# RADIOTHERAPY IN THE TREATMENT OF CARCINOMA OF THE URINARY BLADDER

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MALIGNANT tumors of the urinary bladder arise from transitional epithelium and may be expected to respond well to ionizing radiation, but this favorable response has not occurred in the past. Tumor doses with 250-kv. apparatus were necessarily inadequate and only the most advanced lesions were treated. Currently the availability of high-energy, skin-sparing sources of radiation makes it possible to deliver cancerocidal doses to the tumor volume; therapeutic technics and skill are minimizing or preventing the types of sequelae formerly encountered; and more lesions are now being treated in the early stages by radiation as the effectiveness of some surgical procedures is being challenged. An attempt will be made to review the events that have led some clinicians to reassess the position of radiotherapy in the treatment of carcinoma of the urinary bladder.

## Classification of Tumors and Prognosis

Survival of patients who had undergone surgical treatment for carcinoma of the bladder was evaluated in terms of various therapeutic technics in the early years. Later some investigators began to assess survival on the basis of histologic findings. However, despite improvements in operative management, patients with ostensibly localized lesions of a favorable histologic type were dying of recurrent cancer of the bladder. It remained for Jewett[1] to establish the validity of survival as a function of invasion of the muscularis. He proved conclusively that the stage (extent of tumor) and to a lesser degree the grade (cellular dedifferentiation) were the most significant prognostic indexes. This classification brought into sharper focus the limitations of cystoscopic findings. It led to the development and refinement of transurethral instruments capable of providing the pathologist with tissue more representative of the actual extent of the tumor. It re-emphasized the value of the often forgotten principles of physical examination. In essence, Jewett[1] shored up urologic practice in this special field by classifying tumors of the bladder according to the depth of invasion. He concluded by saying that in most instances the prognosis and a suitable surgical attack could be planned on the basis of cystoscopic findings, bimanual examination, and an adequate histologic search for invasion. *Figure 1* is Marshall's modification of Jewett's[1] original classification as it appears in Milner's[2] report.

Baker,[3] in a further attempt to assess operability for cure, investigated the intravesical lymphatic network. This is circumferential and crosses the midline anteriorly and posteriorly. Experimental work suggested the relationship between the invasion of the muscle and lymphatic involvement. When the muscle was invaded for more than 50 per cent of its depth, involvement of the vesical as well as extra-

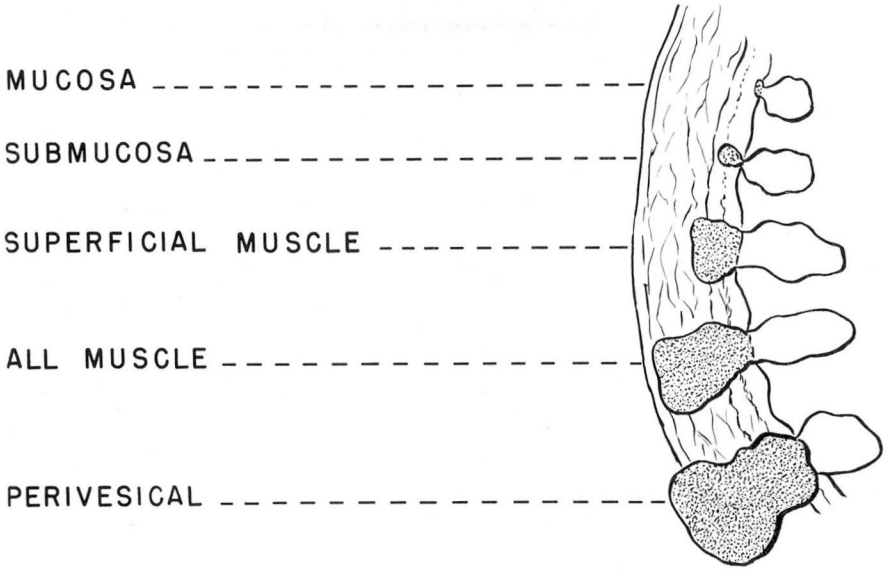


Fig. 1. Marshall's modification of Jewett's original classification of tumors of the bladder. (Courtesy of Milner, W. A.: Role of conservative surgery in treatment of bladder tumours. Brit. J. Urol. 26: 375-384, Dec. 1954; and the British Journal of Urology, Edinburgh and London.)

vesical lymphatics occurred. This prompted Baker[3] to question the value of some radical surgical procedures.

## Surgical Treatment

The study by Baker,[3] and earlier summations by Brice, Marshall, Green, and Whitmore,[4] and Higgins[5] indicate a trend toward conservative treatment as far as statistics for operative mortality and five-year survivals in advanced carcinoma of the bladder are compared. The established role for surgery in small, superficial lesions has been summarized by Nichols and Marshall[6] and needs no repetition here. Riches[7] reported a five-year survival rate of 35 per cent among 85 patients undergoing partial cystectomy for carcinoma, and of 16 per cent among 100 patients subjected to total cystectomy. Marshall, Holden, and Ma[8] reported a 53 per cent five-year survival rate of 123 patients who had undergone partial cystectomy, and 21.2 per cent surviving at five years of 56 patients who had undergone total cystectomy. In each of these series[7,8] there were no patients surviving who had involvement of pelvic lymph nodes; the operative mortality ranged from 12 to 18 per cent. Whether more radical procedures such as total cystectomy combined with regional lymphadenenectomy as advocated by Leadbetter, according to Baker,[3] will improve survival or add to palliation remains to be developed.

Technically, success or failure in radical surgery for carcinoma of the bladder is almost entirely contingent on the prior integrity of the upper urinary tract and

the urinary diversionary method chosen. There are no known survivors among those patients with preoperative evidence of urinary tract obstruction. Certainly other factors such as location of the tumor and previous treatment must be considered.

## Radiotherapy

Radiation by various technics has been utilized in the management of cancer of the bladder. Radon seed implants, interstitial radium needles, intracavitary insertion of radium or cobalt sources, tantalum- or cobalt-wire implants, and external roentgen sources have been tried with a wide range of success by individual cancer therapists. Each technic makes a contribution. The ultimate choice will depend on the extent of the tumor, and to a lesser degree on its histologic characteristics.

The urologist uses radon implants *(Fig. 2A)* usually transurethrally and occasionally suprapubically. This method requires that the tumor be localized and superficially invasive, and that provision for adequate bladder drainage has been established. Others have implanted radium element needles interstitially *(Fig. 2B)*; this method requires two operative procedures and is seldom used now.

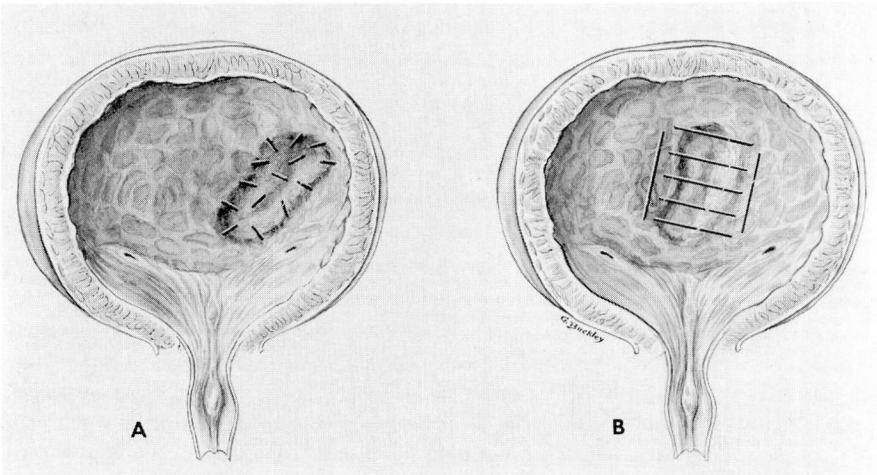


**Fig. 2.** A, sketch showing radon seed implant. B, sketch showing radium needle implant.

Both methods require a basic knowledge of radiation dosimetry to insure a homogeneous distribution of the radioactive sources throughout the tumor volume. These local radiation implants are always preceded by resection and fulguration.

Intracavitary radioactive sources have been used with notable success by Friedman and Lewis[9]. Accurate placement of the sources is essential, and only superficial lesions can be effectively treated. This technic may be useful in cases of multiple superficial papillomata when cystectomy cannot be performed *(Fig. 3)*.

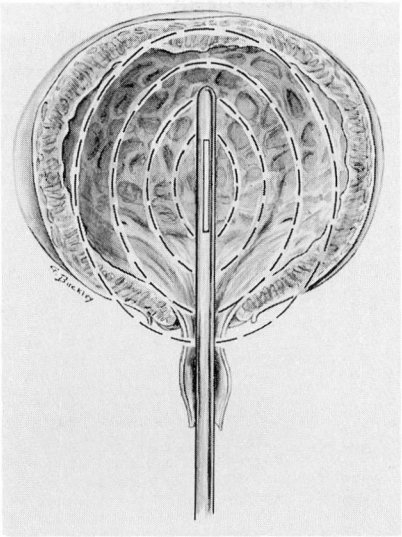

**Fig. 3.** Sketch showing intracavitary method using radium or Co-60 as the source.

External roentgen therapy theoretically would seem to be more promising than the above-mentioned technics. Almost any tumor volume can be included and more homogeneous doses can be delivered. The energy of the primary beam will per se constitute the only physical limitation in increasing the percentage tumor dose. Conventional or orthovoltage methods have a narrow usefulness as the maximum tumor exposure dose can rarely exceed 2500 to 3000 r in four weeks without excessive injury to the integument and to deeper pelvic structures. Even considering the refinement of multiple portal and rotational technics, tumor doses in the cancerocidal range are not attained. Palliation in isolated cases is the best result to be expected.

Sources operating at energies from 2 Mev. to 50 Mev. are currently available in large medical centers keyed to a vigorous program of cancer research and treatment. All these sources produce ionizing radiation that is skin sparing, greater in penetration, and more geometrically pure in its transmission through the body than conventional radiation. Attention to clinical detail and tissue response cannot be neglected. There is no inherent magic associated with these higher energies in terms of five-year survival. The biologic intangibles involved as radiation interacts with matter, parallel earlier radiation experience. Time-dose relationships, selective tissue destruction, and careful follow-up studies are all important factors in radiotherapy. Greater expectations, however, may now be nurtured as independent investigators have the opportunity to treat and to follow comparable groups of patients. The best results will be obtained through closer liaison than has existed heretofore among the urologist, the radiation therapist, and the pathologist.

Tumor exposure doses of 6000 to 8000 r can be delivered in treatment times of from six to eight weeks. The daily tumor exposure dose should rarely exceed 200 r. This dosage assumes that the lesions are potentially curable. When palliation is the best that can be expected, then exposure doses of from 3000 to 4500 r are given in treatment times of from three to four weeks. These figures are an ideal and cannot always be attained as patients vary in their tolerance to treatment. The radiation has to be individualized rather than standardized. The use of multiple portals of entry seems preferable to the use of opposing fields *(Fig.4).*

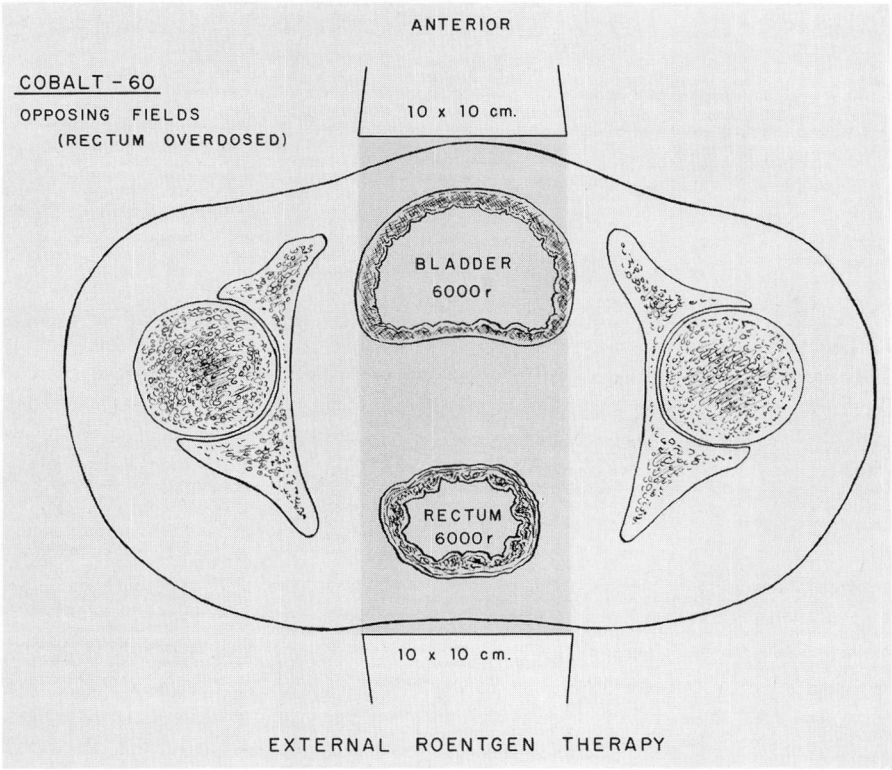


**Fig. 4.** Sketch showing estimated percentage depth dose of Co-60, 80 cm. target skin distance (TSD); half-value layer (hvlayer) 10.5 mm. Pb.

In our practice we employ a single anterior and two posterior oblique (8 by 10 cm. or 10 by 10 cm.) fields *(Fig. 5).* In this way greater doses can be delivered to the tumor volume without overtreating the rectum. Rotation added to supervoltage radiation is the ultimate in precision multiple small-beam therapy as advocated by Trump and associates[10], and Browne and Ogden[11]. Both technics need careful pretreatment assessment of the tumor mass, mapping of isodoses, and roentgen confirmation of the treatment fields.

High energy sources are to be preferred whether for palliative or curative therapy. The comfort experienced by the patients far exceeds other considerations. We use the Picker cobalt-60* teletherapy unit with the Johns-MacKay collimating system. The unit contains a 4620-curie source that delivers 100 r per minute at a treatment distance of 80 cm.

*Pretreatment assessment.* Almost any neoplasm of the bladder with the exception of papillomas should be given a trial of radiation inasmuch as the morbidity in untreated vesical cancer is high. Those that most certainly should be treated by radiation include lesions that are not curable by surgical means, usually classified as stages C or D; infiltrating tumors that recur after resection; and in some isolated

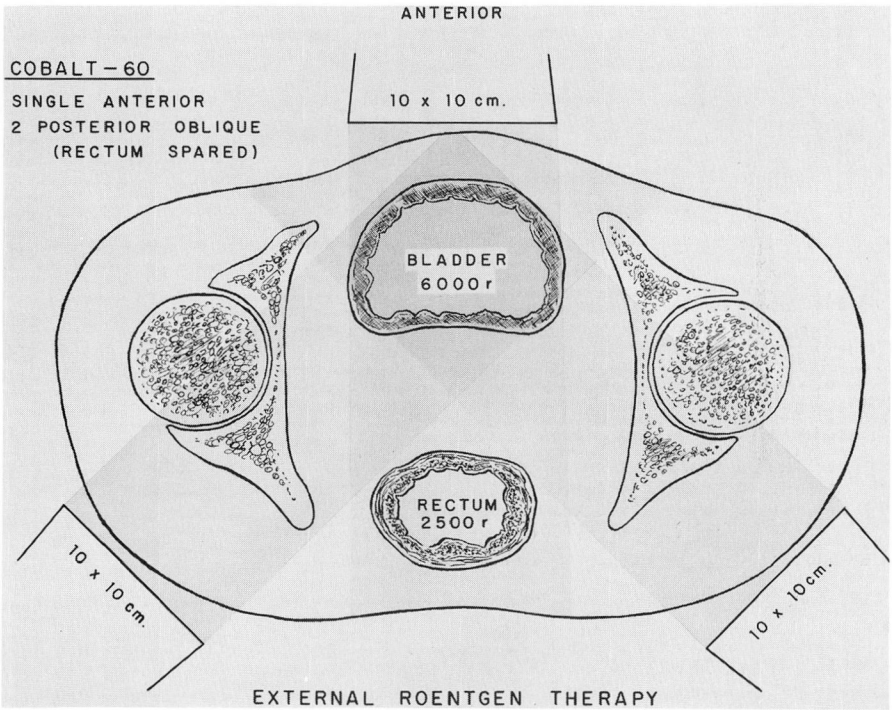


**Fig. 5.** Sketch showing estimated percentage depth dose of Co-60, 80 cm. TSD; hvlayer 10.5 mm. Pb.

instances, tumors extending beyond the line of excision or for which there is histologic proof of vascular invasion.

In advanced lesions (where urinary tract obstruction exists or there is good evidence of perivesical extension of lymphatic metastasis), therapy can only be expected to be palliative in intent. The aim here is to give symptomatic relief and to reduce hemorrhage. This can be accomplished by delivering 3000 to

**The radioactive cobalt was obtained on authorization of the Isotopes Division, the United States Atomic Energy Commission, Oak Ridge, Tennessee.*

4500 r in from three to four weeks, with little discomfort to the patient.

In invasive lesions not suitable for a definitive surgical approach but without extravesical extension, the radiotherapist may assume a more optimistic attitude. Recent reports by Poole-Wilson[12], Cuccia, Jones, and Crigler[13], and Browne and Ogden[11] buttress such thinking. These reviews plus re-evaluation of unfavorable results in surgical treatment suggest that more can be accomplished when joint consultation between the surgeon and the radiotherapist replaces unilateral decisions in cancer therapy. An attempt is made to treat some of these patients radically in an all-out effort to control the primary lesion. While 8000 r can be delivered to the bladder the margin of safety is small, and therefore the average maximum tumor exposure dose is from 5000 to 6000 r in from five to six weeks. Three fields as described above are used. Each field is treated daily and the summated depth exposure dose is 200 r or less. Every attempt is made to minimize the rectal insult. Admittedly this course will not always be feasible, because other factors may delimit the total tumor dose. Previous infection, a reduced bladder capacity, and lesions arising near the vesical neck may be deterrents to intensive therapy. Poor renal function, while in itself not a contraindication to major therapy, may lead to complications requiring interruption of planned treatment. Urinary diversion occasionally may be necessary before the beginning of radiation.

The tumor dose is calculated according to established dosimetry and the fields are checked by exposing industrial roentgen film to the cobalt-60 beam in the treatment position. The patients are followed by the urologist and radiation therapist during and after the treatment course.

*Radiation sequelae.* Ionizing radiation produces peculiar changes in the mucosa of the bladder which require many months and oftentimes a year to heal completely. Evaluation of response to radiation then may not be possible for some time after therapy. Acute changes occur during the third and fourth weeks of treatment and are characterized by frequency, urgency, and dysuria. Cystoscopic findings include bullous edema and a generalized exudative mucositis. As the reaction subsides, edema may persist and mucosal pallor and telangiectasia appear.

Severe chronic changes may supervene, heralded by hematuria, urgency, and frequency. The cystoscope discloses interstitial fibrosis, localized ulceration, and massive telangiectatic areas. These findings are clinically significant and, while unavoidable in some cases, they may be a necessary consequence in the radical radiation treatment of otherwise inoperable cancer of the bladder. This is not to say that the therapist in his attempt to achieve long-term survival will not heed symptoms that may be prodromal in character. It may be mandatory to interrupt treatment or to reduce the daily tumor dose in some instances.

*Comparison of results.* Cuccia, Jones, and Crigler[13] reviewed 100 consecutive cases of cancer of the bladder classified according to Marshall (cited by Milner[2]) and all with histologic confirmation. Cobalt-60 and the betatron were used to deliver tumor exposure doses from 5000 to 6000 r in from five to six weeks as

radical therapy. Palliative treatment consisted in delivering from 3500 to 4500 r in from three to four weeks. One anterior and two posterior fields were used. Of the 64 patients treated radically with radiation, 16 are living and well at two years and 15 of these are apparently free of cancer; 18 are symptom-free at one year and 16 of these are known to be free of cancer; and 14 patients are alive and well less than one year after treatment and 13 are free of tumor. Thirty-six patients received palliative radiation only and eight are living at one year. Complications were distressing in those patients receiving intensive treatment. Eleven patients had minor sequelae. Eighteen patients, however, experienced major reactions; 11 had rectal or vesical hemorrhage; 10 had a contracted bladder; 3 had bladder ulceration. Two of these 18 patients died of uncontrollable rectal bleeding. It is to be noted that each of the three patients with bladder ulceration had radiation therapy previously, and six of the patients with a reduced bladder capacity had undergone surgery previously. Perhaps severe radiation injury may be obviated by a more judicious use of radiotherapy.

Browne and Ogden[11] reviewed the records of 55 patients with histologically proved bladder carcinoma treated with rotational cobalt-60 teletherapy with or without previous surgery between December 15, 1954, and January 1, 1958, and a similar group of 45 patients treated surgically only. All cases were classified in accordance with Jewett's[1] grouping. Of the 55 patients treated with radiation, 47 received tumor exposure doses of from 5000 to 6000 r and eight patients received less than 5000 r. Five of the 55 patients were considered to have operable cancer but received only radiation; all five are living from one and one-half to four years after treatment. Thirty-six patients received radiation postoperatively. Eighteen of the 36 were treated for residual disease within two months postoperatively; 9 of these were living and well from one and one-half to three years after treatment. Eighteen of the 36 were treated for local recurrence more than two months postoperatively; five of these were living and well from one and one-half to three years after treatment. Fourteen of the 55 patients were considered to have inoperable cancer at surgical exploration; two of these were living with disease at one and one-half and two and one-half years after radiotherapy. Clinically, all patients having stages A or B1 lesions were alive and well at the time of the report; 62 per cent of those with stage C lesions were living without evidence of carcinoma; and 14 per cent of those considered inoperable were living but had persisting disease.

Forty-five patients were treated surgically. Thirty-nine patients were classified as having lesions of stage A or B and 28 (72 per cent) of these were alive and well; eleven had died of carcinoma; six patients who had cancer of stage C or D died of their disease.

Fifty-one per cent of all patients receiving radiation experienced minor complications, consisting of diarrhea and cystitis, during the third week of therapy. In five patients severe reactions developed; of the three who had hemorrhagic cystitis, two had been treated previously with radon implants. In two patients intractable

diarrhea developed. One patient with bladder hemorrhage underwent a total cystectomy for relief of symptoms.

Jewett,[1] and Marshall (cited by Milner[2]) by their classification made possible a more realistic clinical assessment of bladder cancer. Transurethral resection and fulguration with or without a radon implant would seem the treatment of choice for lesions staged[2] as O, A, or B. For lesions classified as B2, C, or D, recent experience indicates that well-planned radical radiotherapy may yield superior results.

## Summary

The role of ionizing radiation as a definitive procedure in the treatment of carcinoma of the urinary bladder is reviewed. External gamma-ray therapy with cobalt-60 or alternate high-energy sources may offer more palliation to a greater number of patients than will the other radiation modalities. Careful treatment schemata co-ordinated with urologic and pathologic findings are essential to success. Radical radiation is effective in the control of some bladder carcinomas, and may proffer symptomatic relief in others. Preliminary reports from two independent medical centers suggest that radiotherapy can sometimes control inoperable cancer of the urinary bladder and can prolong survival in other cases. If other tumor centers would report on comparable programs it would serve to advance knowledge and skill in the use of radiation in the management of carcinoma of the urinary bladder.

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