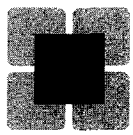

High-stage bladder cancer: bladder preservation or reconstruction?

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■ The availability of potentially effective systemic chemotherapy for transitional cell carcinoma of the bladder and the functional improvements afforded by new methods of urinary diversion have both contributed to significant changes in the treatment of high-stage bladder cancer. The clinician must decide at the beginning of therapy whether to use a bladder-preservation or bladder-reconstruction approach. The decision may be based on survival or on quality of life—two different goals that require different studies. When multiple types of treatments are combined, cumulative toxicity must be examined carefully.

□ INDEX TERM: BLADDER CANCER □ CLEVE CLIN J MED 1990; 57:280–284

THE EVOLUTION of treatment for stage T2 to T4 (invasion of muscle, paravesical fat, or adjacent organs) carcinoma of the bladder (stages B and C) has been significant in recent years. In the early 1980s, the standard in the United States was preoperative radiation therapy, ranging from 1,500 rad to 5,000 rad (15 Gy to 50 Gy), followed by radical cystectomy and urinary diversion with an ileal conduit. In the last 5 to 8 years, the focus has shifted dramatically: Preoperative radiation therapy is rarely used, there has been an extraordinary interest in new methods of urinary diversion, and potentially effective chemotherapy has become available. The decision-making process for arriving at the appropriate treatment for high-stage bladder cancer has become much more complex.

The fundamental choice is between bladder preservation and bladder reconstruction. Different institutions have different philosophies. For example, the University of Southern California group relies almost entirely on bladder reconstruction, possibly combined with adjuvant chemotherapy, whereas the Memorial Sloan-Kettering group focuses more on bladder preservation[1,2] Differences in patient selection, staging evaluations, and follow-up evaluations complicate the scene, and it is not possible to state that one approach is superior. Nevertheless, each physician must make this initial decision before outlining a logical treatment plan. The alternatives involved in the decision process are outlined in *Table 1*.

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BLADDER PRESERVATION

The goal of bladder preservation is to eliminate the bladder cancer and maintain adequate bladder function. Clear documentation of the status of local disease both before and after treatment and a critical evaluation of bladder function have sometimes been inadequate in earlier trials. Objective measurements of the quality of life with the bladder-sparing (or bladder-reconstruction) approach have not been well defined and clearly would be valuable.

Radiation therapy with cystectomy

The treatment philosophy in Britain and Canada for many years has been to use definitive radiation therapy with salvage cystectomy. Although earlier results were disappointing, this may not accurately reflect the potential value of this treatment. For example, if follow-up cystoscopy were not performed for many months after radiation therapy, this would delay the decision that the radiation therapy had failed and that cystectomy was needed. Cystectomy should be strongly considered if a re-evaluation done at 3 months shows that the cancer has not been eliminated.

A recent report from London by Jenkins and associates [3] described an overall, corrected 5-year survival rate of 40% for T2 and T3 lesions; 52% had apparent complete regression of the primary tumor, and 18% received salvage cystectomy.

Patient selection factors make interpretation of these results difficult but similar data have been obtained from Scotland.[4] Shipley and colleagues[5] have stressed factors that are associated with a good response to radiation therapy. For example, patients who underwent apparent complete transurethral resection of the tumor prior to irradiation had a 54% complete response rate compared to 17% in those who did not. Other characteristics associated with good response to radiation therapy were absence of hydronephrosis and an initial papillary growth pattern of the carcinoma.

Shipley[6] stated, "This favorable advantage in patients with maximum tumor debulking prior to radiation therapy is likely the combined result of having tumors of initially smaller size or of an exophytic type as well as a lower number of remaining tumor cells that must be inactivated by radiation therapy." Thus, definitive radiation therapy with salvage cystectomy may be appropriate in patients who have papillary tumors that can be completely resected, no hydronephrosis, and minimal mucosal in situ disease. These criteria have not been widely used in the past. Restaging after radiation therapy is often difficult and the persistence of cancer more than 3 months after radiation therapy indicates a treatment failure.

Chemotherapy with total or partial cystectomy

The success rates of the M-VAC (methotrexate, vinblastine [Velban], doxorubicin [Adriamycin], cisplatin), CMV (cisplatin, methotrexate, vinblastine), or CISCA (cisplatin, cyclophosphamide [Cytoxan], doxorubicin) regimens have prompted consideration of chemotherapy as primary treatment.[2,7,8] In patients with metastatic disease, 50% to 70% have a favorable response to treatment and 20% to 40% of patients have a complete response. The number of patients who have a complete response in the bladder is also in the range of 20% to 50%.[2,8]

TABLE 1
TREATMENT ALTERNATIVES FOR BLADDER CANCER

- Bladder preservation
  - Definitive radiation therapy with salvage cystectomy
  - Primary chemotherapy with salvage total or partial cystectomy
  - Combination of radiation therapy and chemotherapy with salvage cystectomy
- Bladder reconstruction (cystectomy)
  - Ileal conduit
  - Continent cutaneous reservoir
  - Continent orthotopic revervoir to urethra
  - Augmented rectal reservoir
  - Adjuvant chemotherapy

A major disadvantage of primary chemotherapy is the difficulty of the restaging evaluation to confirm a complete response. Three points need to be stressed: (1) Lesions of mixed histologic types—ie, significant elements of squamous cell carcinoma or adenomatous changes in transitional cell cancer—have a poor response rate compared to those with pure transitional cell carcinoma;[1,2,8] primary chemotherapy is ill-advised in this setting. (2) Systemic chemotherapy is not particularly effective against carcinoma in situ;[1,2] a patient who has a solid invasive lesion, but with large amounts of associated in situ carcinoma, may well need treatment at some point with additional intravesical therapy, such as Bacillus Calmette Guerin (BCG), to control the mucosal disease. (3) Since a complete response to chemotherapy does not prevent further cancers from developing, regularly scheduled follow-up endoscopy is essential.

The advisability of a bladder-sparing operation, such as a partial cystectomy, is debatable. Patients who have a complete response to the chemotherapy do not need the surgery. In patients who have only a partial response to the chemotherapy, the precise location of the remaining disease, the potential presence of other mucosal disease, and the temptation to compromise margins are potential sources of failure. Partial cystectomy may work in some cases, but decisions related to its use will remain difficult.

Radiation therapy and chemotherapy combined with salvage cystectomy

If radiation therapy works in 30% to 40% of patients and chemotherapy works in 30% to 40% of patients,

wouldn't it make sense to combine the two regimens to get an additive or synergistic effect? Several groups are investigating this approach.[9–11] Shipley[6] has reported an initial complete response rate of 77% with a combination of platinum and radiation therapy. Rotman and associates[10] reported a complete response in 61% of patients treated with a combination of 5-fluorouracil (5-FU) and radiation therapy. Wajsman and Klimberg[11] have used M-VAC followed by radiation therapy combined with cisplatin and, in "those patients completing the entire treatment," only 17% had remaining disease. However, early studies often focused on a subgroup of patients who were able to complete the entire treatment; the patient who still has disease at the end of the radiation therapy and chemotherapy is often not in optimal condition for a cystectomy. This combination approach may be ideal for patients with minimal invasive disease and pure transitional cell carcinoma.

Essentially all of the above data represent Phase II studies. Phase III studies comparing combination therapy with surgery alone are in progress, but the appropriate endpoint of these studies is survival.

BLADDER RECONSTRUCTION

An alternative treatment philosophy is to use initial radical cystectomy with special efforts at bladder reconstruction, and then add adjuvant systemic chemotherapy in those patients who are deemed at high risk on the basis of pathologic findings in the cystectomy specimen.[1,7,8] This plan has the disadvantage of poor tolerance of postoperative chemotherapy, but it avoids chemotherapy in some patients who may not need it.[7,12]

Radical cystectomy is the most effective local therapy available for invasive bladder cancer. In patients with T2 to T4 lesions, the pelvic recurrence rate is approximately 10% to 20%.[1,13] This must be compared with 50% to 70% pelvic failure rates after either definitive radiation therapy or definitive chemotherapy. Thus, there should be little debate about which treatment is most effective in eliminating the *local* cancer.

The obvious disadvantage of cystectomy is the morbidity in terms of the size of the operation, the functional disability afforded by urinary diversion, and interference with sexual function.[14] Spurred on by the pioneering efforts of Kock, Skinner, and Walsh, functional rehabilitation after cystectomy has been appreciably improved in the last 6 to 8 years.[14,15] Four different categories of urinary diversion are now possible, and ideally all of these options should be available to appropriate patients.

Ileal conduit

The ileal conduit has the advantage of long experience with its use; preservation of upper tract function in the adult is excellent and renal failure is uncommon after a cystectomy unless there is a clear technical failure. The perioperative complications are low, and with the widespread availability of expert enterostomal therapy, long-term stomal complications are uncommon.[16,17] The single undeniable disadvantage is the need to wear an external appliance. Nevertheless, in the elderly patient with a rather sedentary lifestyle, this may have minimal impact on body image and function and often is the wisest approach.

Continent cutaneous diversions

Kock and Skinner have been leaders in the development of this type of diversion; the advantage of this approach is that the patient does not need to wear an external appliance.[18] A stoma is present and needs to be catheterized every 5 to 6 hours. The operation is more difficult and requires significant education for both the surgeon and the patient. Nevertheless, this is an attractive alternative for many patients, especially those with a vigorous, outdoor lifestyle.

While experience has been greatest and follow-up longest with the ileal reservoir popularized by Skinner, modifications of cutaneous reservoirs using the right hemicolon have also shown promise.[19–21] These colonic reservoirs rely on plication of the terminal ileum with reinforcement of the ileocecal valve as their continence mechanism, as opposed to an efferent nipple valve in the ileal reservoirs.

Continent orthotopic reservoir to urethra

Urinary reservoirs have also been placed down to the male urethra and provide reasonable function. The largest experience is that of Camey in France with a U-shaped ileal reservoir to the urethra, but results with this operation in the United States have been disappointing.[22] More favorable results have been obtained with detubularized bowel segments conformed into a spherical shape, made up of either ileum or right hemicolon; these tend to have lower volume pressure characteristics and better long-term urinary continence.[23] The disadvantage of this operation is that a significant percentage of patients will have some degree of nocturnal incontinence when the urethral resistance decreases significantly during sleep. Even so, this procedure is attractive to many patients because it avoids any external appliance or stoma. Unfortunately, this has only been applied successfully in significant numbers in male patients.

Augmented rectal reservoir

Ureterosigmoidostomy is a method of urinary diversion that has been used for more than 50 years. In the last 30 years, since the ileal conduit became available, the method has lost popularity in this country because of the potential for upper tract infections, metabolic disturbances, an increased risk of colon cancer, and fecal and urinary soilage resulting from poor control.[24] Nevertheless, this has been the main form of urinary diversion used in Europe, the Middle East, and South America.

As urologists better appreciate characteristics of other types of diversions that improve reservoir capabilities, it is likely that other procedures will be developed that make use of the augmented rectal reservoir.[25] The increased risk of colon cancer in older patients who need cystectomy must be evaluated, and any conclusions relative to the functional results and safety of this approach are premature.

Adjuvant chemotherapy

Since the major source of treatment failure after cystectomy is systemic disease, cystectomy with any type of urinary diversion will not significantly improve the current survival rates. The previously described adjuvant chemotherapy is one approach that may be worthwhile.[1,7,8] Patients who have undergone a major operation such as a cystectomy often have difficulty tolerating aggressive chemotherapy. However, two or three cycles of chemotherapy may be all that is needed, and longer, more protracted courses may not necessarily provide better results. There is some evidence that the use of adjuvant chemotherapy may delay relapse, but the more important question is whether there will be an improvement in overall long-term survival.[7,8] This question is unanswered at the present time. "Neoadjuvant" chemotherapy is also being evaluated.[2]

COMMENT

An important consideration is the cumulative toxicity of all the therapies. Radical cystectomy previously was considered an extremely dangerous operation; mortality rates in the 1930s to 1950s ranged from 20% to 40%. Operative mortality has consistently decreased, and is now in the range of 1% to 2%. In a Cleveland Clinic series of 229 consecutive cases (including 8% who had preoperative radiation therapy, 9% who had previous definitive radiation therapy, 12% who had a new form of urinary diversion, and 8% who had preoperative systemic chemotherapy), the operative mortality was 0.4% (1/229).[17] Other authors have confirmed the safety of the operation with the improved perioperative support services now available.[26,27]

Systemic chemotherapy also carries attendant risk. In series with large numbers of patients, the incidence of drug-related deaths has ranged from 2% to 6%.[2,28] It may not be entirely appropriate to compare these results with the results of surgery because a patient undergoing surgery is likely to be less sick than one receiving chemotherapy. Nevertheless, we must appreciate that each treatment has its own toxicity; when we combine different treatment modalities, the toxicity may well be additive.

In the evaluation of treatment protocols, it is important to compare patients according to their initial treatment plan and not exclude patients who only complete a portion of the regimen. For example, if the plan is for bladder preservation, we cannot eliminate patients who initially receive chemotherapy but don't complete the entire treatment protocol because of treatment-related side effects. We must resist the temptation to analyze results based on "those patients completing the entire planned treatment regimen."

All of the newer approaches to bladder preservation or bladder reconstruction must be considered investigational. It may well be that no single approach will emerge as clearly superior for all patients and that the treatment must be individualized. Younger patients with large cancers and no significant mucosal disease may be best served by initial chemotherapy with or without radiation therapy. Older patients and those with mixed histologic types or with diffuse mucosal disease may be best served with primary surgery. Unfortunately, there are few ongoing well-designed clinical trials and it is difficult to accrue adequate numbers of patients because many physicians have already arrived at conclusions relative to the efficacy of these approaches.

REFERENCES

1. Skinner DG. M-VAC chemotherapy in the management of locally advanced bladder cancer. J Urol 1988; **139:**570.
2. Scher HI, Yagoda A, Herr HW, et al. Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) effect on the primary bladder lesion. J Urol 1988; **139:**470–474.
3. Jenkins BJ, Caufield MJ, Fowler CG, et al. Reappraisal of the role of radical radiotherapy and salvage cystectomy in the treatment of invasive (T2/T3) bladder cancer. Br J Urol 1988; **62:**343–346.
4. Quilty PM, Duncan W. Primary radical radiotherapy for T3 transitional cell cancer of the bladder: an analysis of survival and control. Int J Radiat Oncol Biol Phys 1986; **12:**853–860.
5. Shipley WU, Rose MA, Perrone TL, Mannix CM, Heney NM, Prout

GR Jr. Full-dose irradiation for patients with invasive bladder carcinoma: clinical and histological factors prognostic of improved survival. J Urol 1985; **134:**679–683.
6. Shipley WU. Optimizing full-dose radiation therapy in the successful bladder-sparing management of patients with invasive bladder carcinoma. World J Urol 1988; **6:**152–147.
7. Freiha F, deVries C, Torti F. Neoadjuvant and adjuvant chemotherapy of transitional cell carcinoma of the urothelium with cisplantin, methotrexate and vinblastine. World J Urol 1988; **6:**153–157.
8. Logothetis CJ. The role of chemotherapy in the management of urothelial tumors: interpretation of the M.D. Anderson Cancer results. World J Urol 1988; **6:**163–166.
9. Raghavan D, Grundy R, Greenaway TM, et al. Pre-emptive (neo-adjuvant) chemotherapy prior to radical radiotherapy for fit septuagenarians with bladder cancer: Age itself is not a contra-indication. Br J Urol 1988; **62:**154–159.
10. Rotman M, Macchia R, Silverstein M, et al. Treatment of advanced bladder carcinoma with irradiation and concomitant 5-fluorouracil infusion. Cancer 1987; **59:**710–714.
11. Wajsman Z, Klimberg IW. Bladder-sparing approach to invasive bladder cancer. World J Urol 1988; **6:**148–152.
12. Debruyne FMJ, Splinter TAW. A review of "upfront" chemotherapy in invasive transitional cell carcinoma of the bladder. World J Urol 1988; **6:**167–169.
13. Montie JE, Straffon RA, Stewart BH. Radical cystectomy without radiation therapy for carcinoma of the bladder. J Urol 1984 **131:**477–482.
14. Schlegel PN, Walsh PC. Neuroanatomical approach to radical cystoprostatectomy with preservation of sexual function. J Urol 1987; **138:**1402–1406.
15. Montie JE, Pontes JE, Smyth EM. Selection of the type of urinary diversion in conjunction with radical cystectomy. J Urol 1987; **137:**1154–1155.
16. Klein EA, Montie JE, Montague DK, Novick AC, Straffon RA. Stomal complications of intestinal conduit urinary diversion. Cleve Clin J Med 1989; **56:**48–52.
17. Montie JE, Wood DP, Jr. Risk of radical cystectomy. Brit J Urol (in press).
18. Boyd SD, Skinner DG, Lieskovsky G. Ongoing experience with the Kock continent ileal reservoir for urinary diversion. World J Urol 1985; **3:**155–158.
19. Lieskovsky G, Skinner DG, Boyd SD. Complications of the Kock pouch. Urol Clin North Am 1988; **15:**195–205.
20. Rowland RG, Mitchell ME, Bihrle R, Kahnoski RJ, Piser JE. Indiana continent urinary reservoir. J Urol 1987; **137:**1136–1139.
21. Bejany DE, Politano VA. Stapled and nonstapled tapered distal ileum for construction of a continent colonic urinary reservoir. J Urol 1988; **140:**491–494.
22. Camey M. Bladder replacement by ileocystoplasty following radical cystectomy. World J Urol 1985; **3:**161–166.
23. Hinman F, Jr. Selection of intestinal segments for bladder substitution: physical and physiological characterics. J Urol 1988; **139:**519–523.
24. Zabbo A, Kay R. Ureterosigmoidostomy and bladder exstrophy: a long-term followup. J Urol 1986; **136:**396–398.
25. Kock NG, Ghoneim MA, Lycke KG, Mahran MR. Urinary diversion to the augmented and valved rectum: preliminary results with a novel surgical procedure. J Urol 1988; **140:**1375–1379.
26. Skinner DG, Lieskovsky G. Technique of radical cystectomy. [In] Skinner DG, Lieskovsky G, eds. Diagnosis and Management of Genitourinary Cancer. Philadelphia, W.B. Saunders, 1988, pp 607-621.
27. Hendry WF. Morbidity and mortality of radical cystectomy. J R Soc Med 1986; **79:**395–400.
28. Wahle SM, Williams RD, Gerstbrein JJ, et al. CMV chemotherapy for extensive urothelial carcinoma. World J Urol 1988; **6:**158–162.