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Basic principles of radiation biology and radiation tolerance are reviewed. The implications for radiation therapy of newer staging techniques in carcinoma of the prostate such as exploratory laparotomy, lymphangiography, and bone marrow acid prosphatase are discussed. A technique for treating the prostate and para-aortic lymph nodes in continuity is presented. Complications and results of therapy are discussed.

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Much change has taken place in the role of radiation therapy in the treatment of carcinoma of the prostate. Improvement in radiation therapy equipment and the development of sophisticated treatment planning techniques are only partially responsible. The greater stimulus has come from the advances in staging procedures, such as lymphography, staging laparotomy, and bone marrow acid prosphatase, which have already been discussed by others.

In only 5% of patients is cancer clinically confined to the prostate. About ¼ to ½ of these will have evidence of extraprostatic extension when radical prostatectomy is performed. We also know that the incidence of lymphatic metastases is very high in this group of patients. We suspect, but have not yet proven, that many of these patients are potentially curable. However, much larger volumes of tissue than previously treated must be irradiated.

Radiation Biology

In order to comprehend the significance of these changes in radiation therapy one must first understand some of the basic principles of radiation interactions with biological systems. As radiation passes through tissues, it causes alterations at the biochemical level primarily through the mechanism of ionization. At the cellular level, the effects appear principally to be mediated by chromosomal damage. The effects we see clinically are the result of disruption of tissues and organs due to cellular damage interacting with homeostatic mechanisms of the body.

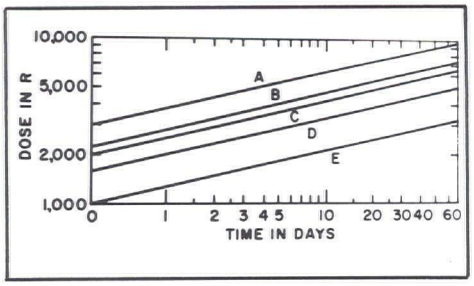

Figure 1
Isoeffect curves relating the total dose to the overall treatment time for A, skin necrosis; B, cure of skin carcinoma; C, moist desquamation of skin; D, dry desquamation of skin; E, skin erythema. (From Eric J. Hall, *Radiobiology for the Radiologist,* Hagerstown, Maryland 1973, Harper & Row Co. Redrawn from Strandqvist M: *Acta Radiol* Supp 55: 1-300, 1944)

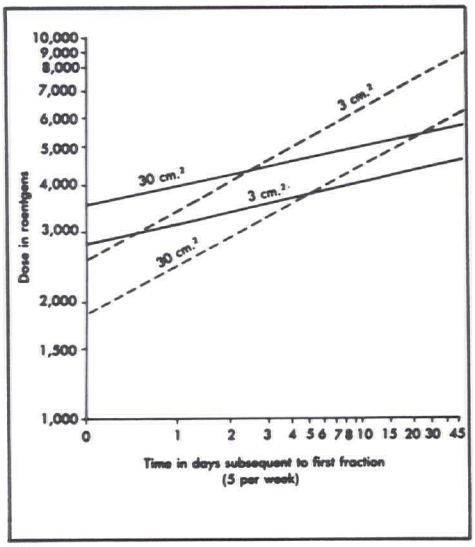

Figure 2
Time-dose-volume relationships for fractionated irradiation of carcinoma of the skin. The solid lines are isoeffect curves for 99% tumor regression for cancers 3 cm² and 30 cm². The broken lines are isoeffect curves for 3% skin necrosis for skin areas of 3 cm² and 30 cm². The curves for tumor regression have less slope than those for skin tolerance. Unlike the classical Strandqvist curves, cancers of similar sizes are grouped together, emphasizing that larger cancers require a higher dose than small cancers. The curves also emphasize that for a given fractionation large volumes tolerate less dose than small volumes. Moving along the graph from left to right, with increased fractionation the curves for necrosis and tumor regression cross, then diverge, emphasizing the benefits of fractionation. (From Moss WT, Brand WN, and Battifora H: Radiation Oncology, ed 4, St. Louis, 1973, The C. V. Mosby Co., modified from von Essen CF: *Radiology* 81:881-883, 1963)

The ability of the body's homeostatic mechanisms to repair the damage due to radiation is dependent upon four main considerations: the time interval during which radiation is administered, the total dose of radiation, the fractionation or size of each dose, and the volume of tissue irradiated.

The first correlations of dose and time were published by Strandqvist in 1944. In Figure 1 curve A shows skin necrosis, curve B tumor control, and curves C, D, and E various degrees of skin reaction. Note that, according to these data, the dose which will cause skin necrosis is above that for tumor control at all levels.

The curves in Figure 2 summarize data which not only take into account the effects of total dose and time, but also include the effects of volume. The solid lines represent 99% tumor control. The dotted lines represent a 3% incidence of skin necrosis. There are two sets of curves according to the size of the field, three square centimeters and thirty square centimeters. These observations have been made on skin carcinoma. They represent an optimal range of doses which are adequate to control the tumor in a majority of cases, with an acceptable level of complications.

For the three square centimeter field the single dose for both skin necrosis and tumor control are reasonably close together. As the dose and the time increase, the curves rapidly diverge, indicating an increasing differential margin of safety. For example, at 20 days about 4000 rads is required for tumor control while the skin will tolerate about 7000 rads. A dose adequate to control the tumor can be delivered without a significant risk of complications.

For the thirty square centimeter field, however, the single dose required for tumor control is much greater than that which will produce skin necrosis. As one follows the curves out in time, one can see that eventually they cross, (in this case 5000 rads at 28 days) and reach a point where the dose required for tumor control is less than that required for skin necrosis. This illustrates graphically the principles of protraction and fractionation. That is, as one reduces the daily dose but increases the overall time and total dose delivered one can gain a therapeutic advantage by increasing the differential between tumor control and normal tissue tolerance. They also emphasize the importance of volume: The larger the volume the less the normal tissue tolerance and the greater the dose required for tumor control.

While the skin is relatively resistant to radiation, a majority of internal organs are not. However, the solid tumors which comprise a majority of internal malignancies require about the same high doses for control as do malignancies of the skin. Tolerance is dependent on how much of the organ is irradiated. The following illustrations will be important to keep in mind when discussing our newer techniques. Radiation myelitis produces a Brown-Séquard syndrome if ½ the diameter of the cord is involved, or a transection if the entire width is involved. Spinal cord tolerance is shown to be dependent on the length of spinal cord irradiated. If the length of cord treated is relatively short, radiation myelitis will usually occur only after doses in the range of 4400 to 5000 rads in 4½ to 5 weeks. If a greater length of spinal cord is irradiated, the risk is increased and the tolerance decreased to a range of 3600 to 4000 rads in about 4 weeks.

The syndrome of acute nephritis is produced in about ½ of patients if the dose to the whole of both kidneys exceed 2300 rads in about 5 weeks. However, if ½ to ⅓ of each kidney is shielded in such a manner as to restrict the dose to less than 2000 rads, the remaining portions of the kidney may be treated to higher doses without clinically significant alterations in function. Similarly, the radiation tolerance of most organs, such as liver, small bowel and lung, is considerably diminished if the entire organ must be included in the radiation field. If only a portion of the organ is irradiated, however, relatively high doses will be tolerated.

What about tumor control? We have seen from the earlier curve (Figure 2) that as tumor size increases, the dose for tumor control also increases. There are several reasons for this. One is that cell kill or survival follows an exponential curve if the cells are well oxygenated. As the tumor grows larger, however, the central portion of the tumor becomes hypoxic and therefore radioresistant. Calculations based on experimental values obtained by Warburg and Crowe have indicated that oxygen concentration will fall to zero about 150 microns from capillaries. Cells more distant than this will be anoxic. Experimentally in animals it has been shown that cells closer to vascular stroma are damaged more than those distant from it during radiation even though those further from the vasculature may receive higher doses. Tomlinson and Grey examined the histological structure of human lung tumors. They noted that the solid tumor cords were surrounded by vascular stroma but no capillaries were seen in the cords. All cords greater than 180 microns in radius had necrotic centers. There is, as well, a transitional zone of hypoxia in which the cells are still viable but metabolically inactive due to a lack of oxygen and nutrients. With a course of fractionated radiation, most radiation therapists feel that the more peripheral, well oxygenated cells are initially killed. As the tumor regresses, they believe that reoxygenation occurs because the surviving previously hypoxic cells become closer to the vascular supply and are rendered euoxic and thus more sensitive to radiation. Reoxygenation, however, is not accomplished 100% of the time.

How does this affect tumor dose? For grossly evident tumors and employing megavoltage radiation such as cobalt 60 or

linear accelerators, permanent local control of most solid tumors requires doses in the range of 6600 to 7000 rads, whether they are epidermoid carcinomas of the head and neck region or adenocarcinoma of the prostate.

Microscopic disease, on the other hand, does not require such high doses. Fletcher and others have demonstrated that doses in the range of 5000 rads in five weeks, delivered to clinically uninvolved but high risk nodes, will prevent tumor development in 90% of cases. In our own series at Henry Ford Hospital, many patients with Stage I and IIA carcinoma of the cervix received pre-operative radiation. The dose to the pelvic lymph nodes is in the range of 3200 to 3600 rads. Several previous studies have demonstrated that the expected incidence of nodal involvement would be about 10 to 20% in this patient group. However, only one patient in our series had positive nodes in the surgical specimen. The conclusion that one is led to draw from this evidence is that microscopic clumps of cells are probably much more radiosensitive than macroscopic aggregates.

The implication in carcinoma of the prostate is that while some of these tumors are beyond the confines of surgical extirpation, they may still be permanently controlled by radiation, if the following criteria can be met:

1. A radiation portal sufficient in size to encompass all the known and suspected areas of disease can be employed.
2. No vital organs will be included in the high-dose volume.
3. A sufficient amount of radiation can be administered to sterilize the tumor without exceeding normal tissue tolerance.

The use of such things as exploratory laparotomy for surgical staging and lymphangiography have shown that carcinoma of the prostate frequently metastasizes to regional nodes and may remain there prior to hematogenous dissemination. The implication is that radiotherapists in recent years are treating larger volumes of tissue to higher doses. Tolerance of normal tissue must be respected, for it is of no value to sterilize the tumor and in the process cause unacceptable complications.

Treatment Technique

Since solid tumors, as previously stated, require high doses of radiation for control, in the range of 6000 to 7000 rads, reduction of the treatment volume to minimal size is essential. The same staging procedures which define the extent of disease allow visualization and minimization of the necessary treatment volume. These factors have stimulated trials of the aggressive radiation therapy.

The specific technique we use depends on the extent of tumor as shown by the staging procedures. In patients whose disease is confined to the prostate or extraprostatic tissues, we know that the risk of pelvic lymph node involvement is relatively high. If the lymph nodes are shown to be negative by lymphangiography and/or exploratory laparotomy, we initially treat the entire pelvis to a dose of 5600 rads. This dose should be adequate to control microscopic disease that may be clinically undetected in the lymph nodes. A booster dose of an additional 1000 rads is then delivered to the area of the primary tumor site to bring the total dose to this area to 6600 rads delivered in 6½ weeks, giving 200 rads per day, five days per week.

Once the lymphatics are grossly involved, we feel that it is necessary to treat the entire abdominal lymphatic chain up to the level of the diaphragm. A technique to treat this large area has been developed here at Henry Ford Hospital. Initially, an anterior posterior coaxial pair of fields, referred to as a spade, (Figure 3) is used to encompass the primary tumor as well as lymphatics up to the diaphragm. This field is treated at the rate of 150 rads per day in order to reduce the daily dose rate to the lower spinal cord segment as well

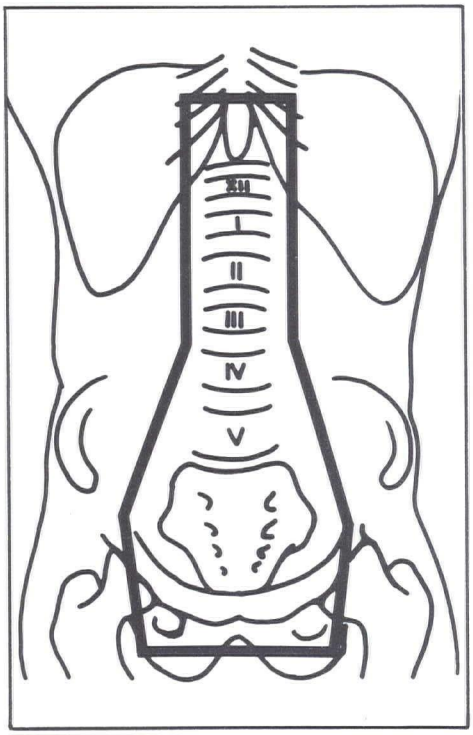

Figure 3
The spade shaped field. This is designed to encompass the lymphatics of the pelvis and the para-aortic chain up to the level of the diaphragm.

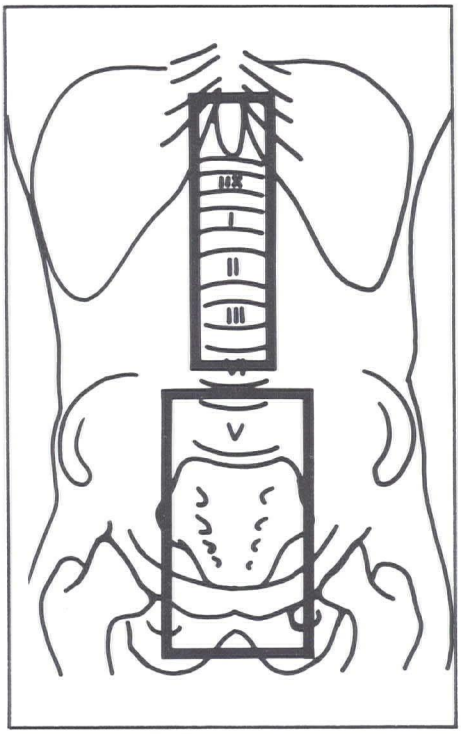

Figure 4
Separate pelvic and para-aortic ports. The pelvic port extends to the L4,5 intervertebral disc space. The para-aortic ports encompass the remainder of the para-aortic lymph nodes up to the level of the diaphragm. The pelvic port is treated at the rate of 200 rads per day and the para-aortic port at the rate of 150 rads per day.

as the small bowel. The kidneys are not in this field. Lateral pelvic fields are also treated during this time so as to boost the daily dose to the prostate and pelvis to 200 rads.

In order to avoid the complication of radiation myelitis and small bowel necrosis caused by delivering the entire course of radiation through the co-axial pair, rotational therapy with a 60° posterior dropout is given on alternate weeks. The para-aortic port (Figure 4) is again treated at 150 rads per day. The pelvic port is treated at 200 rads per day. Computer generated isodose curves are obtained and then superimposed on a contour of the patient's body (Figure 5) which contains the kidneys (as outlined by ultrasonography) and the spine (as demonstrated on transverse tomography). The rotation is designed so as to deliver a maximum dose to the central volume of interest while giving smaller amounts of radiation to the surrounding tissues. The kidneys, which were not in the radiation beam at all for the co-axial fields, are demonstrated to lie in the 50-60% dose region of the rotation. Most of the bowel outside of the central volume will receive much lower doses. The spinal cord is seen to lie within the 40-50% dose region.

The overall treatment scheme is summarized in Table I. Note that the para-aortic nodes are treated at the rate of 750 rads per week while the pelvis is treated at 1000 rads weekly. In the sixth week, the pelvis has reached 5600 rads, the maximum dose this volume will tolerate. The spade field is

TABLE I

Week	WEEKLY DOSE (RADS) "Spade"	Pelvic Boost	Para-Aortic	Pelvis	Prostate Boost
1	750	250	--	--	--
2	--	--	750	1000	--
3	750	250	--	--	--
4	--	--	750	1000	--
5	750	250	--	--	--
6	--	--	750	600	400
	Co-Axial Opposed Para-Aortic				
7	600	--	150	--	600
8	--	--	300	--	--

Summary of the overall treatment technique. On odd weeks, the spade shaped field is treated with a small lateral field to boost the pelvis. During the middle of the sixth week, the larger pelvic field has reached a total dose of 5600 rads and the smaller booster field to the area of the prostate has been started. During the first four treatments of the seventh week, the para-aortic port is treated to a coaxial opposed field. During this week also, the booster field to the prostate is completed.

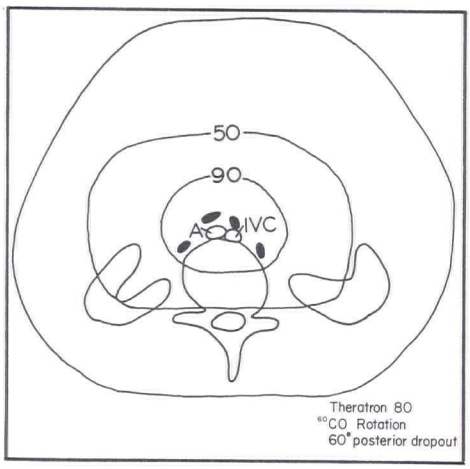

Figure 5
Computer generated isodose curves superimposed on a contour of the body. Note that the lymph nodes and spine are located as visualized on transverse tomography and the kidneys are located as demonstrated by ultrasonography.

TABLE II

TOTAL DOSES (PARA-AORTIC)	
"Spade"	2250 rads
Co-Axial Para-Aortic	600 rads
Rotational Para-Aortic	2700 rads
Total Para-Aortic	5550 rads (7 1/2 weeks)

Total doses to the para-aortic nodes by the combination of techniques.

decreased to a co-axial pair over the para-aortic nodes while the dose to the prostate is boosted with a small field. The para-aortic nodes receive a total dose of 5550 rads in 7½ weeks (Table II). This dose should be adequate to control microscopic disease. The pelvis receives 5600 rads in 5½ weeks (Table III), the prostate receives an additional 1000 rads with a small field designed to encompass only the prostate and its bed. This increases the total dose to the prostatic region to 6600 rads in 6½ weeks.

Using this alternate week technique, doses to critical organs are limited (Table IV). The kidneys receive a total dose in the range of 1200-1400 rads in 6½ weeks. The spinal cord and the entire small bowel receive doses of about 3810 rads in 7½ weeks. Finally, localized areas of small bowel will receive 5500 rads over 7½ weeks.

Results Of Therapy

There have been reports in the literature of biopsy-proven residual tumor after radiation therapy. The incidence of post radiation residual tumor varies considerably (Table V) from a low of 24% up to a high of 87%. In none of these series was there an attempt to obtain biopsy from every patient who was treated. Most of the biopsies were from patients in whom, for some reason, there was a suspicion of residual tumor. Many of the patients, especially those with a higher

TABLE III

TOTAL DOSES (PELVIS)	
"Spade"	2250 rads
Pelvic Boost	750 rads
Pelvic Rotation	2600 rads
Total Pelvis	5600 rads (5 1/2 weeks)
Prostate Boost	1000 rads
Total Prostate	6600 rads (6 1/2 weeks)

A summary of the total doses delivered to the pelvis and prostate by the various techniques.

TABLE IV

TOTAL MAXIMUM DOSES (CRITICAL ORGANS)	
Kidney	1200 rads (6 1/2 weeks)
Spinal Cord	3810 rads (7 1/2 weeks)
Localized S. B.	5500 rads (7 1/2 weeks)
Whole Bowel	3810 rads (7 1/2 weeks)

Total maximum doses to critical organs.

percentage of positive biopsies, initially had more extensive tumors.

Cox and Tijerina reported positive for tumor 26 of 43 biopsies obtained the first nine months post radiation. Twenty of these became negative over the next one to two years. They emphasize that tumors which are slow growing also regress slowly after irradiation.

The question that must be asked is not whether there is actually residual tumor, but *"what is the clinical significance of this residual tumor?"* The old-time radiotherapists used to say that radiation therapy never

TABLE V

POST RADIATION RESIDUAL TUMOR	
RHAMY et. al. (J. UROL., 1972)	87% (13/15)
BAGSHAW et. al. (RADIOL. 1965)	60% (3/5)
GROUT et. al. (J. UROL., 1971)	45% (5/11)
HILL et. al. (CANCER, 1974)	24% (5/21)

Percent of post radiation residual tumor within the prostate as reported by various authors.

TABLE VI

RESULTS OF TREATMENT - 10 YEARS (disease limited to prostate)	
RADICAL PROSTATECTOMY (JEWITT, 1954, 1969)	49%
ORCHIECTOMY AND ESTROGENS (BARNES, 1969)	50%
RADICAL IRRADIATION (BAGSHAW, 1973)	48%

Results of treatments for carcinoma of the prostate utilizing various techniques as reported by various authors.

cured a cancer, but rather prevented further growth. It has long been known in such things as cancer of the cervix, for instance, that patients who are treated with radiation therapy and who undergo pelvic surgery for some other cause, as long as 20 to 25 years later, may suddenly have reactivation of their tumor. In most cases this suggests that radiation induces a fibrotic reaction which entraps the tumor cells. Perez et al demonstrated prostatic fibrosis following irradiation. Most articles reporting post radiation residual have not mentioned the presence or absence of this phenomenon. However, from our point of view, the presence or absence of apparent residual tumor on biopsy is not as important a factor as the results of therapy.

Jewitt reported the largest series of patients treated with radical prostatectomy (Table VI). Even with improvements of the technique over the years between 1955 and 1970, there has been no marked improve-

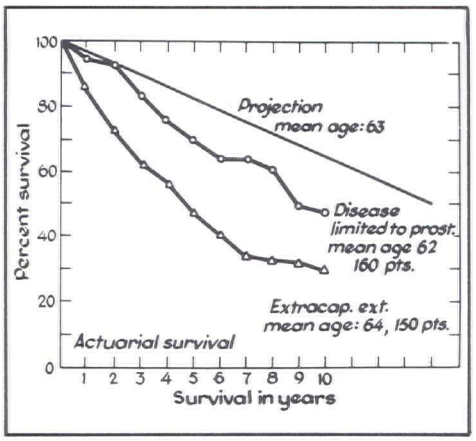

Figure 6
Results of radiation therapy treatments from Gordon R. Ray et al, "Definitive Radiation Therapy For Carcinoma Of The Prostate", *Radiology*, 106, February, 1973, pages 407-418, Figure 2.

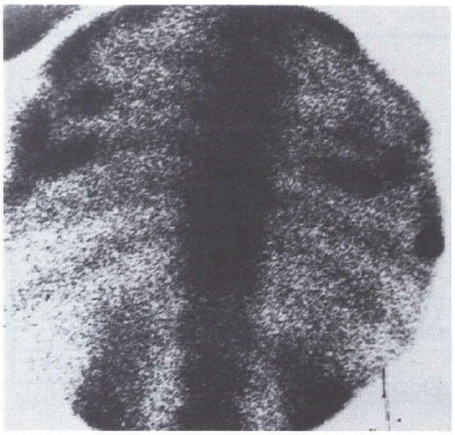

Figure 7
Bone scan six months after treatment of a patient showing densely positive areas of uptake representing metastatic disease. Note that the areas of metastasis start right at the upper border of the radiation therapy treatment portal.

ment in the results. That is, in patients receiving radical prostatectomy for disease limited to the prostate, the overall 10 year survival or 10 year "cure rate" is about 50%. In 1969 Barnes reported a series in which only orchiectomy and estrogen therapy were administered to patients with disease limited to the prostate. This series would be somewhat prejudiced by the fact that many of these patients will not have disease confined to the prostate gland itself. Finally, in 1973, Bagshaw reported their results of therapy using a technique analogous to ours, that is, irradiating the lymphatics as well as the prostate gland. They have an overall 10-year survival again of around 50%. It is of major interest, however, that many of their patients had more advanced disease and would not be candidates for radical prostatectomy.

Figure 6 represents actuarial survival curves taken from Bagshaw's data. At the top is a projection of survival for a population of normal men with a mean age of 63. The survival in the group of treated patients obviously is not as good as in normal individuals. However, in those with disease limited to the prostate gland, survival was fairly close to normal expectancy. The result was 48% at 10 years. An important fact he noted was that, in 85% of the patients with disease limited to the prostate, more than half of the prostate gland was involved by tumor; so this was not a group of patients with early disease. The survival rate was 30% for patients in whom there was extracapsular extension. This is reasonably good when compared with other methods of therapy for this stage.

Complications

As radiotherapists, we like to distinguish between what we consider complications and sequela of radiation therapy. There are certain expected reactions to the radiation which generally will remit within several weeks after completing therapy. In our series, all patients were able to complete their course of therapy. Bagshaw's experience with this large number of patients was that approximately 40% of patients experience acute gastrointestinal or genitourinary symptoms. He also stated that there were approximately 11% of patients who had symptoms which persisted for up to one year. However, it was very rare that patients had symptoms

lasting longer than that. Bagshaw felt that persistent morbidity existed when complications were related either to initial tumor extent or prior surgical procedures. Examples were patients in whom there was persistent tenesmus. In this group of patients it was noted that the anal sphincter was invaded by tumor prior to the initiation of therapy. It is a known phenomenon that fibrosis occurs as the tumor regresses. Urethral strictures were confined almost entirely to patients who had undergone transurethral resection prior to initiation of therapy. In the latter years of their study they found that the incidence of urethral stricture decreased markedly if they waited four to six weeks after transurethral resection before undertaking radiation therapy. Impotence occurs in essentially 100% of patients who undergo radical prostatectomy or orchiectomy with estrogen therapy. In Bagshaw's series, a total of 96 patients reported normal sexual function following therapy.

Figure 7 from our files illustrates the new questions we have created. This bone scan is of a 70-year-old gentleman with prostatic obstruction who was found to have adenocarcinoma at the time of transurethral resection. Lymphangiography revealed abnormal lymph nodes in both the pelvic and para-aortic areas. The initial bone scan results were negative. He was treated by the technique I have described and did fairly well following therapy. However, approximately five months later, the patient developed osseous metastases. The kidneys and lumbar spine were normal but the dorsal spine and ribs were involved with metastases. This bone scan demonstrates that the hematogenous metastases start just above the level of our treatment portal. Similar cases are reported by others. Therefore, we are not yet sure where to classify the patient who already has para-aortic lymph node metastases.

Summary

Advances in our knowledge about the spread of carcinoma of the prostate, as well as improvements in equipment and the development of sophisticated radiation therapy treatment planning techniques, have led us to attempt curative therapy in patients who are beyond the scope of surgical cure. The results reported to date are preliminary. Cooperative randomized trials are necessary in order to accumulate a large enough number of patients for valid statistical data. The dilemma of where to classify the patient with para-aortic lymph node metastasis is yet to be resolved. My impression is that once these nodes are grossly involved, hematogenous dissemination is very likely. Perhaps in the future, some combination of chemotherapy and radiation therapy will provide more satisfying results.

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