Challenges in the treatment of bladder cancer

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Seventy to eighty percent of patients with newly-diagnosed bladder cancer will present with superficial tumors (Ta, Tis or T1). There is, however, a continuum between superficial and muscle-invasive cancer, with the advanced cases usually associated with less-differentiated histology and aneuploidy. Common sites of metastasis include regional lymph nodes, bone, lung, skin and liver. From the low cure rates achieved with radical cystectomy, there is strong evidence that bladder cancer, from the outset, is a systemic disease. The limitations of local treatment are well-documented: a local control rate of 30% with radiation treatment, and 50–70% with radical cystectomy; and no improvement in surgical cure was seen with the use of preoperative radiation. Over the past 30 years, since the initial reports of the effectiveness of cisplatin in the treatment of advanced bladder cancer, there has been a steady flow of chemotherapeutic agents, singly and in combination, shown to be effective in the treatment of this tumor. While response rates and CR rates have increased with the use of combination chemotherapy, this has not translated into survival in advanced disease of greater than 16 months. While the search for more effective agents and combinations continues, attention has also been given to the roles of neoadjuvant and adjuvant chemotherapy in an effort to improve the cure rate achieved with surgery alone. Although radical cystectomy, with continent diversion or neobladder construction in selected cases remains the standard of care in the United States for patients with muscle-invasive bladder cancer, several groups have explored therapeutic strategies that aim at bladder preservation. Early approaches with the goal of bladder preservation consisted of radiation treatment as monotherapy (largely abandoned) or aggressive TURBT for smaller tumors. Over the past 20 years, the Massachusetts General Hospital (MGH) and the Radiation Therapy Oncology Group (RTOG) have studied patients with muscle-invasive bladder cancer utilizing tri-modality treatment: a visibly complete transurethral resection followed by radiation with concurrent radiosensitizing chemotherapy and, subsequently, adjuvant chemotherapy. Thus, chemotherapy has been used in two phases of treatment (1) as radiosensitizers, given concurrently with radiation treatment and (2) as adjuvant treatment, recognizing that survival will only be improved by the successful treatment of micrometastases. Based on preliminary information from reports of the effectiveness of gemcitabine/cisplatin in advanced disease, that combination was chosen as the adjuvant regimen in one of our earlier protocols, recently completed and reported. Our current protocol utilizes the Bellmunt regimen as our adjuvant program with the highest RR in advanced disease. This study is ongoing, with early reports of tolerance of the three-drug regimen encouraging. The treatment options for muscularis propria-invasive bladder tumors can broadly be divided into those that spare the bladder and those that involve removing it. In the United States, radical cystectomy with pelvic lymph node dissection is the standard method used to treat patients with this tumor.

**radical cystectomy**

Radical cystectomy for stage T2–T4a muscle-invasive bladder cancer is an approach that results in 90% local control at five years, but only 40–60% five-year overall survival. It is likely that the low cure rate is due to micrometastatic disease present at the time of cystectomy, and patients so afflicted are therefore destined to die of distant metastases. An analysis of cystectomy by investigators at Memorial-Sloan Kettering Cancer Institute demonstrated a disease-specific survival of 67% and a median overall survival of only 45% with a median follow-up of 65 months [1]. Several studies have established that the clinical and pathologic stage of the disease is important in predicting long-term survival. At the University of Southern California, the 5-year recurrence-free survival for muscle invasive bladder cancer was 89% in P2 node-negative tumors, 50% in P4 node-negative tumors, and 35% in patients with node positive tumors [2].

**selective bladder preservation in the treatment of muscle-invasive bladder cancer**

Conservative management with organ preservation is now the standard of care in numerous malignancies, including carcinomas of the breast, the anus, and the head and neck region, where radical surgery can be avoided in most patients...
without compromising survival. There are several reports from North America and Europe of long-term survival using multimodality treatment of muscle-invasive bladder cancer, with appropriate safeguards for early cystectomy should the bladder preservation treatment fail.

**monotherapy**

Barnes et al. reported a 27% 5-year survival in 85 patients with well and moderately-differentiated T2 transitional cell carcinomas treated with transurethral resection alone [3]. Sweeney et al. found that only 19% of patients with muscle invasive tumors were selected for treatment by partial cystectomy, and these had a local recurrence rate of 38–78% [4]. Local control rates with radiation alone for muscle-invading tumors have been disappointingly low, and radiation as monotherapy has largely been abandoned [5–8]. Hall and Roberts reported a 19% three-year freedom from recurrence with chemotherapy alone in 27 patients with localized disease, utilizing cisplatin, methotrexate, vinblastine, and epirubicin [9]. The local control rates for the monotherapies noted above are unacceptable when compared to radical cystectomy, with its local control rate of 90%.

**trimodality treatment**

Investigators have become interested in clinical trials with the demonstration that some older as well as newer drugs have considerable activity against metastatic bladder cancer (Tables 1 and 2). The list includes cisplatin, methotrexate, vinblastine, ifosfamide, doxorubicin, gemcitabine, paclitaxel, as the principal agents. Not surprisingly, combinations of these drugs have been shown to be more effective than single agents in the percentage of complete remissions (CR) achieved. With the use of combination chemotherapy in advanced measurable disease, CR has become a common achievement as compared to a 15–20% rate of partial remission utilizing a variety of single drugs, and with complete remissions only rarely observed with single-agent treatments.

Successful approaches have evolved over the last two decades following the initial reports of the effectiveness of cisplatin against transitional cell carcinoma and reports of added efficacy when it is given concurrently with radiation. From 1981 to 1986 the National Bladder Cancer Group first used cisplatin as a radiation sensitizer in 68 patients with muscle-invasive bladder cancer who were unsuitable for cystectomy. In a multicenter protocol this approach was shown to be feasible and safe [10]. Furthermore, the long-term survival rate with stage T2 tumors (64%) and even for stage T3–T4 tumors (22%) was encouraging. Single institution studies showed that the combination of a visibly complete transurethral resection of tumor (TURBT) followed by radiation therapy or radiation therapy concurrent with chemotherapy led to improved local control [11, 12].

Houssett and colleagues from the University of Paris reported on 120 patients with stage T2–T4a bladder cancer. The treatment consisted of TURBT followed by cisplatin and 5FU given concurrently with twice a day hypofractionated radiation. They reported a 63% overall survival [13].

Investigators at the University of Erlangen recently updated the largest bladder-sparing study to date, 415 patients treated from 1982–2000 [14]. This report included 126 patients who received radiation without any chemotherapy and 89 patients who were not clinical Stage T2–T4 but classified as ‘high risk T1’. The complete response (CR) rate of all 415 patients was 72% and local control of the bladder tumor after the CR without a muscle invasive relapse was maintained in 64% of the patients at 10 years. The 10 year disease specific survival was 42%, and more than 80% of these survivors preserved their bladder. These results suggest strongly that radiochemotherapy when given concurrently is superior to radiation therapy alone, that carboplatin is less radiosensitizing than cisplatin, and that cisplatin plus 5FU may be superior to cisplatin alone. The authors recognized that their study was compromised by the absence of randomized trial data.

These findings led RTOG to develop the algorithm for bladder preservation to consist of an initial TURBT of as much of the bladder tumor as is safely possible followed by a combination of radiation with concurrent radiosensitizing chemotherapy. One key to the success of such a program is the selection of patients for bladder preservation on the basis of the initial response of each individual patient’s tumor to therapy. Thus, bladder conservation was reserved for those patients who had a clinical complete response to concurrent chemotherapy and radiation. Prompt cystectomy was recommended for those patients whose tumors responded incompletely or who subsequently developed an invasive tumor (Figure 1). All of the protocols developed at MGH or within RTOG since 1986 call for radical cystectomy at the first sign of failure of local control. More than one-third of the patients entering a potential bladder preserving protocol with trimodality therapy (initial TURBT followed by concurrent chemotherapy and radiation) will require radical cystectomy [15].

From 1994 to 1998, twice daily radiation therapy was introduced into RTOG protocols with concurrent cisplatin
or with cisplatin plus 5FU as radiosensitizers [16]. From 1999–2002, twice a day radiation concurrent with cisplatin and paclitaxel as radiosensitizers along with adjuvant cisplatin and gemcitabine was evaluated. The latest North American protocol for bladder sparing treatment (RTOG 02–33) recently opened. This is a randomized Phase II study comparing two combinations of radiosensitizing chemotherapy, (cisplatin plus paclitaxel vs. cisplatin plus 5FU) each given concurrently with an induction course of twice-daily radiation treatment. This is followed in patients whose tumors initially respond completely by consolidation chemoradiation and in those with incompletely responding tumors by radical cystectomy. All patients are then to undergo a three-drug adjuvant treatment consisting of cisplatin, gemcitabine and paclitaxel [17].

The MGH experience with 190 patients with invasive bladder cancers with clinical stages T2–T4a entered on successive prospective protocols has recently been updated [18]. A common feature of all of the protocols was early bladder tumor response evaluation and the selection of patients for bladder conservation on the basis of their initial response to TURBT combined with chemotherapy and radiation. Bladder conservation was reserved for those who had a complete clinical response at the mid point in therapy (after a radiation dosage of 40 Gy). Approximately two-thirds of the total then received consolidation with additional chemotherapy and radiation to a total tumor dose of 64–65 Gy. Incomplete responders were advised to undergo radical cystectomy, as were patients whose invasive tumors persisted or recurred after treatment.

The median follow-up for all surviving patients was 6.7 years with 81 patients having been followed for five years or more and 28 patients for 10 or more years [19]. The five and ten year disease specific survivals are 63% and 59%, respectively.

The overall survival rate is provided in Figure 2, and the disease specific survival rate stratified by clinical stage in Figure 3. The current schema for multimodality treatment of muscle invasive bladder cancer is provided in Figure 1, and the risk of relapse with a superficial tumor following multimodality treatment in Figure 4.

The 5- and 10-year disease-specific survival rate for the 66 patients undergoing cystectomy is 48% and 41%, respectively. This indicates the very important contribution of prompt salvage cystectomy for disease control in the 66 patients who required salvage cystectomy.

The Memorial Sloan Kettering Cancer Center contemporary radical cystectomy series showed that in 184 patients with tumors of pathologic Stage P2–P4, the 5-year overall survival rate was 36%. The results of this contemporary cystectomy series for muscle-invading bladder cancer are similar to the MGH series as well as those from the University of Erlangen [20] and the RTOG [21] (Table 3).

One of the concerns with bladder sparing therapy is the risk of subsequent superficial relapses within the intact bladder, which could progress to life threatening malignancy once again for those patients. Long-term follow-up from the MGH series has examined this issue in detail in the 121 patients with a complete response (Figure 4). Sixty percent of patients did not have evidence of relapse after a median follow-up of 7.1 years. Of the 32 superficial recurrences, 10 required cystectomy and 18 were treated conservatively with tumor-free bladders. Thus, with a median follow-up of over 7 years, 91, or 75% of the 121 complete responding patients have tumor-free bladders. The overall survival of those patients with a superficial recurrence is the same as those CR patients without a bladder recurrence [22].
Thus, lifelong surveillance with cystoscopy is therefore crucial in patients treated with bladder sparing therapy, and prompt salvage therapy for either superficial or recurrent invasive disease results in no survival disadvantage.

The latest national protocol for bladder sparing treatment (RTOG 02–33) was approved in January 2003. This is a randomized Phase II study comparing two combinations of radiosensitizing chemotherapy, each given concurrently with a short course of twice-daily radiation treatment. Patients received either the combination of fluorouracil and cisplatin or paclitaxel and cisplatin. This is followed, in patients whose tumors are successfully controlled with chemotherapy and radiation, by a 3-drug adjuvant treatment program utilizing cisplatin, gemcitabine, and paclitaxel. This regimen has shown the highest response rate yet observed in published reports in advanced measurable bladder cancer [23].

**quality of life**

Radical cystectomy may cause important changes in the lives of patients, not only in urinary and sexual function, but also in social function, daily living activities and satisfaction with body image [24–28]. Nevertheless, as reported by investigators at the University of Southern California, the majority of patients reported good overall quality of life, and very little emotional distress.

Zietman et al. studied patients treated by TURBT, followed by chemotherapy, and radiation in the treatment of bladder cancer at MGH [29]. Of 221 patients with clinical T2–4a cancer of the bladder treated from 1986–2000, 71 were alive with their native bladders and disease free at the time of the report in 2001. These patients were asked to undergo a urodynamic study (UDS) and to complete a quality of life questionnaire. Sixty-nine percent participated in some component of this study with a median time from the completion of tri-modality therapy of 6.3 years, a duration long enough to capture the majority of late radiation effects. Seventy-five percent of patients had normally functioning bladders by UDS. Reduced bladder compliance, a recognized complication of radiation, was seen in 22% but in only one-third of these was it reflected in distressing symptoms. Bladder symptoms were uncommon by questionnaire, especially among men, with the exception of control problems. The majority of men retained sexual function.

A prospective multicenter study from France tracked voiding symptoms and quality of life in 53 patients. Thirty-three of these retained their bladders and these were interviewed 6, 12, and 24 months later. Only 5% of patients reported any EORTC grade 3 symptom. It was also notable that most patients experienced improvement of symptoms in the two years after treatment, presumably because of the eradication of a symptomatic tumor.

Two recent cross-sectional questionnaire studies, one from Sweden and one from Italy, have compared the outcome following radiation with the outcome following cystectomy [30, 31]. As reported in the MGH study, 74% of patients reported good urinary function. Both studies compared bowel function in irradiated patients with that seen in patients undergoing cystectomy. In neither of these studies was there a statistically significant difference in bowel function in the radiation-treated group vs. the cystectomy group.

In the assessment of sexual function, most women in the MGH study preferred not to answer the questions, yielding no data. In men, in contrast to patients who have been irradiated for prostate cancer, the majority of male bladder-sparing

**Figure 3.** Estimates of disease-specific survival according to clinical tumor stage.

**Figure 4.** Outcome of 121 patients with clinical T2-4 transitional cell carcinoma of the bladder who had a complete response.

**Table 3.** Invasive bladder cancer - survival outcomes in contemporary series

<table>
<thead>
<tr>
<th>Series</th>
<th>Stages</th>
<th>Number</th>
<th>5 yr survival</th>
<th>10 yr survival</th>
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<tbody>
<tr>
<td>Cystectomy</td>
<td>P2-P4a</td>
<td>633</td>
<td>48%</td>
<td>32%</td>
</tr>
<tr>
<td>M.S.K.C.C. (1) (2001)</td>
<td>P2-P4a</td>
<td>181</td>
<td>36%</td>
<td>27%</td>
</tr>
<tr>
<td>Selective bladder preservation</td>
<td>cT2-T4</td>
<td>326</td>
<td>45%</td>
<td>29%</td>
</tr>
<tr>
<td>Erlangen (14) (2002)</td>
<td>cT2-T4a</td>
<td>190</td>
<td>54%</td>
<td>36%</td>
</tr>
<tr>
<td>M.G.H. (15) (2002)</td>
<td>cT2-T4a</td>
<td>123</td>
<td>49%</td>
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</tr>
</tbody>
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Thus, lifelong surveillance with cystoscopy is therefore crucial in patients treated with bladder sparing therapy, and prompt salvage therapy for either superficial or recurrent invasive disease results in no survival disadvantage.
patients reported adequate erectile function (full or sufficient for intercourse), and only 8% reported dissatisfaction with their sex lives. These results are in line with those obtained in the Swedish and Italian series in which 38% and 25% of men retained useful erections as compared with 13% and 8% of cystectomy controls.

adjuvant chemotherapy with bladder preservation

Adjuvant chemotherapy as a key component in bladder-sparing protocols has generally included drugs of proven usefulness in metastatic cancer of bladder origin. Newer drugs are appropriately utilized as adjuvant treatment following the initial phases of bladder-sparing with TURB, radiosensitizing chemotherapy and radiation therapy. The major drugs in this category are gemcitabine and paclitaxel. Many recent studies have suggested that paclitaxel is an active agent in transitional cell carcinomas and a Phase II study of the combination of cisplatin and paclitaxel demonstrated a 50% response rate in 52 patients with metastatic disease [32]. Three Phase II trials demonstrated that gemcitabine combined with cisplatin is a well-tolerated active regimen [33–35]. The combination of cisplatin and gemcitabine has been compared to methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) in a Phase III study and the two combinations were shown to have similar efficacy in metastatic disease. The gemcitabine/cisplatin combination, however, was better tolerated and led to fewer hospital days for the treatment of toxic side effects [36]. It was these studies which encouraged us to use this combination in the adjuvant setting.

molecular tumor markers

The natural history of superficial urothelial tumors is that of recurrence, and, therefore, it is unclear whether tumors that occur at separate sites or at separate times in the urothelial tract are derived from the same clone or are polyclonal in origin. A report by Sidranski, Frost & Von Eschenbach et al. demonstrated the clonality of multiple bladder tumors from different sites [37], and Miyao showed concordant genetic alterations in asynchronous tumors from individual patients [38]. These studies suggest, but do not prove, that urothelial TCCs appearing at different times and sites may be derived from the same neoplastic clone. Moreover, many recent studies have reported an increasing frequency of specific genetic abnormalities in bladder tumors of more advanced-stages [39–41]. Many tumor suppressor gene modifications, including those of p53, pRB, p16, p21, thrombospondin-1, glutathione, and factors controlling the expression and function of the epidermal growth factor receptor (EGFR) have been shown in retrospective analyses to influence the outcomes of patients with TCC following various treatments [42–46]. Even in the most intensively studied tumor suppressor gene in advanced TCC, the p53 gene, retrospective analyses give conflicting data on whether a mutation of p53 confers an increased responsiveness or an increased resistance to chemotherapy or radiation [47, 48]. This conflict in the predictability of the responsiveness to adjunctive chemotherapy of TCCs with a p53 mutation is now being tested by a prospective Phase III trial of post-cystectomy MVAC chemotherapy, funded by the National Cancer Institute [49].

The development of novel biologic agents targeted against tumor specific growth factor pathways or against angiogenesis has resulted in positive studies in a variety of solid tumors. Two classes of agents that have received great attention are inhibitors of EGFR, including EGFR1 and EGFR2 (or her2/neu), and inhibitors of vascular endothelial growth factor (VEGF) or its receptors. There is ample preclinical evidence (1) that many, if not most, bladder tumors express products of the EGFR family, (2) that over-expression correlates with an unfavorable outcome, and (3) that inhibition of these pathways may have an antitumor effect [50–55]. A number of cooperative groups, including CALGB, RTOG and SWOG, are planning to study inhibitors of EGFR1 and her2/neu in the treatment of advanced bladder cancer.

Another avenue for potential selective increase in tumor cytotoxicity relative to normal tissues is the inhibition of angiogenic inducers, which are frequently present in bladder tumors. Several studies have correlated elevated VEGF levels or cyclooxygenase-2 (COX-2) expression with disease recurrence or progression, often as an independent predictor by multivariate analysis [56, 57]. This is the basis for combining in prospective clinical trials, anti-VEGF therapy or various COX-2 inhibitors with other forms of cytotoxic therapy [58].

The major challenge for clinical and translational investigators is to design appropriate prospective trials that will identify which molecular tumor markers will be prognostic of outcome and be predictive of whether a patient will do better treated by surgery, radiation, chemotherapy, molecular targeted therapy or a combination of these. Only then can molecular tumor markers be incorporated into clinical decision-making and allow physicians to make better treatment choices on behalf of their patients.

conclusions

We would conclude that selective bladder sparing should be one of the approaches considered in the treatment of invasive bladder cancer. While it is not suggested that it will replace radical cystectomy, sufficient data now exist from many international prospective studies to demonstrate that it represents a valid alternative. This approach contributes significantly to the quality of life of patients so treated and represents a unique opportunity for urologic surgeons, radiation oncologists, and medical oncologists to work hand in hand in a joint effort to provide patients with the best treatment for this disease.

In this symposium, Dr Boccardo will discuss the current status of adjuvant chemotherapy in muscle-invasive bladder cancer. Dr Bellmunt will report on his studies of the 3-day combination cisplatin/paclitaxel and gemcitabine in advanced bladder cancer, and Dr Roberts will discuss long-term results of gemcitabine/cisplatin vs. MVAC in metastatic or locally advanced bladder cancer. Dr Gontero will report his experience with gemcitabine in superficial bladder cancer, and Dr Zustovich and Dal Bianco will discuss the use of gemcitabine in renal cancer.


