Bladder cancer has many unusual characteristics, including a high incidence of local recurrence, an accessible location, and sensitivity to topical chemotherapy and immunotherapy, that make it subject to innovations in cancer treatment. These characteristics are partly responsible for the improvements that have occurred in the treatment of bladder cancer and can be used to advantage in improving the management of bladder cancer and that of other malignancies in the future. This editorial reviews the major advances in bladder cancer over the past 20 years and the remaining challenges that need to be addressed to increase patient survival.

Despite the continued increase in the number of new cases occurring each year, the mortality attributed to bladder cancer has remained relatively constant. The incidence and mortality estimates for the past 20 years as reported by the American Cancer Society are illustrated in the Figure. In 1978, 30,000 new cases were estimated, with an estimated mortality of 9,900, or 33% of the annual incidence. In 1985, with an annual incidence of 40,000 cases, the mortality was 10,800 (27% of the annual incidence). Actual mortality remained lower than that number until 1995, when, with an estimated 50,500 new cases, 11,200 deaths occurred (22% of the annual incidence). Since 1995 mortality has continued to increase, and 54,400 new cases and 12,500 deaths are projected for 1998 (23% of the annual incidence).

These population statistics suggest that survival of patients with bladder cancer has been prolonged as the result of improved care in the early 1980s. The more recent increase in mortality suggests that although bladder cancer mortality has been delayed, patients currently undergoing treatment remain at risk of dying of the disease. Survival is prolonged, but cure remains elusive for many patients.

The most obvious improvements in care during this period are bacille Calmette-Guérin (BCG) immunotherapy for superficial bladder cancer and cisplatin and methotrexate–based combination chemotherapy for advanced disease. BCG immunotherapy for superficial bladder cancer was first reported in 1976 by Morales et al, and the first controlled tri-
al confirming its efficacy was reported by Lamm et al in 1980. The US Food and Drug Administration approved BCG for the treatment of carcinoma in situ in 1990.

In 1985 Harker et al published the results of treatment with cisplatin, methotrexate, and vinblastine, and Sternberg et al reported the efficacy of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) combination chemotherapy in the treatment of advanced bladder cancer.

BCG immunotherapy has radically changed the management of carcinoma in situ of the bladder and aggressive papillary transitional cell carcinoma. Before 1983, an average of 54% of patients with carcinoma in situ developed muscle-invasive disease within 5 years. With BCG immunotherapy, 70% or more of patients will have a complete response, and 65% of complete responders will remain disease-free for 5 years.

With improved maintenance BCG schedules, complete response increases to 83%, and 80% remain disease-free.

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Figure. Despite efforts to reduce exposure to carcinogens in the workplace and decrease cigarette smoking, the number of new patients with bladder cancer has increased each year in the last 20 years. Mortality has remained relatively constant despite the increase in numbers of new cases. Fortunately, most patients present with superficial disease, and even those who develop metastasis after cystectomy for invasive disease may survive for more than 1 year. The annual mortality is therefore more reflective of incidence and treatment failure several years earlier. Nonetheless, percent mortality steadily decreased from 1978 (33%) to 1992 (18.4%).

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About 30% of patients with bladder cancer develop metastasis during the course of their disease.\textsuperscript{30} Cisplatin and methotrexate–based combination chemotherapy has significantly improved the treatment of advanced bladder cancer. MVAC, when combined with aggressive surgical resection of residual masses, has resulted in complete response in more than one-third of patients. Unfortunately, two-thirds of patients with complete response relapse within 2 years.\textsuperscript{31}

Aggressive surgical management before the onset of metastasis therefore remains an important, potentially lifesaving strategy. Advances in surgical techniques, including bladder substitution using intestinal segments that permit urethral voiding (a technique that now can be successfully used in women as well as men), have greatly improved patient acceptance of cystectomy.

What lessons can be learned from the history of the treatment of bladder cancer, and what can be done to reduce the incidence and mortality of this disease further?

**Prevention**

As Dr. Droller points out, approximately half the bladder cancers in men are the result of cigarette smoking, and a large portion of the remainder are caused by industrial or agricultural carcinogens. Reducing exposure to these carcinogens is difficult, but doing so would lower the incidence of bladder cancer and that of other malignancies.

Chemoprevention also may be feasible. In our double-blind study, high doses of vitamins A, B\textsubscript{6}, C, and E plus zinc reduced the long-term recurrence of bladder cancer by 40% in patients receiving intravesical BCG immunotherapy.\textsuperscript{32} The National Cancer Institute’s Five A Day program to increase consumption of fruits and vegetables and the increased public interest in taking supplemental vitamins may be beneficial in reducing the incidence of bladder cancer.

**Early Detection**

Although 70% or more of patients are diagnosed with superficial bladder cancer, 80% to 90% of patients with muscle-invasive cancer already have invasive disease at the time of diagnosis.\textsuperscript{33,34} Patients in the latter group account for most of the bladder cancer deaths, because 50% of patients with muscle-invasive disease already have distant metastasis. Improved treatment of superficial disease, therefore, will have only a limited effect on the overall mortality of bladder cancer. A major reduction in mortality without highly effective treatment for metastatic disease requires improved detection of aggressive malignancy while it is still superficial.

Evidence does suggest that screening men older than 50 years can significantly lower the incidence of invasive disease from the expected 24% to 5% and that of mortality from 16% to 0.\textsuperscript{35} Widespread screening of at-risk populations should reduce mortality, and with the advent of improved urinary markers, as outlined by Dr. Droller,\textsuperscript{1} screening programs may become safe and efficient.

**Improved Treatment of Superficial Bladder Cancer**

Many intravesical chemotherapeutic drugs have been confirmed in controlled studies to reduce the incidence of tumor recurrence when used in conjunction with transurethral tumor resection. Unfortunately, however, no chemotherapeutic drug has been confirmed to reduce disease progression.\textsuperscript{36,37} Increasing data suggest that the optimal time for instillation is immediately after transurethral resection.\textsuperscript{38–40} Presumably, immediate instillation of chemotherapy prevents tumor cells released during resection from implanting on the traumatized urothelium.
Better drugs are needed, but the development and US Food and Drug Administration approval of these drugs are ironically hampered by the success of BCG immunotherapy for superficial transitional cell carcinoma.

BCG immunotherapy now results in complete eradication of transitional cell carcinoma in situ in more than 80% of patients, compared with 50% or less of patients treated with chemotherapy. Unfortunately, despite evidence from Europe that leaving a “marker lesion” to test for sensitivity to intravesical therapy does not increase the risk of disease progression, this practice has been discouraged by institutional review boards in the United States.

This leaves only carcinoma in situ, which cannot be reliably resected, for testing new drugs in phase II studies. Because carcinoma in situ is an aggressive and potentially lethal form of bladder cancer and BCG is highly effective, only patients who fail to respond to or are intolerant of BCG are available for evaluation of new drugs. This leaves very few patients: only 10% of patients have carcinoma in situ (about 5,000 per year), and all but about 20% (1,000 patients) respond to BCG. Moreover, unless new agents are at least as effective as BCG, approval may not be forthcoming. This restrictive policy makes it difficult to introduce new drugs into the treatment of bladder cancer.

Anatomically, superficial bladder cancer is an ideal malignancy for the evaluation of new treatment modalities. In addition to immunotherapy with BCG, photodynamic therapy using a combination of light-sensitive dye and laser light has been effective in the treatment of bladder cancer and has been applied to other malignancies. Because bladder cancer is accessible to topical treatment and the response can be assessed directly, treatments such as antibody-directed chemotherapy and gene therapy can be developed and tested with less concern about systemic inactivation or toxicity.

**Improved Treatment of Advanced Disease**

The prospect for introducing new and more effective drugs and drug combinations is much better in the treatment of advanced bladder cancer than in that of superficial bladder cancer. As noted in Dr. Droller’s review, new combinations hold the promise of being less toxic and at least as effective as cisplatin and methotrexate combinations. Cisplatin combined with paclitaxel, docetaxel, gemcitabine, or both paclitaxel and gemcitabine has been reported to have acceptable toxicity and response rates ranging from 60% to 90%.

A reliable tumor marker for metastatic bladder cancer would facilitate management of advanced disease and, more importantly, identify patients with occult metastasis who could benefit from adjuvant chemotherapy. Beta human chorionic gonadotropin (β-hCG), carcinoembryonic antigen, CA-125, CA 19-9, and others have been evaluated and do correlate with clinical response to chemotherapy. Better tumor markers are greatly needed because none of the current markers, when used alone, is elevated in more than 50% of patients, and we have no marker to detect occult disease reliably.

Meeting the challenges that stand in the way of reducing the mortality of bladder cancer requires considerable research, financial investment, and public education. Despite the frequency of bladder cancer and the toll it takes in human morbidity and mortality, it does not have the public awareness or support that many other malignancies do. Support groups exist for patients with breast, prostate, and kidney cancers, for example, but no national support group or organized lobbying effort exists for those with bladder cancer.

Many patients are reluctant to let
others know of their disease. Although political leaders and famous entertainment and sports figures have had bladder cancer, none has stepped forward to champion the cause. This reticence is not in the interest of patients with bladder cancer. No shame is associated with having bladder cancer, and better education, public awareness, and support for research will result in earlier diagnosis, better treatment, and further reduction in mortality.

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