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Combined chemo-radiotherapy with organ preservation for invasive bladder cancer

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In North America, radical cystectomy remains the standard treatment for patients with muscle-invading bladder cancer. However, despite radical surgery and resulting loss of normal urinary function, the expected 5 year survival is less than 50%. Radiation therapy has long been recognized a standard treatment option, capable of preserving organ function. However local control with radiotherapy is only 30-50%. Incorporation of systemic chemotherapy into the primary management of invasive bladder cancer is an attractive strategy for several reasons. The risk of distant metastases is high and local treatment modalities cannot reduce that risk and preclinical studies have demonstrated synergistic cytotoxicity when cisplatin is combined with concurrent radiotherapy. Phase II clinical trials have established chemo-radiotherapy with selective bladder preservation as an reasonable option for patients with muscle-invading bladder cancer. However, we still need to further improve local control rates, decrease the risk of non-invasive recurrences, decrease the risk of distant metastases and optimize quality of life of patients with muscle-invading bladder cancer.

Key words: bladder neoplasms; combined modality therapy; treatment outcome

In North America, radical cystectomy remains the standard treatment for patients with muscle-invading bladder cancer. However, despite radical surgery and resulting loss of normal urinary function, the expected 5 year survival is less than 50%. The majority of deaths are related to the development of distant metastases. Also, many patients are poor surgical risks or will not agree to radical surgery. Radiation therapy has long been recognized a standard treatment option, capable of preserving organ function. However local control with radiotherapy is only 30-50%. Five year survivals of 20-40% are typically observed for patients selected for radiotherapy.[1,2]

Clinical "radio-responsiveness" has been employed by some to determine which patients are best candidates for definitive radiotherapy and bladder preservation. At some centers, patients are treated with definitive radiotherapy while "salvage cystectomy" is being employed for those with local failure.[3,4] This treatment strategy has allowed bladder preservation for selected patients who achieve a complete response with radical radiotherapy. It also results in long-term survival for approximately 30-40% of patients able to undergo cystectomy at the time of recurrence. In a Danish randomized trial the use of preoperative radiation and cystectomy was compared to radical irradiation and early salvage cystectomy for local recurrence. In that study this delayed use of cystectomy did not seem to impact negatively upon survival.[4]

Incorporation of systemic chemotherapy into the primary management of invasive bladder cancer is an attractive strategy for several reasons. The risk of distant metastases is high and local treatment modalities cannot reduce that risk. Preclinical studies have demonstrated synergistic cytotoxicity when cisplatin is combined with concurrent radiotherapy.[5,6] Combination chemotherapy has also been reported to result in significant responses in both the

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primary tumor as well as distant metastases.[7,8] Therefore its incorporation into the primary management of invasive bladder cancer could potentially have positive effects on both local control and distant failure. Cisplatin-based combination chemotherapy regimens are now considered standard for patients with metastatic disease.

The National Bladder Group treated patients not considered suitable for cystectomy with radiotherapy and concurrent cisplatin.[9] This study demonstrated the safety of such a combined modality treatment approach. The complete response rate of 70% also suggested a therapeutic gain with the addition of cisplatin to radiotherapy. The National Cancer Institute of Canada conducted the only randomized phase III study comparing radiotherapy with concurrent cisplatin-radiotherapy for patients with invasive bladder cancer. Although the use of cisplatin had no effect upon the risk of distant metastases, it did significantly reduce the risk of pelvic failure.[10]

Encouraging results from initial phase II studies have led investigators to further explore the role of transurethral resection followed by chemo-radiotherapy. Goals of this combined modality therapy include the eradication of local tumor, maintenance of normal organ function, improvement in the quality of life, and prevention of distant metastases. Salvage cystectomy has been reserved for isolated bladder recurrence following chemo-radiotherapy. Proponents have assumed that the quality of life of patients treated with organ sparing approaches is better than that of patients treated with radical surgery.

The Radiation Therapy Oncology Group (RTOG) and others have utilized selective bladder preservation for those patients who respond well to initial chemotherapy-radiotherapy. The RTOG initially reported results of its pilot study of cisplatin and concurrent radiotherapy. In this initial trial, 48 patients were treated with cisplatin-radiotherapy and selective bladder preservation for those patients with cystoscopic complete response. The complete response rate was 66%, bladder preservation was 52%, and 4-year overall survival was 52%.[11]

The second RTOG trial employed the addition of two cycles of "neoadjuvant" methotrexate, cisplatin and vinblastine (MCV) prior to cisplatin and concurrent radiotherapy. Results were similar, with complete response rate 75%, bladder preservation 60%, and 4-year overall survival being 62%.[12] The third RTOG trial was a prospective randomized comparison of cisplatin-radiotherapy with and without neoadjuvant MCV chemotherapy. Preliminary results of this third study show increased toxicity, with six deaths occurring during treatment. Unfortunately, no improvement in response nor survival was observed with the addition of MCV prior to cisplatin-radiotherapy.[13]

These combined modality studies confirm the effectiveness of combined chemo-radiotherapy when combined with selective bladder preservation reported by others. In two trials employing MCV chemotherapy and cisplatin-radiotherapy, similar rates of complete response (66% and 66%), survival with bladder preservation (55% vs 43%) and overall survival (62% vs 52%) are reported.[12,15] An additional problem observed in these organ preservation treatments has been the development of superficial non-invasive cancers during follow-up. These are generally managed with transurethral resection and intravesical treatment.

Other phase II trials of cisplatin-based chemotherapy plus radiotherapy have confirmed similar rates of complete response, bladder preservation, and overall survival.[14-17] A summary of these phase II chemo-radiotherapy trials employing selective bladder preservation are summarized in the Table 1. Although similar in design, the results of these trials cannot be directly compared because of differences in patient populations and response criteria. However, these studies show consistent rates of tumor clearance of 57-75% and 3-5 year overall survival of 47-62%. Because of study design and short follow-up, the long term survival is not known exactly, but it appears similar to survival of patients treated with radical cystectomy.

Recognizing the difference between clinical and surgical staging, it is difficult to compare exactly the survival results from these bladder preservation series with those from surgical series. However, for muscle-invading bladder cancers, survival results are similar to those reported in radical cystectomy series where patient eligibility is based upon clinical stage.[18,19] An important component of the success of these organ preserving studies is close follow-up and the incorporation of salvage cystectomy early if local failure occurs.

The toxicity of combined chemotherapy-radiotherapy is substantial. In the above cited phase II trials, 10-38% of patients enrolled were unable to complete the treatment as planned. Grade 3-4 reversible toxicities were fairly common, but treatment-related deaths were uncommon in these early trials. It is of great concern that in the most recent

Table 1. Chemo-radiotherapy and bladder preservation

Reference	Pts	Drugs	CR	Actuarial	
				Survival with Bladder Preserved	Survival
Tester[11]	42	C	66%	52%	52% (5-yr)
Tester[12]	91	MCV-C	75%	55%	62% (4-yr)
Shipley[13]	126	C/MCV-C	57%	36%	47% (5-yr)
Dunst[14]	139	C/P	80%	40%	47% (5-yr)
Kachnic[15]	106	MCV-C	66%	43%	52% (5-yr)
Cervek[16]	105	MCV	62%	49%	62% (3-yr)
Housset[17]	54	FC	74%	-	59% (3-yr)

M = methotrexate; C = cisplatin; V = vinblastine; F = fluorouracil; P = carboplatin; Pts = patients; CR = complete response

RTOG study 6 of 126 patients enrolled died during treatment, 5 on the MCV chemotherapy arm.[13] These deaths were related to either neutropenic sepsis or surgical complications.

In general, bladder function following this treatment has been acceptable. Rare patients will require cystectomy for treatment complications; 2 of 259 in the three RTOG series [11-13] and 3 of 192 patients in the Erlangen series [14] required cystectomy for complications of treatment.

Phase II clinical trials have established chemo-radiotherapy with selective bladder preservation as an reasonable option for patients with muscle-invading bladder cancer. Implicit in this approach has been the assumption that the quality of life of patients treated with bladder preservation strategies is better than that of patients treated with radical cystectomy. However, very little published data is available to support this contention today. Future organ preservation studies should include monitoring of standard quality of life assessments. As surgical techniques improve, and the use of continent reservoirs becomes more available, the negative effects of radical surgery may well decrease.[20]

We still need to further improve local control rates, decrease the risk of non-invasive recurrences, decrease the risk of distant metastases, and optimize quality of life. Also, the development of biologic measures with predictive value for chemo-radiotherapy responsiveness might be extremely useful in the selection of patients for bladder preservation programs. Effective chemotherapy-radiotherapy regimens are needed that will be better tolerated by an elderly population of patients who often have other medical problems. Other active chemotherapy agents that have also demonstrated evidence of radiation enhancement in early preclinical studies include paclitaxel, ifosfamide, gallium nitrate, and gemcitabine. The role of these agents and their effects when combined with radiotherapy remain to be studied.

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