RADIATION INJURY OF THE GASTROINTESTINAL TRACT

INTERNAL MEDICINE GRAND ROUNDS

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HENRIK WESTERGAARD, M.D.

Radiotherapy has become an established treatment modality in a number of neoplastic diseases where it is used either alone or in combination with surgery and/or chemotherapy in an attempt to arrest and cure the neoplastic process. The incidence of all new cancers is about 1 mill per year in the U.S., and it is estimated that about 50 percent of these patients will receive radiotherapy as part of their treatment. The cancer types where radiation is used as an integral or alternate part of the treatment are listed in Table 1.

Integral RX	Alternate RX
Cervical	Breast
Head and Neck	Rectal
Seminoma	Prostate
Skin (except melanoma)	Bladder
Lymphoma	Brain

Table 1. Cancer types treated with radiotherapy.

The radiation field in a given patient will invariably include normal tissue in the proximity of the radiated tumor, and therefore both tumor cells and normal cells may suffer identical damage. Radiation injury of the gastrointestinal tract has been observed since the introduction of radiotherapy, and the radiation tolerance of the intestine is often the limiting factor in terms of total radiation dose that can be delivered to a tumor in the abdomen. It is the purpose of this presentation to review some principles of radiotherapy and discuss the pathophysiologic basis, presentation and treatment of radiation enterocolitis.

Historical background

X-rays were discovered by W. C. Röntgen in 1895, and within two months he reported his findings in Nature (1). He named the observed rays x-rays "for the sake of brevity" and obviously because he was unable to further characterize the

nature of the rays except for their penetrating power and that they were not deviated in an electric field. Importantly, the discovery of x-rays led to the development of diagnostic radiology and radiotherapy. Remarkably, within a few years several reports appeared on the effects of x-rays on a variety of skin diseases (acne, eczema) but also as a cause of severe dermatitis. The first case of gastrointestinal effects of x-rays was published in 1897 (2). Röntgen received the first Nobel Prize given in physics in 1901.

A few years later, Marie and Pierre Curie in Paris described the eminence of rays from uranium salts and coined the term 'radioactivity'. They went on to isolate and purify radium for which they received the Nobel Prize in 1903. A year later the radiation emitted from radium was shown to be composed of three types of rays: α, ß and γ and that γ-rays did not deviate in a magnetic field and could penetrate several centimeters of metal. Thus γ--rays had very similar characteristics to x-rays. As with x-rays radium was rapidly introduced as a radiotherapeutic tool both for surface application for skin cancer and as intracavitary treatment for cervical cancer. In 1915 two large series of patients with carcinoma of the cervix treated with either intracavitary radium or with x-rays from an external beam were published (3,4). The encouraging results from these two studies spurred further developments in radiotherapy. The problems that radiotherapy faced in the early days was that the x-ray tubes generated x-rays in the low energy range (50-150 kv). These x-rays had poor tissue penetration, and the maximum energy was delivered at the surface of the skin. Hence, intolerable skin reactions were often the limiting factor in the treatment of deep-seated tumors. Another problem was the lack of knowledge about the amount of energy delivered by the x-ray tubes or the amount of energy absorbed by the tumor. The treatment of various tumors with radiotherapy therefore relied mainly on guesswork in defining a treatment plan. With time radiotherapists gained increasing experience in the utilization of x-rays and radium

in the treatment of various tumors, but progress was still hampered by X-rays tubes of low energy and the lack of defined units of energy delivered or absorbed by the tissues.

In the 1930s x-ray tubes of progressively higher energy were developed by General Electric, and the first linear accelerators were constructed in the 1940s, which were able to produce x-rays in the megavolt range. Linear accelerators are now the standard equipment in a modern radiotherapy unit capable of delivering x-rays in the 10 to 20 MV range. The advantage of these high energy accelerators is that the x-rays produced has a much deeper tissue penetrance and that the maximum energy can be delivered precisely at the tumor with much less energy deposited in the skin. Thus, skin reactions are no longer a complication in the treatment of deep seated tumors.

The 1930s also was the decade where the units of x-rays were finally defined. The unit of a 'roentgen' was introduced in 1937 and is a measure of dose delivered by an x-ray source. The roentgen unit does not define the amount of radiation received or absorbed by the tissue undergoing radiation. The roentgen unit was substituted by the rad unit (rad = radiation absorbed dose) in 1953. One rad is defined as 100 ergs per gram of energy absorbed in any material. In the S. I. system the gray (Gy) unit is used where 1 Gy equals 100 rad. Thus, by the 1950s radiotherapy had come of age. Radiotherapists now had powerful equipment to deliver a high dose of energy to any lesion in the body, and they could accurately formulate a plan to deliver a prescribed amount of radiation to a defined tumor volume.

<u>Generation of x-rays and gamma rays</u>

X rays and γ–rays are composed of photons, i.e., electromagnetic energy such as light but of a higher frequency. Photons have no charge or mass. The x- and γ–

rays are produced when a high energy electron strikes another bound electron in the inner orbitals of an atom as shown in Fig. 1 (5).

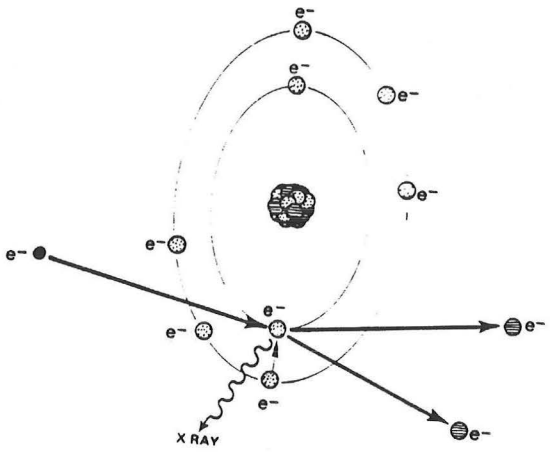

Fig. 1. Generation of x-rays or γ–rays.

The struck electron is ejected and leaves a vacant place in the orbital which is rapidly filled by an electron from the outer orbital. This process leads to the emission of one photon from the atom. The generated photons cause ionizations by three principal interactions: photoelectric effect, Compton scattering and pair production. All three processes lead to the generation of electrons and photons which then interact with other atoms causing further ionization until the energy is dissipated. Because photons are uncharged but generate charged particles (electrons) by deposition of their kinetic energy, γ–rays and x-rays are called indirectly ionizing radiation.

Cellular effects of ionizing radiation

Since water is the major constituent of cells the effect of ionizing radiation is predominantly an interaction with water molecules to generate free radicals. When photons eject an electron from a water molecule an ionized water molecule is generated (6,7).

$$H_2O \rightarrow H_2O^+ + e^-$$

Through a series of reactions with other water molecules, the net result of radiation of water is the formation of a hydrogen (H•) and a hydroxy (OH•) free radical. These free radicals have a very short lifetime (10^{-10} sec) but possess a high energy that can break chemical bonds. Furthermore, they can interact with each other ($2OH• \rightarrow H_2O_2$) by sharing their unpaired electrons or interact with free oxygen ($H• + O_2 \rightarrow HO_2•$) to generate the peroxyl radical. The effect of free radicals on other cellular molecules is counterbalanced by free radical scavengers such as superoxide dismutase, catalase and sulfhydryl containing compounds such as glutathione and cysteine which can reduce free radicals to water.

The deposition of energy directly or indirectly through free radical formation can induce chemical changes in cellular macromolecules such as DNA, RNA and proteins (8,9,10). The chemical changes include breakage of hydrogen bonds, breakage of single or double strands in DNA and crosslinking (intramolecular or intermolecular), which in turn may result in chromosomal aberrations, cellular dysfunction and ultimately cell death. Single strand damage is usually repaired rapidly and efficiently and is not considered critical for cell survival. Double strand breakage, however, may lead to chromosomal aberrations, mutation and cell death. Moreover, it has been shown that the degree of double strand breakage is proportional to radiation dose (9).

Whether cell death induced by radiation is the result of direct DNA damage or a consequence of inadequate repair processes is still a subject of debate in radiobiology. It has been shown that glutathione depletion results in greater radiosensitivity and, conversely, that the addition of sulfhydryl compounds like cysteamine to cells in culture can protect against radiation damage (11). On the other hand other studies have not shown a correlation between glutathione content over a wide range of concentrations in different cell lines and radiosensitivity (12).

The concept of radiosensitivity

The dose-response to radiation has been studied in a variety of cell lines in vitro (13,14,15). A typical example is shown in Fig. 2 for human cancer cells (HeLa cells).

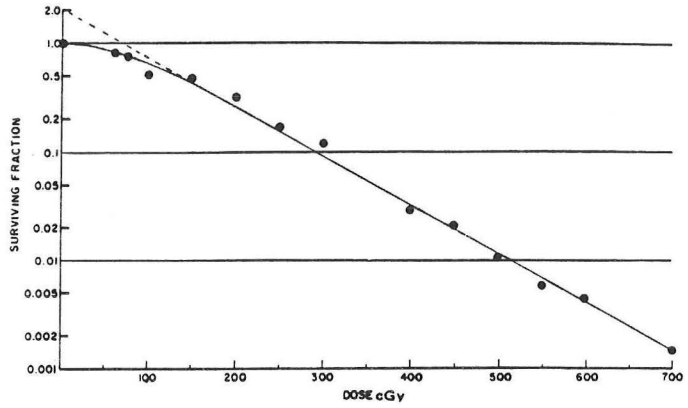

Fig. 2. Dose-response curve of HeLa cells to radiation.

The surviving fraction of cells on a logarithmic scale is plotted against radiation dose on a linear scale. After an initial shoulder region there is an exponential decline in the surviving fraction. This relationship is typical for most mammalian cells that have been studied, when cells have been exposed to a single dose of radiation. The slope of the linear portion of the line is described by the parameter $D_{0,}$ also called the mean lethal dose. It is the dose in cGy required to reduce the surviving fraction to a value of 1/e (0.37). Thus, the mean lethal dose in this example required to reduce the surviving cell fraction from 10% to 3.7% is about 100 cGy. The D_0 value can also be interpreted as the dose required to induce an average of one lethal event per cell. The other parameter that can be derived from the plot is the extrapolation number, N, by extrapolating the slope to the y-axis. The value of N is mainly determined by the shoulder region. The N value is thought to reflect the cells' capacity to repair radiation damage at low levels of radiation dose. Most cells, whether normal or tumor derived, have D_0 values in the range of 100 to 200

cGy when studied in vitro. A representative list of D_0 and N values in various cell lines is shown in table 2 (13).

Cell Population	Do (cGy)	N
Hela	100	2
Human bone marrow	137	1
Human lymphocytes	235	1
Rat endothelium	170	7
Mouse skin	135	–
Mouse melanoma	133	4.2
Mouse small intestine	130	–
Mouse sarcoma	134	9.5
Rat rhabdomyosarcoma	120	10

Table 2. D_0 and N values for human and animal cell lines.

Thus, there is little difference in radiosensitivity between normal cells and tumor cells, at least when they have been removed from their normal environment and propagated in cell cultures. This finding is in contrast to the clinical experience of radiotherapists who find variations in the response of different tumors to radiation.

Cells at various stages in the cell cycle vary in their sensitivity to radiation. In general, cells are most sensitive in the mitosis (M) phase and in the G_2 phase and most resistant in the later part of DNA synthesis (S) phase (6,14,16) as shown in Fig. 3.

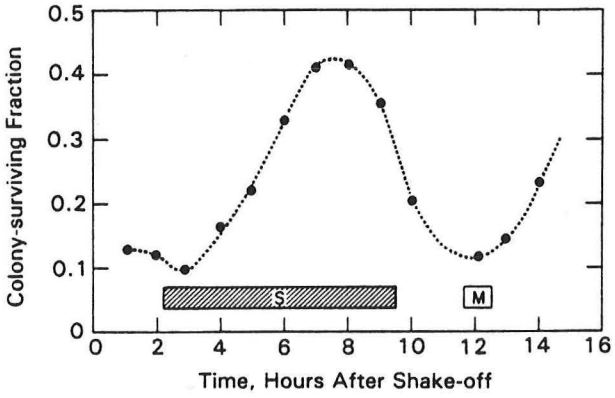

Fig. 3. Cell cycle dependent radiosensitivity of Chinese hamster cells.

The reason for the different sensitivities of cells through the cell cycle is not known but is thought to relate to the compactness of DNA at the various stages. When

DNA is tightly packed as in the M phase the cells are more radiosensitive possibly because repair enzymes may have difficulty in gaining access to the breakpoints in DNA.

Cells lines derived from patients with inherited diseases such as ataxia-telangiectasia have an increased sensitivity to radiation. Fibroblasts derived from these patients have D_0 values in the 35 to 60 cGy range as compared to 100 to 160 cGy in normal fibroblasts (17). A list of inherited diseases where cell lines derived from these patients have increased radiosensitivity is shown in Table 3.

Ataxia-telangiectasia
Huntington's disease
Retinoblastoma
Homocystinuria
Fanconi's anemia
Gardner's syndrome

Table 3. Inherited diseases with increased radiosensitivity.

The reason for the increased radiosensitivity in these diverse inherited diseases is currently not known but could be due to ineffective DNA repair processes.

Deprivation of oxygen cause cells to become more radiation resistant as shown in Fig. 4.

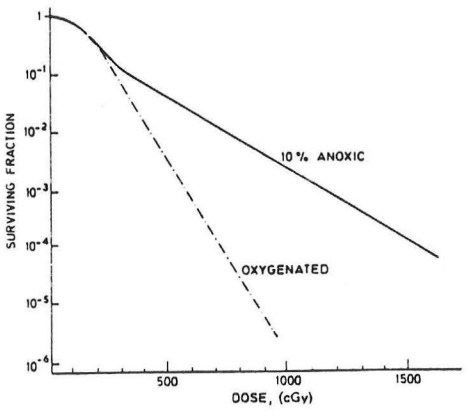

Fig. 4. Cell survival curves for oxygenated and 10% anoxic cells.

which shows the dose response curve for well oxygenated and 10% anoxic tumor cells. In general, D_0 values for anoxic cells are 2-3 fold higher than D_0 values for oxygenated cells (16). Oxygen serves to generate an increased yield of free radicals which is thought to be the underlying mechanisms of the oxygen effect.

In proliferating tissues such as the intestine there is a constant cell turnover and several distinct cell compartments have been defined, which include the stem cell population in the intestinal crypts, the dividing transit population, the transit pool and the mature pool. There are only a few stem cells per crypt and they are relatively undifferentiated. The stem cell products (daughter cells) enter the dividing transit pool in the upper part of the crypts and differentiate into enterocytes, goblet cells and endocrine cells as they continue to divide. These cells enter the transit pool along the sides of the intestinal villi without undergoing further cell division and finally enter the mature pool at the upper part of the villus. Cells in this pool are fully differentiated and have a finite life span. The stem cells and the dividing transit population are very radiosensitive, whereas cells in the transit and mature pool are radiation resistant. The difference in radiosensitivity in these four pools of cells is most likely related to the degree of cell cycling activity as stem cells and the cells in the dividing transit pool are undergoing continuous cell divisions. Other rapidly proliferating tissues such as bone marrow cells, germinal cells and epidermal cells have similar characteristics. As a general rule, tissues that depend on active renewal from a stem cell population will be more radiosensitive than tissues composed of mature, fully differentiated cells independent of stem cell activity such as CNS or liver.

While it has been possible to characterize the effect of radiation on both normal and tumor cells in vitro in considerable detail, it has been difficult to correlate these findings to the effect of radiation on human tumors. The discrepancy is due to the fact that most tumors are heterogeneous in composition,

consisting of tumor stem cells, proliferating tumor cells, differentiated, non-dividing tumor cells and stromal cells each with a different sensitivity to radiation. Furthermore, there appears to be a wide range in cell cycle times within tumor cells in individual tumors which also may account for a differential sensitivity to radiation (18). More recently, however, it was found in an analysis of human tumor cell lines that a correlation existed between radiosensitivity and the response of these tumors to radiation treatment (19). There was a 3-fold difference in sensitivity between the most resistant (glioblastoma) and the most sensitive cells (oat cell carcinoma).

Normal tissue tolerance

The aim of radiation therapy is to kill all tumor cells within the defined target volume and to produce the least possible damage to normal tissues in the proximity of the target. Because the difference in radiation sensitivity between normal cells and tumor cells is relatively small and because normal tissue almost invariably will be included in the radiated field, it follows that the therapeutic gain, i.e., the difference between tumor control and normal tissue damage, is narrow (Fig. 5)

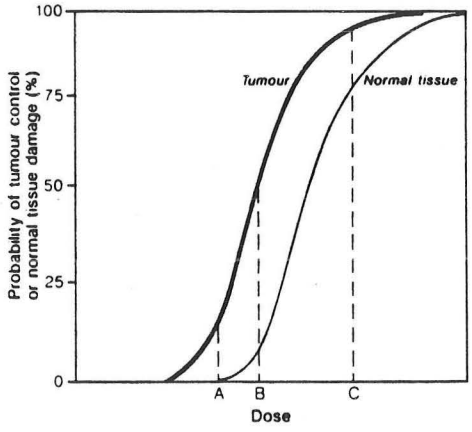

Fig. 5. Theoretical relationship between x-ray dose and outcome of radiotherapy.

This theoretical plot illustrates that with increasing degree of tumor control there is also an increasing risk of normal tissue damage. Fractionation of radiation dose was introduced to decrease normal tissue injury. Generally, radiation therapy is given in five doses per week until the full described dose has been delivered. A usual daily dose is 180 to 200 cGy which results in an exponential decline of surviving tumor cells. The 24-hour delay between each fraction increases the therapeutic gain between normal tissue and tumor cells because of repair processes, repopulation, redistribution and reoxygenation (4R's) (20). The repair of DNA damage is completed within hours and repair processes operate more efficiently in normal tissue than in tumor cells. Repopulation by surviving cells in proliferative tissues such as the intestine functions as an important homeostatic mechanism to maintain tissue integrity. Surviving cells in the dividing transit population will start to divide rapidly to replace the killed cells. Since the rate of repopulation in most tumors is slower than in normal tissues, the difference in repopulation rates also offers a therapeutic gain to fractionated treatment. Redistribution implies a change within the cell cycle. Cells in the M and G_2 phase are most radiosensitive and thus preferentially killed by a radiation fraction. This is thought to partially synchronize the remaining tumor cells which may then pass into the radiosensitive phase of the cell cycle prior to the next radiation fraction 24 hours later. Finally, reoxygenation of hypoxic tumor cells is thought to be important. Hypoxic cells are more radiation resistant (2-3 fold) than normally oxygenated cells. Areas of hypoxia may exist within a solid tumor, and tumor cells in these areas may initially survive radiation. During each fraction the normally oxygenated tumor cells are killed, and the hypoxic cells may then be better oxygenated and become sensitive, hence the concept of reoxygenation. Thus fractionation of the radiation dose into smaller doses separated by a certain time interval not only serves to protect normal tissue but also serves to render the more radioresistant cells to become radiosensitive by

cell cycle redistribution and reoxygenation. Newer methods of fractionation include hyperfractionation where the dose per fraction is reduced and given twice a day which might reduce late tissue effects and allow the delivery of higher total dose in the same treatment period (21).

The tolerance of normal human tissues to radiation is shown in Fig. 6.

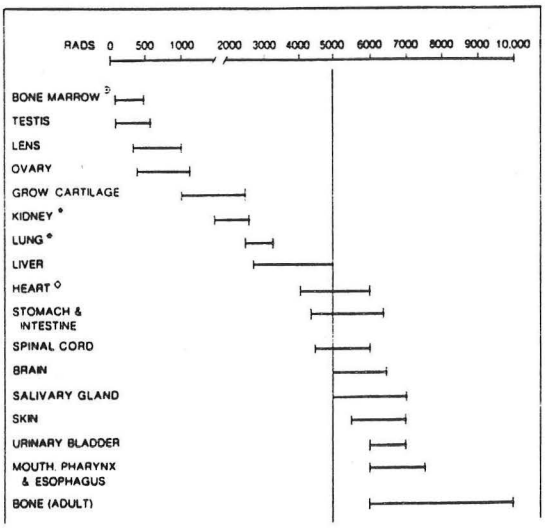

Fig. 6. Normal human tissue tolerance doses (rads).

in a descending order of sensitivity (22). The values in rads have been derived from many years of clinical experience of radiotherapists and refer to standard treatment with five fractions (200 rad) per week. The limits of radiation dose for each organ refer only to late injury. The bars on the horizontal lines indicate two defined tolerance doses (TD 5/5 and TD 50/5 i.e., radiation doses that cause complications in 5% or 50% within 5 years). More recently, a task force has reevaluated the normal tissue tolerance to radiation and included volume considerations (23). The TD 5/5 for the small intestine is estimated to 5000 cGy and the colon to 5500 cGy if 1/3 of the organ is included in the radiated field. It should be emphasized that the tolerance doses are estimates derived from clinical experience. Nonetheless, these are the dose limits that are used in the treatment planning.

The formulation of a treatment plan in a given patient with a defined malignancy involves a simulation with the patient in a fixed position in the

treatment room with assessment of the tumor volume and its precise location within the treatment field by x-ray or CT. The treatment technique is then determined (AP-PA fields, lateral fields etc.), and the total dose that will result in tumor control with minimal normal tissue damage is prescribed. The doses received by the tumor and surrounding tissue are calculated and are usually shown as a series of isodose curves as shown in Fig. 7.

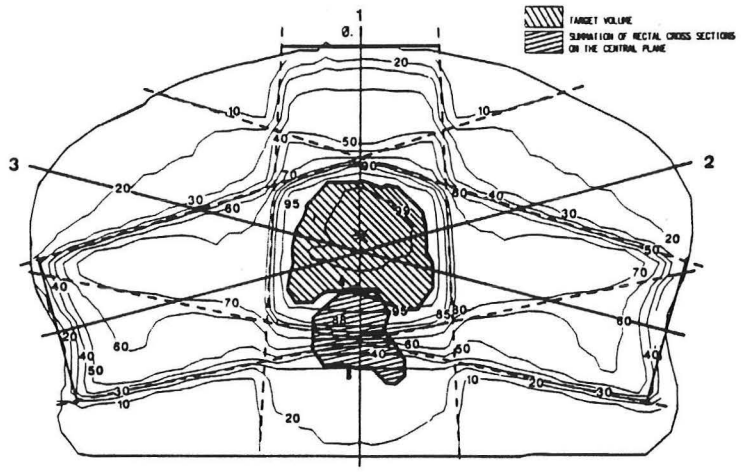

Fig. 7. Isodose curves for a three-field treatment plan for prostate cancer.

which shows a treatment plan for prostate cancer. From these curves it is then possible to estimate the doses received at critical normal tissues (rectum, bladder), and the treatment plan can be modified if these doses exceed accepted tolerance levels. The figure also illustrates the fact that it is difficult to design a treatment plan in prostate cancer where the anterior rectal wall will not receive a high radiation dose.

Radiation enteritis and colitis

The incidence of radiation injury to the gastroinestinal tract appears to be variable but ranges from 3.6 to 21% in recently published large series of patients receiving pelvic radiation as shown in Table 4.

n	Incidence (%)	Ref.
57	21	24
132	15	25
154	20	26
218	19	27
293	11	28
526	10	29
527	13.5	30
784	3.6	31
1418	4.3	32

Table 4. Incidence of late intestinal radiation injuries in patients treated with pelvic radiation.

The incidence refers only to late injuries that become symptomatic months to years after radiation treatment has been completed. The incidence of acute effects that appear during or immediately after radiation is much higher and in the range of 60 to 80% in some series (33).

Pathological changes

The pathological changes that are observed in the gastrointestinal tract following radiation can be divided into acute and chronic (late) manifestations (34,35). The acute injury is mainly restricted to the small intestinal and colonic mucosa, which are both actively proliferative epithelia. Stem cells and cells in the dividing transit population are depleted because of their radiosensitivity, and hence, the normal balance between crypt cell production rate and cell loss from the villus tips, which maintains villus integrity, is disturbed. Temporarily, there is greater cell loss than new cell synthesis which leads to characteristic changes in villus morphology that include shortening of the villi, enlargement of the villus cells and prolonged retention of the cells on the villus, all of which may serve to maintain

epithelial integrity and prevent disruption (ulcer formation). The changes in villus architecture are associated with an increase in inflammatory cells in the lamina propria and submucosal edema as seen in Fig. 8.

Fig. 8. Effect of radiation on small intestinal villus morphology.

which shows three small bowel biopsies from a patient undergoing abdominal radiation (A: before treatment; B: after 3300 rads and C: 12 days after completion of treatment) (36). The remarkably rapid recovery in just twelve days illustrates the concept of repopulation. A higher radiation dose will result in more extensive epithelial damage with desquamation and ulcer formation. The disruption of the epithelial barrier may result in bacterial invasion and sepsis, bleeding from ulcerations and diarrhea. Such severe acute changes are, however, rare with modern radiotherapy. The important fact about the acute epithelial changes is that they probably occur in most patients undergoing radiation, and that the changes are transient and rapidly repaired in most cases.

The pathological changes in late injuries have been studied more extensively due to the fact that patients with these injuries often undergo surgical resections. The gross changes of the affected small intestine may include mesenteric thickening, serosal fibrin deposits and adhesions, segmental narrowing or a concentric stenosis (34). The wall of the intestine is thickened and there may be

focal shallow or deep ulcers occasionally penetrating the wall. Microscopically, the villi are shortened and blunted with fibrosis and telangiectasic vessels in the lamina propria. Characteristically, the most profound changes are observed in the submucosa, where there is extensive fibrosis and extensive vessel damage with endothelial cell loss, intimal proliferation, hyalinization and fibrin-platelet thrombi (37). The nerves and ganglion cells are similarly distorted by the fibrotic process (38). The profound vascular changes may cause local tissue ischemia which then may perpetuate or accentuate the inflammatory changes. The primary target for submucosal radiation injury may be the endothelial cells which serve an important role in local tissue homeostasis and synthesize a number of cytokines that regulate permeability, inflammatory cell trafficking, platelet aggregation and fibrinolysis (39). Endothelial cells have a very slow cell cycle time estimated to be many months (40) which may account for the late onset of these injuries. Vascular changes similar to those observed in human small intestine have been observed in animals subjected to radiation (41,42).

The gross and microscopic late changes in the colon are very similar to those described for the small intestine with fibrosis and obliteration of the vessels in the submucosa (43). Local ischemia may cause tissue necrosis resulting in ulceration, fistula formation or perforation, which are typical sequelae of intestinal radiation injury.

The pathological changes are not pathognonomic for radiation damage but highly suggestive when observed in biopsy specimens from patients who have undergone radiation therapy.

It should also be mentioned that identical changes are observed in the stomach and the esophagus when these organs have been included in the radiation treatment field (34).

Clinical presentation

It is useful to separate the gastrointestinal symptoms that develop in patients receiving abdominal radiotherapy into immediate or early symptoms and late symptoms which correlate with the pathologic manifestations of radiation injury.

Early symptoms

The early symptoms usually start during or immediately following radiotherapy and are most often transient corresponding to the transient nature of the pathological changes. Patients who receive upper abdominal radiation often develop nausea and vomiting during radiation. The pathophysiological mechanisms(s) that cause nausea and vomiting is unknown. Some have argued that these patients develop gastroparesis but studies to document compromised gastric emptying during radiation are currently lacking. Nausea and vomiting usually respond well to dopamine antagonists (metoclopramide or domperidone) and the symptoms will abate shortly after completion of the treatment.

Diarrhea may develop several weeks into the treatment when the small intestine is included in the treatment field. The degree of diarrhea appears to increase with increasing dose of radiation and also to correspond to the length (volume) of exposed intestine (44,45). In radiation for pelvic malignancies distal small intestinal loops are almost always inside the treatment field especially in patients who have had previous abdominal surgery (46). These patients may develop watery diarrhea which in some patients have been shown to be due to bile acid malabsorption (47). Presumably, the loss of mature enterocytes with a normal complement of bile acid transporters leads to replacement with immature enterocytes with a deficient number of bile acid transporters. The increased loss of bile acids to the colon induces electrolyte and water secretion. The diarrhea usually

responds to treatment with a bile acid binding resin such as cholestyramine. If jejunal loops are within a treatment field the diarrhea may conceivably be due to lactose malabsorption because of insufficient lactase activity in immature enterocytes. A direct demonstration of decreased lactase activity in human jejunum during radiation has not been performed. In general, diarrhea will respond to treatment with antidiarrheal medications (loperamide, diphenoxylate) during radiation and resolve after completion.

The most disturbing early symptoms are the development of rectal bleeding and tenesmus which are typical of radiation proctitis and seen in patients treated for pelvic malignancies (cervical, prostate and rectal cancer). The symptoms of radiation procititis are similar to those of idiopathic ulcerative proctitis and so are the sigmoidoscopic findings which will show an edematous inflamed mucosa with loss of vascular pattern and some friability (48). Frank ulcerations and more severe rectal bleeding may eventually develop if radiation is continued at an unchanged dose-rate. Fortunately, only a minority of patients will develop radiation proctitis as an early symptom. The symptoms may respond to a reduction in dose rate. Symptomatic treatment with hydrocortisone enemas usually accelerates the resolution of the inflammatory process.

Although there is no absolute correlation between early and late symptoms there is evidence that patients who have severe early symptoms are more prone to develop late symptoms. However, there is no guarantee that those who are asymptomatic during treatment will not develop late symptoms. In one series of patients radiated for pelvic malignancies more than one half developed late small bowel injuries although they had no early symptoms (49).

Late symptoms

The peak incidence for the manifestations of late injuries is between 6 months to 2 years after completion of radiation but there is a wide variation and some injuries may not become symptomatic until 25 to 30 years later. The symptoms are usually insidious in onset and the first symptom is often abdominal pain which may be meal related and progressive in nature. Other symptoms include development of bloody diarrhea, tenesmus or increasing constipation with a change in stool caliber (50,51). The symptoms reflect the underlying pathologic changes in the small and large bowel. The mucosal changes with multiple telangiectasias and ischemic ulcerations cause rectal bleeding and tenesmus and the submucosal fibrosis causes stricture formation. The combination of strictures and local tissue ischemia may result in deep penetrating ulcers and fistula formation. Basically, these patients may present with chronic proctitis/proctosigmoiditis, partial or total small or large bowel obstruction from stricture formation or diarrhea/malabsorption secondary to stricture or fistula formation. Each type of presentation represents a difficult management problem and include both medical and surgical interventions.

Medical treatment

a. Radiation proctitis.

The initial work-up of patients with chronic radiation proctitis (or proctosigmoiditis) includes a flexible sigmoidoscopy or colonoscopy to evaluate the extent and severity of the lesions and to exclude other lesions. Typically, there are multiple telectasias, small ulcerations and friability or spontaneous bleeding (52). Except for telangiectasia these findings are also typical for ulcerative colitis. Biopsies show findings compatible with radiation injury.

There are no controlled randomized studies of the effect of medical treatment on radiation proctitis. In fact only a few studies on a limited number of patients have been published. The combined administration of azulfidine p.o. and hydrocortisone enemas caused subjective and proctoscopic improvement in one patient but with a very slow response (53). In another study of four patients with radiation proctitis the administration of 5-aminosalicylic acid enemas (Rowasa) for two to seven months failed to cause any improvement (54). A synthetic sulfated polysaccharide, sodium pentosanpolysulfate has recently been tried in a phase I/II study of radiation proctitis (55). Eleven patients were treated with 150 or 300 mg t.i.d. for 3 months and nine patients had a complete response. Four of the nine complete responders had a relapse after about one month and were retreated for another 3 months and again had a complete response. Remission was maintained for a follow-up period of 9 months. The beneficial effect was only evaluated by symptoms and objective improvement on sigmoidoscopy was not documented. The mechanism of action of this compound is unknown. Unusual treatment modalities have been attempted where standard treatment has failed. For example, rectal instillation with formalin (3.6%) was used in a patient with transfusion requiring radiation proctitis (56). The bleeding stopped right after treatment and no further bleeding was observed in the follow-up period (14 months).

Laser treatment with obliteration of mucosal telangiectasia was recently shown to be effective in stopping rectal bleeding in four patients with refractory radiation proctitis (57). No further rectal bleeding was observed in a mean follow period of 6 months.

It is perhaps not surprising that radiation proctitis remains refractory to the administration of antiinflammatory drugs if the late injuries are secondary to ischemia rather than to inflammation.

The natural history of radiation proctitis was analyzed in 88 patients followed over an eight year period by a gastrointestinal clinic (58). The patients were divided into three groups according to the severity of rectal bleeding and bowel dysfunction. Group I (n = 39) had low grade bleeding not requiring transfusions; group II (n = 32) had transfusion requiring bleeding but minimal bowel dysfunction and group III (n = 17) had transfusion requiring bleeding and significant bowel dysfunction (constipation and pain). There was no significant difference in the total radiation dose to the rectum among the three groups. The positive finding of this analysis was that about 2/3 of group I patients and 1/2 of group II patients went into remission after about 2 years as illustrated in Fig. 9.

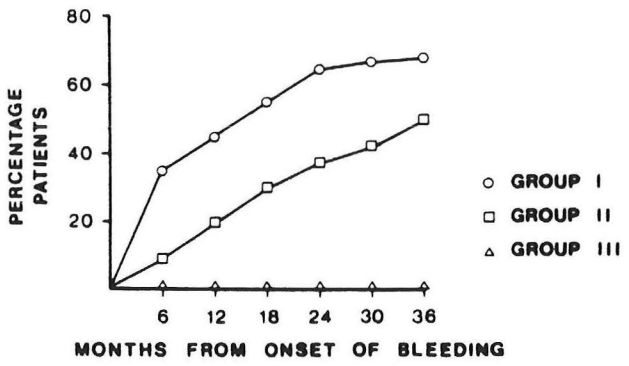

Fig 9. Spontaneous remission of rectal bleeding in radiation proctitis with time.

Patients in group III remained symptomatic with chronic rectal bleeding. More than 80% of the total group was treated with oral azulfidine and hydrocortisone enemas but a beneficial effect of the medical treatment could not be detected. However, it is encouraging that a substantial number of patients with radiation proctitis may recover with time.

b. Radiation enteritis

Patients with radiation enteritis typically present with symptoms and signs of partial or complete small bowel obstruction and medical treatment has a limited role. Small bowel x-rays usually show evidence of ileal disease with strictures, abnormal mucosal folds and proximal dilation (59,60,61). Only one study that involved a total of three patients have documented subjective and radiographic improvement on long term azulfidine treatment (55). Most patients with radiation strictures usually have progressive symptoms with repeated episodes of obstruction and will eventually require surgery.

A minority of patients with radiation ileitis may present with diarrhea and malabsorption of bile acids and B_{12}. B_{12} and bile acid absorption was measured in a series of 26 patients with radiation ileitis and a main complaint of watery diarrhea (62). The results are depicted in Fig. 10.

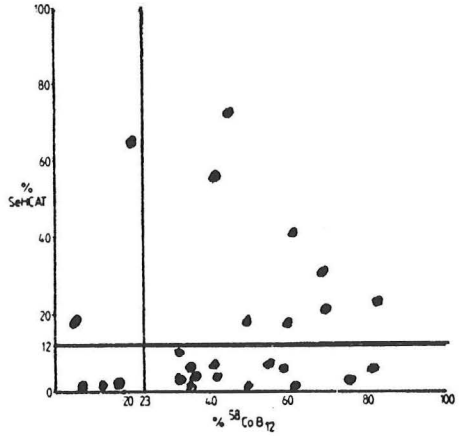

Fig. 10. B_{12} and bile acid absorption in 26 patients with diarrhea and radiation enteritis.

Eight had normal absorption of both compounds, 13 had abnormal bile acid absorption and normal B12 absorption, 2 had normal bile acid but abnormal B_{12} absorption and 3 had malabsorption of both compounds. Fifteen of the 16 patients with bile acid malabsorption had resolution of the diarrhea with cholestyramine treatment. The two patients with B_{12} malabsorption, but normal bile acid

absorption had an abnormal breath hydrogen test following an oral glucose load suggestive of bacterial overgrowth and diarrhea resolved after antibiotic treatment.

Finally, diarrhea may develop due to the presence of a fistula between small and large bowel. The presence of a fistula is best documented with a radiographic study and treatment is surgery.

Surgical treatment

It is estimated that 1-2% of patients treated with abdominal radiation will develop late injuries that require surgical interventions (63-67). There appears to be a trend toward an increasing incidence at least in some centers (32). The indications for surgery are shown in the Table 5.

Rectosigmoid stenosis	19
Rectovaginal fistula	11
Rectal ulcer	8
Intractable proctitis	6
Perforation	5
Obstruction	5
Other fistulas	4
Unknown	4
Total	62
Number of operations:	143
Number of complications:	61

Table 5. Indications for surgery in 62 patients with late intestinal radiation injury.

which illustrates the Mayo Clinic experience. 720 patients with radiation proctitis were seen in the period 1950 to 1983 (68). 62 of these patients eventually required surgery for the problems shown in the table and they underwent a total of 143 operations. 40 patients (65%) had a total of 61 complications and the operative mortality was 13%. The major type of complications were anastomotic leaks, wound infections, intestinal obstruction, abscess and fistula formation. In the series of 88 patients with radiation proctitis previously described 19 required surgery of whom 9 died from sepsis (47% mortality) (58). The high morbidity and mortality rates

underscore the severity of the complications and the difficulties in the surgical management. There has been an ongoing discussion in the surgical literature regarding the benefits of resection and primary anastomosis versus a simple bypass operation where the diseased segment of intestine is left in place. An analysis of 199 patients showed that 36% of patients with resections had complications with a 21% mortality rate whereas bypass operated patients had a 6% complication rate and a 10% mortality (69). Thus, by-pass procedures were recommended for small bowel strictures. In patients with rectosigmoid strictures or refractory proctitis it is now recommended that the initial surgical procedure should be a colostomy (descending or transverse colon) and to follow the patients for one year. If the proctitis resolves secondary to the diversion of the fecal stream the colostomy can be closed. In the case of persistent bleeding or strictures an anterior resection is recommended with wrapping of an omental pedicle graft around the anastomosis to reduce the risk of a leak. Rectovaginal fistulas have been notoriously difficult to treat. Currently, the procedure of choice is rectal mucosectomy and a pull-through of mobilized descending colon with a colo-anal sleeve anastomosis. The fistula is left untouched. Acceptable functional results with a low rate of complications have been reported with this method of repair (70).

The reason for the high complication rate in surgical management of radiation injuries is most likely due to the fact that microscopic radiation damage extends beyond the visible macroscopic changes and thus anastomoses maybe created in tissues with poor healing capacity. Thus, the surgical management of radiation injuries requires a careful preoperative evaluation with radiological and colonoscopic delineation of the extent of injuries and a conservative rather than an aggressive approach during surgery.

Prevention of radiation injury

The aim of radiotherapy remains to achieve the highest possible rate of tumor control and thus improved survival while at the same time inflicting the least possible damage to normal tissues, i.e., to increase the therapeutic ratio. An improved treatment planning strategy is one way to achieve this goal and there has been several technological advances in treatment planning (71). The first step in optimal treatment planning is to define the closest approximation of the treatment volume to the target volume, which will reduce the radiation dose to normal tissues. In the past the target volume was usually assessed with x-rays in two dimensions which may under- or overestimate the true tumor volume. For example , in a review of 409 patients it was found that treatment planning without CT resulted in insufficient tumor coverage in 49% when the plans were reevaluated with CT (72). Thus, CT is clearly superior to two-dimensional x-rays to define the target volume which should lead to a higher geometric accuracy i.e., the tumor volume is covered with the radiation beams. It is likely that CT-assisted tumor volume assessment will improve local control rates and possibly decrease the rate of normal tissue injury. However, the incidence of radiation proctitis in 154 patients treated for prostate cancer with CT assisted planning was still 20% (26). CT images with the patient in the treatment position has also been used to develop computerized 3D treatment planning systems which provide information about optimal beam arrangement, shielding of fields with wedges to protect normal tissue and radiation doses in the target volume and in surrounding tissues (73). Three dimensional planning can be used to conform the maximal dose to the target volume (conformal therapy) and refine the dose distribution to protect normal tissues. This technique was used in a high dose treatment (76 Gy) of stage C prostate cancer in 20 patients (74). All patients were alive at a median follow-up time of 19 months and three developed mild radiation proctitis. It remains to be established in larger

prospective series how much these technological advances will improve tumor control and reduce radiation injuries. It should be noted however that CT assisted dose calculations have shown that 2D dose estimations may underestimate total dose received by normal tissue (bladder, rectum) by a factor of 2 (75,76).

While the rectum and bladder are fixed structures within a radiation field the exclusion of small bowel from the field has been achieved with both simple and more aggressive measures. Simple measures include a prone treatment position, bladder distension and abdominal compression. In a series of 150 patients receiving pelvic radiation these measures reduced the small bowel volume in the radiation field by more than 60%. Only 5 patients developed late radiation injury (small bowel obstruction (46). A more aggressive approach is the displacement of small bowel loops with an absorbable mesh placed during surgery prior to radiation (77,78). The number of patients treated in this manner are too small to evaluate a possible benefit.

The lethal damage of tumor and normal cells by radiation is partly due to the generation of free radicals in the cells. Chemical compounds that can neutralize free radicals and cross cell membranes might be of value in the protection of normal tissue against radiation damage. A number of compounds have been screened and one compound, WR-2721, a phosphorylated aminothiol, was shown in animal studies, when administered prior to radiation, to improve survival and to reduce the rate of late radiation damage (79). WR-2721 has now been tested in a phase I trial and was found to be well tolerated (80). It remains to be shown that this compound will offer selective protection of normal tissues. If the compound enters both normal and tumor cells at the same rate it is possible that it also will result in a less favorable response in terms of tumor control. Interleukin 1 (IL-1) has been shown to protect intestinal crypt cells against radiation injury when given prior to radiation mice (81). The mechanism of protection is unknown.

Release of prostaglandins following radiation has been postulated to play a role in the epithelial injury (82). Administration of a prostaglandin synthesis inhibitor, indomethacin, to mice prior to and following radiation of the esophagus at different doses showed increased survival rates at 3200 cGy as compared to controls (83). Furthermore, epithelial damage was more pronounced in controls than in indomethacin treated mice at 2400 to 3200 cGy. There was no difference in survival or epithelial damage between control and treated mice at higher doses. In addition, it was also shown that administration of indomethacin did not adversely affect the radiation cure rate of an implanted squamous cell tumor in mice. This study suggests that inhibition of prostaglandin synthesis may be of benefit in protection against acute radiation damage. There was, however, no difference in submucosal changes (venous dilation and endothelial cell swelling) between control and treated mice which indicates that indomethacin may not protect against late damage.

A possible role for sulfasalasine or the newer 5-aminosalicyclic acid derivatives as protective agents against intestinal radiation injury has surprisingly not been evaluated. Sulfasalasine is not only a prostaglandin synthesis inhibitor but also a free radical scavenger (84). It is conceivable (but unproved) that oral or rectal administration of these compounds prior to radiation which results in a high mucosal concentration of 5-amino-salicylic acid, might offer selective protection of intestinal mucosal cells and possibly submucosa.

At any rate the search for more effective radioprotective agents continues in parallel with technological advances in treatment planning. Prospective analysis of these combined efforts will hopefully result in a reduction in the rate of acute and late radiation damage of the intestine.

Radiation induced risk of colon cancer

Several reports have raised the issue that the incidence of colon and rectal cancer is increased in patients following pelvic radiation (85,86). These reports are all retrospective analyses of probably inhomogenous patient populations in terms of treatment modality and radiation dose where the incidence of observed and expected colon cancers are compared. Patients who have suffered one malignancy may have an inherently increased risk of a second malignancy irrespective of radiation. Thus, it is difficult to assess a true increased risk from these retrospective studies. In a large series of patients (n = 2068) radiated for a benign condition (uterine bleeding) there was an almost 2-fold increase in observed cases of colon and rectal cancers compared to the expected incidence (87). A similar conclusion was reached in a theoretical calculation of the relative risk in women receiving pelvic radiation at age 40 or 50, and assuming a radiation dose of 30 Gy to the colon (88). The calculated relative risks varied between 2.0 and 3.6 in a follow-up period of 20 and 30 years. The issue of a possible increased colon cancer risk is currently unresolved and previous pelvic radiation is not included in the list of diseases that is recommended for sigmoidoscopic cancer surveillance by the American Cancer Society.

In summary, radiotherapy is an important treatment modality in modern cancer therapy. A large and increasing number of patients are treated with radiation for a variety of cancers within the abdomen and pelvis. Because of the physical characteristics of photon delivery to a tumor target it is not possible to completely eliminate normal tissues within a treatment field and to avoid normal tissue damage. Late intestinal radiation injuries remain feared complications and are difficult to treat. It is hoped that recent advances in treatment planning and delivery and development of more effective radioprotectors will translate into a decreasing incidence of these injuries.

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