Combined Modalities - bladder sparing

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2007: Free online article: Benchmarks achieved in the delivery of radiation therapy for muscle-invasive bladder cancer John J. Coen M.D.a, Anthony L. Zietman M.D.a, Donald S. Kaufman M.D.b and William U. Shipley M.D.a,

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Nov. 2004 Europe:

Current Status of Radiation Therapy and Combined-Modality Treatment for Bladder Cancer. Rodel C. Department of Radiation Therapy, University of Erlangen, Erlangen, Germany.

...Several phase II studies and one phase III study indicate that concomitant radiochemotherapy is superior to RT alone. In modern series of CMT, 5-year survival rates in the range of 50-60% have been published, and about three quarters of the surviving patients maintained their own bladder. Recent data suggest that incorporation of newer chemotherapeutic agents, particularly gemcitabine and taxanes, in CMT protocols is feasible and promising. Clinical criteria helpful in determining patients for bladder preservation include such variables as early tumor stage, unifocal tumor, a visibly and microscopically complete TURBT, and absence of ureteral obstruction. CONCLUSION:. CMT for bladder cancer is a reasonable treatment option for patients who are deemed medically unfit for cystectomy and for those seeking an alternative to radical cystectomy. PMID: 15549188

RTOG 97-06: Initial report of a Phase I-II trial of selective bladder conservation using TURBT, twice-daily accelerated irradiation sensitized with cisplatin, and adjuvant MCV combination chemotherapy.

After aggressive TURBT, twice-daily accelerated RT initiated in concomitant-boost format is well tolerated and results in a rate of complete response (74%) similar to that in previous bladder-sparing trials. The projected 2-year values for locoregional control, bladder-intact survival, and overall survival were also consistent with previously reported trials of bladder-sparing treatment. With only 45% of patients completing three cycles of MCV, this form of adjuvant chemotherapy appears to be poorly tolerated by most patients.

PMID-Medline abstract:14529770 Hagan MP, Winter KA, Kaufman DS, Wajsman Z, Zietman AL, Heney NM, Toonkel LM, Jones CU, Roberts JD, Shipley WU.

Int J Radiat Oncol Biol Phys. 2003 Nov 1;57(3):665-72. Medical College of Virginia Hospitals, Richmond, VA, USA

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For the story of one man's success with this approach, see Mike Mann's page

Further reading, below

The combined modalties/bladder sparing protocols, which use trans-urethral resection followed by chemotherapy with concurrent radiation, has long been in trials around the world for aggressive early stage tumors as well as more invasive later stage lesions; Cisplatin, carboplatinum, 5FU, and methotextrate- and more recently paclitaxel and gemcitabine (Taxol and Gemzar)- have been used singly or combined to enhance the effect of radiation, and some sources claim that

these protocols are showing results similar to those of radical cystectomy. The combined modalities of TUR, radiation and chemotherapy may be considered as a potential option for a select group of patients with no distant metastases, T1-T4 who are not candidates for, or refuse surgery.

The results of conservative surgery (TUR and in some cases partial cysectomy), radiation therapy and systemic chemotherapy as monotherapy, as well as strategies of combined modality treatment were reviewed by experts in 1995, and based on this review many areas of consensus were reached which include:

1. The primary goal of any treatment for a patient with muscle-invading bladder cancer is survival; bladder preservation in the interest of quality of life is a secondary objective.

2. Only a small proportion of carefully selected patients may be cured by transurethral surgery alone, or by partial cystectomy alone.

3. Radiation therapy is currently the standard bladder-preserving therapy against which all other bladder-preserving methods must be compared.

4. Systemic chemotherapy as monotherapy is inadequate and cannot be recommended.

5. The addition of cisplatin-containing systemic chemotherapy to radiation therapy or conservative surgery appears to improve local control. Deferring the patient from immediate cystectomy does not appear to compromise survival, nor does the addition of primary systemic chemotherapy appear to significantly increase the morbidity of cystectomy or radiotherapy.1

Experts in bladder preservation emphasize early cystectomy for individuals not achieving an early complete response.

A growing body of evidence is suggesting that one half or more of patients who receive combination bladder-preserving therapy will remain disease-free 3 to 4 years after treatment, and 5 year survival rates of approximatley 50%. have been realized. Treatments consist of initial TUR of as much tumor as possible followed by the ‘combined modalities’ of chemoradiotherapy. Radical cystectomy is reserved for patients who do not achieve a complete response. Expert teams using these protocols feel that within a subset of patients with aggressive tumors, surgery can be postponed or avoided. 2 3 4

There are many doctors and institutions around the world who are studying this approach, and you may be able to get connected to a team/institution offering the combined modality approach; its use should be by experienced multi-modality teams of urologic oncologists which would include an oncologist, urologist, surgeon and radiologist. .

I have heard from bladder cancer warriors that Dr. Shipley’s team from Boston, Mass. does long distance consults, will consider your case with the rest of his team and will sometimes oversee a person’s treatment via long distance in co-operation with a corresponding team of experts (see study summary below, and references 3 6 7).

Dr. Wm. Shipley (Head of Genitourinary Oncology Unit, Department Radiation Oncology, Massachusetts General Hospital, Professor of Radiation Oncology, Harvard Medical School, Chair Genitourinary Oncology Section, Radiation Therapy Oncology Group [RTOG]) has a web page here; http://www.mgh.harvard.edu/depts/RadOnc/bio_wus.htm where it states that ‘the Department of Radiation Oncology at the Massachusetts General Hospital is internationally recognized for its experience and pioneering approaches in this field and is the only hospital in the USA to routinely offer patients the chance to keep their own natural bladders.’

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In a study from ’97, the expert team from Mass. General Hospital reported their good results using multimodality treatment, particularly in patients with clinical T2 and T3a disease who did not have a ureter obstructed by tumor. The authors state that individually, the local monotherapies of radiation, TURBT, or multidrug chemotherapy each achieve a local control rate of the primary tumor of from 20 to 40%. When these are combined, clinical complete response rates of from 65 to 80% can be achieved. 4

A complete response predicts long term survival; and patients with deeply invasive lesions (T3b to T4) usually are not considered as good candidates for bladder preservation. However, under certain circumstance those with T3b and T4 tumors are accepted, though distant metastasis would normally preclude candidacy. To optimize patients selection, new prognostic factors are necessary. Many biologic variables based on expression of tumor-related proteins are under study. Additional research is required to determine whether these approaches improve survival and to identify better markers of treatment outcome.5

Researchers in France recently concluded that the regimen of cisplatin+5FU (5fluorouracil) combined with radiotherapy was tolerable with low toxicity and good results. A complete response was achieved in 30 out of the 42 evaluable patients (65.2%), after a median follow up of 38 months. Projected 3-year locoregional control was 49% for the 46 patients. Projected overall 3-year survival was 53%. The protocol (see 'trials'below) is presented as a potentially curative and conservative treatment for patients with localized muscle-invasive bladder cancer. 6

A recently completed Phase III clinica trial unfortunately concluded that the use of two 28 day cycles of methotrexate, cisplatin and vinblastine, followed by radiotherapy and concurrent cisplatin was of no added benefit while also having a higher toxicity which made treatment much less tolerable.7

In 1996 a study conducted on 42 women with muscle invasive bladder cancer who had undergone treatment of TUR, cisplatin and radiation, showed that after a median follow up of 56 months actuarial overall survival for all 42 women was 58% at 5 years. Actuarial overall survival with an intact bladder was 47% at 5 years. The functional quality of the conserved organ, the rectum, and the vagina, as reported by the women in the study, was excellent.8

Trials (this is not a complete listing of combined modality trials; please consult with your physician for more information)

Phase I/II Trial of Transurethral Surgery and Cisplatin;: protocol # RTOG 9706

Chemotherapy plus Twice-a-Day Irradiation Followed Either by Selective

Bladder Preservation or Radical Cystectomy and Adjuvant Chemotherapy in

Operable Patients with Muscle-Invading Bladder Cancer.

Patients must have histologic evidence of a muscle invading bladder primary

cancer without evidence of lymph node involvement. Bladder function must be

adequate following an evaluation by a urologist, and must have undergone a

transurethral resection of the bladder tumor. Patients must also have not

received prior irradiation or chemotherapy, and must not be receiving drugs

that have potential nephrotoxicity or ototoxicity.

There is currently a phase I/II trial in progress led by Dr. Shipley, which combines the chemos 5FU, cisplatin with concurrent radiation; Protocol # RTOG 95-06

In Europe and Israel there is a phase II trial also using 5FU, cisplatin and radiation; Protocol # EORTC-22971 Michel Bolla, Chair, EORTC Radiotherapy Cooperative Group

http://cancertrials.nci.nih.gov/

Excellent online article: Bladder Preservation Protocols in the Treatment

of Muscle-Invasive Bladder Cancer; Javier F. Torres-Roca, MD" Bladder-preserving therapy is a safe and effective alternative to cystectomy for carefully selected patients with bladder cancer." 2004 Department of Interdisciplinary Oncology and the Radiation Oncology, Genitourinary Oncology, and Experimental Therapeutics Programs at the H. Lee Moffitt Cancer Center & Research Institute, Tampa Florida.

Excellent review - online article: Non-invasive Management of Invasive Bladder Cancer: Lectures by Professor William U. Shipley; Japanese Journal of Clinical Oncology 33:592-594 (2003) http://jjco.oupjournals.org/cgi/content/full/33/11/592

Read this excellent abstract of the latest review article: Overview of bladder cancer trials in the Radiation Therapy Oncology Group Shipley WU, Kaufman DS, Tester WJ, Pilepich MV, Sandler HM; Radiation Therapy Oncology Group.Genitourinary Oncology Committee, Radiation Therapy Oncology Group, American College of Radiology, Philadelphia, Pennsylvania, USA. Cancer. 2003 Apr 15;97(8 Suppl):2115-9

For an outline of the arguments Against Bladder Sparing click here.

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6. Treatment of infiltrating cancer of the bladder with cisplatin, fluorouracil, and concurrent radiotherapy: results of a pilot study Chauvet B; Felix-Faure C; Davin JL; Berger C; Vincent P; Reboul F Clinique Sainte-Catherine, Avignon, France.

Cancer Radiother 1998 Apr;2 Suppl 1:77s-81s PMID: 9749084 UI: 98420908

7. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. Shipley WU; Winter KA; Kaufman DS; Lee WR; Heney NM; Tester WR; Donnelly BJ; Venner PM; Perez CA; Murray KJ; Doggett RS; True LD Department of Radiation Oncology, Massachusetts General Hospital, Boston 02114, USA. J Clin Oncol 1998 Nov;16(11):3576-83 PMID: 9817278 UI: 99032190

8. Combined Modality Treatment with Selective Bladder Conservation for Invasive Bladder Cancer: Long-Term Tolerance in the Female Patient

Kachnic LA; Shipley WU; Griffin PP; Zietman AL; Kaufman DS; Althausen AF; Heney NM

Genitourinary Oncology Unit, Departments of Radiation Oncology, Urology, and Medical Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Cancer J Sci Am 1996 Mar;2(2):79 v PMID: 9166504 UI: No Cit. ID assigned

Against Bladder Sparing

After reviewing the literature regarding the relative success of bladder preservation therapy compared with total cystectomy, expert urologist James E. Montie, from the University of Michigan, Ann Arbor, Michigan, reported in the August 1999 issue of the Journal of Urology that current strategies are substantially inferior to cystectomy for elimination of the existing cancer and prevention of pelvic recurrence (soft tissue after cystectomy or in the bladder after bladder preservation).1

The best bladder preservation protocols eliminate cancer from the bladder at first evaluation in 10 to 20% and 50 to 80% of patients with T3b and T2 cancers, respectively, while later recurrences in the bladder are seen in 40 to 60%. Cystectomy provides a local failure rate of 10 to 25% for T2 and T3b disease, respectively.

While Montie agrees that clinical strategies for bladder preservation are necessary, he concludes that the above concerns argue in favor of bladder removal, and adds that bladder reconstruction with a neobladder after cystectomy minimizes deterioration of quality of life which is the motivating rationale for bladder preservation.

Montie argues that a remarkably consistent figure of approximately 50 to 60% of complete responders get new tumors in the bladder. He also states that since those who have recurrences after attempts at bladder preservation fails have already demonstrated a propensity for life threatening bladder cancer, that it would be naive to hope that new cancers in this same bladder are likely to be indolent. It is these invasive recurrences that influence overall survival after bladder preservation strategies, and give results that are less desirable than those obtained by immediate cystectomy.

Most importantly, long-term results of bacillus Calmette-Guerin (BCG) for carcinoma in situ are disturbing with 30 to 40% failure in the bladder, 25% in the upper tracts and 25% in the prostate.2,3,4 The risk for extravesical recurrences is much more common than previously appreciated. It is conceivable that earlier cystectomy has the opportunity to alter the natural history of carcinoma in situ by intervening before diffuse mucosal spread occurs. Noninvasive recurrences are a red flag waved high to indicate a remaining malignant bladder.

Montie's article states "It is clear that cystectomy provides the best local control in the pelvis. For organ confined cancers the pelvic recurrence rate is 5 to 15%. For clinical T3b cancers (palpable mass) pelvic recurrences are higher than commonly appreciated, approximately 25%, and additional strategies to improve this figure are needed."

Montie points out the necessity of further research in the area of bladder preservation, and makes a very interesting point by stating; Future successes may rest with molecular fingerprinting of a cancer to select a patient who is exquisitely sensitive to either radiation therapy or chemotherapy. Early data suggest that Rb or p53 status, or the presence of a mediator of drug resistance (metallothionein) may influence tumor susceptibility to chemotherapy or radiation therapy. Favorable patients could then be treated with a higher expectation of success.

In a commentary following Montie's article in the Journal of Urology,1 esteemed expert Harry W. Herr, Urology Service, Department of Surgery Memorial Sloan-Kettering Cancer Center New York, New York remarks:

Bladder preservation raises 3 issues of concern for patients with invasive bladder cancer. 1) Is preserving a normal bladder a realistic long-term goal? 2) Can an initial attempt to spare the bladder fail and result in life threatening tumor progression that may be prevented by immediate cystectomy? 3) Can new tumors develop within the retained bladder that may spread and ultimately cause cancer death? The answers to each of these 3 related questions is yes.

There is no doubt that not all invasive bladder cancers need immediate cystectomy. In about half of the patients the bladder can be preserved, often for up to 10 years, with maximum transurethral resection and aggressive chemotherapy regimens combined with either radiation or bladder sparing surgery. Such patients are selected because they have low volume invasive tumors that are confined to the bladder and respond completely to combined modality treatment. It is equally true that probably 10 to 20% of cases in which a complete response is not achieved will not be salvaged by cystectomy. These unfortunate patients, either because of local tumor progression or new invasive tumors, will die of bladder cancer that might have been prevented by immediate cystectomy.

Nonetheless, attempts at bladder preservation should not be abandoned altogether. As Montie suggests, risk directed treatment strategies based on clinical and molecular fingerprinting of bladder cancer may improve the likelihood of successful bladder preservation and survival. In the meantime, patients who elect to preserve the bladder must accept frequent followup evaluations and multiple invasive procedures to detect local tumor recurrence, the possibility that cystectomy may eventually become necessary and the uncertainty that a tumor relapse may lead to death.5

back to invasive bladder cancer

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Urology Service, Department of Surgery Memorial Sloan-Kettering Cancer Center New York, New York