Rx of Bladder Cancer: Complex and Controversial

Complex decisions regarding the choice of treatment for the patient with bladder cancer may pose many often controversial questions. On what criteria is this choice best made? What is the role of combined preoperative irradiation and surgery? How are the complications of high dose irradiation best managed and prevented? Is chemotherapy of value in the treatment of bladder cancer? In the following series of questions and answers, these and other practical questions are discussed by some outstanding specialists in the field, including:

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What are the most common pretreatment signs and symptoms of bladder cancer?

Dr. Grabstald: Gross, painless hematuria is the most common symptom in patients with bladder cancer. The exception occurs in patients with in situ carcinoma which is often asymptomatic or associated with symptoms of cystitis; that is, frequency, urgency, dysuria. It must be emphasized that it is the first, and not the second, episode of hematuria which requires complete urologic investigation. It is frustrating to have a patient appear with a very large bladder tumor, following an episode of hematuria who, upon close questioning, reveals that he had an episode of hematuria one year previously and was treated by antibiotics. Tumors do not bleed day and night. For this reason, it is the first and not the second episode of hematuria that requires investigation.

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Frequency, urgency and dysuria occasionally accompanied with clots may be the second most common symptom complex in patients with bladder tumors. Total retention is very rare except in children with sarcoma botryoides. Flank pain may be a manifestation of hydronephrosis secondary to the tumor. Back pain is an ominous sign and may reflect nodal involvement with nerve pressure.

Once bladder cancer is suspected, how is the patient most accurately evaluated prior to treatment?

Dr. Grabstald: Cystoscopy, superficial and deep biopsies and bimanual examination are the most accurate means of evaluating patients for therapy. Therapy is always predicated on stage of disease. Other tests to be utilized include cytologic studies of urinary sediment (Pap urines) which should be obtained both before and after transurethral resection and may often be helpful in detecting small tumors which have been missed or may indicate incomplete resection of tumors. The intravenous pyelogram is mandatory. Cystography may be of some value especially in patients with tumors in diverticula. Pelvic arteriography may be useful in better staging the disease.

Which form of clinical staging is most widely used and accepted today?

Dr. Wizenberg: Clinical staging is of utmost importance since treatment of bladder cancer must be adapted to the exact nature of the disease. Indeed, the lack of consensus on one classification of clinical staging which should be utilized contributes to the controversy on the effectiveness of various forms of treatment; investigators using different staging classifications supply often widely divergent data. We generally use the Marshall modification of the Jewett and Strong classification (Table 1) although the one used by the International Union Against Cancer (UICC) also is widely accepted. The dif-

| Table 1: Current Classifications of Bladder Cancer |
|-----------------------------------------------|
| **Jewett and Strong Classification** | **International Union Against Cancer Classification** | **Description** |
| Stage 0 | T1s | Carcinoma in situ |
| Stage A | T1 | Tumor with infiltration into subepithelial tissue |
| Stage B1 | T2 | Tumor with infiltration into superficial muscle |
| Stage B2, C* | T3 | Tumor with infiltration into deep muscle |
| Stage O | T4 | Tumor with infiltration into adjacent organs |
| Stage D1 | N1, (regional) | Tumor with lymph-node invasion below bifurcation of iliac arteries |
| Stage D2 | M1 (distant)†† | Tumor with lymph-node invasion in periaortic region |

* One difference between the two classifications is the designation of a Stage C tumor infiltration into perivesical fat in the Jewett and Strong system. This is not utilized in the International Union Against Cancer classification.
† The separate use of "N" for defining lymph node involvement in the International Union Against Cancer system is placed into Stage D of the Jewett and Strong staging.
†† "M" is used for distant visceral metastases as well as for periaortic lymph nodes.
The difference between these two classifications is the designation of Stage C in the Jewett and Strong which is not utilized by the International Union Against Cancer. Both systems, however, rely on the depth of penetration into the bladder wall as the indicator of the clinical stage of the cancer. It should be recognized that all systems are at best crude, and no information about node involvement is available except in those patients surgically staged. Many patients clinically classified as Stage B or C actually have lymph node metastases.

**Dr. Caldwell:** The Broders’ classification (Table 2) is most frequently used. Grades I and II refer to low grade cancers; Grades III and IV to poorly differentiated, high grade cancers.

**Table 2: Broders’ Grading Classification**

| Grade | Description |
|-------|-------------|
| I     | Low grade, well differentiated, no mitoses, no stromal invasion |
| II    | Low grade, well differentiated, low mitoses, no stromal invasion |
| III   | Low grade, well differentiated, high mitoses, no stromal invasion |
| IV    | Poorly differentiated, high grade, high mitoses, stromal invasion |

**Dr. Grabstald:** In one sense yes, if cancer is defined as a tumor which recurs. One must remember, however, that just because a wart recurs does not make it a cancer. Papillomas are different in that 15–20 percent of patients with bladder papillomas will at some time develop bladder cancer.

At our institution, a papilloma, if histologically benign, is called just that—namely, a benign papilloma. I would have no quarrel with those institutions which classify papillomas as Grade I cancers because they recur. One, however, must not compare statistics from one institution where the term papilloma is used with those of another institution where the term low grade cancer is used since it would appear that the cure rate of cancers is very high at the latter institution when indeed they are curing papillomas. Given 100 patients with
adequately resected solitary papillomas, 50 percent will develop further tumors; if there are two or more papillomas, two thirds will recur.

**Dr. Caldwell:** I agree with Dr. Grabstald that a papilloma, strictly interpreted, is a benign tumor with a low incidence of malignant potential.

_How accurate is clinical staging compared to surgical staging?_

**Dr. Bagshaw:** In a controlled clinical study, we found that six out of 10 patients were found to have more advanced tumors at laparotomy due largely to the identification of positive nodes. We now feel that it is essential to have surgical staging prior to any treatment.

**Dr. Caldwell:** When Marshall presented his modification of the Jewett and Strong clinical staging classification, he also compared clinical staging to surgical staging. One hundred and four patients were clinically staged prior to cystectomy. Forty-two percent of these patients were underestimated in the clinical appraisal and 16 percent were overestimated. This discrepancy was greatest for clinical Stages B₂ and C lesions. Although subsequent information obtained by operative intervention or postmortem examination cannot alter the clinical stage, knowledge of this discrepancy between clinical and surgical stage is extremely important for treatment planning and for evaluating treatment results; surgically or pathologically staged cancers will have a better prognosis, stage for stage, than clinically staged cancers. In spite of these shortcomings, however, clinical staging is valuable in guiding and directing the choice of therapy and helps in determining which patients are best suited for laparotomy.

_Are data available to help predict lymph node involvement in clinically staged patients?_

**Dr. Wizenberg:** There are very few definitive studies which indicate the extent of lymph node involvement in patients with bladder cancer. Generally, however, we feel that 30–60 percent of patients have node involvement. The lower figures would apply, of course, to Stages B₁ and B₂ and become progressively higher with Stages C and D.

_What therapeutic alternatives are available in the management of the patient with bladder cancer?_

**Dr. Grabstald:** This is, indeed, a very big question because it covers the entire spectrum of bladder tumors and would best be answered by assuming that proper staging has been done.

One can generalize that the transurethral resection is the treatment of choice for papillomas and for low grade and low stage tumors. General surgeons who cannot use the resectoscope and who feel they can “get a better look” by opening
the bladder are deceiving themselves, I think. One gets a better look via the cystoscope. As indicated previously, the fact that a large number of lesions recur would suggest that repeated cystostomies certainly can't be done every three months. Multiplicity of tumors, rapidity of recurrence, location and size of tumors might dictate a more aggressive approach. This would especially be true in patients with small bladders, diverticula or urethral strictures in whom repeated transurethral resections become very difficult.

Those patients with deeply infiltrating tumors, Stages B2 or C, need more aggressive measures. Transurethral resections will very rarely cure a tumor which deeply infiltrates muscle.

It is unfortunate that only 10–15 percent of bladder tumors occur in the dome of the bladder. Were it not for this fact, cystectomy would be rarely indicated. Segmental resection of a tumor in the bladder dome is the treatment of choice even for Stages B1 and C cancers. When the tumor is near a ureteral orifice so that reimplantation of the ureter becomes necessary, it is doubtful that segmental resection is the procedure of choice.

Radical cystectomy, which implies concomitant lymph node dissection is necessary when nothing else will do! While the cure rate is very low when there are metastases in the regional nodes, there are patients with involved obturator nodes or perivesical nodes who may be cured by radical cystectomy. A radical cystectomy, rather than a simple cystectomy, accomplishes better removal of the bladder by better delineating the surrounding structures.

Dr. Wizenberg: Patients with Stages B1 and early B2 cancers may also be treated with megavoltage radiations. With anything less than these energies, it is almost impossible to safely deliver a therapeutic dose. We treat the entire pelvis either with opposed anterior and posterior fields (in a thin patient), with a three-field arrangement (anterior and two posterior oblique fields) or other multiple field arrangements to a dose of about 4,000 rads. Rotational therapy is generally used to supplement the dose to the bladder to at least 6,000 rads. With well-differentiated tumors, the whole treatment may be given by rotational therapy. In rotational therapy or treating with lateral fields, you must use a field that is at least 10 cm. wide and which usually also includes the prostate and the prostatic urethra. The bladder should be empty during treatment especially when small fields are used. The split-course method is another approach to radiation therapy for more advanced bladder cancers and appears to be associated with better tolerance and regression than a continuous course of treatment. Patients are given 3,000 rads in two weeks, rested for three weeks and then given an additional 3,000 rads in two and one half weeks. Three thousand rads in two weeks, without the second course, may also be useful for palliation.
Dr. Caldwell: When treating bladder cancer to cancericidal dose levels with 60 cobalt or with four or six mvp X-rays, you must resort to other than two opposed fields. The dose in the mid-pelvis of a patient who is 20 or 22 cms. thick is at least 15 percent less than the maximum dose regions which are anterior and posterior to the bladder; tissue absorption even of these megavoltage beams accounts for this dose falloff in the mid-pelvis.

Dr. Grabstald: Stage of disease is perhaps the most important consideration. However, the patient’s choice would also dictate the treatment utilized after, of course, he has been given the facts. Some patients adamantly refuse cystectomy; radiation therapy then becomes the treatment of choice for deeply infiltrating tumors. The reverse may be true if the patient refuses irradiation and prefers total removal of the bladder.

Dr. Wizenberg: The five-year survival figures for cystectomy in several series show tremendous differences (Table 3). Survival rates are obviously lower for patients with Stages B2 and C cancers than for those with superficial, low grade cancer; the five-year survival for irradiated patients is also markedly lower for Stages B2 and C cancers (Table 4). There is no clear
evidence that either of these treatment methods provides better survival rates than the other.

Dr. Caldwell: One must remember, however, when examining Tables 3 and 4 that in the operative series the patients were operatively staged, whereas in the radiotherapy group the patients were all clinically staged. Since there is almost always more extensive disease found at operation than is detectable clinically, one cannot expect to do as well on a stage for stage basis with a clinically staged group as compared to those operatively staged.

When is a combined approach of preoperative radiation and operation indicated?

Dr. Grabstald: Whenever cystectomy is planned, we feel that preoperative irradiation is indicated to seal off lymphatics, alter cell viability so that implants will not occur or grow, and to sterilize microscopic or macroscopic foci in the lymph nodes. The fact that irradiation can actually eliminate disease is well known.

When administering preoperative irradiation, are the entire pelvis and prostate always included in the treatment fields?

Dr. Wizenberg: If you confine preoperative irradiation strictly to the area you are later going to resect, I think you are setting a very limited goal. We irradiate the entire pelvis in the hope of controlling microscopic or macroscopic metastases.

Dr. Caldwell: I agree with Dr. Wizenberg and prefer to treat not only the bladder but also the pelvis, prostate and proximal urethra, particularly for advanced cancers. A treatment dose of approximately 5,000 rads in five weeks is recommended. This is most beneficial in eradicating clinically nondetectable disease in lymph nodes which is not managed well operatively. Indeed, a negative exploration prior to a preoperative course of irradiation would not deter me from treating the whole pelvis, but would rather encourage me to do so.

Have any controlled clinical trials been performed to evaluate the effectiveness of combined treatment?

Dr. Bagshaw: Since data comparing the effectiveness of irradiation alone versus the combined technique are so indefinite, we decided to inaugurate a controlled clinical trial. All patients are evaluated by the same team and staged clinically. Yet, prior to treatment, each patient has an exploratory laparotomy and lymph node biopsies, when indicated, so that we not only clinically stage but operatively stage, as well. Those patients with Stages B2, C or D cancers are included in the program. Patients are randomized in either irradiation alone (7,000 rads in seven weeks: 6,000 rads to the whole pelvis with four fields and then an extra 1,000 rads to the bladder) or
combined therapy (5,000 rads in five weeks to the whole pelvis followed by total cystectomy). Patients in the combined therapy group have an ileal loop diversion at the time of the surgical staging procedure and, following recovery, they are given preoperative irradiation. Four to six weeks later, a total cystectomy is performed.

Our data comparing survival statistics for patients treated by radiotherapy alone versus preoperative radiotherapy followed by cystectomy is still too small to be meaningful. We have, however, gathered some striking information on the effectiveness of preoperative clinical staging compared to surgical staging. One of the important features of this study is that before a patient is randomized into one or the other treatment groups, the extent of the disease must be determined by operative staging. To date, 23 patients have been clinically as well as operatively staged. Eighteen or 78 percent of these patients were found to have more advanced tumors at laparotomy. The change in stage, in almost every instance, was due to the discovery of occult metastases in pelvic or para-aortic lymph nodes. This unexpectedly high incidence of lymph node metastases casts serious doubt on the credibility of any prospective randomized study which assigns patients to treatment groups on the basis of clinical staging alone.

**Dr. Grabstald:** Our experience indicates that irradiation is valuable in patients with high stage tumors and not so valuable in patients with tumors of lesser stage. Papillomas and especially in situ cancers are notoriously radioresistant. We have removed the bladders of patients with both invasive and in situ cancer who had been irradiated and found that all invasive cancer had disappeared while all in situ cancer remained.

In about 20 percent of patients in whom we combined 4,000 rads of preoperative radiation therapy with cystectomy, the removed specimens had either no tumor or tumors of lesser stage than noted at the time of cystoscopy. The five-year survival figures following combined radiation therapy and cystectomy appear to be better in patients with deeply invasive bladder cancer.

**Dr. Caldwell:** I disagree with Dr. Grabstald’s comment that in situ cancers are radioresistant. Some in situ carcinomas respond well to a high dose, limited volume irradiation.

*When is irradiation indicated postoperatively and how is it best delivered?*

**Dr. Bagshaw:** Irradiation is employed following segmental resection when the margins of the resected specimen are inadequate and after total cystectomy when there is evidence of residual tumor either at the primary site or in regional lymph nodes.

**Dr. Caldwell:** In my opinion, patients with Stages B2 and C cancers should have postoperative irradiation of the entire pelvis, because of the high percentage of local failures from cystectomy (or
lesser resection) alone. Those patients with operative Stage D disease (particularly if the lymph node involvement is gross) have a high probability of disease in the periaortic lymph nodes or more widespread metastases and, therefore, are less likely to benefit from local irradiation of the pelvis. Following cystectomy in those patients with high grade tumors or when we anticipate recurrence, we irradiate using the three-field arrangement to provide an adequate dose to the anterior abdominal wall and in the hope of preventing wound recurrence which is invariably fatal.

What are the most common complications of high dose radiotherapy?

Dr. Wizenberg: Approximately 50 percent of radically irradiated patients will develop moderate reactions such as cystitis, urinary frequency or diarrhea. About 10–20 percent of patients will develop severe reactions—severe either in terms of degree at the time of treatment or in terms of persistence. An increase in bowel problems, particularly of the small bowel, is expected in patients who undergo laparotomy prior to irradiation and is probably related to adhesions trapping loops of bowel in the pelvis. Infection may be seen in patients with obstruction of the bladder neck or ureters.

How are complications of high dose radiotherapy best managed and prevented?

Dr. Wizenberg: Cystitis is usually satisfactorily controlled with antispasmodics. Belladonna and opium rectal suppositories are often useful. Diarrhea or cramping can be managed by putting the patient on a low residue diet, administering stool softeners during the entire course of treatment and prescribing antispasmodics if indicated for diarrhea or small bowel symptoms. If reactions are very severe or persistent, we usually interrupt treatment. Infection is, of course, managed with antibiotics; however, in the presence of obstruction, or a necrotic ulcerated tumor, this may be difficult. Approximately one third of the patients with serious and persistent reactions will recover with only conservative treatment; one third of these will develop rectal ulceration, sigmoiditis or chronic bladder symptoms and may require corrective surgery and one third may die of either fistula or necrosis.

Perhaps the most important preventive measure is to wait at least three to four weeks following surgery before starting irradiation. If one irradiates these patients sooner, treatment will almost always have to be interrupted because of marked reaction in the bladder. Those patients who have had multiple segmental resections should probably be irradiated, bearing in mind that they will most likely require a cystectomy as part of their treatment because of loss of bladder capacity. If the patient has unilateral or bilateral obstruction of the ureter with an elevated BUN, urinary tract diversion must
be done prior to radiotherapy. If not, there is an excellent likelihood that these patients will not survive the course of treatment. Also, those patients who have been previously irradiated by any method to virtually any dose level cease to be candidates for radical irradiation.

Does chemotherapy have a place in the treatment of bladder cancer?

Dr. Grabstald: Topical Thiotepa has a definite place in the management of patients with rapidly recurring low stage and low grade tumors. It is of no value in patients with deeply infiltrating tumors. Systemic chemotherapy including 5-FU and Bleomycin are occasionally of use for metastatic carcinoma.

What are the most effective methods of determining early recurrences?

Dr. Grabstald: Cystoscopy every three months is mandatory after the first transurethral resection if conservative therapy is to be utilized. Cytologic studies of urinary sediment (Pap urines) are extremely useful in following bladder cancer patients since one may detect early recurrence before the lesion becomes cystoscopically visible, either by ordinary light or by ultraviolet light cystoscopy. It is ironic that we who constantly urge patients to report the earliest signs and symptoms of cancer now have a diagnostic aide, the Pap urine, which can diagnose cancer at the cellular level, and yet we do not know what to do with this information.

How frequently should these follow-up studies be performed?

Dr. Wizenberg: There is little advantage in cystoscopying a patient for whom you've planned a cystectomy following irradiation. The presence or absence of disease at two weeks, a month or even six weeks following irradiation should not affect the treatment program. Also, there is little point in cystoscopying patients carried to a full dose of irradiation sooner than three months after treatment. Subsequently, however, these patients need frequent cystoscopy at perhaps three month intervals for the first three years. Most patients who will die of bladder cancer do so in the first three years following treatment.

Is metastasis the major cause of death in patients with bladder cancer?

Dr. Bagshaw: Each year, many patients die of metastatic disease. Yet, 50 percent of patients die because the local disease in the bladder had not been adequately controlled. It is toward this end that we must focus our major efforts.