

Original Research Article

Bladder preserving chemoradiotherapy compared to surgery for variants of urothelial carcinoma and other tumors types involving the bladder: An analysis of the National Cancer Database



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ABSTRACT

Purpose: For muscle-invasive bladder cancer, bladder preserving chemoradiotherapy (BPCRT) has shown to be a viable alternative for patients with urothelial carcinoma (UCa). Traditionally bladder cancer with variant histology UCa or other tumors types involving the bladder have worse outcomes and BPCRT has been contraindicated. However, there is limited high level evidence for this recommendation.

Materials/methods: The National Cancer Database (NCDB) was queried for all patients with Bladder cancer treated from 2004 to 2015 restricted to clinical stage T2–4, N0, M0 who had variants of UCa or other tumors types involving the bladder (e.g. adenocarcinoma and squamous cell carcinoma). Only patients treated with definitive intent with either radical cystectomy or BPCRT after maximal transurethral tumor resection were analyzed. Propensity-score matching was used.

Results: 356 patients had BPCRT and 2093 patients had definitive surgery for muscle-invasive bladder cancer limited to variants of UCa and other tumors types involving the bladder. On multivariable analysis worse prognosis was associated with age >65 years old (HR 1.24, $p = 0.004$) and T4 disease (HR 1.90, $p < 0.001$). In propensity score weighted sample, there was no statistical significant difference in OS for patients with BPCRT as compared to cystectomy ($p = 0.387$) and for neuroendocrine, micropapillary or not otherwise specified histology subgroups there was no significant difference. Patients with adenocarcinoma (HR 1.75) or squamous cell carcinoma (HR 1.49) had worse OS associated with BPCRT compared to surgery.

Conclusion: From 2004 to 2015, BPCRT in muscle-invasive bladder cancer was associated with similar overall survival compared to cystectomy in patients with selected variant histology but with worse OS for adenocarcinoma or squamous cell carcinoma specifically. As our study has inherent limitations, these hypotheses require validation in a prospective setting and/or with a larger sample size.

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1. Introduction

Bladder cancer affects an estimated 81,400 people in the USA annually with an estimated 17,980 deaths per year [1]. The vast majority of cases have conventional urothelial cancer histology

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(UCa). For muscle-invasive bladder cancer (MIBC), the traditional standard of care has been radical cystectomy [2]. However, bladder preserving chemoradiotherapy (BPCRT) has been shown to be a viable alternative for patients with UCa [3–6]. BPCRT avoids the morbidity and mortality of radical surgery and allows preservation of the natural bladder through concurrent chemotherapy and radiation after aggressive transurethral tumor resection in select patients. BPCRT is preferred by some patients for better quality of life and psychological benefits.

Traditionally bladder cancer with variants of UCa or other tumors types involving the bladder have worse outcomes and often present with more advanced disease [7]. A National Cancer Data Base (NCDB) analysis of squamous cell histology showed inferior survival with BPCRT compared to definitive surgery [8]. With limited data on the efficacy of BPCRT, bladder cancer with variant histologies and other tumors types involving the bladder have often been a contraindication to bladder preservation and these patients are often excluded from clinical trials. Notably the National Comprehensive Cancer Network (NCCN) guidelines do recommend upfront BPCRT for patients with small-cell component of histology [9]. Here we utilize the NCDB to directly compare the outcomes of patients with MIBC with variants of UCa or other tumors types involving the bladder treated with radical cystectomy to BPCRT in a real-world practice setting.

2. Material and methods

2.1. Patient cohorts

The NCDB was used to identify study subjects. The NCDB is a national clinical oncology database sourced from hospital registry data collected from over 1,500 Commission on Cancer accredited facilities and captures at least 70% of new cancer cases in the United States [10]. The NCDB was queried for all patients with bladder cancer treated from 2004 to 2015 restricted to American Joint Commission on Cancer clinical stage T2–4, N0, M0 who had variants of UCa or other tumors types involving the bladder. The NCDB does not code for proportion of variant histology. For example, micropapillary carcinoma is only recorded as such and not as a proportion of variant histology and traditional UCa. The BPCRT cohort was restricted to patients who had local therapy including transurethral resection of bladder tumor but not including partial cystectomy followed by definitive radiation (total dose ≥ 40 Gy or ≥ 20 fractions) with concurrent chemotherapy. The definitive surgery cohort was restricted to patients who had at least a complete cystectomy without radiation. The selection of patients is summarized in Supplemental Table 1.

2.2. Statistical analysis

Statistical analyses were conducted using SAS Version 9.4 and SAS macros developed by Biostatistics Shared Resource at Winship Cancer Institute [1]. The significance level was set at $p < 0.05$. Descriptive statistics for each variable were reported. Association between variables of interest and the study cohort were examined using Chi-square for categorical variables and ANOVA for continuous variables. The overall survival is the primary endpoint and defined as the months from the treatment started date to death or the last follow-up (censor). The association with OS was generally modeled by the Cox proportional hazards model and Kaplan-Meier method, and the multivariable models were built by a backward variable selection procedure with an alpha = 0.25 removal criteria. The Subgroup analysis was carried through estimating the interaction effect between the histology group and study cohort.

An inverse probability treatment weighting schema called matching weights used in other publications [2,3] was implemented to balance patient baseline characteristics. A logistic regression model was utilized to estimate the probabilities that a patient would receive Surgery based on their baseline covariates (Histology groups, Facility type, Insurance, Age, T stage, Race, Charlson Score, Sex). The balance of covariates among cohorts was evaluated by the standardized differences (SD), and value of < 0.1 was considered as negligible imbalance. See Supplemental

Table 2 for the distribution of baseline characteristics and SD change before and after the weighting.

3. Results

3.1. Patient and tumor characteristics

Between 2004 and 2015, there were 577,674 cases of bladder cancer in the NCDB queried for this study. Of these patients, 356 and 2093 patients met our criteria for definitive treatment with BPCRT and definitive surgery, respectively. Median follow-up for patients with BPCRT was 78.1 months (IQR: 35.6–101.9 months) and for patients with definitive surgery was 60.8 months (IQR: 34.4–96.3 months). At baseline, there were significant differences between the groups in several patient and tumor characteristics (Table 1). Patients who were treated with BPCRT were older, treated less frequently in Academic/Research Programs, had higher proportion of T4 disease, and had fewer lymph nodes evaluated (Max 13, IQR 0–0), all $p < 0.001$. Less than half of the surgical cohort received chemotherapy (Supplemental Table 3) with the median number of lymph nodes evaluated 13 (IQR 6–22).

3.2. Outcomes

On multivariable analysis, there was a trend towards worse OS with BPCRT compared to surgery (HR 1.15, 95% CI 1.00–1.33, $p = 0.052$). Age, Charlson-Deyo co-morbidities, and higher T-stage were associated with worse overall survival ($p < 0.05$) Table 2. There was no difference in OS associated with race (HR 0.79, 95% CI 0.55–1.13, $p = 0.233$) and a trend towards worse OS associated with treatment in a community or integrated network cancer program (HR 1.12, 95% CI 0.97 – 1.28, $p = 0.058$).

In propensity score weighted sample, there was no statistical significant difference in OS for patients with BPCRT as compared to surgery (HR 1.08, 95% CI 0.90–1.30, $p = 0.387$) (Table 3). However the Kaplan-Meier curves crossed (Fig. 1) violating proportional hazard assumption. For < 12 months of follow-up there was trend toward better OS with BPCRT (HR 0.80, 95% CI 0.62–1.02, $p = 0.077$), but there was worse OS with BPCRT at > 12 month follow-up (HR 1.51, 95% CI 1.18–2.02, $p = 0.0017$). By subgroup there was no OS difference for neuroendocrine, micropapillary, or not otherwise specified variants of UCa (Table 3). There was worse associated overall survival with BPCRT as compared to surgery for adenocarcinoma (HR 1.75, 95% CI 1.36–2.25, $p < 0.001$) and squamous cell carcinoma (HR 1.49, 95% CI 1.25–1.77, $p < 0.001$).

The Kaplan-Meier curves for the propensity-score-weighted cohorts are displayed in Fig. 1. For the BPCRT the median OS was 19.0 months with 5-year OS 26.4%. The surgery cohort had median OS of 19.1 months with 5-year OS 33.2% (Fig. 1). For squamous cell carcinoma, the median OS and 5-year OS were 12.6 months and 21.7% for BPCRT and 14.2 months and 33.8% for surgery. For adenocarcinoma, the median OS and 5-year OS were 13.4 months and 19.3% with BPCRT and 31.9 months and 31.2% with surgery. For neuroendocrine variants the median OS and 5-year OS were 25.2 months and 32.0% with BPCRT and 18.5 months and 33.8% with surgery. For micropapillary variants the median OS and 5-year OS were 38.5 months and 0% with BPCRT and 22.5 months and 24.1% with surgery. For other variants of UCa not otherwise specified the median OS and 5-year OS were 23.3 months and 29.9% with BPCRT and 16.7 months and 33.9% with surgery (Fig. 2).

4. Discussion

The outcomes for non-conventional UCa remain poor. Fischer-Valuck et al [8] showed that BPCRT outcomes were worse when

Table 1
Patient Characteristics.

		Surgery (n = 2,093)	Bladder Preservation (n = 356)	P-value
Age at Diagnosis (median)		66	72	<0.001
Sex	Male	1,338 (64%)	228 (64%)	0.966
	Female	755 (36%)	128 (36%)	
Race	White	1,881 (91%)	308 (87%)	0.025
	Black	138 (6.7%)	38 (11%)	
	Other	54 (2.6%)	10 (3%)	
Treatment Facility Type	Community or Integrated Network Cancer Program	354 (17%)	82 (23%)	<0.001
	Comprehensive Community Cancer Program	526 (26%)	159 (45%)	
	Academic/Research Program	1,186 (57%)	114 (32%)	
Charlson-Deyo Score	0	1,400 (67%)	233 (65%)	0.594
	1+	693 (33%)	123 (35%)	
T-Stage	T2	1,571 (75%)	237 (67%)	<0.001
	T3	325 (16%)	50 (14%)	
	T4	197 (9%)	69 (19%)	
Histology	Squamous Cell	728 (35%)	94 (26%)	<0.001
	Adenocarcinoma	318 (15%)	38 (11%)	
	Neuroendocrine	310 (15%)	135 (38%)	
	Micropapillary	206 (10%)	16 (5%)	
	Other	531 (25%)	73 (21%)	

Table 2
Multivariable analysis for patient and treatment characteristics with overall survival.

		Hazard Ratio (95% CI)	HR P-Value
Treatment Group	BPCRT	1.15 (1.00–1.33)	0.052
	Surgery	–	
Age	>65	1.24 (1.07–1.43)	0.004
	≤ 65	–	
Charlson-Deyo	1+	1.24 (1.12–1.39)	<0.001
	0	–	
T-Stage	T4	1.90 (1.60–2.22)	<0.001
	T3	1.20 (1.03–1.38)	0.017
	T2	–	

Bold = statistically significant (P < 0.005).

comparing patients with conventional UCa to squamous cell carcinoma. This study was done to examine if worse outcomes with non-conventional UCa or other tumor types involving the bladder are associated with treatment modality. Specifically this study aimed to assess the association of definitive intent BPCRT as compared to definitive intent surgery on OS in patients with MIBC with other tumors types involving the bladder or variant histology.

Our findings demonstrate that from 2004 to 2015, BPCRT in MIBC was associated with similar overall survival compared to cystectomy in patients with variant histology. However, by subgroup analysis there was worse OS with bladder preservation approach in patients with adenocarcinoma and squamous cell carcinoma. This is consistent with general understanding of radiosensitivity of adenocarcinoma particularly as compared to neuroendocrine tumors,

which are generally quite sensitive to radiotherapy [11,12]. Additionally, our data confirms patient and disease characteristics previously reported to be negatively associated with survival, such as advanced age and primary tumor stage [5,13].

International guidelines still recommend against bladder preservation in definitive management of most variant histology or other tumors types involving the bladder [14]. However multimodality treatment with neoadjuvant chemoradiation for neuroendocrine variants of UCa has been increasingly used, and is associated with lower cancer-specific mortality [15]. Notably neoadjuvant chemoradiation followed by radical cystectomy was not associated with improvement in cancer-specific survival for adenocarcinoma or squamous cell carcinoma variants of UCa [15]. However, salvage cystectomy at time of failure is a viable option in select patients [16–18]. Given that many patients with other tumors types involving the bladder present with advanced age and stage, up to 48% pursue no treatment [19]. Additionally, with more advanced presentations, patients with MIBC with variant histology or other tumors types involving the bladder would benefit from refinement of systemic therapy regimens given high risk of distant relapses.

Our study highlighted the limits of proportional hazard assumptions. Notably the Kaplan-Meier curves for the overall and multiple subgroups crossed. This aligns with intuition about likely lower short-term mortality with non-operative approach (BPCRT) corresponding to similar or trend to better OS without surgery, but better OS for those that survive surgical complications. This has been shown in multiple other studies [20–22]. This study

Table 3
Propensity Score weighted sample for overall survival based on treatment by histology.

Cohort	Treatment Group	N	Hazard Ratio (95% CI)	HR P-Value
Overall	BPCRT	350	1.08 (0.90–1.30)	0.387
	Surgery	2011	–	
Squamous Cell	BPCRT	92	1.49 (1.25–1.77)	<0.001
	Surgery	695	–	
Adenocarcinoma	BPCRT	38	1.75 (1.36–2.25)	<0.001
	Surgery	308	–	
Neuroendocrine	BPCRT	133	1.02 (0.80–1.29)	0.89
	Surgery	299	–	
Micropapillary	BPCRT	16	0.60 (0.41–0.87)	0.007
	Surgery	197	–	
Other	BPCRT	71	0.95 (0.77–1.18)	0.66
	Surgery	512	–	

Bolded = statistically significant at p < 0.005.

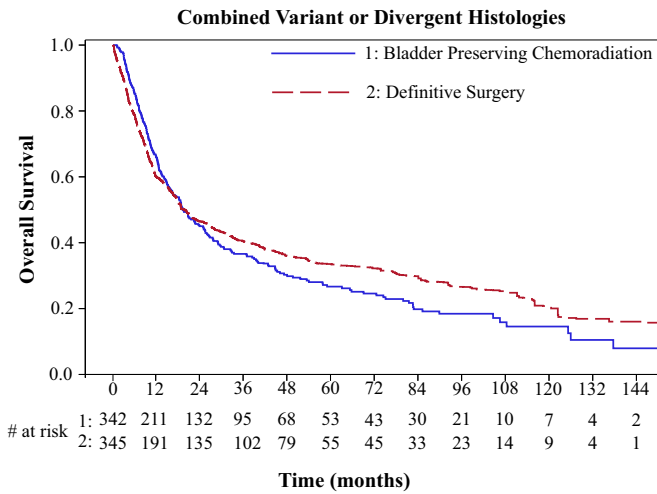


Fig. 1. Kaplan Meier Curves for overall survival in propensity matched cohorts treated with BPCRT or definitive surgery.

highlights that long term control is best achieved with surgery for multiple subgroups of variant histology MIBC. However that conclusion is limited by construction of cohorts, which, due to NCDB limitations, prevented inclusion of patients who had initial BPCRT but subsequently had salvage cystectomy. As such some of the more fit patients who elected for upfront bladder preservation would not be included in the survival analysis for BPCRT.

Our analysis has several limitations. This study is a retrospective analysis of a national registry with inherent limitations and selection biases. Histology was not reviewed by a central institution, nor is there information about specialization or fellowship training of pathologist. Distinctions between pure variant histology and proportion of mixed histology are not available. Additional details about treatment such as completeness of TURBT, dose reductions for chemotherapy, or possibility of missing traditional urothelial component are not available in the NCDB. Patients were not randomized and so selection bias, overall fitness, and unmeasured confounders are not completely captured in propensity score matching. The NCDB registry also lacks data regarding local control, treatment-related morbidity, and specific cause of death. Patients with salvage cystectomy following radiotherapy were

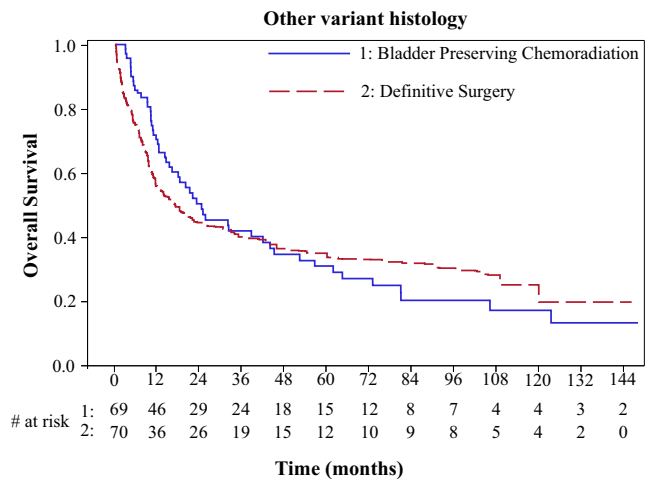
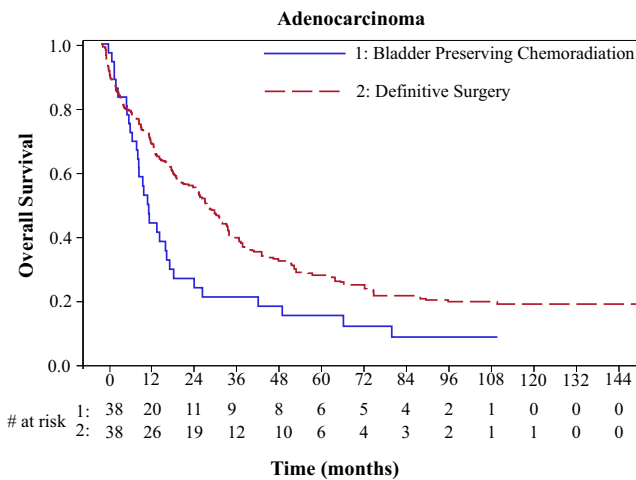
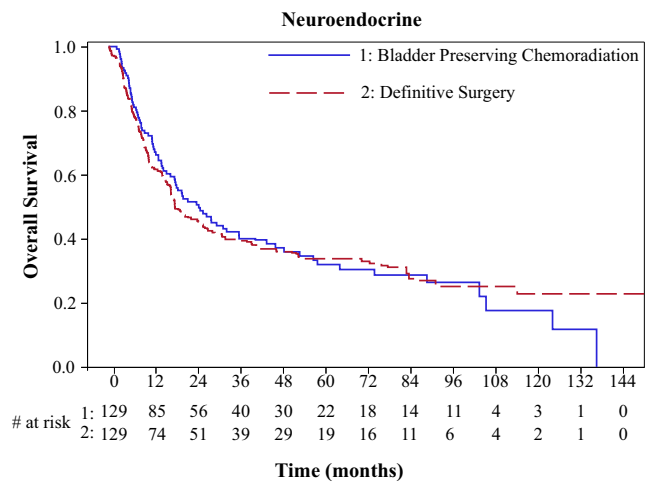
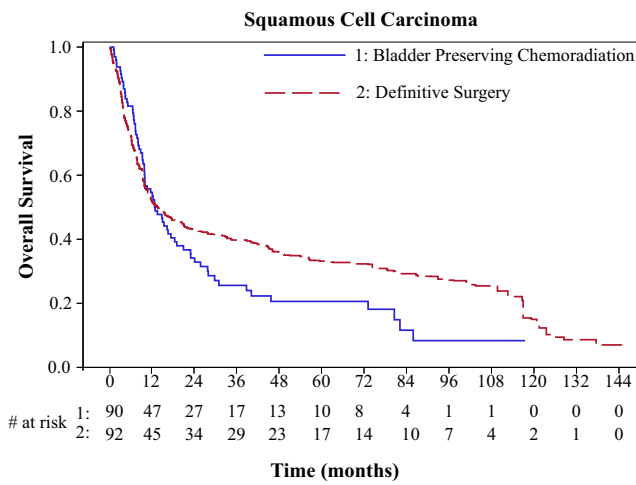


Fig. 2. Kaplan Meier curves for overall survival in propensity matched cohorts by histology.

excluded as it is impossible to identify patients who had definitive intent BPCRT following TURBT and later had salvage cystectomy in the NCDB. Therefore, the overall benefit of the initial BPCRT is not completely captured by excluding patients that were salvaged with surgery. Furthermore, this study has limited numbers of patients particularly for individual histologies such as micropapillary ($n = 15$ with BPCRT). However, given that the NCDB captures an estimated 70% of all cancer diagnoses in the USA [10] the limited numbers in this study highlight inherent challenges of studying local therapies in patients with muscle invasive bladder cancer with variant histology or other tumors types involving the bladder.

5. Conclusions

Despite several limitations, this study contains data from a significant number of patients and can compare outcomes of patients with T2–4N0M0 bladder cancer with variants of UCa and other tumors types involving the bladder treated with definitive surgery versus BPCRT. Our results suggest that patients can be treated with bladder-preserving approach outside the clinical trial setting with results comparable to radical surgery. However squamous cell and adenocarcinoma variants had worse outcomes with BPCRT and so multi-disciplinary tumor board discussion would likely help guide local treatment decisions in those scenarios, particularly since salvage cystectomy patients were excluded from this analysis. The poor survival in all cohorts by histology and local treatment further highlight the need for improved systemic therapy. In the absence of prospective randomized trials, this study may help guide treatment decisions in the multi-disciplinary setting and provide additional options for patients contemplating high-risk or morbid therapies.

Declaration of Competing Interest

M.A. Bilen has acted as a paid consultant for and/or as a member of the advisory boards of Exelixis, Bayer, BMS, Eisai, Pfizer, AstraZeneca, Janssen, Genomic Health, Nektar, and Sanofi and has received grants to his institution from Xencor, Bayer, Bristol-Myers Squibb, Genentech/Roche, Seattle Genetics, Incyte, Nektar, AstraZeneca, Tricon Pharmaceuticals, Peleton Therapeutics, and Pfizer for work performed as outside of the current study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2020.11.002>.

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