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Post prostatectomy outcomes of patients with high-risk prostate cancer treated with neoadjuvant androgen blockade

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Abstract

Background—Patients with high-risk prostate cancer have an increased likelihood of experiencing a relapse following radical prostatectomy (RP). We previously conducted three neoadjuvant androgen deprivation therapy (ADT) trials prior to RP in unfavorable intermediate and high-risk disease.

Methods—In this analysis, we report on the post-RP outcomes of a subset of patients enrolled on these studies. We conducted a pooled analysis of patients with available follow-up data treated on three neoadjuvant trials at three institutions. All patients received intense ADT prior to RP. The

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primary endpoint was time to biochemical recurrence (BCR). BCR was defined as a PSA ≥0.2 ng/mL or treatment with radiation or androgen deprivation therapy for a rising PSA <0.2 ng/mL.

Results—Overall, 72 patients were included of whom the majority had a Gleason score ≥8 (n=46, 63.9%). Following neoadjuvant therapy, 55.7% of patients (n=39/70) had pT3 disease, 40% (n=28) had seminal vesicle invasion, 12.9% (n=9) had positive margins, and 11.4% (n=8) had lymph node involvement. Overall, 11 (15.7%) had tumor measuring ≤0.5cm, which included four patients (5.7%) with a pathologic complete response and seven (10.0%) with residual tumor measuring 0.1-0.5cm. Compared to pretreatment clinical staging, 10 patients (14.3%) had pathologic T downstaging at RP. The median follow-up was 3.4 years. Overall, the 3-year BCR free rate was 70% (95% CI 57%, 90%). Of the 15 patients with either residual tumor ≤0.5cm or pathologic T downstaging, no patient experienced a recurrence.

Conclusions—In this exploratory pooled clinical trials analysis, we highlight that neoadjuvant therapy prior to RP in unfavorable intermediate and high-risk patients may potentially have a positive impact on recurrence rates. Larger studies with longer follow-up periods are warranted to evaluate the impact of neoadjuvant hormone therapy on pathologic and long-term outcomes.

Introduction

Despite generally outstanding results for radical prostatectomy (RP), patients with high-risk prostate cancer (PC) have an increased risk of biochemical recurrence (BCR) and PC mortality despite treatment.(1) Biochemical recurrence may not be indolent since approximately one third of men with high-risk disease who suffer a BCR will die of PC within 10 years.(2) While adjuvant and salvage therapies can improve outcomes for patients with local recurrences, the overall relapse rate is still unacceptably high, in part due to occult systemic disease and radiation resistance. Consequently, novel strategies that integrate multimodality therapy are warranted to improve cure for high-risk patients.

Neoadjuvant systemic therapy is a widely accepted paradigm for the treatment of malignancies including breast(3), bladder(4, 5), and esophageal(6, 7). Neoadjuvant therapy offers the potential for systemic control of microscopic metastases, while optimally treating the primary disease.(8) In some cases, neoadjuvant therapy may facilitate resection and provide prognostic information with an *in vivo* assessment of treatment sensitivity.(8) A key principal of neoadjuvant therapy is that local response correlates with long-term survival. In breast cancer, pathologic complete response (pCR) has been used as a surrogate for long-term survival resulting in FDA approval of pertuzumab.(9) Additionally, residual cancer burden (RCB), a method to quantify residual disease after neoadjuvant chemotherapy for breast cancer that incorporates number and size of nodal metastases and percent cellularity of the primary tumor bed, has been shown to correlate with long-term survival.(10)

Historically, androgen-deprivation therapy (ADT) is the primary systemic therapy for men with PC.(11) The utilization of neoadjuvant ADT prior to RP was evaluated in the 1990's and while initially demonstrated improvements in the rate of organ-confined disease and decreased positive surgical margins, there was no benefit in recurrence rates.(12-23) These studies were underpowered to detect significant differences between disease-free survival

(DFS) and overall survival (OS) given limited reporting of these endpoints, lack of long-term follow-up, and inclusion of primarily low and intermediate-risk patients.(24)

These studies primarily utilized treatment with luteinizing hormone releasing hormone (LHRH) agonists and/or first-generation anti-androgens. Treatment with LHRH agonists and first-generation anti-androgens results in incomplete suppression of tissue androgen, which is hypothesized to be another possible explanation for the lack of efficacy of these former studies.(25) While serum androgens are reduced by approximately 90% with standard ADT, tissue androgens only decline by 75%, providing rationale for more complete androgen blockade.(25)

The development of more potent hormonal agents provides the opportunity to investigate these therapeutic options in the neoadjuvant setting. In addition to LHRH suppression, further androgen receptor (AR) axis suppression can be achieved by targeting CYP17 mediated androgen synthesis (ketoconazole, abiraterone) or with AR inhibition (enzalutamide). Abiraterone and enzalutamide improve OS in metastatic castration resistant PC. We hypothesized that intense ADT can improve outcomes in high-risk localized PC and have published three neoadjuvant studies utilizing these hormonal agents.(26-28) Herein, we report on the post-RP outcomes of patients with available follow-up data enrolled on these studies.

Patients and Methods

Patients

We conducted a pooled analysis of patients treated on three neoadjuvant trials at three institutions: Dana-Farber/Brigham and Women's Cancer Center, University of Washington, and Beth Israel Deaconess Medical Center (Table 1). Post-RP follow-up, including frequency of clinic visits, prostate specific antigen (PSA) and radiographic evaluations, was not predefined on the studies given funding restrictions. Given that long-term follow up after RP was not mandated, patients included were those with available PSA and follow-up data. Clinical, laboratory, and radiographic data following RP were obtained. The decision to initiate adjuvant or salvage therapy was at the discretion of the treating physician. Informed consent was obtained from all subjects. This study was approved by the Institutional Review Board at each institution.

Statistical analysis

The primary endpoint was time to BCR, defined as the time from RP to BCR, censored at the last PSA follow-up for those without progression. BCR was defined as a PSA $\geq$0.2 ng/mL, with a second confirmatory level $\geq$0.2 ng/mL, or treatment with salvage radiation therapy or ADT for a rising PSA that was <0.2 ng/mL at the time of therapy initiation. A secondary endpoint included time to metastasis (TTM), defined as the time of RP to the first evidence of metastasis on imaging, censored at the date of last PSA or imaging follow-up for those without progression. The distributions of time to BCR or TTM were estimated using the Kaplan Meier method.

Median time to BCR and BCR-free rate at 2 and 3 years along with 95% confidence interval (CI) were summarized in overall cohort and by pathological response groups. Two pathological outcomes were analyzed: 1) minimum residual disease (MRD) defined as tumor in the RP specimen measuring ≤0.5cm, and 2) improved pathologic T stage compared to clinical staging defined by the American Joint Committee on Cancer (AJCC) staging system at baseline. Patients who had an improvement in T stage either between T stage categories or within T stage categories were counted as having downstaging. The subgroup analyses of BCR by pathological response groups were explorative with limited statistical power; no formal comparison was provided.

Time to testosterone recovery was estimated by the Kaplan Meier method. The recovery time was calculated from the date of RP to testosterone >200ng/dL, or censored at the last sample date if testosterone had not reached a normal level. If patients received ADT prior to testosterone recovery, their time to testosterone recovery was censored at the date of ADT initiation.

We conducted a descriptive exploratory analysis to evaluate the predicted pathologic RP outcomes of matched patients with comparable high-risk features planned to undergo RP alone. Using the Memorial Sloan Kettering Cancer Center (MSKCC) pre-RP nomogram (https://www.mskcc.org/nomograms/prostate/pre-op), we used the baseline parameters of patients in our cohort to determine the predicted pathologic outcomes including extracapsular extension, seminal vesicle invasion, and lymph node involvement of RP alone. No formal test could be made for this descriptive comparison.

Results

Baseline Characteristics

Overall, 72 patients (50% of those enrolled on the trials) were included (Table 2). The median PSA prior to neoadjuvant therapy was 8.3 ng/mL. The majority of patients had a Gleason score ≥8 (n=46, 63.9%). Fifty-two patients (72.2%) had high-risk disease by NCCN criteria.

Pathologic RP Outcomes

Of the 72 patients, 70 (97.2%) had pathologic data available (Table 3). Two patients discontinued study treatment early and subsequently received RP at outside hospitals. The majority of patients (n=39, 55.7%; 95% CI: 43%, 68%) had pT3 disease at RP and eight patients (11.4%; 95% CI: 5%, 21%) had lymph node involvement. The rates of seminal vesicle involvement and positive margins were 40% (n=28; 95% CI: 28%-52%) and 12.9% (n=9; 95% CI: 6%, 23%), respectively.

Overall, 11 (15.7%; 95% CI: 8%, 26%) had tumor measuring ≤0.5 cm at largest cross section dimension in the RP specimen, including four patients (5.7%) with a pCR and seven (10.0%) with residual tumor measuring 0.1-0.5 cm. Of the patients with residual tumor measuring ≤0.5 cm, eight (72.7%) were treated on the Neo-Abi trial and three (27.3%) on the Neo-Enza trial.

Compared to pretreatment clinical staging, 10 patients (14.3%; 95% CI: 7%, 25%) had pathologic T downstaging at RP, including four patients (5.7%) with downstaging from T3 to pT2, four patients (5.7%) with downstaging from T1/T2 to pT0 and two patients (2.9%) with change in subcategories. Six patients achieved both tumor measuring ≤0.5 cm and pathologic T downstaging. Overall, 15 patients (20.8%; 95% CI: 13%, 33%) had either tumor measuring ≤0.5 cm or pathologic T downstaging at RP.

MSKCC Pre-RP Nomogram Prediction

The predicted rates of extracapsular extension, seminal vesicle invasion, and lymph node involvement for matched patients undergoing RP alone were 78%, 23%, and 25%, respectively. The predicted 3-year BCR-free rate was 50%.

Time to BCR, TTM, and OS

Overall, the median follow-up post-RP was 3.4 years (range 0.1-7.0): 5.7 years for TAPS, 4.3 years for Neo-Abi, and 2.6 years for Neo-Enza. Twenty-three patients had a BCR and median time to BCR was 5.1 years (95% CI: 4.4, not reached) (Figure 1A). The 2-year BCR-free rate was 75% (95% CI: 63%, 84%) and 3-year rate was 70% (95% CI: 57%, 80%). Five patients (6.9%) developed metastases and median TTM was not reached. The 3-year metastasis-free survival was 95% (95% CI: 0.86, 0.98). Overall, there was one death from PC and 3-year OS rate was 98% (95% CI: 88%, 100%).

Time to BCR by pathologic parameters

In an exploratory analysis evaluating time to BCR by pathologic T downstaging, no patient with pathologic T downstaging (n=10) had a BCR and median time to BCR was not reached (Table 4, Figure 1B). Similarly, there were no recurrences in patients with a residual tumor ≤0.5 cm (n=11) (Table 4, Figure 1C). Median follow-up was 2.7 (range 0.6, 5.0) years in those with residual tumor ≤0.5 cm or pathologic T downstaging (n=15).

Testosterone Recovery

Post-RP testosterone data were available for 47 patients from two institutions. Overall, median time to testosterone recovery from RP was 4.0 months (95% CI: 3.4-4.9). The cumulative testosterone recovery rate was 31% (95% CI: 20%, 47%) by 3-months, 77% (95% CI: 63%, 88%) by 6-months, and 88% (76%, 96%) by 1-year, respectively.

Forty out of 47 patients had testosterone recovery, of whom 27 (67%) were BCR-free at last follow-up. The BCR-free rate at 2-years post testosterone recovery was 73% (95% CI: 55%, 85%). Four patients with low testosterone were lost to follow-up and were censored at the last testosterone test date. Three patients who received ADT prior to testosterone recovery were censored at time of ADT initiation.

Discussion

This exploratory analysis was designed to investigate the post-RP outcomes of patients treated with intense neoadjuvant androgen deprivation. We demonstrate that at a median of three years following RP, 70% of patients remain disease free. Furthermore, no patient with

pathologic T downstaging or residual tumor ≤0.5 cm experienced a recurrence. While our series is limited by the small number of patients and low failure events, neoadjuvant therapy prior to RP in unfavorable intermediate and high-risk patients may potentially have a positive impact on recurrence rates. These data are hypothesis generating and larger randomized studies with longer follow-up are needed to evaluate the benefit of neoadjuvant hormone therapy.

Currently, RP alone is insufficient for many patients with high-risk PC. Historic trials have evaluated the role of neoadjuvant hormonal therapy. The largest randomized trial included 547 men with cT1-T2 randomized to leuprolide and flutamide for three or eight months before RP.(20) Eight months of therapy was associated with improved preoperative PSA, lower positive surgical margin rate, and higher organ-confined disease rate.(20) Though the pCR rate was higher in the eight month group compared to the three month group (9.3% versus 5.1%), this was not statistically significant.(20) A meta-analysis including 10 studies of neoadjuvant ADT prior to RP demonstrated statistically significant improvements in pathologic parameters at RP, however these did not correspond to improved DFS or OS.(24)

The more contemporary clinical trials included in this meta-analysis evaluate more potent androgen blockade beyond LHRH therapy and first-generation anti-androgens. This is the first report of the post-RP outcomes data of patients enrolled on these studies. While neoadjuvant ADT remains under investigation, our data highlight that a subset of patients may have a favorable response to treatment. This is consistent with recent data from the Systemic Therapy in Advancing or Metastatic PC: Evaluation of Drug Efficacy (STAMPEDE) trial evaluating abiraterone in patients never previously treated with hormone therapy.(29) Of the 1,917 patients randomized, 27% had newly diagnosed high-risk locally advanced disease.(29) Overall, abiraterone added to ADT was associated with a 37% improvement in OS compared to ADT alone (hazard ratio (HR) 0.63; 95% CI: 0.52-0.76, $p<0.001$).(29) The benefit of abiraterone was seen in those with non-metastatic (HR=0.71) and metastatic disease (HR=0.65).(29)

Additionally, there is an increasing interest in surgery as part of an integrated multimodal treatment paradigm for patients with locally advanced or oligometastatic PC.(30) Radical surgery to remove the primary in metastatic disease has been associated with improved survival in several solid tumors including colorectal(31) and renal cell carcinoma(32). With regards to PC, though prospective studies are lacking, a number of retrospective studies have demonstrated the potential benefit of RP in patients with advanced disease.(30) A Surveillance Epidemiology and End Results-based study compared the survival of 8,185 men with metastatic PC receiving RP, brachytherapy or no local treatment, and demonstrated an improvement in 5-year OS with local treatment.(33) The safety and efficacy of RP in very-high risk or oligometastatic PC is being investigated in a single arm phase 1/2 clinical trial (NCT02971358). Additional randomized trials will be necessary to evaluate the role of multimodal therapy for locally advanced or metastatic PC.

In our cohort, 11% of patients were observed to have microscopic lymph node involvement at RP. These results are comparable to historic studies documenting rates of nodal involvement at ~10% in high-risk patients undergoing RP.(34) Additionally, in the

exploratory analysis evaluating predicted pathologic outcomes of matched patients having undergone RP alone, the predicted rate of nodal involvement was 25%. Though patients did not have clinical lymph node involvement at baseline in our cohort, whether microscopic lymph node involvement was present at baseline is unknown. Direct comparisons cannot be made between these analyses, which highlight the differences between clinical and pathologic staging.

The impact of the pathologic response on long-term outcomes in PC has not been established. In our study, the pCR rate was low, though a subset of patients experienced pathologic T downstaging or MRD. Interestingly, there were no recurrences in these patients. It is possible that pathologic response may correlate with long-term clinical benefit, however the duration of follow-up was short. Our analysis was exploratory and not powered to investigate the association of pathologic and survival outcomes.

In this analysis, we defined MRD as a residual tumor ≤0.5 cm. However, this definition does not account for tumor volume and cellularity. In the Neo-Abi trial, we investigated the significance of MRD defined as RCB (tumor volume corrected for tumor cellularity) ≤0.25 cm^3.(26) The rates of RCB ≤0.25 cm^3 ranged from 44-52%. Similar results were seen on the Neo-Enza trial with rates of RCB ≤0.25 cm^3 of 36%-74%. Consensus criteria for the measurement and reporting of pCR and MRD are important in the planning and interpretation of future neoadjuvant trials.

Despite more effective blockade of the androgen axis, the rate of testosterone recovery in our cohort was 85% and median time to testosterone recovery was 4 months. The short recovery time may be related to the young age of our population. We anticipate additional recovery with longer follow-up. Historic trials of neoadjuvant ADT evaluating variable durations of ADT ranging from 3-8 months did not report on testosterone recovery. For reference, we previously evaluated the efficacy of a LHRH agonist, bicalutamide with or without bevacizumab administered for six months in recurrent PC.(35) The rate of testosterone recovery in the ADT only cohort of this study was 71% and median time to testosterone recovery was 10.1 months. Though direct comparisons cannot be made, it appears that testosterone recovery following 6-months of potent androgen blockade was not inferior to that with standard ADT.

In our cohort, the 3-year BCR-free rate was 70% post-RP with eight patients receiving adjuvant radiation therapy or ADT. Using the MSKCC pre-RP nomogram, the predicted 3-year BCR-free rate was 50% for matched patients undergoing RP alone. Numerous questions remain regarding the long-term impact of neoadjuvant therapy on rates of BCR, need for salvage therapy, metastasis development, and OS. Though promising, the significance of our observation on BCR is indeterminate and the benefits can only truly be determined by a phase 3 trial.

Despite neoadjuvant therapy, the majority of patients had residual disease, underscoring the need to identify and target resistance in these patients. We previously demonstrated that persistent intraprostatic tissue androgens and continued AR activity in residual tumor cells may drive resistance.(26, 27) These data suggest that more potent AR inhibition or

potentially longer therapy may be warranted. We are investigating these questions in two subsequent neoadjuvant studies. One study, which recently completed accrual, is evaluating the combination of abiraterone and enzalutamide (NCT02268175). The other study, currently open to accrual, is a two-part phase 2 study evaluating neoadjuvant and adjuvant abiraterone and apalutamide, a potent AR antagonist (NCT02903368). Additional correlative analyses are evaluating the genomic and expression profiles of baseline prostate biopsy and RP tissue for biomarkers of exceptional responders and resistance.

This post-hoc exploratory analysis has several limitations. Though patients were enrolled on prospective clinical trials, post-RP follow-up was variable between patients and data were collected retrospectively. Direct comparisons between the three trials is limited given differences in baseline patient and disease characteristics and small sample size. The endpoint of T downstaging at RP is weak given that clinical T stage at baseline was compared to pathologic T stage at RP. The analysis evaluating predicted pathologic outcomes is limited and direct comparisons cannot be made to our cohort. Furthermore, the endpoint of 3-year BCR is short and number of failure events was low.

Our subset analysis from three contemporary multi-center trials evaluating neoadjuvant intense ADT, demonstrates a favorable BCR compared to MSKCC nomogram predicted BCR. Ultimately, a randomized phase 3 study will be necessary to challenge the current treatment paradigm for men with unfavorable-intermediate and high-risk disease and prove the value of neoadjuvant/adjuvant intense ADT. The development of such a study poses challenges in terms of the best choice of an intermediate clinical endpoint that is a surrogate for OS and funding. Our preliminary data support that pCR plus MRD (≤0.5 cm tumor or RCB <25%) could be an endpoint that will correlate with BCR and ultimately freedom from metastasis. Despite these challenges, conduct of future neoadjuvant/adjuvant studies is needed to improve the current standard of care for these patients.

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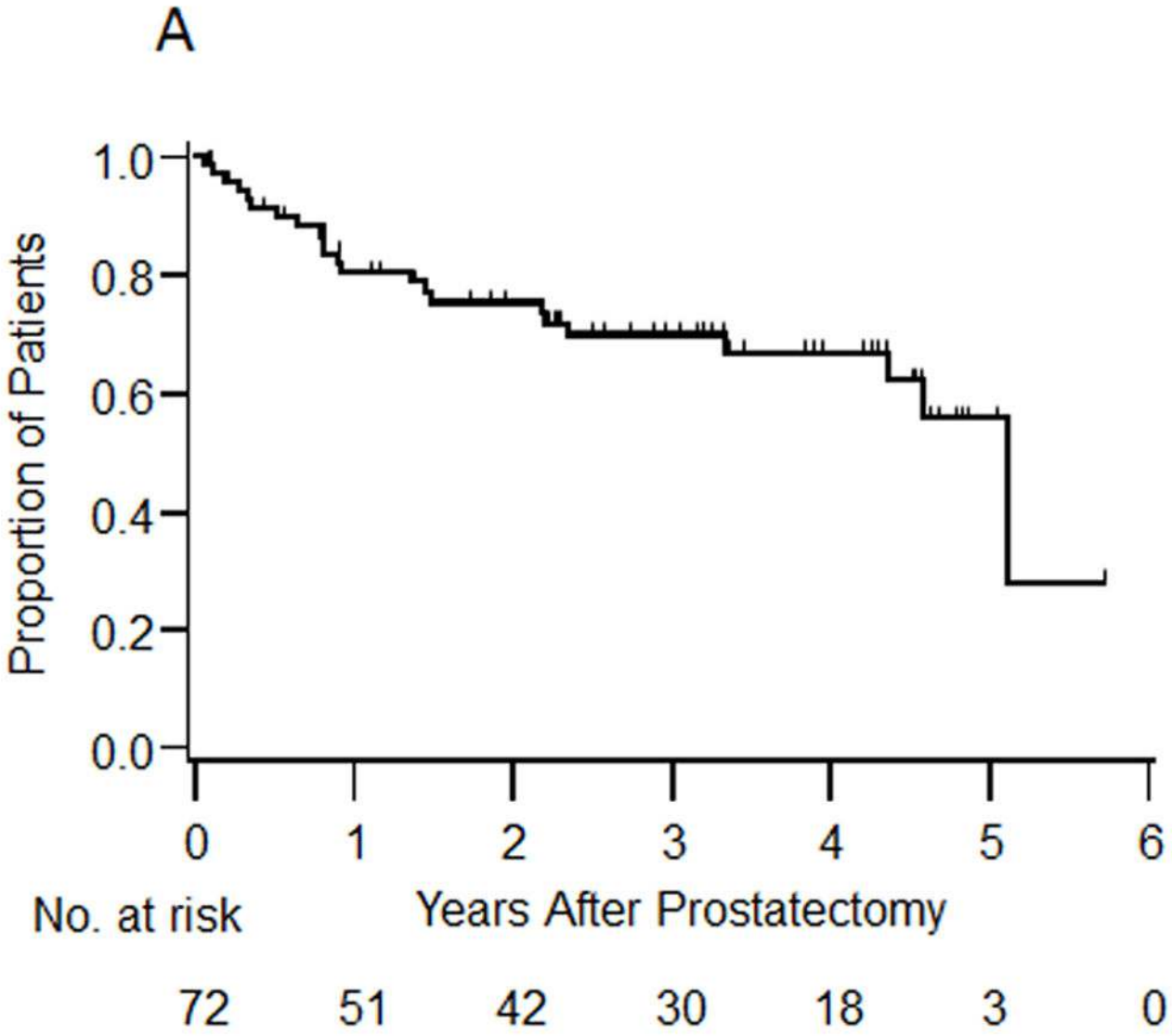

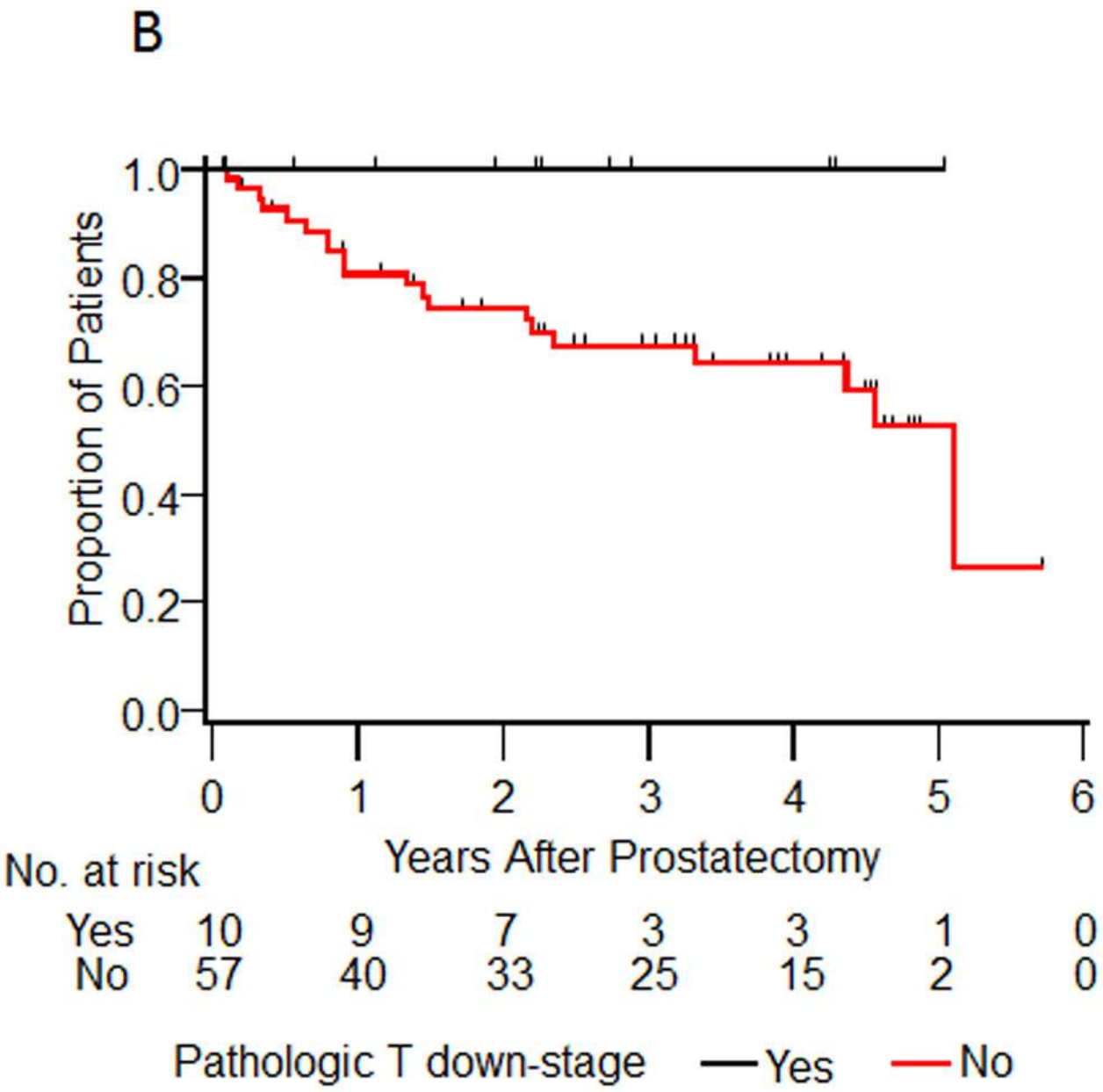

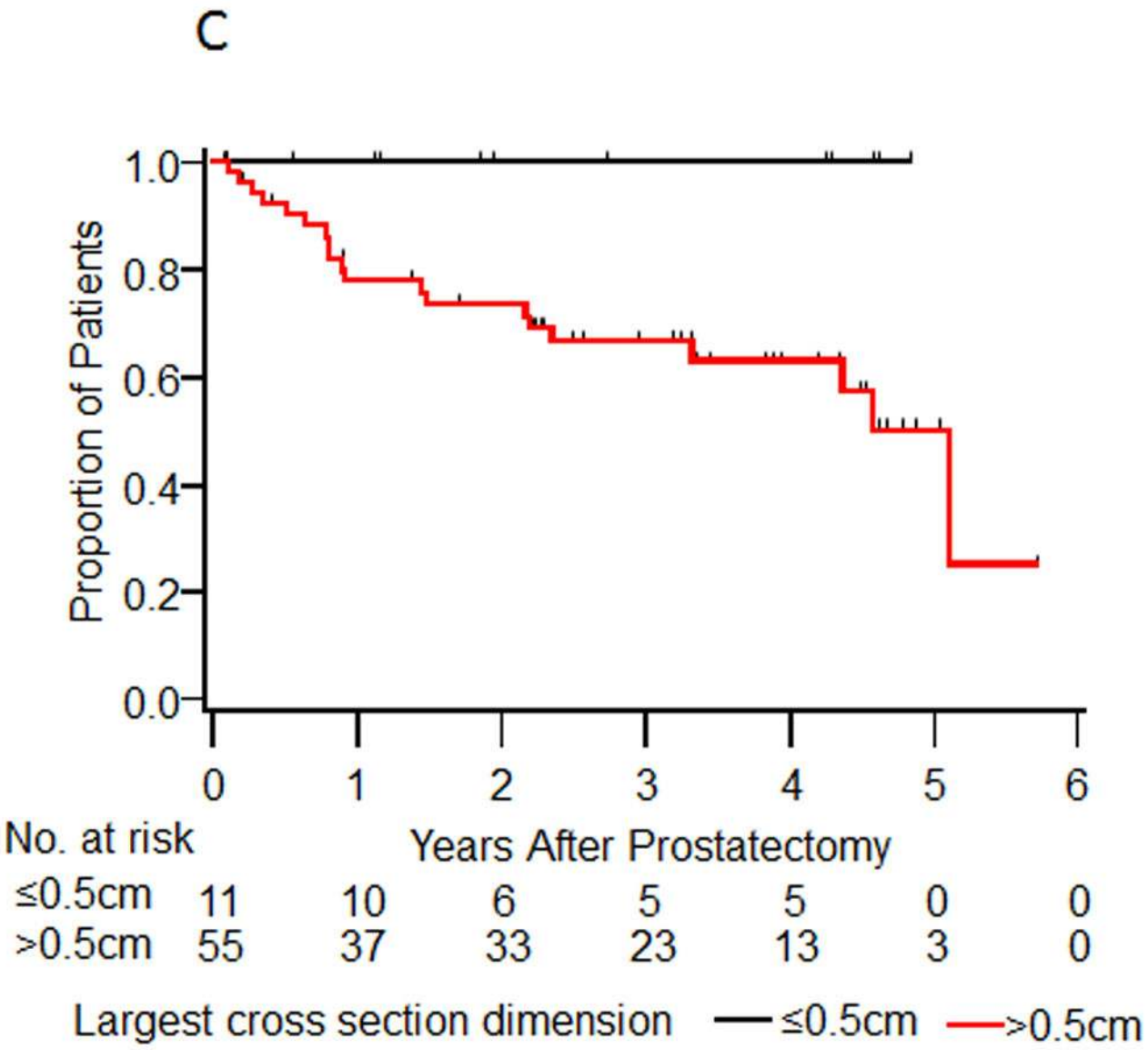

Figure 1.
Kaplan Meier estimates of BCR (Panel A) for the total cohort. Time to BCR by pathologic T downstaging (yes vs. no) (B) and largest cross section dimension (≤0.5cm or >0.5cm) (C).

Table 1

Summary of neoadjuvant trials.

Study	Enrollment Period	Patients Enrolled	Selection Criteria	Arms	Duration of Neoadjuvant Therapy	Primary Endpoint
TAPS(27) (NCT00298155)	July 2006 – December 2009	35	cT1-T3 AND PSA < 40 ng/dL AND Gleason 7-10	**1** Goserelin + Dutasteride **2** Goserelin + Dutasteride + Bicalutamide **3** Goserelin + Dutasteride + Bicalutamide + Ketoconazole (1:1:1)	3 months	Prostate tissue DHT levels
Neo-Abi(26) (NCT00924469)	September 2009 – June 2011	58	Positive biopsies ≥3 AND Gleason score ≥7 OR PSA > 10 ng/mL OR PSA velocity > 2 ng/mL/year	**1** 12 weeks Abiraterone acetate/24 weeks LHRH agonist **2** 24 weeks Abiraterone acetate/24 weeks LHRH agonist (1:1)	24 weeks	Prostate tissue testosterone and DHT levels
Neo-Enza(28) (NCT01547299)	March 2012 – November 2013	52	Positive biopsies ≥3 AND PSA > 10 ng/mL OR Gleason score ≥7 (4 + 3); T4 excluded	**1** Enzalutamide **2** Enzalutamide + Leuprolide + Dutasteride (1:1)	6 months	Pathologic complete response rate

PSA=prostate specific antigen, DHT=dihydrotestosterone, LHRH=luteinizing hormone-releasing hormone.

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Table 2

Baseline patient and disease characteristics.

	Current Analysis cohort (N=72)	Original Trial Cohorts					
		TAPS (n=35)		Neo-Abi (n=58)		Neo-Enza (n=52)	
	N (%)	Included	Excluded	Included	Excluded	Included	Excluded
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total N	**72**	**4**	**31**	**41**	**17**	**27**	**25**
Institution							
BIDMC	7 (10)						
DF/BWCC	48 (67)						
UW	17 (24)						
Gleason Score							
Gleason 7	26 (36)	1 (25)	24 (77)	15(37)	3 (18)	10 (37)	10 (40)
3+4	5 (7)						
4+3	21 (29)						
Gleason 8-10	46 (64)	3 (75)	7 (23)	26(63)	14 (82)	17 (63)	15 (60)
3+5	3 (4)						
4+4	18 (25)						
4+5	16 (22)						
5+4	6 (8)						
5+5	3 (4)						
Clinical T Stage							
T1	20 (28)	1 (25)	9 (29)	13 (32)	3 (18)	6 (22)	8 (32)
T2	37 (51)	2 (50)	16 (52)	24 (59)	6 (35)	11 (41)	13 (52)
T3	12 (17)	1 (25)	6 (19)	3 (7)	7 (41)	8 (30)	4 (16)
Unknown	3 (4)	0	0	1 (2)	1 (6)	2 (7)	0
NCCN Risk Group							
Intermediate	20 (28)	1 (25)	-	12 (29)	1 (6)	7 (26)	4 (16)
High	52 (72)	3 (75)	-	29 (71)	16 (94)	20 (74)	21 (84)
	Median (IQR)	Median by treatment arm[a] (Range)		Median by treatment arm[a] (Range)		Median by treatment arm[a] (Range)	

	Current Analysis cohort (N=72)	Original Trial Cohorts					
		TAPS (n=35)		Neo-Abi (n=58)		Neo-Enza (n=52)	
	N (%)	Included	Excluded	Included	Excluded	Included	Excluded
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PSA at Baseline (ng/mL)	8.3 (5.0-14.2)	11.9/5.8/7.9 (-)		12.1/6.4 (2-316.6)		10.9/12.8 (0.6-61.1)	
Median age at RP, years	59 (54-63)	62/66/60 (-)		55/60 (50-74)		61/60 (46-75)	

BIDMC=Beth Israel Deaconess Medical Center, DF/BWCC=Dana-Farber/Brigham and Women's Cancer Center, UW=University of Washington, NCCN=National Comprehensive Cancer Network, NA=not available, IQR=interquartile range, PSA=prostate specific antigen, RP=radical prostatectomy.

- denotes not available.

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Table 3

Pathologic outcomes at radical prostatectomy.

	Current Analysis Cohort (n=70)		Original Trial Cohorts					
			TAPS (n=32)		Neo-Abi (n=56)		Neo-Enza (n=48)	
	N	%	N	%	N	%	N	%
Pathologic T stage								
pT0	4	5.7	2	6.3	4	7.1	1	2.1
pT2	27	38.6	21	65.6	22	39.3	15	31.3
pT3	39	55.7	9	28.1	30	53.6	32	66.7
Pathologic T Down-Stage *								
Yes	10	14.3	-	-	-	-	-	-
No	57	81.4	-	-	-	-	-	-
Unknown	3	4.3	-	-	-	-	-	-
Pathologic N Stage								
N0	61	87.1	-	-	46	82.1	41	85.4
N1	8	11.4	-	-	10	17.9	7	14.6
Unknown	1	1.4	-	-	0	0	0	0
Positive Margin								
Yes	9	12.9	-	-	8	14.3	9	18.8
No	61	87.1	-	-	48	85.7	39	81.3
Seminal Vesicle Involvement								
Yes	28	40.0	5	15.6	17	30.4	16	33.3
No	42	60.0	27	84.4	39	69.6	32	66.7
Largest Cross Section Dimension								
≤0.5cm	11	15.7	-	-	-	-	-	-
>0.5cm	55	78.6	-	-	-	-	-	-
Unknown	4	5.7	-	-	-	-	-	-
Pathologic Complete Response								
Yes	4	5.7	2	6.3	4	7.1	1	2.1

	Current Analysis Cohort (n=70)		Original Trial Cohorts					
			TAPS (n=32)		Neo-Abi (n=56)		Neo-Enza (n=48)	
	N	%	N	%	N	%	N	%
No	66	94.3	30	93.7	52	92.9	47	97.9

* Downstaging of clinical T stage as defined by AJCC staging system at diagnosis to pathologic T stage at radical prostatectomy. Improved from T1c to pT0 (N=2), T2a to pT0 (N=1), T2b to pT2a (N=1), T2c to pT0 (N=1), T3 to pT2 (N=1), T3a to pT2a (N=2), T3a to pT2c (N=1), T3b to pT3a (N=1).

- denotes not available.

Table 4

Time to BCR in the total cohort and by pathologic parameters.

Pathologic Parameter	N	Number of Events	Median, year (95% CI)	BCR Free Rate	
				2-Year (95% CI)	3-Year (95% CI)
All patients	72	23	5.1 (4.4, NR)	75% (63%, 84%)	70% (57%, 80%)
Pathologic T Downstaging					
Yes	10	0	NR	100%	100%
No	57	20	5.1 (3.3, NR)	74% (60%, 84%)	67% (52%, 79%)
Largest cross section dimension					
≤0.5 cm	11	0	NR	100%	100%
>0.5 cm	55	20	5.1 (3.3, NR)	74% (60%, 84%)	67% (52%, 79%)

NR=Not reached.

*Exclude patients who did not have pathologic parameters because surgery was done at outside hospitals or tumor measures (i.e. T stage or Largest Cross Section Dimension) were not available from the original trials.

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