lung may also receive irradiation incidental to treatment for lymphomas and Hodgkin's disease [18, 19], or lymphatic irradiation for mammary carcinoma [20]. With smaller irradiated volumes, the acute effects are usually evanescent, the late effects are predominantly radiologic, and the physiologic changes are compensated [21, 22]. Early pneumonitic changes will occur in all irradiated volume exceeding 25 Gy at 1.8–2.0 Gy daily. With large irradiated volumes, debilitated patients, and significant preexisting lung disease, the pneumonitic process may be complicated by infection with involvement of nonirradiated lung and may be fatal (less than 2% of irradiated cases) [23]. Corticosteroids may ameliorate the acute process, but must be carefully withdrawn to avoid relapse. Judicious supportive care (oxygen, bed rest, antibiotics, bronchodilators) may assist the patient through the acute-subacute phase, but does not reverse the late fibrotic changes [24–27]. Prophylactic steroids for high-risk patients have

been advocated by some, but never prospectively tested.

The ultimate degree of late fibrotic injury increases up to complete and permanent loss of functional lung in the irradiated volume above 50 Gy at 1.8–2.0 Gy daily. The ability to compensate for such loss depends on pretreatment pulmonary function, the volume treated, and other patient factors. Improvements in pulmonary function resulting from radiation response of lung tumors may compensate for losses due to radiation fibrosis [28–30]. Several authors have recently correlated radiation-related changes in lung density with computed tomographic (CT) findings [31, 32].

For both whole or partial lung irradiation, prior, concurrent, or even subsequent chemotherapy may augment radiation effects and lower the threshold dose for symptomatic pneumonitis through either additive or synergistic mechanisms. Actinomycin D, cyclophosphamide, methotrexate, bleomycin, and BCNU are among the more commonly used agents that have pulmonary toxicity and may increase the risk of pulmonary injury [4, 8, 9, 33].

The key to avoidance of excessive radiation lung injury lies in careful evaluation of tumor extent and tailoring of the treatment fields to that extent with custom-shaped blocking. Since volume irradiated is such a key factor, "shrinking field" techniques, in which the irradiated volume is reduced as the tumor responds, are essential. Pretreatment assessment of pulmonary function, avoidance of infection, and awareness of the risks of sequential or concurrent chemotherapy are also important.

With consideration for these factors, even elderly patients with chronic lung disease can be successfully irradiated [34]. Ongoing studies of altered fractionation schedules (hyperfractionation), normal tissue protective drugs, and optimization of radiation-chemotherapy sequencing may further reduce the frequency of significant radiation lung injury.

### *Cardiac Effects of Irradiation*

Until recently, the heart was felt to be rather tolerant to radiation effects. However, the effects of incidental cardiac irradiation received during treatment of mediastinal tumors have shown that the heart cannot be discounted in radiation treatment planning. While effects on the coronary vessels [35–37], myocardium [38], and valves [39] have been reported, they are rare and not always clearly related to radiation effects alone.

Radiation-related cardiac injury may present clinically, either early or late, with signs and symptoms ranging from silent functional abnormalities to constrictive pericarditis with tamponade. The frequency and severity of cardiac effects are related to the effective biologic dose of radiations and the volume of heart irradiated. Involvement of the pericardium by tumor may contribute to some of the effusions seen after mediastinal-cardiac irradiation. At cardiac doses of 40 Gy in 4–5 weeks, the frequency of clinically symptomatic radiation pericarditis is 4–7% [40–42].

Clinical pericarditis presents within the first 12–24 months after treatment [43]; it is characterized by chest pain, fever, friction rub, and development of a pericardial effusion which may be apparent either by changes in the transverse cardiac diameter or cardiac silhouette, or electrocardiographic and echocardiographic changes. Chronic pericardial effusion may appear as a transient or persistent effusion, either form of which may be asymptomatic. The persistent form may progress to tamponade or chronic constrictive pericarditis; in this event, pericardiocentesis and/or pericardiectomy may be required. While clinical cardiac status is reported to return to normal thereafter, recent reports indicate that finer measures of cardiac function can detect functional abnormalities not apparent clinically.

In an evaluation of patients with stage I–III Hodgkin's disease receiving mediastinal irradiation, in which cardiac doses averaged 35 Gy, left ventricular ejection fraction (LVEF) was reduced in more than one-half of the irradiated patients in comparison to normal controls [44]. The authors emphasized that these changes were subclinical and that none of the patients presented with congestive heart failure or constrictive pericarditis. They also observed a decreased transverse heart diameter. A diffuse subclinical myocardiopathy was suggested. Wehr et al. [45] have described subtle electrocardiographic changes suggesting a transient, clinically silent, perimyocarditis following cardiac irradiation received during prophylactic internal mammary irradiation for left-sided carcinoma of the breast.

In another review of patients receiving cardiac doses greater than 40 Gy [46], the authors observed decreased systolic left ventricular function at rest and decreased left ventricular functional reserve in asymptomatic patients 5–15 years after irradiation for Hodgkin's disease with predominantly anterior fields. The mid-cardiac dose in such patients was in the range of 50–55 Gy in 5–6 weeks. There was a high frequency of pericardial effusion (36%) reflecting the high cardiac dose.

Other investigators have reported frequencies of symptomatic pericarditis ranging from 3% at doses of 40–45 Gy to 30% when cardiac doses exceeded 50 Gy [47, 48]. These studies also related the frequency of symptomatic pericarditis to the presence or absence of intrathoracic tumor, the size of the

mediastinal tumor, and the fractional volume of heart exposed. Miller showed that venous and lymphatic channels of the heart drain to mediastinal lymphatics [49]. Alteration of mediastinal lymphatics by tumor involvement may facilitate pericardial effusion and account partially for the correlation of mediastinal tumor extent to post-therapy effusions.

Histopathologically, radiation pericarditis affects both the parietal and visceral pericardium, but the parietal pericardium is more commonly and severely involved. Late diffuse interstitial fibrosis of the myocardium has been reported. The period of transient effusion after irradiation reported by several authors [43, 46] correlates with the period of latency reported by Stewart and Fajardo [41] (2–70 days postirradiation); no cardiac abnormalities are noted by light microscopy, but electron microscopy reveals swelling of the cytoplasm of myocardial capillary endothelium, as well as fibrin and platelet thrombi and extravasation of red blood cells. After 70 days, fibrosis of all structures is noted. Using tritiated labeled thymidine, activity is highest after 39–70 days; this is most likely due to capillary and endothelial cell proliferation, i.e., repair of radiation-damaged endothelial cells. If capillary damage is excessive, there is death of myocytes and replacement by fibrosis. It has also been speculated that fibrosis of the pericardium is secondary to fibrosis of nonorganized fibrinous exudate produced by the pericardium.

To minimize the risk of cardiac effects from irradiation, it is important to recognize the dose response relationships noted above. Limiting the cardiac dose to 36–40 Gy in 4–5 weeks should limit the frequency of clinically significant changes to 5% or less. When the anatomic location of tumor requires irradiation of more than 50% of the cardiac volume, total doses should probably be diminished or the daily dose reduced, with protraction of the overall treatment course. Poussin-Rosillo et al. [50] reported a 2% incidence of pericarditis in 101 Hodgkin's patients treated with 38–40 Gy using a split-course technique.

Chemotherapeutic agents known to be cardiotoxic, such as doxorubicin, given before, during, or after irradiation may also dictate reduction in cardiac radiation dose or volume. While the mechanisms of myocardial injury for radiation and drug are probably dissimilar, they are nevertheless additive in effect. In view of the subtle functional effects of irradiation now being reported at commonly used doses, techniques of limiting cardiac dose and volume irradiated are especially important. Clinically asymptomatic changes may become more significant as the treated population ages. While the key to management of radiation-related cardiac injury is prevention, careful follow-up of patients receiving cardiac irradiation in any form is mandatory. These evaluations should include a careful clinical history with regard to signs and symptoms, which may be transient, careful attention to cardiac diameter and silhouette on chest roentgenograms, electrocardiography, echocardiography, and periodic radionuclide angiography. In the presence of overt pericardial effusion, pericardiocentesis and anti-inflammatory agents may be sufficient for transient episodes. However, chronic recurrent effusions, especially with the development of constrictive changes and tamponade, may require therapeutic pericardiectomy [51, 52].

### *Esophageal Effects of Irradiation*

Esophageal effects of irradiation may either be acute, occurring during the course of irradiation to mediastinal structures, or late, following irradiation by weeks or months. The effects may be augmented by concurrent chemotherapy, and "recall" of radiation effects may be seen with subsequent chemotherapy [4, 53].

The response of the esophagus to irradiation is similar to that of other squamous mucous membranes. The germinal layer of epithelium is most sensitive to the effects of radiation. During a course of irradiation, there can be a range of changes from minimal degeneration of the germinal (dividing) epithelial cells and temporary hyperemia to total necrosis. In a course of radiation treatment to the mediastinum for an intrathoracic neoplasm, the effects on the esophagus are usually intermediate between the two extremes noted above, as long as there is no intervening infection or tumor recurrence.

Thus, the acute effects are due to pseudomembranous inflammation, often incorrectly called "mucositis" or "radioepithelitis," resulting in symptoms of dysphagia occurring 10–14 days after the start of treatment and a dose of 15–20 Gy. The symptoms then abate, even though treatments continue, but they may increase again near the end of the fourth or sixth week of therapy. The esophageal mucosa is a rapidly renewing cellular system; thus, recovery from acute effects is usually rapid.

Typical symptoms of acute radiation esophagitis are mild to moderate substernal burning, dysphagia manifest at the level of the suprasternal notch, and occasional sharp chest pains. Recovery from these acute symptoms usually occurs within a few days after interruption or completion of therapy. Radiographic changes during this time are usually unrevealing unless there is associated responding tumor [54].

Therapy of acute radiation esophagitis is usually symptomatic. Recommendations include a soft

bland diet, avoidance of irritants such as acidic fruit juices, and restriction of alcohol intake. Analgesics, frequently in liquid or elixir form, may be helpful, as well as topical anesthetics such as viscous lidocaine although the latter may be hazardous in certain patients since it may decrease sensation of food in the pharynx and promote aspiration.

Late effects of irradiation on the alimentary tract are characterized by progressive endarteritis, which is the critical late radiation lesion, resulting in either ulceration and infarction necrosis with more rapid obliteration of vessels or a progressive slow fibrosis and stricture. Thus, the most common late effect of radiation is stenosis due to scarring and contraction. Slowly progressive dysphagia is the clinical manifestation of late effects. Changes may be present radiographically as a smooth tapering lesion on barium swallow; they should not be confused with recurrent carcinoma of the esophagus, which tends to have ulcerations, irregular edges, and filling defects. These latter findings, including fistulas, sinus tracts, and ulcers, are usually not found with late radiation effects [53]. Stenoses or strictures may be managed with conservative dilatations and dietary alterations. Dilatations done under endoscopic guidance are preferred since direct visualization decreases the risk of perforation.

The normal esophagus (not involved by tumor) can probably tolerate total doses in the range of 60–70 Gy in 6½ to 7½ weeks with a frequency of severe stricture well below 5% [54]. While the total dose alone has been implicated as the most important feature [55] protraction of the treatment course and reduction of the volume of esophagus irradiated are also important factors. When the esophagus is only incidentally irradiated in the course of treatment of other mediastinal malignancies (e.g., lung, lymphoma), the dose and volume can usually be kept below 50 Gy in 5 weeks. The risk to the esophagus at this dose level for late effects is probably less than 2%. In definitive irradiation treatment for esophageal cancer, however, large segments of esophagus will, of necessity, receive much higher total doses, up to 70 Gy in 7 weeks. The frequency of late stricture of the esophagus at this dose level is higher, anticipated, but accepted owing to the high risk of uncontrolled tumor. The effects of tumor invasion and destruction of the esophagus, and associated inflammation, may increase the risk of scarring.

The cervical esophagus may also be incidentally irradiated during treatment of tumors of the head and neck, and some degree of acute esophagitis is to be expected. The esophageal dose usually does not exceed 50 Gy/5 weeks when the cervical nodes are treated prophylactically or primary tumors are treated preoperatively. Field reductions keep the esophageal dose below 60 Gy/6 weeks when primary tumors are treated definitively above 60 Gy. The frequency of late cervical esophageal stenosis is no more than 1–2% below 60 Gy/6 weeks, but may reach 5–6% above this dose [56]. In a randomized prospective study, the Radiation Therapy Oncology Group observed an incidence of late stenosis in 7/121 (6%) patients treated to 60 Gy/6 weeks postoperatively versus 1/120 (<1%) at 50 Gy/5 weeks preoperatively [57].

Many chemotherapeutic agents are known to augment radiation effects on the esophagus, especially doxorubicin [58–60], cyclophosphamide [4], bleomycin [61], fluorouracil [62], dactinomycin [62], and etoposide [63]. The severity of radiation esophagitis, augmented by chemotherapy, may be sufficient to lead to catastrophic and lethal complications [55, 64]. Even chemotherapy administered subsequent to radiation may result in a recall of radiation esophagitis. The mechanism for this is speculated to be depletion of stem cells by chemotherapy in zones of focal radiation ischemia [4]. Several reports suggest properly sequenced, nonconcurrent administration of radiation and drug can minimize these serious early and late esophageal effects [59, 65, 66].

## Pelvic Irradiation

Nearly all patients receiving radiation therapy to the abdomen or pelvis experience transient acute effects of irradiation of the bowel. Depending on the volume and intensity of the treatment, predominate symptomatology consists of diarrhea, nausea, abdominal cramps, and tenesmus of variable severity. These symptoms, manifested during the treatment series and persisting for a short time after its completion, are secondary to reparable cellular damage sustained by the normal bowel epithelium [67]. Satisfactory clinical response is usually obtained with the administration of anticholinergic drugs, opiates, cholestyramine [68], or aspirin [69] so that interruption or abandonment of the treatment is rarely necessary. These expected transient reactions are sometimes misconstrued as a complication of radiation therapy, but this is no more valid than it would be to consider postoperative ileus a complication of laparotomy.

Although acute effects of irradiation of the gastrointestinal tract are commonly observed, severe late sequelae are not. Moreover, there is no relationship between the occurrence or severity of the acute syndrome and the development of late morbidity. A latency interval of 6 to 24 months [70] between the irradiation and the appearance of bowel complications is typical, although late effects

may appear after periods of problem-free survival of up to 20 years [69, 71].

Frequencies of significant complications following abdominal or pelvic irradiation have been estimated to occur in 0.5–11.6% [71–74] of all patients treated. Figures vary depending on the case mix, the influence of predisposing factors, and the intensity and scope of the treatment. Sequelae are most likely to occur in patients treated with radical high-dose irradiation, particularly with combined external and intracavitary irradiation. Troublesome chronic sigmoiditis and cystitis which may be refractory to medical management are the most common of these difficulties. Intractable symptoms requiring skilled surgical intervention for correction or palliation [72, 75, 76] are observed in approximately a third of patients with late morbidity. These include painful ulceration in the bladder, vagina, or rectum; fistulas; small bowel obstruction; and rectal stenosis. The etiology and location of these lesions can usually be correlated with the previously described radiation parameters on review of the dosimetric data in the case. Ureteral stricture related almost exclusively to a laterally deviated intrauterine tandem is relatively rare.

Balanced against the success rates of curative radiation therapy both in terms of local tumor control and improved survival, this level of morbidity appears justifiable. Reports of large series of patients treated at leading institutions for carcinoma of the cervix [77–80] or prostate [81–83], neoplasms that are appropriately managed with irradiation of the most radical sort, show major complication rates less than 10%, even in patients with advanced lesions treated with "maximal" combinations of external and intracavitary irradiation. In a review of reported series of irradiation therapy for prostatic carcinoma since 1974, containing a total of more than 1,100 patients, Dewit et al. [84] found that the frequency of either late gastrointestinal or genitourinary complications was less than 5%.

### *Predisposing Factors*

Multiple factors that are independent of the radiation technique employed and associated with an increased rate of complications following abdominal or pelvic irradiation have been identified. Among these are the extent of the disease treated [70], the number and scope of prior abdominal or pelvic operations [70, 85], and any postoperative morbidity (adhesions, infection, etc.) related to these operations. Host factors including gender (female > male) [86], pelvic inflammatory disease [87], thin physique [80, 86, 88], diabetes mellitus [87], cardiovascular disease (including hypertension) [73, 87, 88], diverticulosis [80], and preexisting vascular compromise of the bowel [88] have also been implicated in many series. Several reports [4, 89, 90] suggest that the frequency of severe delayed complications may also be greater in some patients treated with combined chemotherapy and irradiation.

Potish and Twiggs [85, 91] have shown that epidemiologic methods can be used to determine the probability of enteric complications following irradiation related to the above factors. Assessments of this type may eventually determine modifications in the radiation technique to be employed in individual patients or to the substitution of alternative therapy when the cumulative risk is determined to be unacceptable. Until such methods are further developed, however, treatment decisions continue to be based largely on clinical empiricism.

### *Treatment-Related Parameters*

The frequency of gastrointestinal or genitourinary complications following radiation treatment is most directly dependent on the total absorbed dose and the volume of tissue concerned. Accordingly, efforts are made to limit the irradiation administered in order to minimize or eliminate the risk of adverse effects.

With external irradiation, the use of multidirectional, sharply collimated, high-energy photon and electron beams allows concentration of the radiation dose in tumor-containing areas and avoidance of normal structures [92]. Augmented by highly accurate computer-assisted dosimetric planning and calculations, and sophisticated tumor localization systems, these advances enable delivery of tumoricidal doses of radiations where needed (Fig. 2). Sparing of uninvolved tissues or critical organs is achieved with the use of individualized custom-blocking techniques and by progressively "shrinking" the radiation field size during the treatment course.

When intracavitary or interstitial implants are employed, other more complex physical concepts come into consideration. Since the radiation dose provided by an implant is extremely high near the sources, but falls off precipitously away from the system, there is no single spatial point (i.e., point A or B) at which the dose is representative of the entire system. Therefore, the complex dose, time, and volume relationships involved cannot be adequately expressed by the calculation of a dose at one point [93] nor can implant doses be simply added to a dose given with external beams. Computer dosimetry allows determination of the actual dose received by the bladder wall, rectum, and sigmoid in every case without resorting to quasi-dose expressions such as milligram-hours. Only

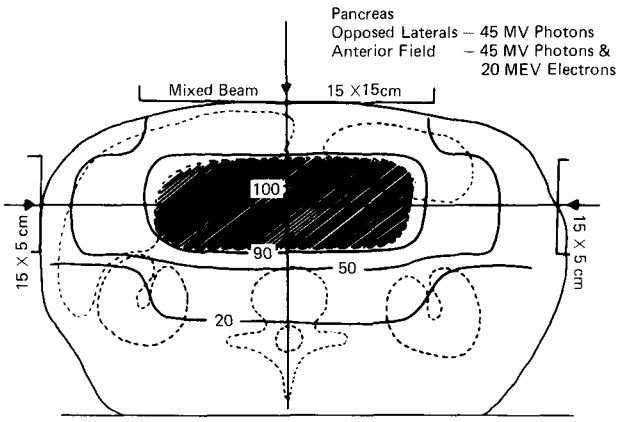


**Fig. 2.** Representative contour and isodose distribution of a patient with pancreatic carcinoma treated with a 3-field mixed electron (45 MeV) and photon (20 MV) beam technique. From Dobelbower, R. et al., Cancer *41*:1088, 1978 [163], reproduced by permission of the authors.

critical analysis of extensive clinical experience [70, 78, 80, 94] has determined the optimal physical characteristics of implant systems and how best to integrate them with external irradiation to yield maximum tumor control with acceptable morbidity.

Better control of the irradiation from implants has also been achieved through the development of intracavitary applicators which are more readily adaptable to individual anatomy than earlier instruments. Extensive use of afterloading in applicator design has expanded the time allowable for meticulous placement of the devices to obtain an optimal anatomic and geometric arrangement of the sources. Strategically positioned bladder and rectal shields have been incorporated into the ovoids of some applicators.

Simple measures may contribute to the degree of safety with which radiation therapy can be administered. For example, efforts to displace the small intestine out of the pelvis when pelvic irradiation is given may contribute to avoiding small bowel complications. Maneuvers such as treating patients in prone, rather than supine position and with the urinary bladder distended or with pelvic compressive devices in place may be effective in some patients.

Surgical techniques of reperitonealization and use of omental flaps to keep the small intestine out of the pelvic cavity if postoperative pelvic irradiation is planned have also been shown feasible in cadaver [86] and clinical studies [95]. At the least, it is prudent for surgeons to detect and lyse adhesions binding loops of small bowel deep in the pelvis when laparotomy is performed in patients who will receive irradiation later so that the bowel is free to migrate out of the pelvis. Ileal loops and colostomy stoma should be placed out of the treatment field when possible.

## Irradiation of Upper Respiratory and Digestive Tracts

### *Mandibular Effects*

The frequency of osteoradionecrosis varies considerably from one series to another. This may be related in part to the lack of a uniform definition of this complication and variation in the reporting of less and more severe cases. Some variation may be the result of limitations in length of follow-up since osteoradionecrosis can occur years after therapeutic irradiation. The average time to onset of necrosis has been reported to be approximately 22 months. The frequency of osteonecrosis has been reported from 4% to 35% [96] but the majority of reports are in approximately the 5–20% range. Severe necrosis is less common; among 315 patients reported by Parsons et al. [97], severe necrosis, defined as not healing spontaneously and requiring eventual mandibular resection or prolonged hospitalization, occurred in only 1% of patients treated with external-beam irradiation alone and 3% of patients treated with a combination of external-beam and interstitial irradiation; mild or moderate necrosis, which healed spontaneously, occurred in 5% and 18% of patients, respectively. The vast majority of osteonecrosis involve the mandible; maxillary necrosis is uncommon.

The location of the primary tumor in relation to bone influences the risk of mandibular necrosis [98, 99]. Carcinoma of the hard palate or upper or lower gingiva is associated with higher probability of necrosis than other sites [98]. The frequency at sites adjacent to bone such as the floor of the mouth and retromolar trigone is intermediate while the incidence at more distant sites such as the buccal mucosa, oral tongue, base of tongue, soft palate, and tonsillar region is still lower. Paradoxically, the size or T stage of the tumor may not influence the risk of necrosis.

The total dose of radiation received by the mandible has a strong influence on the risk of necrosis [98, 100, 101]. In one series, the risk was found to be 0 for patients receiving less than 6,500 rad to the mandible and 50–85% for those receiving more than 7,500 rad depending on whether they were dentulous or edentulous [100]. Technique of irradiation also influences risk. Patients receiving interstitial irradiation in addition to external-beam treatment are at higher risk than those receiving external beam alone. Dental status prior to irradiation is also critically important. Patients who are edentulous prior to radiation therapy and prior to any dental

intervention have approximately half the risk of mandibular osteoradionecrosis of dentulous patients, or about 10–14% [98, 100]. This should not be taken to imply that edentulation, or even removal of all teeth within the high-dose volume prior to treatment, is appropriate. While this was recommended in the past [102], it now appears that more conservative management, with preservation of those teeth that can be salvaged is preferable [98, 103, 104]. Patients must have thorough dental evaluations with extraction of all nonsalvageable teeth. In addition, fluoride gel treatments have been shown to be of value. The location and extent of the primary tumor may largely dictate field arrangement, total dose, and whether interstitial and/or external-beam irradiation is appropriate. The dose to the mandible and volume of mandible irradiated are, therefore, controllable to a limited extent. Tumors in certain locations, such as those involving the gingivae and hard palate, may be treated preferentially by resection in view of the high risk of necrosis.

Histologic studies have shown that the walls of regional blood vessels become thickened and the marrow cavity is infiltrated by loose connective tissue and inflammatory cells. Such devitalized bone is susceptible to infection and has a limited capacity for repair. This is important in view of the fact that the overlying mucosa is generally thin and atrophic, so that the bone becomes exposed easily and may remain exposed for long periods of time. Exposure of bone is seen in conjunction with osteoradionecrosis approximately 95% of the time [96]. Small areas (less than 1 cm) of exposed mandible will frequently heal with conservative management given sufficient time. Such cases should be distinguished from the more severe and fortunately less frequent instances in which surgical intervention is required. Mild or moderate cases are frequently associated with pain, especially when eating, and inability to tolerate dentures. More severe cases may be complicated by osteomyelitis with very severe pain and difficulty with deglutition, speech, or even respiration. Recognition of predisposing factors (age, tumor site, oral hygiene, dental status) and treatment-related factors (beam quality, field size, total doses, interstitial implants) permits individualization of radiation therapy to achieve the lowest risk of osteonecrosis.

### *Soft Tissue Effects*

Necrosis of soft tissues after irradiation is a less serious problem than osteonecrosis. Many of these necroses, particularly the smaller ones, may be asymptomatic, although in certain sites (lateral tongue and floor of mouth) even small necroses may be painful. The typical appearance consists of a yellowish ulcer with induration. The majority of necroses appear within 2 years. Mucosal trauma, however, may lead to later necrosis. It is sometimes difficult to distinguish between soft tissue necrosis and tumor recurrence, especially if necrosis occurs at the site of the original tumor. Certain features of the gross appearance may be helpful. The induration around a tumor is generally more pronounced and the margins have a rolled rather than a flat, sharply demarcated appearance. Observation may be helpful since the vast majority (over 95%) of soft tissue necroses will heal with conservative treatment given sufficient time [96].

The factors that place patients at higher risk for necrosis of the soft tissues of the oral cavity and oropharynx are essentially the same as for osteoradionecrosis. Patients with primary carcinomas of the oral cavity and oropharynx are at the highest risk while those with tumors of the supraglottic larynx, nasopharynx, and hypopharynx are at less risk [97]. Similar treatment-related factors are involved. The use of large total doses, large daily fractions, large field sizes, and the need to employ interstitial techniques in conjunction with external-beam irradiation are associated with a higher risk of soft tissue necrosis. Fortunately, that risk is quite small. Parsons et al. [105] observed only 1 case of soft tissue necrosis among 50 patients treated with twice a day irradiation to total doses of 74–77 Gy for advanced and moderately advanced squamous cell carcinomas of the upper aerodigestive tract. In a series of 198 patients with carcinoma of the oral cavity or oropharynx treated with either conventional irradiation or a split course, the frequencies of necrosis were found to be approximately 10% among patients receiving external-beam irradiation alone compared with 20% among those receiving external-beam and interstitial irradiation. Most of these necroses, however, were characterized as only mild or moderate and healed spontaneously with conservative measures [97]. Marcial et al. reported soft tissue necrosis in 13% of 141 patients with carcinoma of the base of the tongue who were treated in a randomized study of continuous versus split-course irradiation [106]. The frequency of necrosis was not appreciably different with continuous-course or split-course irradiation. Attention to all the factors that may contribute to osteonecrosis will diminish the frequency and severity of soft tissue necrosis following irradiation.

### *Pituitary Effects*

The pituitary gland may be irradiated in the course of treatment of tumors arising in the nasopharynx, paranasal sinuses, brain, or retina. It was once

believed that hypopituitarism secondary to radiation therapy was distinctly uncommon. With the advent of more sensitive endocrinological radioimmunoassays and the availability of synthetic releasing hormones, it has become apparent that the frequency of postirradiation hypopituitarism is higher than was previously appreciated. The frequency increases with time after irradiation up to 10 years. Difficulties in estimating the frequency of pituitary dysfunction include the choice of endocrinologic tests, the difficulty distinguishing pituitary from hypothalamic abnormalities, and the absence of prospective data with sequential as well as baseline (i.e., pre-irradiation) measurements of pituitary function. Samaan et al. [107] reported a high frequency of pituitary dysfunction in 110 patients treated for cancer of the nasopharynx and paranasal sinuses; 43 patients had abnormalities following doses to the pituitary of 30–88 Gy (median 50 Gy). The most common abnormality was diminished growth hormone secretion. Hypothyroidism was demonstrated by low $T_3$–$T_4$ levels and failure of thyroid-stimulating hormone to rise following the administration of thyroid-releasing hormone. Growth hormone deficiency in children following irradiation has been found by several investigators [108–111]; it may be associated with clinically significant growth retardation and diminished bone age. This may occur even after moderate doses of radiations (i.e., less than 40 Gy). It may occur more frequently when radiation therapy and chemotherapy are administered concomitantly [108].

The hormone-secreting cells of the pituitary are not believed to be particularly radiosensitive. It may be, however, that this apparent lack of radiosensitivity is the result of slow proliferation with clinically and biochemically apparent pituitary dysfunction becoming manifest only after a considerable period of latency. This is consistent both with the basic biological observation that cells undergo several mitoses following therapeutic doses of radiation and with the clinical observation that the various forms of hyperpituitarism generally occur months to years following therapeutic irradiation [112]. The exact pathophysiology of pituitary dysfunction following irradiation is unknown. Little is known about the morphological changes that follow pituitary irradiation aside from the fact that the gland undergoes progressive fibrosis and depletion of hormone-secreting cells, particularly those secreting thyroid-stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH). Posttreatment evaluation of pituitary function at regular intervals is mandatory so that any endocrine abnormalities that occur may be detected and treated by hormonal replacement.

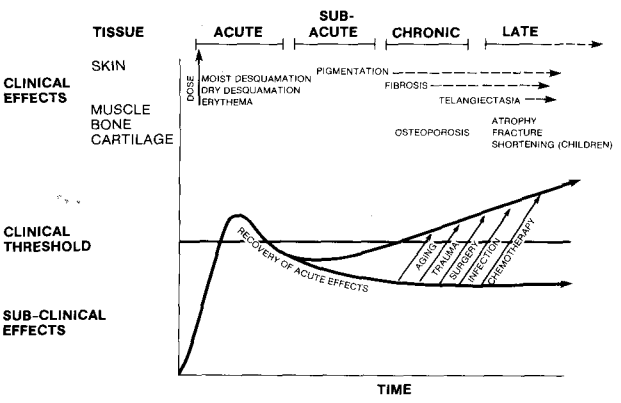


**Fig. 3.** Spectrum of effects following therapeutic radiation to skin, muscle, bone and cartilage. Effects of ionizing radiations on soft tissue, bone, and cartilage. Modified with permission from Rubin, P. and Casarett, G.: Clinical Radiation Pathology, vol. 2., Philadelphia, W.B. Saunders Co., 1968 [120]

## Irradiation of Soft Tissues, Bone, and Cartilage

### *Cutaneous Effects*

Skin, soft tissues, and bone that are adjacent to a tumor cannot be spared some dose of radiations (Fig. 3). Megavoltage therapy machines, multiple daily treatment portals, protracted fractionation, and custom blocking may contribute to a decrease in acute reactions and long-term complications in irradiated soft tissues and bone.

A predictable pattern of skin response will be seen with daily fractionated skin doses of 1.8–2.0 Gy given over 4–5 weeks with conventional x-rays. Mild erythema over the treated area is clinically apparent by the second week, and hair loss begins after 10–14 days of irradiation. As skin doses increase to 30–45 Gy, brown, dry scales of superficial skin flake off to expose the underlying new skin. If higher doses of radiations are given, this process will develop into moist desquamation. Multiple small vesicles will develop throughout the treatment field, eventually coalescing so that the dermis is denuded. Healing occurs as islands of epidermal cells in the central and peripheral regions of the treatment area begin to expand and reform the epidermis [113].

Long-term sequelae of radiation to the skin develop over many years. The late effects are related to the total dose, the length of the treatment course, and the volume of tissue irradiated. The new epidermis may be hyperpigmented initially, but may eventually become pale. Telangiectasia can develop in the hypochromic regions. Variable degrees of subcutaneous fibrosis and atrophy may develop. Subsequent trauma, including surgery, infection, and the normal aging process may contribute to the acute or chronic radiation effects on the skin. Ex-

cept for irradiation of cancer of the skin [114] and carcinoma of the breast [115], cutaneous and subcutaneous effects of radiations are almost entirely avoidable. If the dose of radiation is high, or a higher dose per daily fraction is given, or certain chemotherapeutic agents are combined with radiation, the frequency of severe late effects will increase [116–118].

Patients undergoing reconstructive surgery can be operated 4–6 weeks after completing radiation treatment. Because of early scarring, compromised blood supply, and decreased elasticity, irradiated tissues may be more susceptible to injury during surgical manipulation and must be handled carefully [119]. The tolerance of skin grafts is similar to that of normal skin when the graft is well established. Irradiation of fresh grafts may suppress development of fibroblasts and small nutrient vessels necessary for graft viability [114].

### *Muscular Effects*

Although smooth and/or striated muscle will be within most radiation portals, it is rare for acute or even long-term effects of radiation therapy to be manifest in these tissues. Chronic muscular sequelae may, however, be seen in children irradiated to high doses. Atrophy can develop in paraspinous muscles in children irradiated for Wilms' tumor, or in the sternocleidomastoid of patients treated for Hodgkin's disease [120].

### *Skeletal and Cartilaginous Effects*

Bone and cartilage of adults are relatively insensitive to ionizing radiations, although with high doses some long-term effects may be observed. Suppression of the growth of bone and cartilage was recognized shortly after the discovery of x-rays. The risks of developing late effects from radiations and the severity of such changes increases with higher doses of radiations, interval from the time of irradiation, and the younger the child at the time of treatment [121]. Children receiving cranial-spinal irradiation for medulloblastoma exhibited shortening of the spine with a decreased sitting height from vertebral body growth retardation [122]. Radiation-induced scoliosis was first described in 1950 in a child treated for Wilms' tumor [123]. Radiographic findings have been reported by several groups since that time [124, 125]. The severity of scoliosis correlates with higher doses and younger age. It has been suggested that irradiation of the entire width of the vertebral body may prevent scoliosis but not shortening. However, Rubin et al. [124] reported scoliosis in 7 of 13 children even when the entire vertebral body was irradiated. Other postirradiation changes in children include abnormality of bone modeling resulting from alterations of periosteal activity, and epiphyseal injury secondary to aberrations in chondrogenesis [126].

While mature bone is less susceptible to the effects of ionizing radiation than developing bone, it is a dynamic tissue that can sustain vascular or cellular injury that may result in a number of radiation-induced sequelae. Injury to osteoblasts results in reduction of new bone formation, subsequent thinning, and eventual osteoporosis in some patients. Radiation-induced vascular thickening of the small nutrient vessels of bone can contribute to this effect, and in certain locations results in avascular necrosis several years after irradiation. Irreversible changes resulting from radiation may be enhanced by the aging process. Any subsequent adverse factors such as infection, trauma, or surgical intervention may precipitate the development of necrosis of soft tissues or fracture of involved bone.

Portions of the pelvis and the proximal femurs receive high doses of radiation during therapy for pelvic cancer. In more than 300 patients irradiated to high doses for prostatic cancer, no fractures of the pelvic bones were seen [127]. However, the femoral neck is more susceptible to developing postirradiation fracture than the pelvic bones. The isolated vascular supply of the femoral neck and the stress of weight-bearing distributed over a relatively small volume of bone tissue may account for the greater frequency of radiation-related fractures at this site. Conventional x-rays, with their increased absorption in bone, resulted in femoral neck fractures in 2–3% of patients following high doses of radiations to the pelvic bones and proximal femurs [128–130]. With current practice using megavoltage accelerators, the frequency of femoral neck fracture following radiation therapy is less than 1 patient per 1,000 [126].

The ribs may receive high doses of radiations during primary breast treatment or postmastectomy chest wall irradiation. The frequency of rib fracture is 2–5%; it may be higher for patients who require interstitial implants adjacent to the bone [118, 130, 131]. Reports of bone injury with high-dose radiation therapy combined with chemotherapy for mammary cancer, Hodgkin's disease, malignant lymphoma, and Ewing's sarcoma have been reported [117, 132, 133].

Adult cartilage is relatively insensitive to ionizing radiation even at high-dose levels. Cartilage is composed of cells with low metabolic activity in a matrix of inert material and lacks blood vessels—factors that probably contribute to its resistance to injury. Costal cartilage is irradiated during therapy for mammary cancer without obvious clinical prob-

lems. Cartilage of the hip joints may receive considerable doses during pelvic irradiation with no apparent sequelae. Cartilage necrosis following radiation therapy of laryngeal carcinoma is a serious late effect that occurs more frequently as the tumor size, total dose of radiations, and volume of radiated tissue increase. The belief that underlying cartilage prohibits successful radiation therapy of cancer of the skin is a myth. Parker has reported treatment of several hundred cutaneous carcinomas overlying the pinna, nasal ala, and nasal septum with only 3 cases of cartilaginous necrosis [114, 134].

## Irradiation of the Nervous System

The effects of ionizing radiation on the nervous system are usually categorized as early or late, but they are not truly acute in the sense of occurring during the course of radiation therapy. The frequency and severity of radiation effects, especially late effects, are influenced by many factors including prior surgical intervention, underlying disease, prior or concomitant chemotherapy, total dose of radiation administered and the fractionation, the volume irradiated, and the quality of the beam (conventional x-rays versus high-energy photons versus neutrons).

### *Effects on Brain*

Acute effects of radiations with fractional doses in the usual therapeutic range (1.0–5.0 Gy) have been postulated and assumed, but they are poorly documented. Headaches, temperature elevations, nausea, and vomiting during a course of radiation therapy that includes the brain may be taken as evidence of acute effects, but they are more plausibly the result of the underlying process. Even with individual fractions of 6.0 to 10.0 Gy to the entire brain, there have been no consistent symptoms or signs of acute effects [135]. High total doses of radiations (70–80 Gy at 2.0 Gy/fraction) have not been accompanied by acute effects [136].

Subacute effects have been manifested as a "somnolence syndrome" consisting of marked lethargy without focal neurologic findings occurring 4–8 weeks after irradiation of the brain. This syndrome has been seen in patients who received prophylactic cranial irradiation for acute leukemia [137] or small cell carcinoma as well as those treated for intracranial tumors. The pathogenesis is thought to involve transient demyelination [138].

Necrotizing leukoencephalopathy may be seen 4–12 months after cranial irradiation, almost invariably combined with systemic chemotherapy, although it has been seen in patients treated only with chemotherapy. Such patients may have seizures, dementia, ataxia, hemiparesis, decerebration, and even coma. The clinical course may range from complete recovery to death. Computed tomography (CT) reveals ventricular dilatation, widening of the subarachnoid spaces, and hypodense areas [139]. Histopathologic examination reveals focal demyelination, coagulative necrosis, and gliosis [140].

Mineralizing microangiopathy is seen in the gray matter as a consequence of irradiation and chemotherapy [141, 142], although it has been described on the basis of CT findings [143] following radiation therapy for brain tumors. In contrast to patients with leukoencephalopathy, the majority of patients with mineralizing microangiopathy are asymptomatic.

Late effects may be seen months to years after irradiation of the brain. these effects are most serious because they are irreversible and they may be progressive even to death. Symptoms and focal signs are related to the site of damage in the brain. Necrosis of the brain is thought most likely to be the result of vascular damage, but direct effects on the cellular components of the brain may also be important. Fortunately, severe late effects on the brain are rare. In 1980, Sheline et al. [138] reviewed approximately 100 cases from the literature. The risk of necrosis of the brain is extremely small with total doses of 50 Gy delivered in daily fractions of 2.0 Gy. A few cases have been reported with lower total doses, but large fraction sizes have been responsible. Corticosteroids have been administered in attempts to retard the progression of brain necrosis, with questionable benefit. Very localized areas of necrosis have been resected [144].

### *Effects on Spinal Cord*

Transient radiation myelopathy may be seen weeks to months following irradiation of the cervical or upper thoracic spinal cord. Lhermitte's sign of electrical paresthesias is the only clinical feature of this subacute effect. Electric-like shocks are noted by the patient, radiating down the extremities, especially the buttocks and legs, on ventral flexion of the neck. It is thought most likely to be the result of transient demyelination of the spinal cord [145]. It has been reported in 3% [146] to 15% [147] of patients who received simultaneous irradiation of supradiaphragmatic lymph nodes with a "mantle" field. It may also be seen in patients who have undergone irradiation for carcinomas of the upper respiratory and digestive tracts and for tumors of the thyroid gland.

Late effects on the spinal cord consist of progressive radiation myelopathy, often presenting with

clumsiness and weakness of the legs. Common early findings are those of the Brown-Sequard syndrome. The onset is invariably 6 months or more after completion of radiation therapy, and symptoms may begin 3 or more years after treatment. Dynes and Smedal [148] reported an average latent period of 23 months. Radiographs are normal, spinal fluid pressure is normal, no obstruction in the canal can be demonstrated, the cerebrospinal fluid (CSF) protein is normal, and no unusual cells are seen in the fluid.

Data collected by Phillips and Buschke [149] indicate that 50 Gy in 5 weeks to 60 Gy in 7 weeks are tolerated by the thoracic spinal cord. The cervical cord and thoracic cord seem to have similar tolerances to ionizing radiations. In most cases of radiation myelopathy, unconventional fractionation schemes have been employed. Wollin and Kagan [150] found fraction size and overall treatment time to be important factors in the development of radiation myelitis. There is no known treatment for radiation progressive myelopathy; paraplegia is the usual eventuality.

### *Effects on Peripheral Nerves*

Peripheral nerves have a very high tolerance to ionizing radiations; they infrequently are damaged in spite of very high total doses. There are no recognized acute or subacute effects. Late effects result from marked inhomogeneities of dose with very high areas, or they are seen after altered fractionation with large fraction sizes.

Cranial nerve injuries have been reported following irradiation to high total doses for carcinomas of the upper respiratory and digestive tracts [151, 152]. The higher the total dose, the less the interval from treatment to symptoms.

Stoll and Andrews [153] reported neurologic symptoms and signs referable to the brachial plexus in a high proportion of patients who received irradiation to the supraclavicular region with 4 megavoltage (MV) photons. However, patients with involvement of the brachial plexus by regional metastasis were not consistently excluded. When more strict criteria for radiation-related damage to the brachial plexus were used, Thomas and Colby [154] found injury in only 1.2% (14/1,202) of patients treated. As is the case with late effects on other parts of the nervous system, there is no recognized treatment for radiation-related injury.

## Fractionation and Avoidance of Radiotherapeutic Complications

Throughout the preceding discussion, total doses and treatment volumes have consistently been noted as having important bearing on the risk of late effects of radiation therapy. It is important to emphasize, however, that the total dose administered is only one element of the biologic effects of ionizing radiations. At least as important is the individual dose (fraction size) received. The interaction of total dose, fraction size, and time during which a course of treatment is administered, usually incorporated in the terms "fractionation" or "dose/time relationships," has been recognized as important by radiation oncologists and biologists for three-quarters of a century [155].

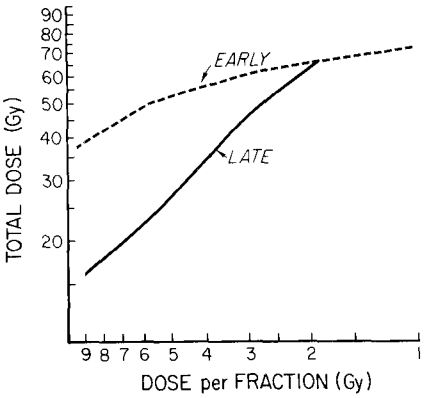


**Fig. 4.** Comparison of isoeffect curves for acute and late effects on normal tissues. From Thames, H.D., Jr., Withers, H.R., Peters, L.F., Fletcher, G.H., Int. J. Radiat. Oncol. Biol. Phys. *8*:219, 1982 [160], modified with permission

Many investigators have attempted to develop expressions, either graphic or numerical [156–159], which were to represent biologic isoeffectiveness; it was hoped that normal tissues, at least, could be predicted to manifest similar effects for different fractionation regimens, based on these isoeffect expressions. Although some crude predictability was achieved, all these expressions were flawed. More recently, it has been realized that fraction size is a much more important determinant of late radiation effects on normal tissues than acute effects [160, 161]. Figure 4 gives some indication of the differences in late effects versus acute effects as a function of fraction size. Clinical and laboratory studies are underway to provide a more complete understanding of the biologic effects of alterations of dose/time relationships [162]. It is hoped that a better understanding of such factors, combined with the appreciation of volume considerations, host factors, and interactions with other agents briefly discussed, will contribute to improvements in therapeutic ratios in the management of patients with cancer, at least one part of which will be a reduction in serious late radiation effects.

## Résumé

L'irradiation de la majorité des tumeurs malignes implique le fractionnement des doses susceptibles d'être tolérées par les tissus normaux voisins. A l'exception de la moelle osseuse et du poumon dont la morbidité après irradiation peut être diminuée en réduisant le volume irradié, les autres structures anatomiques imposent de limiter les doses de manière à réduire les effets secondaires. Au niveau du thorax, le poumon est particulièrement sensible à l'irradiation alors que l'oesophage et le coeur le sont moins. L'irradiation pelvienne comporte de plus grands risques de morbidité en particulier en ce qui concerne l'intestin grêle et moins souvent en ce qui concerne le colon et la vessie. L'irradiation de la partie supérieure de l'appareil aéro-digestif peut être suivie de la nécrose des parties molles et du squelette spécialement du maxillaire. Le traitement des affections dentaires implique un risque indubitable de complications. En revanche les os et les parties molles des autres parties du corps sont moins sensibles, sauf chez l'enfant. L'hypophyse peut être irradiée lors du traitement des tumeurs situées au niveau de la base du crane. La production de l'hormone de croissance peut être compromise quand l'irradiation est pratiquée chez l'enfant. Les effets immédiats secondaires et tardifs de l'irradiation du cerveau sont bien connus. Alors que la myélopathie fugace secondaire à l'irradiation est fréquente et peu grave, la forme progressive est rare mais extrêmement sévère. Les facteurs propres au malade, les autres maladies, les conditions techniques de l'irradiation ne sont pas sans affecter les risques et la gravité des effets secondaires sur les tissus normaux. Les méthodes chirurgicales pour prévenir ces complications ou les traiter revêtent une grande importance.



## Resumen

La terapia de irradiación para la mayoría de los tumores malignos requiere regimenes de fraccionamiento de la dosis cercanos a la tolerancia de los tejidos vecinos normales. Con excepción de la medula ósea y del pulmón, donde la morbilidad puede ser minimizada reduciendo el volumen irradiado, otras estructuras exigen la limitación de la dosis total para minimizar los efectos adversos. En la irradiación torácica la estructura más sensible es el pulmón, en tanto que el corazón y el esófago frecuentemente exhiben efectos tardíos. La irradiación pélvica conlleva un riesgo mucho más alto de morbilidad, primordialmente a cargo de los segmentos fijos de intestino, y con menos frecuencia a cargo del intestino grueso y de la vejiga. La irradiación del tracto aerodigestivo superior puede complicarse por necrosis de los tejidos blandos y del hueso, especialmente de la mandíbula. El manejo dental afecta en forma importante el riesgo de complicaciones. Los huesos y los tejidos blandos en otras regiones del cuerpo rara vez se ven afectados, excepto en los niños en crecimiento. La pituitaria puede resultar irradiada en el curso del tratamiento de tumores cerca de la base del cráneo. La producción de hormona del crecimiento puede verse especialmente comprometida en los niños. Los efectos agudos, subagudos y tardios de la irradiación del cerebro son bien conocidos. En tanto que la mielopatía transitoria de irradiación es frecuente y no grave, la mielopatía progresiva de irradiación es rara pero extremadamente grave. Factores relativos al huésped, otras enfermedades, los aspectos técnicos de la radioterapia, son factores que afectan los riesgos y la severidad de los efectos adversos sobre los tejidos normales. Los procedimientos quirúrgicos pueden ser importantes en la prevención de las complicaciones así como en el manejo de ellas.


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