

## SESSION IV

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**Advanced bladder cancer: options of therapy****Key words** Advanced bladder cancer · Therapy**Introduction**

Little progress has been made on the treatment of invasive transitional-cell carcinoma over the last 30–40 years. The lack of accurate staging modalities, which carries approximately 20%–30% understaging and 20% overstaging, makes evaluation of small gains attributed to any forms of therapy questionable. Furthermore, the lack of proper comparative studies among the different options of therapy continues to confuse the issues [21].

In the United States, until recently, the traditional approach to invasive bladder tumor has been radical cystectomy. Although there is an excellent control of local disease with this approach, approximately half of the patients will die of metastatic disease following this procedure. In other countries, radiation therapy has been used as a traditional method of treating invasive disease. Recently, combinations of chemotherapy, radiation, and surgery have been tried in an attempt to improve the survival of patients with invasive cancer. Herein I discuss the different approaches to invasive bladder tumors and the recent reported results.

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**Review of treatment modalities****Radical cystectomy**

Several reviews in the technical aspects of radical cystectomy have been published [16]. This procedure in large centers is now done routinely with a perioperative mortality of approximately 1%–2% [16]. Radical cystectomy is effective in controlling the local disease with a recurrence rate of less than 10% [9]. Although in the past, preoperative radiation therapy was believed to have a role in the treatment of invasive bladder tumor of patients undergoing cystectomy, recent work shows no advantage for the addition of radiation therapy [17]. Although cystectomy is effective in controlling local disease, the survival of patients undergoing this procedure for invasive disease has remained unchanged for the last 40 years [21]. Another aspect of this treatment modality is that it always requires some form of urinary diversion and, until recently, external diversion (ileal loop) has been necessary. Recently, attempts at creating continent forms of urinary diversions either to the skin or to the urethra have been successful [10]. Although these new surgical techniques do not change survival, they improve significantly the patients' quality of life [10].

**Adjuvant chemotherapy**

The concept of adjuvant chemotherapy is well founded in basic oncological principles. Several protocols designed for preventing the development of metastasis by starting immediate postoperative chemotherapy have been attempted [7, 18]. Three studies have recently been published, two being done in the prospective randomized fashion and the other being a concomitant randomized study showing some advantage for the use of adjuvant chemotherapy. In the two randomized studies, methotrexate, platinum, Adriamycin, and Velban (MVAC) were used, and the nonrandomized study employed cisplatin, Adria-

mycin, and cyclophosphamide (CISCA) [7, 18, 20]. In all three studies advantages in favor of patients receiving adjuvant chemotherapy was noted [7, 18, 20].

### Neoadjuvant chemotherapy

Because it is believed that distant metastases arise from micrometastases that are present at the time of treatment of the primary tumor, the concept of up-front chemotherapy became popular in the mid 1980s. Besides the potential prevention of distant metastasis, and added benefit is downstaging of the primary lesion with the possibility of bladder salvage. Responses to neoadjuvant chemotherapy using either CISCA or MVAC were significant and led to an increased utilization of this modality of therapy, sometimes indiscriminately. The lack of consistency in evaluation of response, the inherent problems with clinical evaluation versus pathological staging, and the lack of an end point led to a loss of some of the initial enthusiasm for this therapy.

### Radiotherapy and combined radiation and chemotherapy

Radiation therapy has been the chosen modality of treatment for invasive bladder cancer in certain countries, such as England. The response rate to radiation therapy is approximately 30%, with the additional patients failing radiation therapy undergoing salvage cystectomy. A recent revision of the Canadian experience was published with approximately the same results [4]. Because of the potential synergism between cisplatin and radiation, attempts to combine both modalities have been made. The results of a phase I–II trial of cisplatin plus radiation therapy done by NBCCG showed a 67% local response rate [14]. The survival of those patients, however, was not superior to that achieved by other forms of therapy [14]. Recently, multidrug chemotherapy and radiation have been utilized with success in preserving bladder function and in treating invasive disease.

## Results and discussion

### Radical cystectomy

Radical cystectomy has been an integral part of the treatment of invasive bladder cancer for many years. In the past, the magnitude of the surgical procedure in association with the lack of appropriate medical support led to acceptably high morbidity and mortality. Operative mortality in modern cystectomy series has been reported to range between 1% and 5% as compared with 12%–22% for historical series [17]. In an attempt to decrease local recurrence, preoperative radiation therapy was proposed and was used in the 1970s as an adjunct to cystectomy

[11]. Although initial reports suggested an advantage for integrated preoperative radiation plus cystectomy, these reports were based mostly on a historically controlled series [11]. In several comparative studies using either long- or short-course radiation therapy plus cystectomy as compared with cystectomy alone, no significant difference was observed [17]. Presently in the United States, cystectomy alone is the most common therapy utilized for invasive bladder cancer. Although the success of this surgery in controlling the primary tumor is excellent, some form of urinary diversion is necessary following cystectomy.

In the United States, the most common form of urinary diversion is the ureteroileal anastomosis (ileal loop), which in adults has the least amount of long-term complications. The psychosocial aspects of this procedure, however, make it undesirable for a significant number of patients. Because of this, in the last few years several procedures have been developed to provide patients with continent urinary diversion either to the skin or to the urethra. A recent review of those procedures has been published [10]. Despite advances with this technique, 50% of all patients undergoing cystectomy for invasive bladder cancer will die of metastatic bladder cancer.

### Adjuvant chemotherapy

The concept of adjuvant chemotherapy is well recognized in oncology. In patients at high risk of developing metastasis, it is likely that micrometastasis is present at the time of cystectomy. The first attempt at utilizing adjuvant chemotherapy for bladder cancer in the United States was a protocol proposed by the National Bladder Cancer Group (NBCG) using cisplatin as a single agent for six courses after radical cystectomy [19]. The results of that study were inconclusive due to the large number of patients not completing protocols and the suboptimal chemotherapy schedule [19]. Recently, three studies utilizing multimodality chemotherapy have suggested an advantage for adjuvant chemotherapy for patients at risk of developing metastasis [7, 18, 20]. Logothetis et al. [7] reviewed 36 patients with invasive bladder cancer who received CISCA (5 courses) postsurgery and compared this group with a similar high-risk group not receiving chemotherapy. There was a significant survival improvement in patients undergoing adjuvant chemotherapy (61% versus 38% survival,  $P = 0.03$ ) [7]. Two other studies done in a prospective randomized fashion have confirmed the advantage of adjuvant chemotherapy [18, 20]. In the study published by Skinner et al. [18], there was a significant delay in disease progression and the median survival of patients in the adjuvant chemotherapy group was 4.3 years as compared with 2.4 years for the control group. Although some criticism has been made toward the work published by Skinner et al. [18], it appears that there is some advantage for adjuvant chemotherapy in selected patients

## Neoadjuvant chemotherapy

After the encouraging results obtained with MVAC chemotherapy in treating metastatic transitional-cell carcinoma of the bladder, the group led by A. Yagoda at Memorial Sloan-Kettering Cancer Center (MSKCC) initiated a phase II study using the same regimen as neoadjuvant chemotherapy [13]. Although the principles of this approach were known, namely, the elimination of micrometastasis present in about 50% of patients with invasive bladder cancer, some of the significant clinical responses obtained in the primary tumor led this group of investigators to evaluate as well the probability of bladder sparing in this group of patients [13]. Among 87 patients treated with this regimen, 64% were clinically down-staged and 23% of those undergoing either cystectomy or partial cystectomy had no evidence of tumor.

Long-term follow up of these patients done at MSKCC showed that 51% of the patients were alive at 5 years and 28% of these had functional bladders [2]. It was also observed that the accuracy of clinical staging of the primary tumor after chemotherapy was inadequate, with approximately 32% of the tumors being understaged [5]. Similar observations have been made by other authors [3, 6, 8]. In reviewing the literature on the subject, Herr et al. [5] stated that if the goal was survival, a cystectomy would have to be performed in all patients. Several other phase II studies have been performed with similar results [3, 6, 8]. A variation of the traditional MVAC approach includes the use of CISCA, MCV, or both of these chemotherapeutic regimens utilizing intra-arterial cisplatin [3, 6, 8]. Our experience using CISCA with intra-arterial platinum is similar, with patients responding to therapy doing well with an overall survival of 76% and approximately 10% of the cases involving bladder preservation [3].

It appears that neoadjuvant chemotherapy selects responsive tumors, eliminating early on (after two courses of therapy) those tumors not likely to respond. Phase III trials comparing neoadjuvant chemotherapy with cystectomy or radiation therapy are presently in progress.

## Radiotherapy and combined radiation and chemotherapy

External radiation therapy alone has been extensively used in the past for the treatment of invasive bladder cancer and continues to be the treatment of choice in some countries [1]. Although in many series the choice of radiation therapy was made on the basis of inoperability due to either local extension or an associated medical condition, the survival reported at 5 years ranged from 20% to 39% [15]. As pointed out by Shipley et al. [15], one of the problems noted is the permanent local control with preservation of bladder function that is achieved in only 30%–50% of patients. In a recent study of patients treated with external radiation therapy in Canada by Gospodarowicz et al. [4], 121 patients treated showed an overall actuarial survival of 31% at 5 years with a cause-specific survival of 44%.

In an attempt to improve the local results of external radiation therapy and the overall survival, a combination of

chemotherapy and radiation has been proposed [12]. In a pilot study sponsored by the NBCG, 70 patients with invasive disease not suitable for cystectomy were treated with a combination of cisplatin plus small-field radiotherapy [14]. Among the 57 patients completing the planned treatment, an overall complete response rate of 77% was observed [14]. The overall survival of those patients did not differ significantly from that of patients treated by cystectomy [14]. A similar experience has been observed in other series. Recently, on the basis of the results obtained with multimodality chemotherapy, a combination of neoadjuvant chemotherapy with radiation has been proposed [12]. In a large phase II study, Prout et al. [12] treated 53 patients with neoadjuvant MCV followed by radiation therapy and cisplatin. Among the 42 patients completing the protocol, 70% were alive at 26 months with bladder preservation [12]. In an analysis of their data, however, it is clear that factors such as complete transurethral resection of the tumor and multiple restaging during the course of therapy had an influence on the overall results. Furthermore, a certain number of the patients whose bladders were preserved experienced recurrent bladder tumors.

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## Conclusions

The treatment of invasive bladder cancer continues to be controversial. Now that several modalities of therapy are available and combination therapy has been optimized, there has been a proliferation of small studies evaluating one or another type of therapy many times without a specific end point. It is necessary that end points be defined in advance. If the goal is bladder preservation, protocols in the future will include combinations of chemotherapy and radiation. If the goal, however, is elimination of local disease and potential cure with improvement of survival, then cystectomy should be the treatment of choice, perhaps with the addition of adjuvant chemotherapy for those patients at risk. This alternative is particularly attractive to urological surgeons, especially now that continent urinary diversion can be done successfully. In the future, advances in molecular genetics will allow for improved selection of patients undergoing extensive therapy.

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