

Neoadjuvant (NACT) and Adjuvant Chemotherapy (ACT) for Muscle-Invasive Bladder Cancer (MIBC):

A Population-Based Outcomes Study in Ontario Canada

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Disclosures

None



What is KNOWN about NACT/ACT for MIBC?

- RCTs and 2 meta-analyses suggest modest (~5%) improvement in OS with NACT
 - Treatment guidelines recommend use of NACT in MIBC
- RCTs for ACT are limited with conflicting results
 - Cochrane meta-analysis shows a 9% improvement in OS. However quality of evidence is poor.
 - Current guidelines do not endorse ACT given the limited evidence

ABC Meta-Analysis Eur Urol 2005
Sternberg Urology 2007
Winquist J Urol 2004
Segal Can J Urol 2002



What is NOT KNOWN about NACT/ACT for MIBC?

- Utilization of NACT/ACT in general population
- Factors associated with utilization and how to improve utilization in routine practice
- **Does ACT improve survival in this disease?**
- What are the outcomes and toxicities of NACT/ACT in the general population?



Population-Based Outcome Studies

- RCTs provide excellent internal validity but their external validity is uncertain.
- Large electronic databases allow exploration of uptake, toxicity, and outcomes in the “real world”
 - ➔ are physicians following guidelines?
 - ➔ are benefits/toxicities as expected based on results of RCTs?
- These studies can also answer questions for which RCT data is not available/conclusive



Methodologic Principles

- Including an entire population minimizes referral bias of traditional institution-based studies.
- Very large sample size provides statistical power to detect even small, but potentially meaningful differences in toxicity and outcome.
- Availability of detailed demographic, disease, and treatment information enables adjusted analyses using instrumental variable and propensity score techniques



Study Design

Objective: To evaluate utilization of NACT/ACT for MIBC and to explore the survival benefit of ACT at the population-level.

Methods:

- Population-based, retrospective cohort study to describe management and outcome of all cases of resected MIBC in the Canadian province of Ontario 1994-2008.
- Cases identified using the Ontario Cancer Registry (OCR).



Methods (2)

- Electronic records of treatment were linked to the OCR to describe use of surgery, RT and chemotherapy.
- The OCR does not have detailed stage information. Accordingly, surgical pathology reports were obtained to assign pathologic T and N stage.
- For the NACT/ACT analyses we included only those cases with muscle-invasive TCC.
- Survival analyses performed using Cox model and propensity score techniques.



Results: Study Cohort

- Among 4876 cystectomy cases pathology reports have thus far been obtained for 3429 (70%)

➔ 2738 cases with muscle-invasive TCC

- Characteristics of 2738 MIBC cases

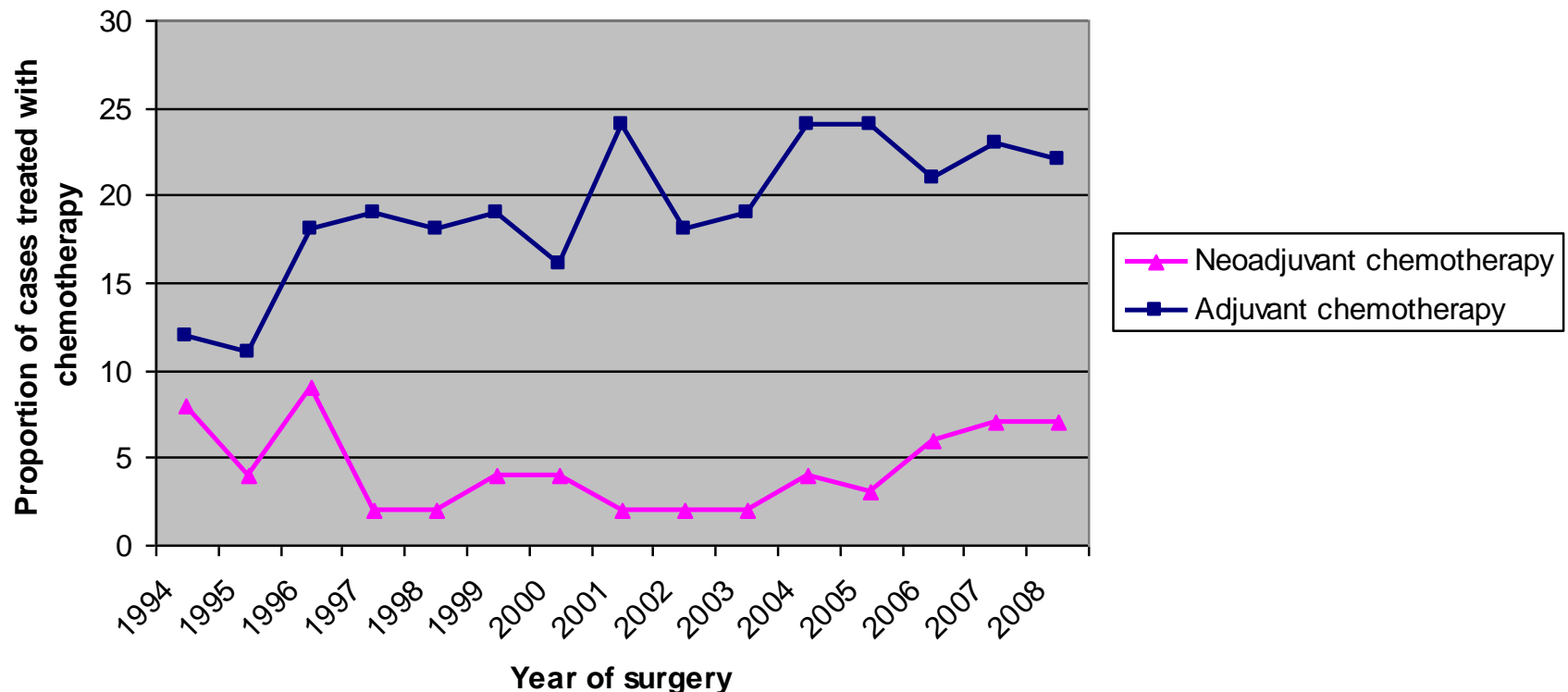
Age, years	
20-49	95 (3%)
50-59	335 (12%)
60-69	681 (25%)
70-79	1095 (40%)
80+	532 (19%)
Sex	
Male	2061 (75%)
Female	677 (25%)
T stage	
<T3	807 (29%)
T3-T4	1931 (71%)
N stage	
N negative	1195 (44%)
N positive	702 (26%)
NX	841 (31%)



Results: NACT/ACT Utilization

- Utilization of NACT was fairly stable over time (4%)
- Utilization of ACT increased over time

➡ 16% (94-98), 19% (99-03), 23% (04-08), $p=0.001$



Results: Patterns of Care

- Treatment regimens included cisplatin or carboplatin in 83% and 13% of cases respectively.
- Patient factors associated with greater use of NACT/ACT:
 - ➡ younger age, less co-morbidity, higher SES, surgery at comprehensive cancer center
- Pathologic factors strongly associated with greater use of ACT:
 - ➡ T3/T4 tumors (OR 2.1)
 - ➡ node positive disease (OR 7.2)
 - ➡ presence of LVI (OR 1.7)



Results: Outcomes

- Among all MIBC cases
 - ➔ 5 yr OS 30% (95%CI 28-31%)
 - ➔ 5 yr CSS 34% (95%CI 32-36%)
- Patients treated with ACT had much worse disease characteristics compared to cases without ACT
 - 83% vs 68% T3/T4 tumor
 - 61% vs 17% node positive disease
- Despite having worse prognosis ACT cases had outcomes comparable to cases without ACT
 - 5 yr OS 30% vs 30%



Results: Survival Analyses

	Overall Survival			Cancer Specific Survival		
	5 year OS	Multivariate analysis		5 year CSS	Multivariate analysis	
		HR (95%CI)	P value		HR (95%CI)	P value
Age, years			<0.001			0.012
20-49 (n=88)	42%	0.6 (0.5-0.8)		45%	0.8 (0.5-1.1)	
50-59 (n=305)	39%	0.7 (0.6-0.8)		37%	0.9 (0.7-1.1)	
60-69 (n=646)	35%	0.7 (0.6-0.8)		38%	0.9 (0.7-1.0)	
70-79 (n=1051)	28%	0.9 (0.8-1.0)		31%	1.1 (0.9-1.2)	
80+ (n=524)	21%	Ref		30%	Ref	
Charlson co-morbidity score			<0.001			0.023
0 (n=1799)	32%	0.7 (0.6-0.8)		35%	0.7 (0.6-0.9)	
1-2 (n=676)	26%	0.8 (0.7-1.0)		33%	0.8 (0.6-1.0)	
3+ (n=139)	16%	Ref		21%	Ref	
T stage			<0.001			<0.001
<T3 (n=754)	50%	Ref		55%	Ref	
T3-T4 (n=1860)	22%	1.7 (1.6-2.0)		25%	1.9 (1.7-2.2)	
N stage			<0.001			
N negative (n=1132)	42%	Ref		46%	Ref	<0.001
N positive (n=672)	18%	1.9 (1.7-2.1)		18%	2.0 (1.7-2.2)	
NX (n=810)	24%	1.4 (1.3-1.6)		30%	1.4 (1.3-1.6)	
ACT			<0.001			<0.001
Yes (n=514)	30%	0.7 (0.6-0.8)		29%	0.7 (0.6-0.8)	
No (n=2100)	30%	Ref		35%	Ref	

➡ ACT is associated with improved OS (HR 0.70) and improved CSS (HR 0.70).

➡ Results consistent in propensity score analysis

Clinical Implications

Case #1: 54 year old male with minimal co-morbidity
T3 tumor, node positive disease

Predicted 5 yr OS

➡ Surgery alone = 12% (95%CI 8-19%)

➡ Surgery with ACT = 23% (95%CI 17-31%)

Case #2: 76 year old female with moderate co-morbidity
T2 tumor, NX disease, LVI

Predicted 5 yr OS

➡ Surgery alone = 22% (95%CI 16-29%)

➡ Surgery with ACT = 35% (95CI 27-45%)



Study Strengths/Limitations

- Very large sample size and resulting statistical power; study population includes all cases of bladder cancer within Ontario and is therefore unselected.
- ACT results are consistent in standard Cox model and Propensity Score Analysis.
- Detailed information related to drugs, performance status, and stage was not available for all patients. This limits our ability to evaluate the appropriateness of case selection for NACT/ACT.
- Despite adjusted analyses it is possible that other unmeasured confounders may have contributed to the observed survival benefit with ACT.



Conclusions

1. Contrary to treatment guidelines use of NACT is low and use of ACT is increasing.
2. In 2004-2008 only 28% of patients with resected MIBC received any form of peri-operative chemotherapy.
3. Poor risk pathology is associated with greater use of ACT.
4. Survival of NACT and ACT cases is substantially lower in the general population than outcomes reported in clinical trials.
5. ACT is associated with a substantial improvement in OS and CSS in the general population.



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