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What is the correct staging and treatment strategy for locally advanced prostate cancer extending to the bladder?

Özgür Haki Yüksel, Ayhan Verit, Ahmet Ürkmez

Fatih Sultan Mehmet Research & Training Hospital, Dept. of Urology, Istanbul, Turkey

__Summary__ *In locally advanced prostate cancer with bladder invasion, frequently encountered problems such as bleeding, urinary retention, hydronephrosis, and pain create distress for the patients. Therefore patients' quality of life is disrupted and duration of hospitalization is prolonged. Relevant literature about accurate staging and treatment of locally advanced prostate cancer with bladder invasion was investigated.*
Locally advanced prostate cancer can present as a large-volume aggressive tumor extending beyond boundaries of prostate gland, and involving neighboring structures which can be involved as recurrence(s) following initial local therapy. Survival times of these patients can range between 5 and 8 years. Their common characteristics are adverse and severe local symptoms unfavorably affecting quality of life Control of local symptoms and their effective palliation are independent clinical targets influencing survival outcomes of these patients.
The treatment outcomes of locally advanced prostate cancer into the bladder are currently debatable. Although in the current TNM classification, it is defined in T4a, we think that this may be categorized as a subgroup of T3 and thus encourage surgeons for the indication of radical surgeries (radical prostatectomy, radical cystoprostatectomy) in selected patient populations after discussing issues concerning consequences of the treatment alternatives, and expectations with the patients. Cystoprostatectomy followed by immediate androgen deprivation therapy may be a feasible option for selected patients with previously untreated prostate cancer involving the bladder neck because of excellent local control and long term survival.

KEY WORDS: *Bladder neck invasion; Cystoprostatectomy; Locally advanced prostate cancer; Radical prostatectomy; Staging.*

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INTRODUCTION

Locally advanced prostate cancer (LAPC) has been clinically described as a cancer extending beyond prostate capsule, with invasion of pericapsullar tissue, apical region of the bladder, bladder neck or seminal vesicles without lymph node involvement or distant metastases. In clinical staging, they are categorized as T3-T4 N0 M0 prostate cancer (PC) and constitute 10-20% of the cases with newly diagnosed cases of PC (1). While in previous reports, nearly 40% of the cases with newly diagnosed PC were categorized in clinical stage T3 (cT3), currently

its incidence ranges between 5-15% (2). Approximately 5-15% of the PC cases are located in clinical stage of T4. In current TNM staging, bladder neck invasion (BNI) has been categorized as stage T4 disease (Table 1).
Management of localized PC and metastatic disease has been summarized in algorithms, although optimal treatment of clinical stage T3-T4N0M0 PC is intensively debated. One of the main reasons of these debates is related to inaccurate local clinical staging over T2 or under staging of positive lymph node (LN) (3).
According to *European Association of Urology* (EAU) guidelines, watchful-waiting, radiotherapy (RT), radical retropubic prostatectomy (RRP), androgen deprivation therapy (ADT) and various combinations of these treatment modalities based on general clinical condition of the patient and local invasion of the tumor can be used (Table 2). According to the current scientific data, multimodality therapy was recommended for the majority of patients. Treatment of locally advanced disease aims at two fundamental goals; the first goal is complete elimination of the disease and the second one is achievement of local control. In terms of biological behavior of PC, low, medium and high risk groups are defined. For high-risk disease, 'clinical T3', 'locally advanced', 'bad differentiated' terms are used and however these are not sufficient to identify the disease (4). Definition of high-risk PC is associated with different criteria according to different sources as summarized in Table 3.
D'Amico risk classification grouping is the most widely used. Accordingly, prostate-specific antigen (PSA) ≥ 20 ng/mL or Gleason score (GS) 8-10 or clinical stage ≥ cT2 are considered as high-risk criteria of prostate cancer (5). American Urological Association (AUA) has also used this risk stratification since 2007 (6). Traditionally, urologists prefer RT and ADT rather than RRP for the treatment of high risk PC. Population-based Surveillance, Epidemiology and End Results (SEER) cancer data examination results showed us that in clinical T3 disease the rate of patients who underwent RRP, decreases from 18.1 to 9.1% and RT rates increase of 20% (7). In patients under the age of 70 who were diagnosed with high-risk prostate cancer, 25% of them could not receive an effective local treatment (2). According to the *Cancer of the Prostate Strategic Urological Research Endeavor* (CaPSURE) data, most of the newly diagnosed patients with high-risk localized PC canalize to the ADT as if the unique

Table 1.
2009 TNM staging system of the PC.

T: Primary tumor
Tis: No evidence of primary tumor
T1a: Tumor detected in less than 5% of the total TUR [transurethral prostate resection] material, normal DRE findings, total Gleason score < 7 pts
T1b: Tumor detected in more than 5% of the total TUR material, normal DRE, Gleason score > 7 pts
T1c: Tumor diagnosed based on the results of the fine needle biopsies performed because of increased PSA levels in a group of patients with normal DRE estimates
T2a: Tumor involving only half or less than 50% of one lobe of the prostate
T2b: Tumor involving more than one half of one lobe
T2c: Tumor involving both lobes
T3a: Uni or bilateral extra-capsular invasion
T3b: Seminal vesicular involvement
T4a: Involvement of bladder neck, external sphincter or rectum
T4b: Tumor invading pelvic wall
N: Regional lymph nodes
N0: No evidence of invasion
N1: A single metastatic lymph node measuring 2 cm in diameter
N2: A single metastatic lymph node measuring 2-5 cm or multiple metastatic lymph nodes each measuring < 5 cm in diameter
N3: A metastatic lymph node larger than 5 cm in diameter
M: Distant metastases
M0: No evidence of metastasis
M1a: Metastasis to non-regional lymph nodes
M1b: Bone metastasis
M1c: Distant rgan metastasis

Table 2.
2013 EAU guidelines in the light of the treatment of locally advanced PC, some of the alternatives.

Mode of treatment	Indications and general information	Degree of evidence
Watchful waiting	Asymptomatic, well and moderately differentiated tumors and patients with low life expectancy and a life expectancy ≤ 10 years	3
Radical prostatectomy	Selected cT3a, Gleason ≤ 8, PSA ≤ 20 ng mL and life expectancy ≥ 10 years	3
	Selected cT3b-T4, N0 or someone T and N1: Multimodality practicable treatment	3
	T3a: Unilateral nerve-sparing surgery	4
	RP+Adj HT [Bicalutamide 150 mg1x1] useful in increasing progression-free survival	
	NHT+RP: ineffective overall survival or disease-free survival	
Radiotherapy	T3NoMo In the early postoperative period in patients with adjuvant RT [positive surgical margins, especially in the] progression-free survival helpful	1
	T2-T3NoMo, in patients with persistent elevated PSA recurrence of elevated PSA and PSA 0.5 ng ml before RT can be given in recovery	3
	T3-T4NoMo ve WHO performance status-2 for patients; concomitant and adjuvant hormone therapy [3 yr] is beneficial to overall survival	1
	T2c-T3 No-x, Gleason 2-6 in patients neo-adjuvant and concurrent with short term ADT overall survival was helpful	1b
	High-risk N1Mo and without severe comorbidities in patients pelvic external beam RT and concurrent long-term adjuvant hormone therapy, overall survival, biochemical control is useful, due to disease and the development of metastases associated with failure delays	2b
Hormonotherapy	Symptomatic, T3-T4, PSA > 25-50 ng mL, PSA doubling time < 1 year for patients	1
	Patients suitable for RT are not suitable for hormonal monotherapy	
	Nonsteroidal antiandrogen monotherapy is an alternative to castration	2a

Table 3.
Definitions of high-risk prostate cancer

Source	Definition
D'Amico et al. (3), AUA (4)	PSA ≥ 20 ng/ml or GS 8-10 or Clinical Stage ≥ T2c
EAU (5)	PSA ≥ 20 ng/ml or biopsy G 8-10 or Clinical stage ≥ T3a
RTOG (6)	PSA 20-100 ng/ml, biopsy GS 8-10 and Any clinical stage or clinical stage ≥ T2c or PSA < 100 ng/ml and GS8-10
NCCN (7)	PSA > 20 ng/ml or GS 8-10 or clinical stage ≥ T3 or T2b/c, GS = 7, PSA > 10 any two of the parameters
Eastham et al. (8)	Kattan nomograms in the 5-year progression probability ≤ 50%
D'Amico et al. (9)	Preoperative PSA velocity > year 2 ng/ml

AUA: American Urologic Association; PSA: Prostate Spesific Antigen; GS: Gleason Score; EAU: European Urologic Association; RTOG: Radiation Therapy Oncology Group; NCCN: National Comprehensive Cancer Network

valid treatment option (8). Although in the current TNM classification it is defined in clinical stage of T4a, we think that LAPC invading the bladder may be categorized as a subgroup of cT3 in order to encourage surgeons to the indication of radical surgeries (RRP, cystoprostatectomy) in selected patient populations and after discussing with the patients issues, concerning consequences of the treatment alternatives and expectations. Altogether, we think that clinicians should not strictly obey the classical staging systems in every cases, especially when LAPC invaded the bladder.

DISCUSSION

In LAPC, RT and ADT are considered as standard treatment modalities, however in selected cases, RRP is recommended as a primary treatment alternative. An advantage of RRP which should not be overlooked is that RRP can demonstrate true histopathological stage of the primary cancer and evaluate potential LN invasion. By this modality, patients with disease recurrence and progression risks can be determined. In fact, patients with organ-confined disease (pT2) can be spared from morbidities of adjuvant treatment modalities.

Extracapsular invasion is found in 88-91% of the cases with clinical manifestations of LAPC, while surgical margin positivity (PSM) and seminal vesicle involvement (SVI) have been reported in 22-53% and 23-29% of the cases, respectively (9).

Whether BNI conveys a high risk for biochemical progression following RRP is a debatable issue. In TNM staging system, BNI is not defined in detail with respect to its microscopic and macroscopic characteristics.

Independent prognostic value of microscopic BNI in PC is not clear. In a study encompassing 1845 patients, conically resected bladder neck specimens were evaluated and true BNI was defined as PC focus within thick smooth muscle bundles without intermixed benign prostatic tissue. While false BNI was described as PC cells intermixed with benign prostatic tissue. BNI was evaluated and analyzed within the context of preoperative serum PSA levels, extra prostatic invasion, SVI, PSM, LN involvement, previous RRP (if any), GS and tumor volume in 90 of 1845 patients diagnosed with BNI. Sixty-three cases of 90 (4.9% of 1845) patients with microscopic BNI were classified as true BNI and 27 cases were categorized as false BNI. In patients with BNI, time to biochemical failure was similar in patients with negative and positive surgical margins (Kaplan-Meier curves). Even though BNI is related to other pathologic features, as demonstrated in previous studies, it is not an independent marker of PSA recurrence. In the light of previous and currently available data, the authors had expressed their expert opinions about TNM staging system and indicated that staging system should be reviewed with respect to BNI and these group of patients should be included in the clinical stage of T3a with favorable prognosis (10).

Dash et al. performed a univariate analysis on their 1123 cases with localized PC and estimated relative probabilities for PSA recurrence risks as 1.52, 3.05 and 8.59 for patients with BNI, extraprostatic tissue invasion and SVI, respectively (11).

In a study conducted by *Ruano et al.* in a series of 290 consecutive patients, 55 cases who presented with BNI and a subgroup of 18 cases also showing PSM according to microscopic criteria of Yossepowitch were compared to patients with extraprostatic extension or seminal vesicle invasion showing no statistically significant intergroup difference as assessed by Cox proportional hazard model. In conclusion, patients with microscopic BNI after RRP had higher preoperative PSA values and GS, higher PSM, advanced pathologic stage and larger sized tumors when compared to those with extraprostatic involvement but showed similar biochemically detected recurrence-free rates. Furthermore, their outcomes were more favorable in comparison to the patients with seminal vesicle involvement and the Authors indicated the need for inclusion of these tumors in clinical stage T3a (12).

Problems encountered in radical surgery performed for LAPC with BNI include higher rates of SVI and LN positivity when compared to the patients with localized disease. However some studies have demonstrated absence of any biochemically detected disease progression within 10 years after RRP in 25% of the patients with SVI and without metastatic LN (13). As a reason for this outcome, discrepancies in the definition of SVI have been indicated (14).

Secin et al. evaluated 387 preoperatively treatment naive patients with SVI who had undergone RRP and published their 15-year follow-up outcomes (15). In this study, 10 and 15 year disease-free survival rates of 296 (76%) patients with SVI but no LN involvement were reported as 89 and 81%, respectively. However their biochemical recurrence rates were indicated as 64 and 68%, respectively. In the same study, 10-year biochemical disease-free and disease-specific survival rates for 92 patients with SVI and LN involvement were reported respectively as 10 and 74%. Nevertheless, at the end of 10 years, 66% of the patients were still surviving (7).

Masterson et al. analyzed 24 patients with LN positivity and SVI and reported 5-year biochemical disease-free survival rate as 25.9% and they estimated mean time interval up to the PSA progression as 6 months (16). Boorjian indicated that in cases with only one LN involvement, the risk of disease-specific mortality had increased 4-fold which was two times higher in patients with multiple LN involvement (17).

In a higher-stage LAPC, as supported by the outcomes of some literature studies, extended LN dissection can be recommended instead of standard pelvic LN dissection. In standard pelvic LN dissection, lymphadenectomy is confined within obturator fossa, whereas in the extended approach, whose importance has been currently emphasized in many publications, in addition to the boundaries of the standard procedure, the target of lymphadenectomy is extended to include external iliac vein, internal iliac vessels, and femoral canal. In a study conducted by *Heidenreich et al.*, the *Authors* reported that LN positivity had been 12% in patients who had undergone standard pelvic LN dissection, but it had raised up to 26% in the extended procedure. For high-risk patients as those with BNI, extended pelvic LN dissection has been recommended, because, especially in the presence of low-volume, micrometastatic LN involvement, relatively

longer disease-free survival can be achieved (18). Morbidity of RRP in high-risk PC is similar to that in low-risk patients (4). For these reasons, nowadays RRP in high-risk patients began to be proposed and implemented more frequently. *Berglund et al.* reported that in patients of high-risk groups who underwent RRP; recovery time, duration of catheterization and continence turnaround time were similar with patients of low risk group (19). In RRP patients with clinical T3, perioperative mortality rates were similar with clinical T2 patients (20). In major centers RRP results of the 5-year and 10-year biochemical recurrence free rates were 30-70% and 15-60%, respectively (21-22). In another study, clinical T1c-T3b PC patients who underwent RRP or RT were retrospectively compared. At 8-year follow-up results when poor-risk patients treated with RRP were compared to those treated with RT showed that metastatic progression rate of RT group was 9.5% more than to RRP group (4). One of the most important advantage in RRP is the ability to accurate pathological staging. Approximately 15-25% of the clinical stage T3 tumors reported as high-graded (23). Consequently RRP may provide more information in determining the need for additional treatment. In addition, LN dissection that was performed during RRP helps us to detect micrometastases which cannot be detected by imaging methods. Otherwise; removal of the seminal vesicles increases the effectiveness of adjuvant treatment (23). In high-risk patients, considering age, general health status and 10 year life expectation, RRP should be recommended as primary treatment. Ten-year biochemical recurrence-free survival rate was 68% in 35% of 175 RRP patients who were reported as organ-confined disease according to D'Amico risk classification and at the end of follow-up, metastasis-free survival rate and cancer-specific survival rate were 84% and 92%, respectively (24).

In a retrospective multicenter study, 3828 patients with high risk of PC who underwent RRP were evaluated between years of 1987 and 2010. Ten-year cancer-specific and non-cancer-cause mortality rates were 5.9% and 14.3%, respectively (25).

In a multicenter European study, were evaluated 1366 patients who were diagnosed as high-risk PC (26). In 37% of overall patients, organ-confined disease has been identified. This rate in presence of only one of the preoperative risk factor was 45%, but in presence of three risk factors (GS, PSA, clinical stage) organ-confined disease detection rate dropped to 9%.

Fowler et al. reported that the 5-year survival rate of patients with LAPC who were treated with hormone therapy alone was 92% with a mean follow-up of 78 months (27). *Bolla et al.* compared the results of combined ADT and RT with those of RT alone in LAPC and reported that overall survival at 5 years was 79% in the combination group and 62% in the RT alone group (28). However, patients with PC BNI were generally high-grade (GS 9-10). In the majority of patients short time to progression and lower urinary tract symptoms were observed. We know the high incidence of complications that occurr when salvage surgery performed after RT (29-30). Patients with clinical stage T4 PC are rarely encountered and in only few centers surgical treatment are applied for these patients. Evaluation of this group of patients provides little information about treatment outcomes. Johnstone et al. followed up 1093 clinical stage T4 PC patients at diagnosis and divided them into 5 categories: RRP, only RT, only ADT, RT and ADT combination, and untreated group. The Authors reported that RRP applied for clinical stage T4 PC patients had provided better survival rates when compared with patients who received mono-RT or mono-ADT. Survival rates achieved with surgery were found to be comparable with those obtained with RT and ADT combination therapy (31). Furthermore, the study indicated the survival of RRP over combined RT with ADT for clinical T4 PC with lymph node metastases (32).

When performing cystoprostatectomy (CP) for PC involving the bladder neck, the possibility of overtreatment should be considered. Among clinical T4, compared to patients with PC involving the rectum or pelvic floor muscles, those with BNI may be better candidates for CP to achieve local cancer control and improvement of quality of life (QOL).

Manifestations of BI consist of hematuria, urinary urgency, pelvic pain, and bladder outlet obstruction. Besides, bladder outlet or ureteral obstruction can lead to renal failure. Many patients might be dependent on lifelong requirement for nephrostomy tubes, ureteral, and urethral stents, and more than one invasive procedure might be needed for routine tube replacements or revision operations. Complications of long-term tube drainage of the urinary tract comprise obstruction, bladder spasms, bleeding, infection, and stone formation. Local symptoms related to BI determine quality of life and reveals the clinical condition. Among adjuvant procedures applied for the management of locally advanced and symptomatic PC patients, systemic treatments as ADT and chemotherapy, local therapies including cryotherapy or surgery (TUR), and local palliative approaches (nephrostomy, and ureteral stent implantation) can be enumerated. The beneficial effect of androgen therapy is restricted with the development of androgen insensitivity. *Still*, in 89% of the patients under systemic chemotherapy, local symptoms were maintained (1). Cryotherapy has been tried after failure of RT, but could not prevent lower urinary tract symptoms (33). On the other hand relieve of outlet obstruction by transurethral resection (TUR) is short-lasting and repeated transurethral procedures might be required (34).

Previous reports on patients who had undergone salvage surgery including CP have demonstrated that they have rarely provided cure. However, in these reports palliative role of CP on patients with local symptoms was not investigated. Leibovici et al. performed palliative CP on a total of 38 T4 PC patients who developed recurrence following primary disease (n = 17), and RT (n = 21). The authors compared local symptoms, and the need for surgical intervention for the relief of obstruction before the operation, and at postoperative 3 month follow up during a mean follow-up period of 23 months (35) showing that the role of palliative CP was not statistically significant.

In several institutions, CP was performed in PC patients with BNI showing severe LUTS for the purpose of relieving those symptoms. *Kumazawa et al.* published out-

comes of CPs they performed on 17 stage T4 patients between the years 1989 and 2005. All the patients in this study, including patients who developed local recurrence, had no local symptoms or no need for catheters for urinary tract obstruction until death. Although no study has compared QOL after conservative treatment and surgical intervention in PC patients with BNI, results indicate that CP may be a treatment option in these patients. Postoperatively, all patients received additional surgical or medical castration therapy during the mean postoperative period of 89 months. The authors determined 5-year disease-free biochemical survival rate as 62 percent. They demonstrated that palliative CP can be performed even for lymph node positive patients (36).

In the light of these data, we need further researches in order to achieve a more accurate assessment and alternative treatments for LAPC patients.

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Correspondence

Özgür Haki Yüksel, MD (Corresponding Author)
ozgurhaki@gmail.com

Ayhan Verit, MD. Prof,

Ahmet Ürkmez, MD

Dept. of Urology, Fatih Sultan Mehmet Research & Training Hospital
Içerenköy/Ataşehir Tr- 34752 Istanbul, Turkey