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Research Article

Genomic analysis and long-term outcomes of a phase 1 clinical trial on cytoreductive radical prostatectomy

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ABSTRACT

Purpose: Approximately 7% of patients with newly diagnosed prostate cancer (PCa) in the US will have have metastatic disease. The dogma that there is no role for surgery in this population has been questioned recently. Here we report long-term outcomes of a phase 1 clinical trial on cytoreductive radical prostatectomy.

Materials and methods: This is a multicenter phase 1 trial. The major inclusion criterion was biopsy proven N1M0 or NxM1a/b PCa. Primary end point was the Clavien-Dindo-based major complication rate. Secondary outcomes were biochemical progression and overall survival. RNA-seq correlative study was conducted in nine select cases as a pilot study.

Results: Final accrual was 32 patients of which 25 and 7 were cNxM1 and cN1M0, respectively. With the median follow-up of 46 months (interquartile range 31.7 - 52.7 months), 25 out of the 32 patients (75%) were alive at the time of last contact. There were three disparate groups based on the oncologic outcome: favorable, intermediate, and poor. In seven men with favorable response, androgen deprivation therapy was switched to intermittent approach and five remain free of any evidence of disease after more than two years off all systemic therapy with the normalization of serum testosterone. Of these five patients, three had M1 disease. Long-term use of one pad or less per day was 80%. RNA-seq analysis revealed an enriched downregulation of tumor necrosis factor (TNF)-α signature in the favorable group.

Conclusion: Overall long-term oncologic outcome of cytoreductive radical prostatectomy was significantly higher than historical results. Importantly, the combination of surgery with systemic therapy may result in a long durable response in a minority of men who present with metastatic PCa.

1. Introduction

Prostate cancer (PCa) is the most common cancer diagnosis among men and is the second-leading cause of cancer death in men.[1] Although most patients present with localized, curable disease, approximately 7% have distant disease at diagnosis.[1]

Abbreviations: PCa, prostate cancer; mPCa, metastatic prostate cancer; CP, cytoreductive radical prostatectomy; IQR, interquartlie range; TNF, tumor necrosis factor; PSA, prostate specific antigen.

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Metastatic PCa (mPCa) inevitably becomes castration resistant, resulting in a 5 year survival rate of only 29%.[2] Over the last two decades, there has been no meaningful overall outcomes improvement in men with mPCa.

Commonly used guidelines currently do not include surgery for men who present with mPCa.[3] Both the NCCN and AUA recommend androgen deprivation therapy (ADT) with luteinizing hormone releasing hormone agonists or antagonists, novel hormonal therapies, chemotherapy, or surgical castration depending on severity of mPCa.[3,4] More recently, the European Association of Urology has included local radiotherapy as a reasonable treatment in men with low metastatic burden.[5] Nevertheless, there is a large body of retrospective data that support cytoreductive radical prostatectomy (CP) in men who present with mPCa.[6-9] In 2014, Culp et el examined the SEER database and reported the 5-year overall survival to be 67.4% in men who had CP compared to 22.5% in those without local therapy.[8]

In this framework, our group completed the first prospective study on CP in 2015.[10] This multi-institution phase 1 feasibility and safety trial enrolled thirty-two men with mPCa on diagnosis and reported the overall major complication rate to be 6.25%. Importantly, we saw potential oncologic benefit as nineteen of the twenty-eight patients that reached the six-month follow-up had prostate specific antigen (PSA) nadir of less than or equal to 0.2 ng/mL. Therefore, this report provides the long-term follow up and genomic analysis of this phase I study on CP.

2. Materials and methods

2.1. Clinical trial

The design of the clinical trial has been described in our previous publication.[10] Briefly, the study was conducted at 4 international institutions: Rutgers Cancer Institute of New Jersey (New Brunswick, NJ, USA), City of Hope (Duarte, CA, USA), Seoul National University Bundang Hospital (Bundang, South Korea), and Juntendo University (Tokyo, Japan). The study was approved by the appropriate regulatory bodies in each participating country: NCT02458716 (USA), UMIN000021303 (Japan), and KCT0002633 (South Korea).

Key inclusion criteria were histologically proven adenocarcinoma of the prostate, evidence of lymph node or bone metastasis (N1Mx or NxM1a/b) by magnetic resonance imaging/computed tomography, bone scan, or biopsy, clinical stage T3 or less (pelvic magnetic resonance imaging shows no rectal and ureteral invasion), no prior systemic therapy for mPCa, and ECOG performance status of 0 or 1.

Key exclusion criteria were clinical stage T4 or M1c, deemed a poor surgical risk per primary medical doctor, received prior therapeutic intervention for mPCa, known spinal cord compression, or deep vein thrombosis or pulmonary embolism in the past 6 months.

2.2. Genomic analysis

As a pilot study, RNA sequencing was performed in samples from nine patients. Both prostate tumors and matching adjacent normal tissues were analyzed. Samples were stored in RNAlater™ (ThermoFisher Sci, Waltham, MA) and profiled on Illumina HiSeq (with rRNA depletion selection), with ~80M paired-end 2 × 150 bp reads per sample. Raw data were mapped to hg19 human genome using STAR 2.5.2a aligner[11] with Refseq gene annotations. Counts were normalized and variance was stabilized using DESeq2[12] Bioconductor R package. The resulting normalized profiles were utilized to define a responder differential gene expression signature, comparing three tumor samples and three matching adjacent normal samples from each group, using two-sample two-tailed Welch t-test. This signature was then subjected to the pathway enrichment analysis, where pathways were obtained from MSigDB C2 collection, which included Biocarta, KEGG, REACTOME, and HALLMARKS gene sets. The pathway enrichment analysis was performed using Gene Set Enrichment Analysis[13], where the responder differential gene expression signature was used as a reference and genes from each individual pathway were used as a query gene set. Enrichment of each pathway in the reference signature was defined using Normalized Enrichment Score and p-value, which were estimated with 1,000 gene permutations.

2.3. Statistics

Descriptive statistics was assessed. Kaplan-Meier curve was used to assess the overall survival. All statistical analyses were performed using STATA software (version 15.0, StataCorp, College Station, Texas) and 2-sided α was set to 0.05.

3. Results

3.1. Oncologic outcome

The total accrual for this study was 32 patients and their characteristics are shown in Table 1. Both clinical N1M0 and M1a/b patients were eligible for this trial. M1c was excluded. Following CP, all men continued with ADT-based systemic treatment. The median age was 64.5 years with the interquartile range (IQR) of 57.5 to 70. Pre-operatively, median PSA was 22.9 (IQR 11.1 - 103.9), biopsy Gleason score was 8 or higher in 20 men (61%), and clinical stage was M1 in 25 patients. Pathologically, positive surgical margin rate was 66% and pelvic lymph node metastasis was confirmed in 62%.

With the median follow-up of 46 months (IQR 31.7 - 52.7 months), 25 out of the 32 patients (78%) are still alive at the time of last contact. Fig. 1A illustrates overall survival for all 32

Table 1
Overall patient characteristics

	Median/Count	IQR/Frequency	
N	32		
Age (years)	64.5	57.5	70.0
Follow up (months)	46.0	31.7	52.7
Status			
Alive	25	78%	
Deceased	7	22%	
PSA at diagnosis	22.9	11.1	103.9
Clinical N and M stage			
N1M0	7		
N0M1	10		
N1M1	15		
ISUP grade group (Biopsy)			
NA (diagnosed by biopsy of met)	2	6%	
1	1	3%	
2	6	19%	
3	4	12%	
4	7	22%	
5	12	38%	
ISUP grade group (Prostatectomy)			
1	0		
2	1	3%	
3	9	28%	
4	2	6%	
5	20	62%	
Positive lymph node	20	62%	
Operative time (min)	225.0	198	311.8
Estimated blood loss (ml)	200.0	100.0	400.0
Major complication rate	6%		

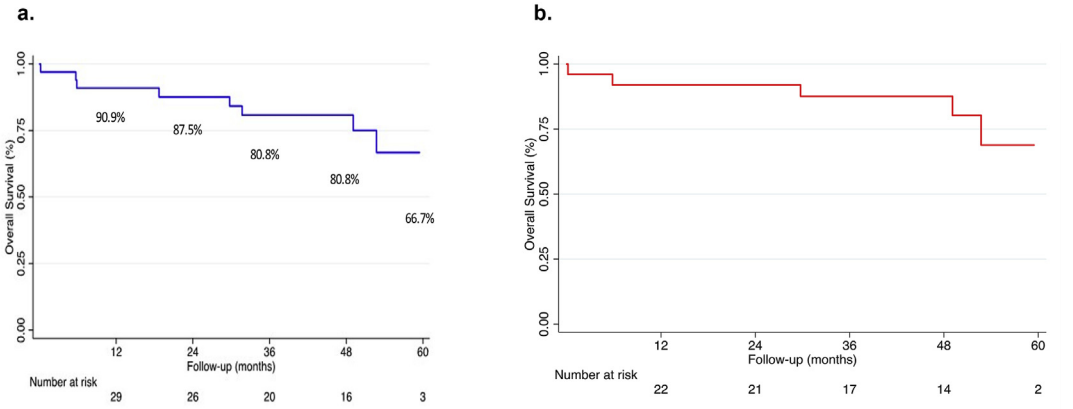

Fig. 1. a) Overall survival of all patients. Kaplan-Meier analysis was used to assess survival. (**b)** Overall survival of M1 patients. Kaplan-Meier analysis was used to assess survival.

patients in the study. The survival of 25 patients with M1 disease is described in Fig. 1B. 5-Year estimated overall survival for the entire cohort and M1 patients are 67% and 69%, respectively. Fifteen patients still have an undetectable PSA and seven have been switched to intermittent ADT after consultation between the treating medical oncologist and patient. After more than two years off all systemic therapy, five remain free of any evidence of disease with the normalization of serum testosterone (Table 2). Of the five, three have M1 disease on diagnosis.

3.2. RNA-seq analysis of favorable responders

To identify unique features of patients with mPCa who have favorably responded to CP, RNA sequencing was carried out. Based on the clinical outcome, patients were divided into three groups: (1) favorable group - undetectable PSA off all systemic treatment, (2) intermediate group - survival longer than two years but requires systemic treatment, and (3) unfavorable - survival less than two years.

Table 2
M1 patient characteristics

	Median/Count	IQR/Frequency	
N	25		
Age (years)	63.9	57	70.0
Follow up (months)	49.6	33.3	53.2
Status			
Alive	18	78%	
Deceased	7	22%	
PSA at diagnosis	89.57	11.1	130
Clinical M stage			
M1a	3		
M1b	22		
ISUP grade group (Biopsy)			
NA (diagnosed by biopsy of met)	2	8%	
1	0		
2	0		
3	5	20%	
4	7	28%	
5	11	44%	
Gleason score (Prostatectomy)			
1	0		
2	0		
3	7	28%	
4	1	4%	
5	17	68%	
Positive lymph node	14	56%	
Operative time (min)	255.4	190 300	
Estimated blood loss (ml)	269.6	100	402.5
Major complication rate	8%		

RNA-seq profiles of tumor samples and matching adjacent normal tissues from three patients each with favorable, intermediate, and unfavorable CP response were used to define a responder differential gene expression signature. Initial principal component analysis demonstrated a significant heterogeneity (Fig. 2A). When the signature was subjected to pathway enrichment analysis, we identified TNFα signaling via NF-kB from Hallmarks database as the most significantly downregulated pathway in patients with favorable response to CP (Fig. 2B; patients #3, 4 and 5 in Table 3). Gene Set Enrichment Analysis, which utilized the responder differential gene expression signature as a reference and TNF-α signaling as a query gene set (Fig. 2C, NES = −4.92, $p < 0.001$), highlighted genes that significantly contributed to this enrichment (Fig. 2D**,** leading edge genes). This analysis nominates downregulation of TNFα signaling to aid the selection of the optimal patients for CP.

3.3. Functional outcomes

Of the 25 men who are alive at last contact, the overall pad-free rate was 48%. Of the fourteen men who were pad-dependent, eight wore 1 pad per day (ppd) for security. Pre- and post-operative mean AUAss in M1 patients were 12.1 and 8.9 ($p = 0.297$), respectively. Interestingly, four men remain potent following surgery (16%).

4. Discussion

In the present study, we report the long-term results of our phase 1 study on CP. With a median follow-up of 46 months, the overall survival was 78%. Among 25 men with M1 disease on presentation, 72% were still alive at last contact and the estimated 5-year overall survival was 69%. Importantly, fifteen patients still have an undetectable PSA. With the implementation of intermittent ADT in seven of these men, five remain free of any evidence of disease off all systemic therapy with the confirmed normalization of serum testosterone for at least two years. Among these five patients, three patients had M1 PCa on diagnosis. Taken together, these results may have a significant clinical implication in treating men with mPCa on presentation.

Although mPCa is considered incurable, our present observations suggest that a minority of men with mPCa have a long-term durable response with the combination of CP and systemic treatment. Specifically, of the five men with an undetectable PSA off all systemic treatment, three had either M1a or M1b disease on diagnosis. These men have confirmed restoration of serum testosterone after more than two years off off ADT. Previously, O'Shaughnessy et al reported undetectable serum PSA in 4 of 20 patients by combining ADT with

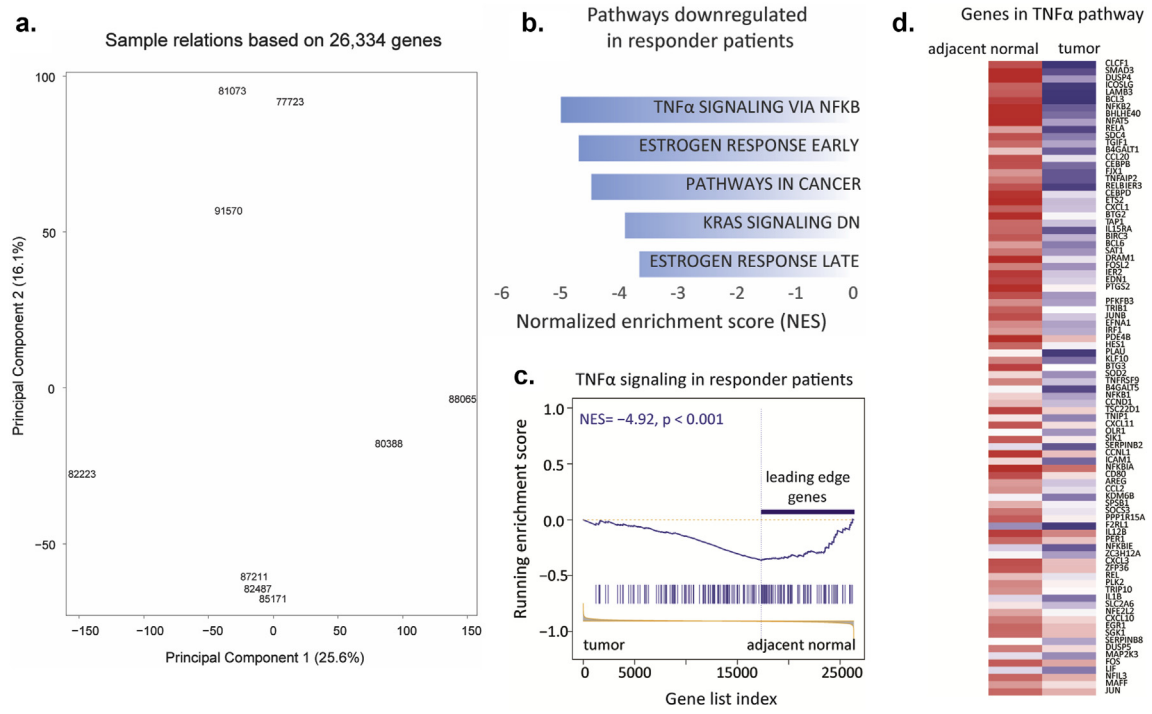

Fig. 2. Molecular analysis identifies the downregulation of TNFα signaling in responder patients. (**a**) The principal component analysis of RNAseq study revealed significant tumor heterogeneity in newly diagnosed mPCa. (**b**) The pathway enrichment analysis, using tumor (n = 3) vs. adjacent normal (n = 3) samples in responder patients as a reference signature and molecular pathways from KEGG, Biocarta, REACTOME, and HALLMARKS databased as query genesets. NES = Normalized Enrichment score. (**c**) Gene Set Enrichment Analysis (GSEA) using tumor vs. adjacent normal samples in responder patients as a reference signature and genes from the HALLMARKS TNFα signaling via NF-kB pathway as a query gene set. NES and p-values were estimated with 1,000 gene permutations. Leading edge genes are indicated with a blue horizontal line. (**d**) Heatmap representation of the leading edge genes from B. Each cell corresponds to the average of the scaled (z-scored) values for either adjacent normal or tumor samples and corresponds to the relative expression levels between these two phenotypes.

Table 3
Characteristics of patients with undetectable PSA off all systemic therapy

Number	Age	Pre-operative PSA	Biopsy gleason	Clinical stage	Last testosterone (ng/ml)
1	64	14.17	3 + 4	T1cN1M0	645
2	70	20.76	3 + 3	T2bN1M0	371
3	56	7.8	4 + 4	T1cN0M1b	444
4	62	5	5 + 5	T3aN1M1b	302
5	71	11.1	5 + 4	T1cN1M1a	248

local surgery and metastases directed radiotherapy.[14] Importantly, when ADT was discontinued in these men, PSA remained undetectable with confirmed non-castrate testosterone levels 20 months later. Interestingly, the authors reported that such result was observed only in men with M1b disease and not M1a. In contrast, one patient in our cohort had M1a disease. Although the numbers are small, these results collectively suggest that up to 10-20% of men with mPCa on diagnosis may have a durable long-term response with a multimodal treatment regimen that includes CP. We plan to continue following these patients to assess whether such patients with durable response to CP are cured.

To start defining men who may or may not benefit from CP, we utilized RNA-seq and found certain genomic signatures that warrant further investigation. Based on the oncologic outcome, we divided the patients into three categories - favorable, intermediate, and unfavorable. Although the principal component analysis revealed a significant tumor heterogeneity, a significant downregulation of TNF-α signature was detected in the favorable group. Previously, TNFα has been shown to promote PCa dissemination[15] and to be elevated in serum of patients with mPCa when compared to patients with localized disease.[16] Here, we show that downregulation of TNF-α signaling is characteristic for patients with good response to CP and thus can be potentially utilized to pre-select patients for this intervention. As for those in the poor group, one patient had elevated neuroendocrine markers. Although these results are preliminary, genomics analysis suggest that the incorporation of CP in treating mPCa may be personalized.

The oncologic outcome for the entire cohort and M1 patients in our phase 1 study reports an estimated 5-year OS of 67% and 69%, respectively, with a median follow-up of 46 months. Such result is similar in magnitude to the one observed in the previously reported analysis of the SEER database.[8] Despite such promising oncologic results, we also observed a potential cost of urinary incontinence for being aggressive. In men who were alive at last contact, 48% were pad-free. However, when the use of 1 ppd was included, 80% had a good urinary control. Since most men with mPCa are destined to have severe local urinary symptoms, such risk may be acceptable to most patients.

To definitively answer the role of CP on treating mPCa, there are two major ongoing randomized trials.[17] The Southwest Oncology

Group study (SWOG 1802), although not specifically focused on CP, investigates whether local treatment of primary tumor in mPCa provides any clinical benefit. It is a phase III study comparing standard systemic therapy to standard systemic therapy combined with combined with local treatment (surgery or radiotherapy) of the primary tumor. Due to the study design, however, the role of CP may not be clearly ascertained as it is offered in the same treatment arm as RT. Another trial, Surgery in Metastatic Carcinoma of Prostate (SIMCAP), is a phase 2.5 multi-institution clinical trial evaluating whether CP combined with systemic therapy has an impact on oncologic and quality of life outcomes in men with newly diagnosed mPCa. Both SIMCAP and S1802 are not oligometastatic studies as there are no limit on the volume of metastases. Key differences between S1802 and SIMCAP are as follows: (1) S1802 requires response to lead-in systemic therapy prior to randomization while SIMCAP does not; (2) S1802 eligibility criteria include clinical N1M0 disease (stage IVA, PCa AJCC vs 8)[18] while SIMCAP is limited to clinical stage M1 (stage IVB, AJCC vs 8)[18]; (3) SIMCAP's initial readout from the phase 2 portion will be available in 2-3 years. Accordingly, these two studies are complementary and will add meaningful and different perspective on the role of CP in treating patients with mPCa.

While surgery is the focus of the current investigation, local radiotherapy may also have a role in treating mPCa. Specifically, two studies on the effect of local radiation in treating men with newly diagnosed mPCa have been completed - HORRAD and STAMPEDE.[19,20] Both studies did not show any significant benefit of local radiation on overall survival. However, on a pre-specified subgroup analysis, the larger STAMPEDE trial demonstrated a 4 months increase in failure-free survival in men with 3 or less bone metastases. On the other hand, HORRAD study with a significantly lower sample size did not show any clinical benefit in men with low metastatic burden (5 or less bone metastases). Collectively, these data suggest that the local radiation at best has a marginal clinical benefit in mPCa and additional studies are needed to clearly define the optimal clinical context in implementing local radiotherapy for men with metastatic disease.

In conclusion, the current study reports an excellent long-term oncologic outcome in men who present with mPCa. Importantly, 10-20% of patients with mPCa may have a long-term durable response off all systemic therapy by combining CP with a limited period of ADT. Although urinary risk is not negligible, the potential therapeutic value of CP warrants further investigation. In this regard, we eagerly await the results of the currently ongoing randomized studies on CP - SIMCAP and S1802.

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Conflicts of interest

All authors have no significant conflict of interest.

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