BLADDER CANCER: EVOLVING PERSPECTIVES IN ORGAN PRESERVATION AND PELVIC TUMOR CONTROL

OTTAWA REGIONAL CANCER CENTRE

CONTINENT DIVERSION
INCREASING # - NODES

SYSTEMIC MICROMETASTASES
NEOADJ / ADJUVANT CHEMO

1990

BLADDER CANCER

ORGAN PRESERVATION

ORGAN PRESERVATION

- PATIENT SELECTION
  - PATHOLOGY
  - TURBT
  - URETERIC PATENCY
  - BLADDER FUNCTION
- STRATEGY
  - BRACHYTHERAPY
  - HIGH LET
  - ALTERED FRACTIONATION
  - CHEMORADIOTHERAPY

CHEMORADIOTHERAPY

- SINGLE AGENT
  - 5FU
  - CISPLATIN
- COMBINATION
  - CMV-RT MGH
    RTOG
  - 5FU-PLATIN PARIS

BLADDER PRESERVATION

RT ALONE	RT-CMV	RT-PLATIN
30-35% LONDON EDINBURGH AUSTRIA	55% HARVARD RTOG	50% COPPIN/NCI SAUER

ROUTE

INTRAVENOUS

INTRAARTERIAL

PEAK EXPOSURE
AUC
TUMOR CONCENTRATION IV vs IA

INTRAARTERIAL CISPLATIN – CONCURRENT RADIATION
OTTAWA REGIONAL CANCER CENTRE

OBJECTIVES:

INCREASED RATE OF COMFORTABLE BLADDER PRESERVATION

NON COMPROMISE OF SURVIVAL VIS A VIS CYSTECTOMY

ELIGIBILITY CRITERIA

- STATE T2 – T4B
- NON SQUAMOUS HISTOLOGY
- NO HEMATOGENOUS METASTASES (CT ABD/CHEST X-RAY/BONE SCAN)
- NO ENLARGED NODES ABOVE ILIAC BIFURCATION
- NO CONTRAINDICATIONS TO FEMORAL ACCESS
- ADEQUATE RENAL/MARROW FUNCTION

TREATMENT PROTOCOL

- DAY 1 #1 I.A. PLATIN
- DAY 10 RT COMMENCES
  60 GY/30/6WEEKS
- DAY 21 #2 I.A. PLATIN
- DAY 42 #3 I.A. PLATIN
- 6-10 WEEKS

RESPONSE EVALUATION: CYSTOSCOPY
BIOPSY
CYTOLOGY

CHEMOTHERAPY

- INPATIENT – OUTPATIENT
- SALINE HYDRATION
- MANNITOL DIURESIS
- DECADRON – ZOFRAN EMESIS PROPHYLAXIS
- BILATERAL TRANSFEMORAL INTERNAL
- ILIAC ARTERY CATHETER PLACEMENT
- CISPLATIN 90-120 MG/M^2 HALVED AND INFUSED INTO EACH ARTERY OVER 1 HOUR
- PRESSURE AT CATHETER SITES x 4 HOURS

RADIOTHERAPY

SIMULATION: SUPINE
PLANNING CYSTO-RECTOGRAM

- VOLUME: PELVIC NODES/BLADDER 40 Gy/20
- BEAM ARRANGEMENT:
  4 FIELD BOX
  L5-S1
  OBTURATOR FORAMINA –ISCHIAL TUBEROSITIES
  S2/S3
  ANT 3CM TO BLADDER. **BOOST**: 4 FIELD, WHOLE BLADDER 20 Gy/10

PATIENT CHARACTERISTICS

- 1986 – 2003
- 200 PATIENTS
- 165 MALES/35 FEMALES
- AGE RANGE 30 – 88 YEARS
- MEDIAN: 69 YEARS

PATHOLOGY

TCC 175		GRADE 1	4
ADENOCA	9	2	46
MIXED	15	3	142
NOS	1	NOS	8

STAGE

- TA 6
- T1 15
- T2 46
- T3A 47
- T3B 54
- T4A 15
- T4B 15
- TX 2

NODE + 14

\- 186

UPPER RENAL TRACTS

- NORMAL 137
- UNIL HYDRO 54
- BILAT HYDRO 9 = 32%

SURGICAL DEBULKING

TURBT YES 172 = 86%
NO 28

GROSS RESIDUAL YES 157 = 78.5%
NO 25
UNCERTAIN 18

TREATMENT DELIVERY/COMPLIANCE

- 196/200 COMPLETED RADIOTHERAPY
- 186/200 COMPLETED CHEMO AS PLANNED
- 7/200 I.A. → I.V. CHEMO

FOLLOW UP

- 2 – 180 MONTHS MEDIAN 30

RESULTS

COMPLETE RESPONSE

BLADDER STATUS

SURVIVAL

PATTERNS OF FAILURE

TOXICITY

LOCAL RESPONSE

- 185 EVALUABLE/15 NON EVALUABLE

TABLE 1
COMPLETE LOCAL RESPONSE

STAGE	ALL PATIENTS	EVALUABLE PATIENTS
Ta=6	5/6	5/6
T1=15	13/15=86.6%	13/15=86.6%
T2=46	41/46=89%	41/43=95%
T3a=47	42/47=89%	42/43=98%
T3b=54	41/54=76%	41/47=87%
T4a=15	13/15=86.7%	13/14=93%
T4b=15	9/15=60%	9/12=75%
Tx=2	2/2	2/2
TOTAL	166/200=83%	166/185=90%
EXCLUDING T4b	157/185=84%	157/173=91%

Table 3
BLADDER PRESERVATION (TUMOUR FREE ± BCG)

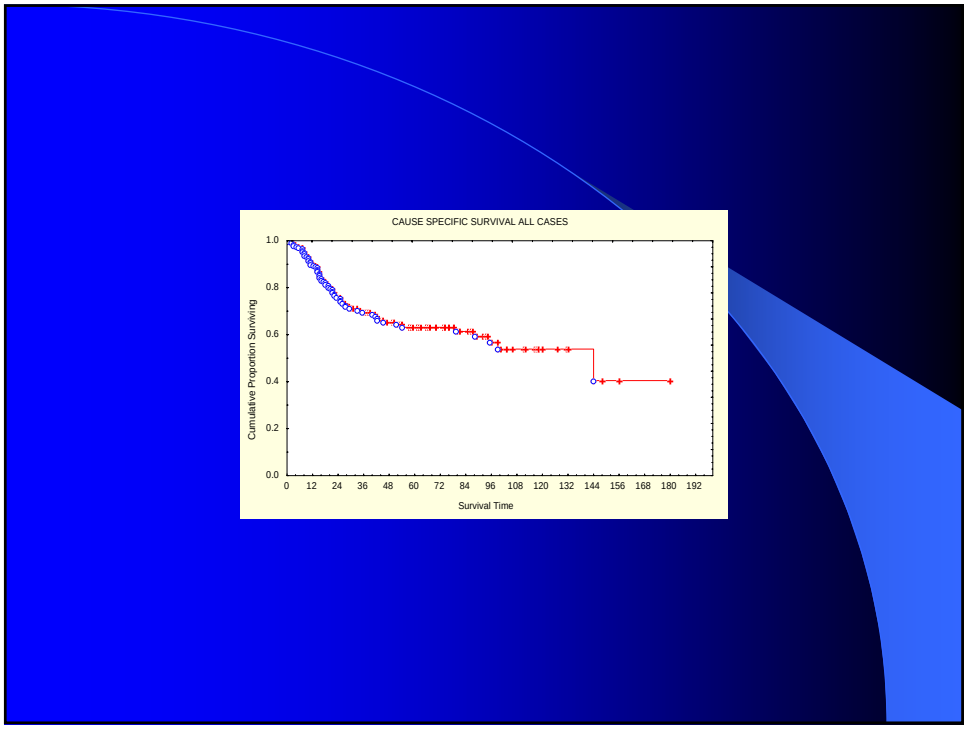
STAGE	ALL PATIENTS	UNKNOWN	EVALUABLE
Ta	5/6	0	5/6
T1	11/15=73%	0	11/15=73%
T2	35/46=76%	5	35/41=85.4%
T3a	31/47=66%	4	31/43=72%
T3b	33/54=61%	7	33/47=70%
T4a	12/15=80%	2	12/13=92.3%
T4b	6/15=40%	4	6/11=54.5%
Tx	1/2	0	½
TOTAL	**134/200=67%**	**22**	**134/178=75%**
Excluding T4b As per tester	**128/185=69.2%**		**128/167=76.6%**

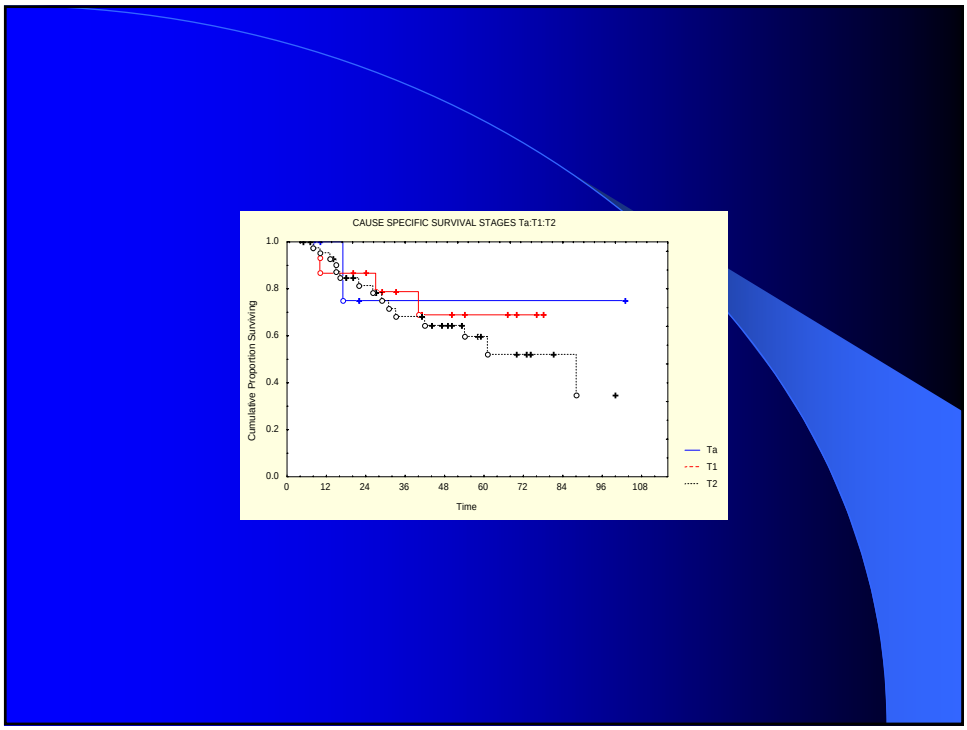
TABLE 2

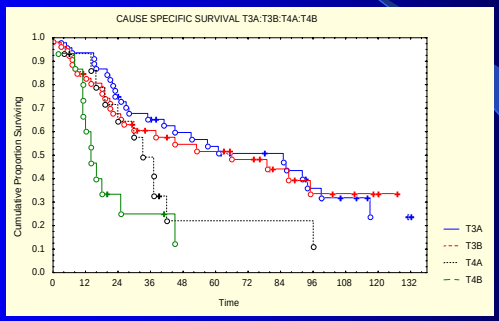
BLADDER STATUS	NUMBER
Non evaluable	22
Tumour free	126
Tumour free with BCG	8
Salvage cyst. for invasive	22
Salvage cyst. superficial	8
Unsalvaged invasive	15
Unsalvaged superficial	0

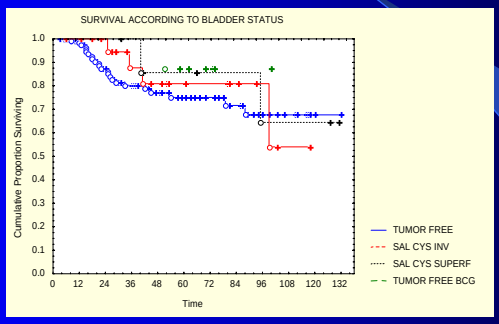
TABLE 5
CURRENT STATUS
NED CANCER

STAGE	UNK.	ANED	DNED	ALIVE	DEAD	A/D LOC ONLY	A/D DIST ONLY	A/D LOC + DIST
Ta=6	0	5	0	0	1	0/1	0	0/0
T1=15	1	11	0		3		0/2	0/1
T2=46	4	26	5	2	9	1/0	1/9	0/0
T3a=47	2	19	13	1	12	½	0/6	0/4
T3b=54	6	25	11	1	11	0/1	0/6	¼
T4a=15	1	3	6	0	5	0/0	0/3	0/2
T4b=15	1	2	0	1	11	1/3	0/5	0/3
Tx=2		2	0	0	0	0	0	0
TOTAL	15	93	35	5	52	3/7	1/31	1/14


CAUSE SPECIFIC SURVIVAL ALL CASES
Cumulative Proportion Surviving
1.0
0.8
0.6
0.4
0.2
0.0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192
Survival Time


CAUSE SPECIFIC SURVIVAL STAGES Ta:T1:T2
Cumulative Proportion Surviving
1.0
0.8
0.6
0.4
0.2
0.0
0 12 24 36 48 60 72 84 96 108
Time
Ta
T1
T2


CAUSE SPECIFIC SURVIVAL T3A:T3B:T4A:T4B
Cumulative Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
12
24
36
48
60
72
84
96
108
120
132
Time
T3A
T3B
T4A
T4B


SURVIVAL ACCORDING TO BLADDER STATUS
Cumulative Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
12
24
36
48
60
72
84
96
108
120
132
Time
TUMOR FREE
SAL CYS INV
SAL CYS SUPERF
TUMOR FREE BCG

ACUTE TOXICITY

2 DEATHS

1 VASCULAR REPAIR FEMORAL PUNCTURE

1 PLASTIC REPAIR GLUTEAL SOFT TISSUE NECROSIS

1 MALLORY-WEISS/M.I.

1 PULMONARY EMBOLUS

35% PATIENTS MEDS FOR G.I. IRRITATION

30% PATIENTS MEDS FOR BLADDER IRRITATION

CHRONIC TOXICITY

1 HEMORRAGHIC CYSTITIS

1 VESICOENTERIC FISTULA

2 RTOG GRADE 1 BLADDER

2 RTOG GRADE 2 BOWEL

1 PELVIC GIRDLE OSTEITIS

SACRAL NEUROPATHY

NEUROPATHY

NONE	64%	129
MILD	20.5%	41
MODERATE	11.5%	23
SEVERE	2%	4

NERVE CONDUCTION/FERRET GANGLIA/DOSE

SUMMARY

WELL TOLERATED OUTPATIENT TREATMENT

COMFORTABLE/FUNCTIONAL BLADDER PRESERVATION

SAFE WITHOUT WORSENNING SURVIVAL

CORROBORATES HYPOTHESIS OF 15-25% GAIN IN RADIOSENSITIZATION **I.A. VS IV** PLATIN

CONTINENT DIVERSION **SYSTEMIC MICROMETASTASES**

2005

BLADDER CANCER

ORGAN PRESERVATION

LONG TERM ORTHOTOPIC BLADDER FUNCTION BERNE 2002 STUDER

- 83/176 MEN
- DAYTIME INCONTINENCE 2/5/10 YRS
  5 / 5 / 10%
- NIGHT INCONTINENCE 2/5/10 YRS
  20% / 30% / 45%

QUALITY OF LIFE STANFORD-USC 1999 HART-SKINNER

- ILEAL CONDUIT
- KOCK TO SKIN
- KOCK TO URETHRA

- EMOTIONAL/BODY IMAGE/SOCIAL LIMITATION/DAILY ACTIVITIES
- ***** NO DIFFERENCE*****

PELVIC CONTROL MSKCC

- J. UROLOGY 2003 169:177-181
- 214 CYST-ORTHOTOPIC BLADDER
- ****INITIAL RELAPSE PATTERN****
- LOCAL ONLY : LOCAL+DIST 11%:8% OF ALL 214 PATIENTS = 19%
- LOCAL ONLY : LOCAL+DIST 22%:13% OF 103 **PT3A/T3B/T4A** PATIENTS
- = 35% INITIAL PELVIC FAIL.

SWOG-INTERGROUP NEOADJUVANT MVAC TRIAL HERR JCO JULY/04

- 268 CYSTECTOMY PATIENTS
- 191 ILEAL CONDUIT/ 77 CONTINENT DIVERSION
- BIOPSY CONFIRMED LOC.RECURRENCE
- CRUDE NON ACTUARIAL RATE=

pT3-T4 27/84 **** 32%****

UNAFFECTED BY MVAC RX OR NOT

Table 4. Multivariate Logistic Regression Model for Probability of a Local Recurrence

Variable	OR*	95% CI	P*†
Treatment RC *v* MVAC + RC	0.5	0.2 to 1.3	.16
pT stage 3-4 *v* 0-2	3.8	1.2 to 12.2	.02
Node status positive *v* negative	1.7	0.5 to 5.2	.37
Margins positive *v* negative	11.2	3.3 to 37.8	.0001
Nodes removed < 10 *v* ≥ 10	5.1	1.8 to 14.7	.002

Abbreviations: OR, odd ratio; RC, radical cystectomy; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin.
*Each OR and *P* value is adjusted for all other covariates in the model.
†*P* values are two sided and based on the Wald χ^2 test.

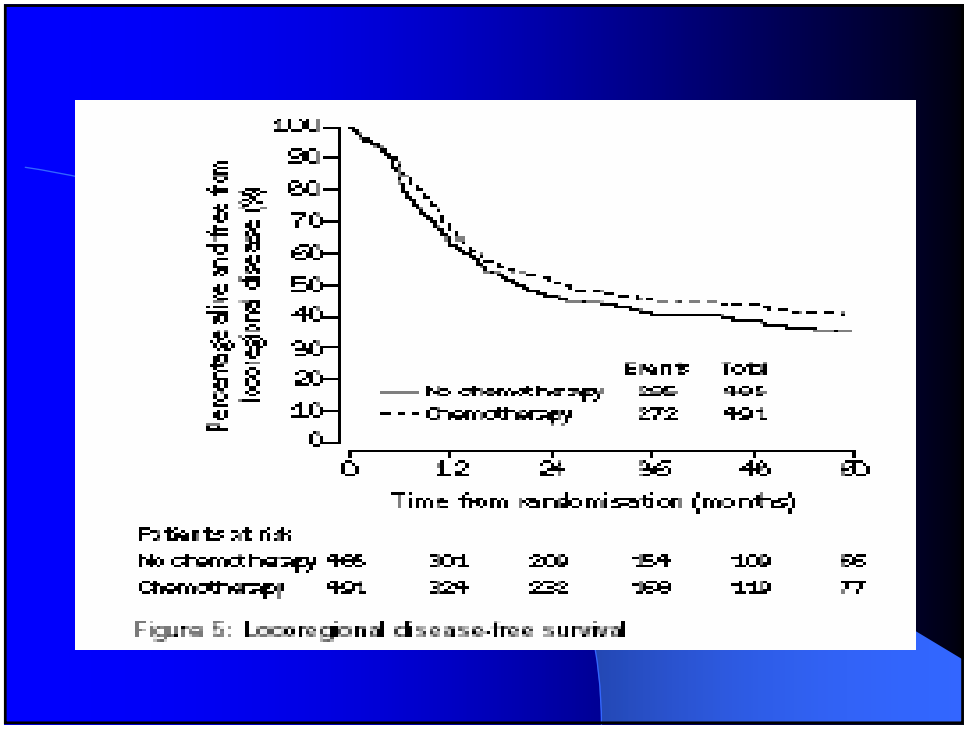


Figure 5: Locoregional disease-free survival

CONTINENT DIVERSION

SYSTEMIC MICROMETASTASES

2005

BLADDER CANCER

ORGAN PRESERVATION

SYSTEMIC MICROMETASTASES

- ADJUVANT
- TO DATE INCREASED DFS WITH NO INCREASE IN OVERALL SURV.
- ?SUBGROUP/ P53/PLOIDY CURRENT TRIALS
- NEOADJUVANT
- METAANALYSES SHOW PAN-T STAGE SURVIVAL GAIN OF
- ***5%***

ISSUES

- EXTRA VESICAL PELVIC CONTROL FOR T3/T4 IS HIGHER WITH CHEMO-RT ORGAN PRESERVATION STRATEGY THAN CYSTECTOMY+/- CHEMO !!!
- IA PLATIN-RT DOES NOT INCREASE SURVIVAL …SYSTEMIC METS
- NEOADJUVANT CHEMO MODEST 5% INCREASE IN SURVIVAL
- INTEGRATING NEOADJUVANT CHEMO AND CHEMO-RT UNSAFE WITH STANDARD RADIOTHERAPY TECHNIQUES

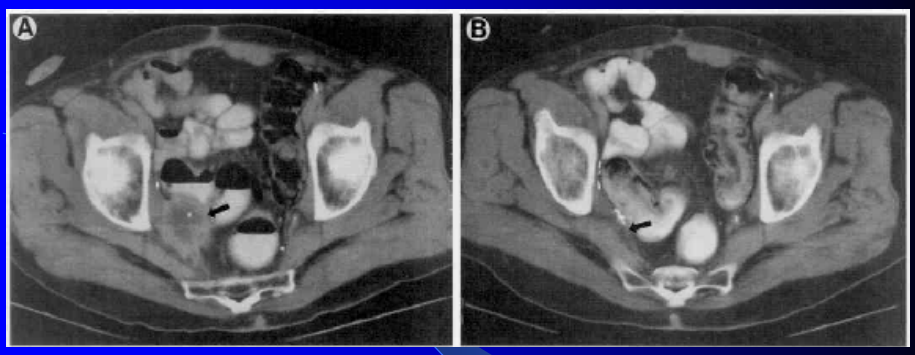


Figure 1. Routine followup CT of 46-year-old asymptomatic patient 4 months after radical cystoprostatectomy. A, 4.5 x 3.0 cm. right pararectal mass (arrow) is visible. B, 4 months after treatment with 3 courses of vinblastine, ifosfamide and gallium, there was stable resolution of disease (arrow).
From: WESTNEY: J Urol, Volume 159(3).March 1998.792-795

OTTAWA 05

- USE DOSE SCULPTING AND IMAGE GUIDANCE OF TOMORADIOTHERAPY
- INTEGRATE NEOADJ.CHEMO WITH IA PLATIN-RT
- INTEGRATE NEOADJ.CHEMO-PREOP RT WITH CYSTECTOMY
- PHASE 1 STARTED DOSIM/TOXICITY(GEM-CIS)

CONCLUSIONS

- BLADDER CONSERVATION IS SAFELY ACHIEVABLE FOR THOSE WHO WISH IT
- FAILURE TO REDUCE THE UNDERDOCUMENTED PELVIC RECURRENCE RATE POSTCYSTECTOMY IN T3/4 DISEASE NEEDS TO BE ADDRESSED
- THE (TO DATE) MODEST SURVIVAL GAIN WITH CHEMO AWAITS BETTER PELVIC CONTROL AND BETTER AGENTS