Integrating chemohormonal therapy and surgery in known or suspected lymph node metastatic prostate cancer

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Abstract

Background—Prostate cancer persisting in the primary site after systemic therapy may contribute to emergence of resistance and progression. We previously demonstrated molecular characteristics of lethal cancer in the prostatectomy specimens of patients presenting with lymph node metastasis after chemohormonal treatment. Here we report the post-treatment outcomes of these patients and assess whether a link exists between surgery and treatment-free/cancer-free survival.

Methods—Patients with either clinically detected lymph node metastasis or primaries at high risk for nodal dissemination were treated with androgen ablation (ADT) and docetaxel. Those responding with prostate-specific antigen (PSA) concentration <1 ng/mL were recommended surgery 1 year from enrollment. ADT was withheld postoperatively. The rate of survival without biochemical progression 1 year after surgery was measured to screen for efficacy.

Results—Forty patients were enrolled and 39 were evaluable. Three patients (7.7%) declined surgery. Of the remaining 36, 4 patients experienced disease progression during treatment and 4 more did not reach PSA <1. Twenty-six patients (67%) completed surgery, and 13 (33%) were also progression-free 1 year postoperatively (8 with undetectable PSA). With a median follow-up of 61 months, time to treatment failure was 27 months in the patients undergoing surgery. The most frequent patterns of first disease recurrence were biochemical (10 patients) and systemic (5).

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Conclusions—Half of the patients undergoing surgery were off treatment and progression-free 1 year following completion of all therapy. These results suggest that integration of surgery is feasible and may be superior to systemic therapy alone for selected prostate cancer patients presenting with nodal metastasis.

Keywords

lymphatic metastasis; prostate cancer; hormone therapy; docetaxel; prostatectomy

Introduction

In everyday practice, surgery or radiation are frequently considered futile in the treatment of prostate cancer patients presenting with clinically detected metastases in lymph nodes (LN).[1] Although the prognosis of these patients is generally poorer than that of those whose disease has not disseminated, specific features of the primary tumor remain of critical importance.[2,3] Gleason score (tumor grade), primary tumor bulk (T-stage), and extent of LN involvement (including number of positive nodes, tumor burden within nodes, and extrapelvic metastasis) have all been noted to affect outcomes.[4,5] Poorly differentiated primary tumors and 3 involved nodes confer the highest risk of systemic progression and cancer–specific death.[1,2,6,7] The optimal integration of systemic and local therapies for these patients remains a dilemma.

Men presenting with nodal metastases are commonly treated with long-term androgen-deprivation therapy (ADT) alone or with radiation. The use of single modality ADT is associated with a high probability of eventual local disease progression (up to 60%), which may result in urinary retention, hematuria, and pain, among other symptoms.[8] Results from studies integrating ADT and curative-intent surgery/radiation in men at risk for or with regional cancer spread have led to an increasing recognition that local therapy is an essential part of the optimal treatment for these patients (see Verhagen et al.[9] for a recent review).[3,6,7,10–18]

We hypothesized that in patients clinically presenting with nodal metastasis or with primaries unlikely to be completely resected upfront, prostate cancer progression might be prevented or delayed using surgical consolidation of systemic therapy. A trial was designed that included 1 year of presurgical treatment followed in responding patients by prostatectomy. We previously reported on the molecular characterization of the residual cancers, and demonstrated that potentially lethal cancer foci persist in the removed prostate.[19] Here we present the post-treatment outcomes of these selected patients, with the primary goal to determine the rate of prostate-specific antigen (PSA) <1 ng/mL at 1 year following completion of therapy and treatment-free survival, and secondary goal to link outcomes to morphologic and clinical characteristics.

Materials and Methods

Patients and treatment

In this single-arm phase II clinical trial (NCT01076335), patients were required to have histologically confirmed prostate adenocarcinoma and no surgical contraindications. Enrollment took place from April 21, 2005 through March 31, 2008. At least one of the following inclusion criteria was needed: biopsy/pretreatment dissection confirming LN metastasis; pelvic and/or abdominal lymphadenopathy 2 cm in typical distribution (aortic/common iliac); or features in the primary tumor implying very high risk for lymph node dissemination ("suspected"), including at least 1 of the following: (1) Gleason score 8 plus PSA 25 ng/mL, (2) clinical (c)T3 disease together with Gleason score 7, or (3) cT4 disease. Patients with small-cell/sarcomatoid variants, clinical/radiological evidence of bone or visceral metastatic disease (M1b or M1c) or with prior chemotherapy or >6 months of ADT were excluded. All patients signed an institutional review board-approved written informed consent form before treatment.

ADT was combined with docetaxel and followed by surgical consolidation in eligible patients. Luteinizing hormone–releasing hormone agonist therapy was given for approximately 1 year until the actual surgical date. Oral bicalutamide (50 mg daily) was permitted. Docetaxel (35 mg/m^2) was administered intravenously on days 1, 8, 15, and 22 every 6 weeks for a total of three cycles in the first 6 months of the preoperative period.

Patients with PSA <1 ng/mL at the end of the systemic treatment period and no clinical progression were offered open or robot-assisted laparoscopic radical prostatectomy (per surgeon's preference) and extended bilateral pelvic LN dissection, scheduled within 6 weeks of completion of 1 year of ADT (from study enrollment). Surgery was not attempted in patients with grossly unresectable–appearing disease.

Disease evaluation and monitoring

PSA concentrations were assessed before initiation of each chemotherapy cycle, every 3 months, and within 6 weeks of surgery. Tumor imaging (bone scan, chest x-ray, computed tomography or magnetic resonance imaging of abdomen-pelvis) was performed before treatment and surgery and whenever felt indicated. After surgery, PSA and testosterone measurements were obtained every 3 months (first 12 months) and every 6 months thereafter until progression (in the case of testosterone, until recovery or return to baseline levels).

Toxicity

Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. Two docetaxel dose reductions (30 mg/m^2 and 25) were allowed. Patients needing more than two reductions or delays beyond 2 weeks owing to toxicity were withdrawn.

Surgical complications were assessed during and within 90 days of the procedure by using Clavien grading.[20] Urinary continence was evaluated by patient-reported daily pad usage 6 months postoperatively, and potency at 12 months.

End points and definition of treatment failure

The primary end point of the study was to define the rate of event-free survival (ie, freedom from treatment failure) 1 year postoperatively. Secondary end points included pathological complete response (pCR) rate, perioperative/postoperative morbidity, and tissue biomarker analysis.

Treatment failure was defined as objective tumor progression during therapy or in the year after surgery, confirmed postoperative PSA 1 ng/mL, or any postoperative radiation, hormonal, or other systemic therapy. The PSA 1 ng/mL level to determine failure was chosen because of (1) the very low probability of lower concentrations to relate to clinically visible metastases, and (2) its use in clinical practice as threshold to initiate ADT after recurrence following surgery. Patients who did not undergo surgery within 8 weeks of completing 1 year of therapy on protocol (for any reason, including patient refusal) were counted as treatment failure, as were patients whose surgery was begun and aborted.

Statistical analyses

The study was designed to enroll a maximum of 40 patients and to be stopped early if the data suggested that p (θ>0.50 | data) <5% (θ being the proportion of patients PSA-progression-free at 1 year postoperatively), assuming prior beta distribution with mean 0.5 and variance 0.083. Time to treatment failure (TTF) was estimated using the Kaplan-Meier method and calculated from the date of study enrollment to the date of progression or off-treatment date (or last follow-up, if missing), whichever first. All statistical analyses were performed with SAS 9.3 (SAS Institute Inc., Cary, NC) and S-Plus 8.2 (TIBCO Software Inc., Palo Alto, CA).

Results

Patients' characteristics

Forty patients were enrolled. Table 1 details demographics and baseline tumor features. Twenty-one patients (52.5%) had cN1 disease, 12 (30%) suspected LN involvement, and 7 (17.5%) clinical disease extension to nonregional LNs (M1a). Pathologic LN involvement at presentation was demonstrated on biopsy in 18/28 patients (64%) with N1/M1a disease. One patient (2.5%) declined presurgical therapy after enrollment and was excluded from subsequent analyses.

Presurgical therapy

Systemic treatment took place as planned in 39 patients. Of these, 37 (95%) completed the intended 12 weekly doses of docetaxel; the other 2 patients missed a single dose. Two patients (5%) required docetaxel dose reduction to 30 mg/m^2 during cycle 1. No dose reductions occurred during cycles 2–3. The most common treatment-related events were anemia (15 patients, all grade 1), fatigue (11), hyperglycemia (7), aspartate and/or alanine aminotransferase elevation (5), and limb edema (5). Table 2 shows grade >2 chemotherapy–related side effects. No patient withdrew for toxicity. Fourteen of the 39 patients (36%) received bicalutamide.

Surgery

Three patients (7.7%) voluntarily declined surgery following completion of the systemic therapy portion of the study. After approximately 1 year of presurgical therapy, 28 of the remaining 36 patients (78%) demonstrated no clinical progression and had PSA <1 ng/mL, moving to prostatectomy and pelvic LN dissection. However, surgery could not be completed in 2 of those patients (dense pelvic adhesions and intraoperative hypoxemia, one patient each). Twenty of the 26 patients (77%) underwent open procedures; the remaining 6 (23%) had robot-assisted surgery. The median hospitalization length was 2 days (range, 1–16).

Four patients (11%) of the 39 had no clinical progression, but their PSA was ≥1 ng/mL (mean, 2.9 μg/L; range, 1.6–4.4). All 4 elected to have surgery off study. Another 4 patients (11%) experienced clinical progression preoperatively and discontinued treatment; of these, 2 eventually underwent cystoprostatectomy for symptom control. Figure 1 shows the study profile.

Perioperative complications

The median intraoperative blood loss was 0.7 L (range, 0.1–2.9 L). Four of the 26 patients who underwent surgery on study (11%) required intraoperative blood transfusion (one unit, n=1; two, n=2; six, n=1). One patient experienced an intraoperative rectal injury that was successfully repaired. No perioperative deaths occurred. Clavien-graded complications and functional recovery data are respectively shown in Supplementary Table and Supplementary Results.

Pathology

Table 3 summarizes the surgical specimens' pathological characteristics. The median number of lymph nodes excised was 17 (range 4–49). Although most (20/26; 77%) demonstrated extraprostatic extension, the negative surgical margins rate was high (24/26; 92%). Two patients (8%) experienced pCRs. We reported the biomarker analysis in a separate publication.[19]

Postsurgical outcomes

Among the 26 patients who completed chemohormonal therapy and underwent surgery per protocol, 13 (50% [33% of the initial 39]) experienced treatment success, ie, PSA <1 ng/mL for at least 1 year postoperatively without clinical progression/additional treatment. PSA remained <0.1 ng/mL at 1 year in 8 of these patients (31% [21% of the initial 39]). The disease of 6 (23% [15% of the initial 39]) has not yet recurred (median follow-up 52.9 months); 4 continue to have undetectable PSA. These 6 patients include 5 with locally advanced adenocarcinoma at diagnosis, 2 of them with PSA >120 ng/mL and a separate 1 with high-volume Gleason score 10 (5+5) in the diagnostic biopsies; and 1 patient with biopsy-confirmed lymphadenopathy up to retrocrural space who achieved a pCR.

Total testosterone measurements for the first 4 months postoperatively were available for 22/26 patients who completed treatment. In 11/22 (50%), testosterone had recovered to >150

ng/dL. Twelve of the 13 patients who experienced treatment success had determinations available 1 year postoperatively: testosterone was >150 ng/dL in 11 (92%).

Of the 20 patients whose disease recurred after completion of treatment (Table 4), 4 (15% of the 26) experienced local recurrence; only 2 (8%) were symptomatic (including ureteral obstruction). The surgical margins were negative in all 4 patients.

With a median follow-up of 61 months, the overall median TTF in the 39 patients receiving presurgical therapy was 21.6 months (95% CI 12.1–26.7) (Figure 2a). The median TTF in the 26 patients who underwent surgery per protocol was 27.0 months (95% CI 21.7–44.4). With 10 deaths (9 prostate cancer-related, 1 due to an accident), the median overall survival has not been reached (Figure 2b). Four of the deaths occurred in patients who had completed protocol treatment.

Discussion

Participants in this clinical trial presenting with clinically evident nodal disease or advanced primaries not meeting criteria for curative surgery upfront (70% and 30% of the patients, respectively), received systemic treatment for 1 year combining ADT and chemotherapy. We reasoned that this strategy would help identify those most likely to benefit from consolidative surgery. Analysis of the residual tumors also allowed characterization of molecular changes associated with the development of the lethal castrate-resistant phenotype.[19]

We envisioned a twofold benefit from this approach: to allow for a meaningful temporal break in androgen ablation (favored by setting the PSA threshold to pronounce failure at 1 ng/mL) and, more importantly, to prevent or delay prostate cancer progression. Withholding hormonal therapy for at least a year probably resulted in decreased morbidity and improved quality of life for the individuals in whom it was withheld, although this was not formally tested in the study. Regarding disease progression, our results show a respectable TTF >2 years for the patients completing surgery, a significant number of whom (50% here) may remain with PSA <1 ng/mL and clinically disease-free for a minimum of 1 year while at very low risk for recurrence at the local site. Our 15% total and 8% symptomatic local relapse rates are better than those reported in retrospective series of prostatectomy alone[8,14] and comparable to prostatectomy and adjuvant ADT and/or radiotherapy.[8,21] Moreover, that 15% of patients remained free from recurrence with almost four-and-a-half years median follow-up is worth noting for this prostate cancer set. Our limited sample size, follow-up time and lack of comparator nonsurgical arm, though, warrant caution in making comparisons.

Tolerance to the combination of weekly docetaxel and ADT was good and predictable. This study was designed at a time when docetaxel was the only systemic therapy having shown a survival advantage for castrate-resistant prostate cancer and its preoperative use still considered promising. Unfortunately, the results of studies of taxanes as single agents or in combination with ADT in previously untreated high-risk patients have suggested no enhanced benefit over the use of ADT alone concerning pathologic as well as long-term

outcomes, even when the docetaxel was administered every 3 weeks and at doses higher than that in our trial.[22–26] Consistently, >75% and approximately 50% of our patients had evidence of respectively residual locally advanced and pelvic LN–metastatic disease after completing treatment, and 9 have died of progressive prostate cancer. Very recent data from a randomized phase III clinical trial (CHAARTED) suggests that, among patients newly diagnosed with metastatic hormone sensitive prostate cancer, those presenting with visceral disease and/or 4 bone lesions are the ones that benefit the most from the early use of docetaxel.[27]

In current clinical practice, the decision to offer surgery and/or radiation to patients presenting with LN metastasis after a period of ADT is not well established. It depends on careful assessment of the quality of the achieved response and the patient's context, including general health, comorbidities, and treatment preferences. We chose 1 year of presurgical therapy to allow for slow responders to be considered for prostatectomy but, in retrospect, 6- 9 months would have probably been enough since chemotherapy was completed in the first half and few additional symptomatic/PSA responses occurred in the second (not shown). Six months is also a useful time frame for identifying prostate cancers with an "anaplastic" phenotype, which demonstrate decreased dependence on androgen-regulated pathways by their behavior.[28] In considering consolidative treatment, it is important to notice that the PSA response alone is not enough and can be misleading, as demonstrated by our observed 77% patients with PSA <1 and high residual (extraprostatic) volumes of cancer.

To the best of our knowledge, this is the first prospective study of presurgical therapy and consolidative surgery primarily directed to patients newly diagnosed with lymph node-metastatic prostate cancer. Although significantly limited by a relatively small patient set and lack of a comparator ADT-only arm, precluding any practical conclusions, our results suggest that such integrative strategy is feasible, and at a minimum likely to enhance disease control in carefully selected prostate cancer patients presenting with LN metastasis. The use of weekly docetaxel did not result in better pathologic or survival outcomes than might be seen with ADT alone, but the presurgical therapy still helped select patients for surgery. Removal of residual treatment-resistant foci in the primary site and lymph nodes may retard metastatic progression in some patients, thus allowing for the opportunity to delay hormonal therapy after surgery, or cure others. However, the effectiveness of presurgical therapies must be improved before this approach can be considered for phase III testing, since the greatest survival benefit is to likely be obtained in those achieving major responses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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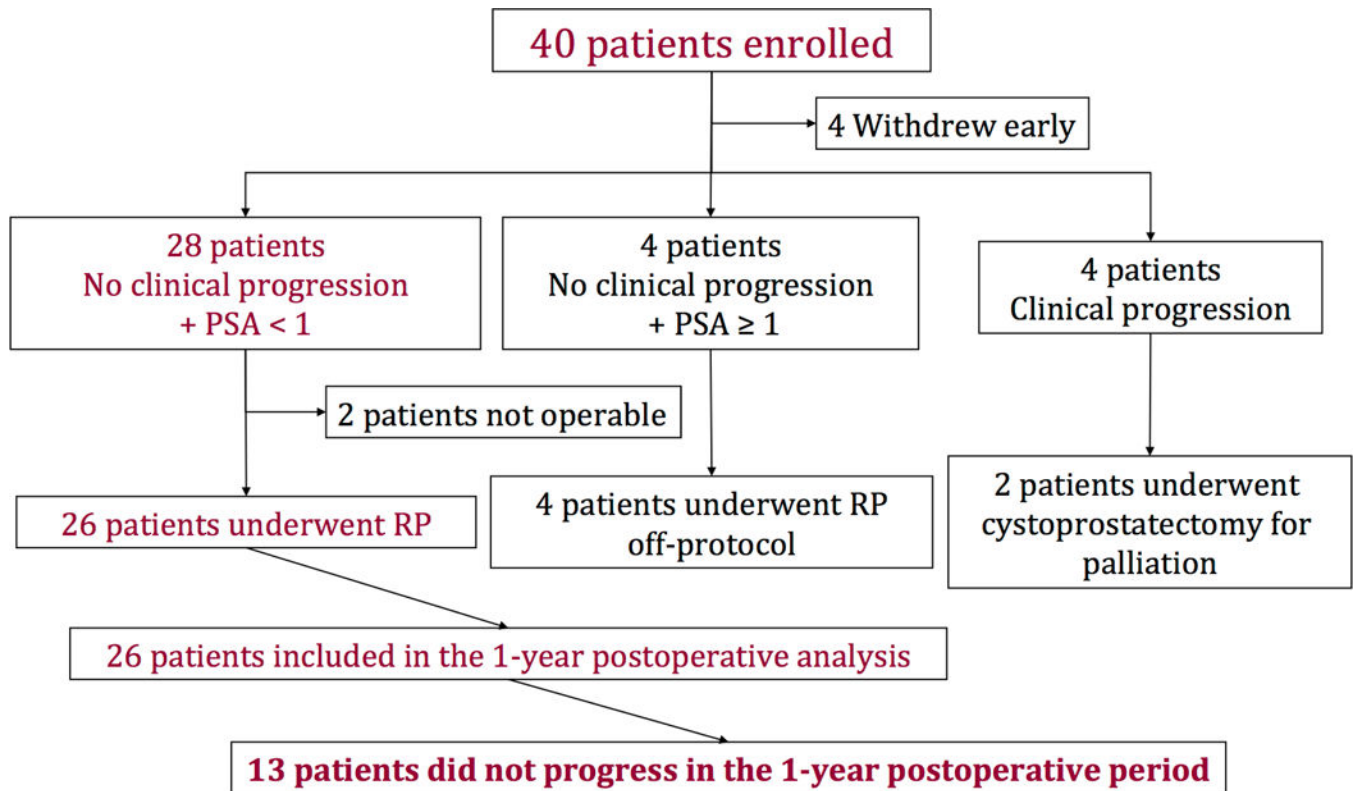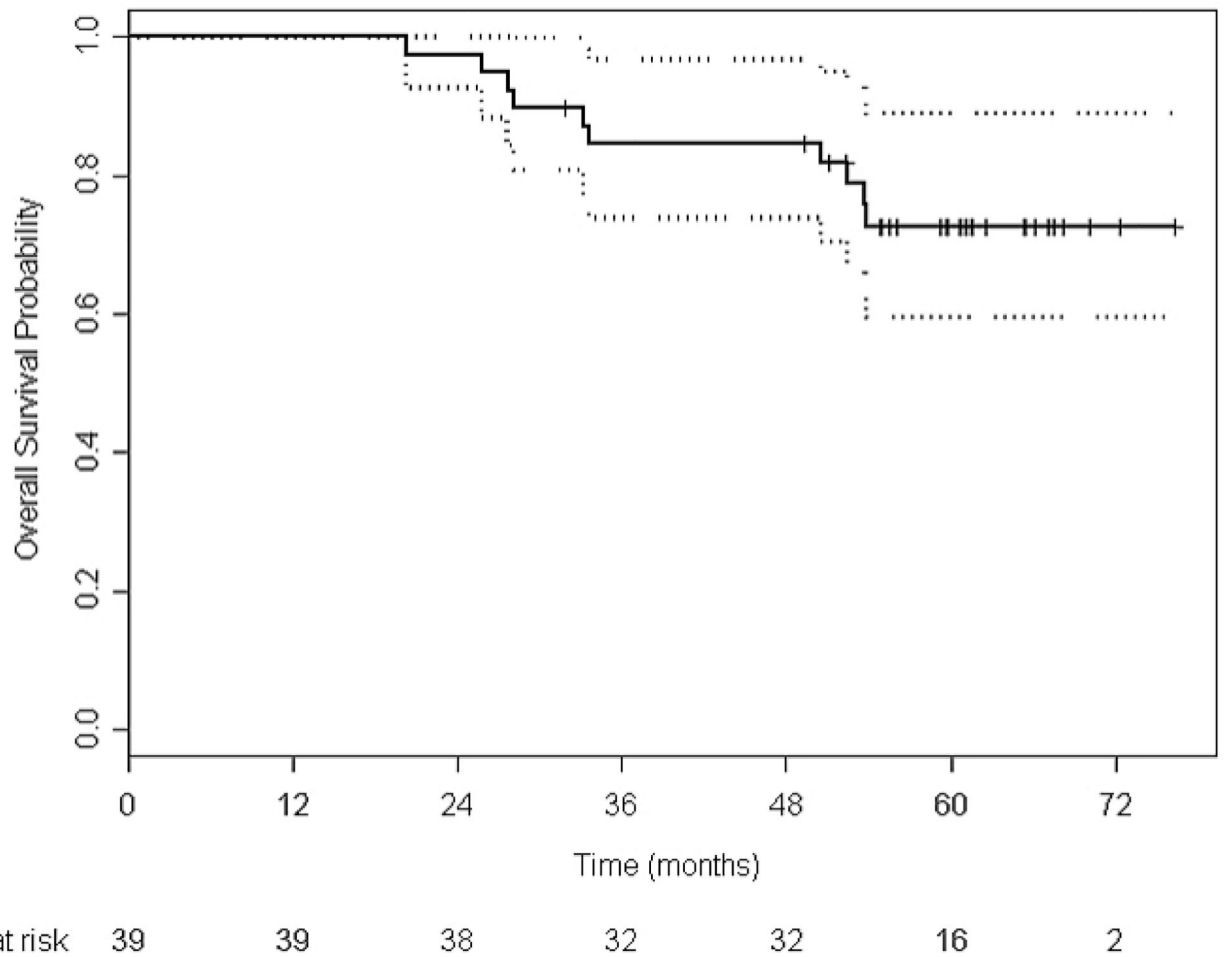
Figure 1. CONSORT diagram showing study's profile
RP, radical prostatectomy with bilateral pelvic lymph node dissection.
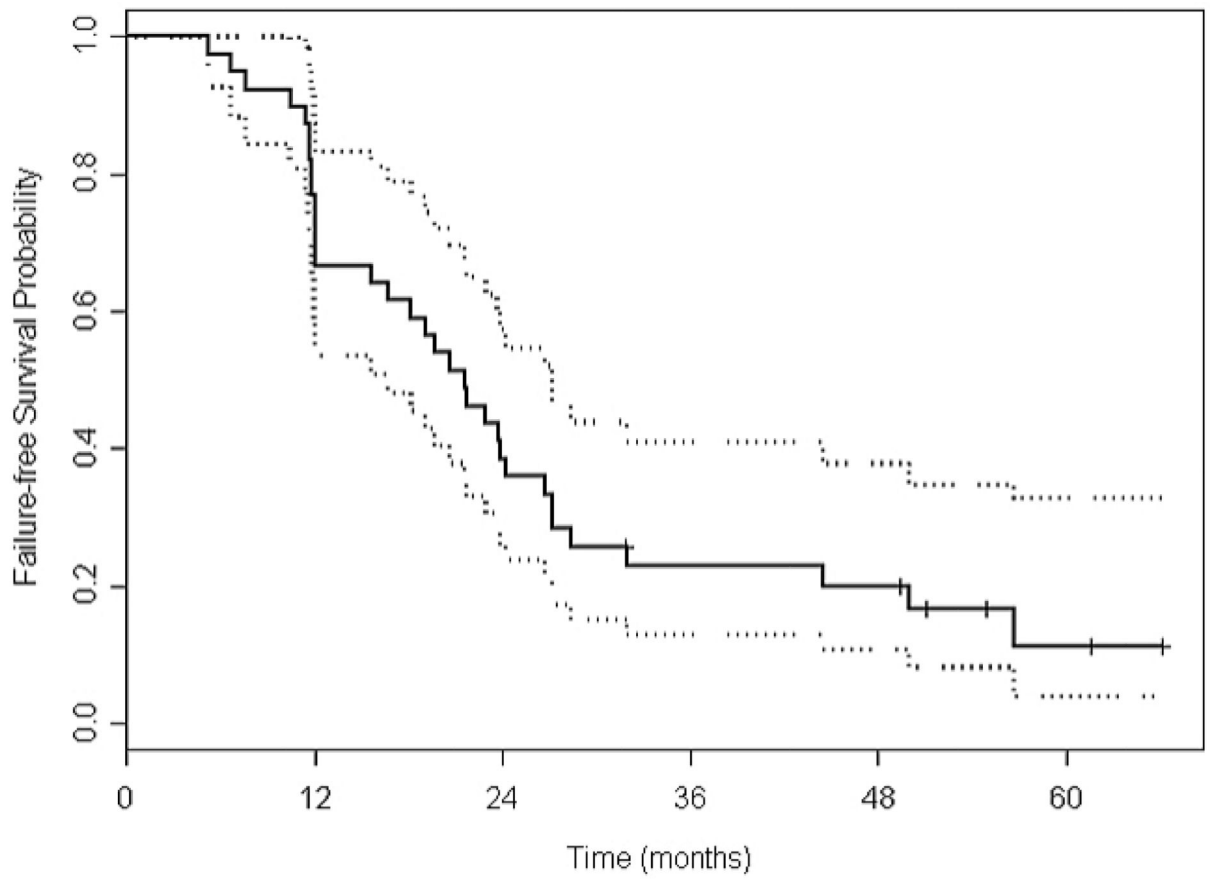
Number at risk   39   30   15   8   7   2

Figure 2. Kaplan-Meier estimates of event-free survival (A) and overall survival (B) in the 39 patients receiving presurgical therapy

The median time to treatment failure was 21.6 months (95% CI 12.1–26.7 months [dashed lines]). Among the six patients who were failure free at their last assessment, the median follow-up time was 52.9 months.

Table 1

Patients' characteristics

Characteristic	Patients (n=40)
Median age at enrollment, years (range)	61.5 (38–75)
Race/ethnicity, no. (%)	
Caucasian	36 (90)
African American	3 (7.5)
Hispanic	1 (2.5)
Clinical T stage, no. (%) [*]	
T2b	5 (12.5)
T2c	5 (12.5)
T3a	9 (22.5)
T3b	14 (35)
T4	7 (17.5)
Lymph nodes status, no. (%) [*]	
Suspected [**]	12 (30)
N1	21 (52.5)
M1a	7 (17.5)
Biopsy Gleason score, no. (%)	
7	3 (7.5)
8	7 (17.5)
9	27 (67.5)
10	3 (7.5)
PSA before presurgical therapy, ng/mL (range)	26.7 (1.4–479.5)
>25	15 (37)
25	26 (63)

[*] 2002 American Joint Committee on Cancer (AJCC) staging system.

[**] Features in the primary tumor implying very high risk for lymph node dissemination (see Materials and Methods, Patients and Treatment section for description.

Table 2

Chemotherapy-related grade >2 preoperative medical toxicity (n=39)

Toxicity	Grade 3	Grade 4	Total
Hyponatremia	0	1	1
Atrial fibrillation	1	0	1
Pericardial effusion	1	0	1
ALT/AST elevation	1	0	1

Common Terminology Criteria for Adverse Events v3.0.

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4

Patterns of disease recurrence among patients completing treatment (n=20)

Pattern	No. (%)
Biochemical (PSA only)	10 (50)
Local [*]	4 (20)
Asymptomatic	2 (10)
Symptomatic	2 (10)
Systemic [*]	7 (35)
Lymph nodes	4 (20)
Lymph nodes + bone	1 (5)
Liver + lymph nodes + peritoneum	1 (5)
Brain [†]	1 (5)
Unknown	1 (5)

[*] Two patients experienced synchronous local and systemic disease recurrence.

[†] Prostatic adenocarcinoma in resected cerebellar mass