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Original article

Tumor cytoreduction results in better response to androgen ablation—a preliminary report of palliative transurethral resection of the prostate in metastatic hormone sensitive prostate cancer

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Abstract

Objectives: To investigate the oncologic influence of transurethral resection of the prostate (TURP) as a cytoreductive surgery in metastatic hormone sensitive prostate cancer (mHSPC), in the setting of continuous complete androgen blockade (CAB).

Materials and methods: Medical histories of 146 consecutive Chinese males with newly diagnosed mHSPC, registered in our institution in 2006 and 2007, were reviewed. All of these patients received CAB as initial systematic therapy. Demographics and cancer control outcomes from 39 mHSPC patients who underwent TURP for a relief of bladder outlet obstruction were compared with those of the other 107 who received CAB only when they were still hormone-sensitive. Median follow-up was 15 months (3 to 27 months).

Results: Age at diagnosis, baseline PSA, and biopsy Gleason score were comparable between the 2 groups. Patients who underwent a TURP had lower PSA nadir (median 0.15 ng/ml vs. 0.82 ng/ml, $P = 0.015$) and longer time to PSA nadir (11.2 months vs. 6.4 months, $P < 0.001$). More patients in the non-TURP group developed hormone refractory prostate cancer ($P = 0.007$). The TURP group had a tendency towards longer disease-specific survival and overall survival (24.4 months vs. 24.1 months and 24.4 months vs. 22.9 months, respectively), though this did not reach statistical significance.

Conclusions: TURP resulted in a better and more prolonged response to hormone therapy in mHSPC, with a trend towards positive influence in disease specific survival and overall survival. To date, our preliminary report is the first study regarding long-term survival of cytoreductive surgery in mHSPC, and further investigations are warranted.

Keywords: Cytoreductive surgery; Hormone sensitive metastatic prostate cancer; Hormone therapy; Prognosis; Transurethral resection of the prostate

1. Introduction

Androgen-suppressing strategies are the mainstay of the management of advanced prostate cancer (CaP). CaP usually responds to androgen deprivation therapy (ADT), but on average, after 12 to 18 months, the malignant cells become resistant. Once hormone refractory prostate cancer (HRPC) develops, the median survival is approximately 24 to 36 months.

Although its use has decreased, transurethral resection of the prostate (TURP) for bladder outlet obstruction (BOO) due to CaP or concomitant benign prostatic hyperplasia (BPH) is occasionally required for palliation. As a form of cytoreductive surgery, TURP potentially has some cancer control benefits, however, most previous studies focused on the peri-operative morbidities and short-term clinical outcomes rather than long-term oncological results [1]. There are virtually no studies to support or refute the concept of a

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tumor control benefit with cytoreductive surgery in men with advanced CaP.

We retrospectively investigated the oncological outcomes after TURP in addition to complete androgen blockade (CAB) and compared these results with those receiving continuous CAB alone in patients with metastatic hormone sensitive CaP (mHSPC). To our knowledge, this preliminary report is the first study evaluating response to treatment and survival after TURP in mHSPC.

2. Methods

From January 2006 to December 2007, 146 consecutive Chinese males with newly diagnosed metastatic CaP were registered in our institution. They all received CAB (ADT + anti-androgens) as initial systematic therapy. Altogether, 39 mHSPC patients underwent TURP for a relief of BOO, and they were termed as TURP group; no matter whether they were experiencing BOO or not, the other 107 patients who did not receive TURP when still hormone-sensitive were termed as non-TURP group; a very limited number of TURP were also carried out in patients who developed BOO when disease progressed, but such patients were grouped into the non-TURP group. Patient demographics and cancer control outcomes were documented and compared between these two groups. Prostate specific antigen (PSA) was routinely tested every month after hormone therapy was initiated. The time to PSA nadir (TTN) was defined as the duration of time from the initiation of ADT to the date the lowest PSA value (PSA nadir) after initiation of ADT [2]. HRPC was defined as follows: (1) serum castrate levels of testosterone with (2) three consecutive rises of PSA at least 2 weeks apart, resulting in two 50% increases over the nadir, (3) anti-androgen withdrawal for at least 4 weeks*, (4) PSA progression despite secondary hormonal manipulations*, or (5) progression of osseous or soft tissue lesions (*either anti-androgen withdrawal or one secondary hormonal manipulation should have been done in order to fulfill the criteria for HRPC) [3].

After patients developed HRPC, they were observed or received one of several treatment regimens, such as estramustine, mitoxantrone, and/or docetaxel.

SPSS15.0 was employed in statistical analysis. Independent sample t-test and χ^2 t-test were used to determine statistical differences in pre- and post-treatment characteristics between these two groups. Primary end point was progression-free (from mHSPC to HRPC) survival (PFS), and secondary end points were disease-specific survival (DSS) and overall survival (OS). Cox univariate and multivariate proportional hazard analyses were also conducted. Kaplan-Meier method was used in survival analysis and the Log rank test was used for statistical significance testing. Statistical significance was set at $P \leq 0.05$.

3. Results

Age at diagnosis, baseline PSA, and biopsy Gleason score were comparable between the two groups (Table 1). In the TURP group, a mean of 20.0 g (range 12–30 g) of tissue were removed at the time of TURP. An improvement of voiding was reported in all the cases, and no serious complications were documented. Median follow-up was 15 months (range 3–27 months).

At last follow-up, patients in TURP group had a lower PSA nadir median (0.15 ng/ml vs. 0.82 ng/ml, $P = 0.015$), and it took a longer time to reach the nadir (mean 11.2 months vs. 6.4 months, $P < 0.001$). Median PSA nadir was 0.46 ng/ml in the entire population, and it was used as the cut-off point in our study. Sixty-six percent of the patients in the TURP group realized a PSA nadir less than 0.46 ng/ml compared with 44% in the non-TURP group. Significantly more patients in the non-TURP group failed CAB therapy and developed HRPC (52%) compared with 33% in the TURP group ($P = 0.007$). Multivariate analyses only

Table 1
Patient characteristics and outcomes of two groups

	Total	pTURP + CAB	CAB alone	P value
Patients (N)	146	39	107	—
Median age (year)	69.0 (52.0–89.0)	68.0 (53.8–87.8)	69.0 (52.0–89.0)	0.367
Median biopsy analysis Gleason score (range)	7.7 (5–10)	7.9 (5–10)	7.7 (5–10)	0.366
Median baseline PSA (ng/ml) (range)	150.00 (4.54–6060.00)	107.00 (4.54–6060.00)	158.00 (5.27–5600.00)	0.471
Median follow up (mo) (range)	14.8 (4.0–29.5)	15.0 (7.1–27.1)	14.5 (4.0–29.5)	0.947
Median PSA nadir (ng/ml) (range)	0.46 (0–357.52)	0.15 (0.00–130.00)	0.82 (0.00–357.52)	0.015
PSA nadir $<$ 0.46 (N)	73	26	47	
PSA nadir $>$ 0.46 (N)	73	13	60	
Mean time to PSA nadir (mo) (95% Confidence Interval)	7.2 (6.4–8.0)	11.2 (9.0–13.4)	6.4 (5.6–7.2)	$<$0.001
HRPC (N)	76	13	63	0.006
Die of prostate cancer (N)	29	5	24	0.198
Die of all reasons (N)	34	5	29	0.071

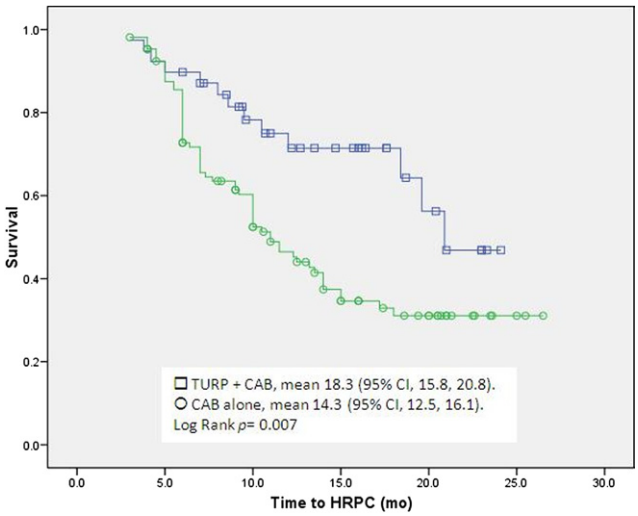

Fig. 1. TURP + CAB vs. CAB alone for progression-free survival. (Color version of figure is available online.)

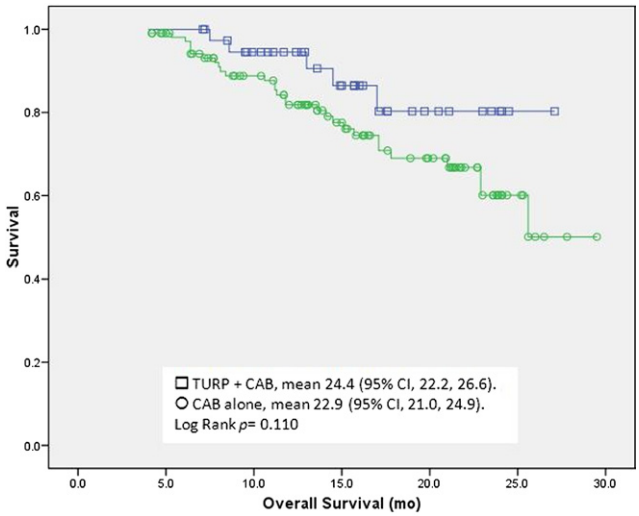

Fig. 3. TURP + CAB vs. CAB alone for overall survival. (Color version of figure is available online.)

detected a statistically significant benefit of TURP towards longer PFS, but no statistical significance was found for DSS or OS; however, there is a trend towards longer DSS ($P = 0.198$) and OS ($P = 0.071$) in those who underwent TURP compared with those who did not (Table 1, Figs. 1, 2, and 3).

4. Discussion

The standard therapy for men who present with metastatic CaP is systemic therapy. CAB appears to provide a small survival advantage compared with ADT monotherapy [4,5]. For patients with metastatic disease, treatment directed to the prostate, in the form of either surgical resection or radiation therapy, is usually administered to either palliate or improve local symptoms [6,7]. The guiding principle for this approach is that mortality is driven by distant disease, not the local tumor. The notion that treating the primary tumor may influence the clinical course of metastatic disease is not generally accepted.

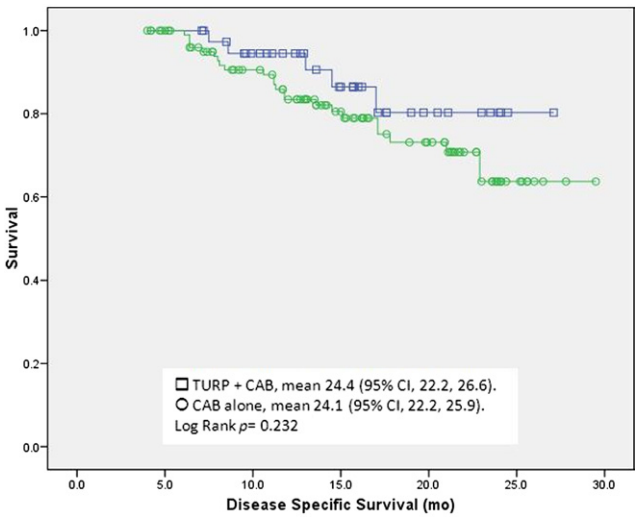

Fig. 2. TURP + CAB vs. CAB alone for disease-specific survival. (Color version of figure is available online.)

Although the ultimate prognosis of metastatic CaP is dismal, unlike in other cancers, there has hardly been any clinical exploration as to whether treating the primary may be of benefit. With some other tumor cell types, such as gastric cancer [8], colorectal cancer [9], breast cancer [10], and renal cell carcinoma [11], there is good evidence that cytoreductive surgery of the primary tumor provides a survival benefit in select patients. In CaP, locally advanced CaP (T3, T4) has been long considered not curable by surgery; however, previous studies have suggested an improvement of survival in patients undergoing radical prostatectomy rather than just hormone therapy alone [12,13]. In addition, retrospective studies of patients with lymph node positive CaP suggest that radical prostatectomy with early adjuvant orchiectomy may provide a significant advantage in overall and cause specific survival compared with orchiectomy alone [14]. Also, in a long-term retrospective study, patients with treatment failure after radical prostatectomy had a better response to androgen ablation than those in whom radiation failed. Time to subsequent failure after androgen ablation for disseminated disease was prolonged in patients with prior surgery compared with patients who were previously treated with prostate radiation (2.67 vs. 1.16 years). Since patients with radiation had a high rate of uncontrolled local disease, it would appear that the bulk of local disease impacts the response to systemic therapy [15]. In total, these studies and others [16] would suggest that removing the primary tumor allows a better response of metastatic disease to androgen ablation.

In our preliminary study carried out in mHSPC, we also found patients receiving TURP responded better and significantly longer to CAB than patients who received CAB alone. This is consistent with the Southwest Oncology Group (SWOG) study that showed those with a better PSA response had a more durable PSA response [17]. Patients in the TURP group had a lower PSA nadir and longer TTN after CAB was initiated and lower PSA nadir and longer TTN have been shown to have a positive influence on survival of mHSPC patients [2].

Currently, men with metastatic CaP for which hormone therapy fails are destined to die of the disease. While they can respond to subsequent chemotherapy, those responses are transient and minimally impact on survival. Clearly, a deeper and more durable response to hormonal therapy will likely prolong survival, as is the trend in our study. Longer follow-up should confirm the significance of the PSA response. If nothing else, we have realized a delay in having to consider chemotherapy in some of the patients.

Although our study seems to support the concept that cytoreduction results in a better response to systemic therapy, this could be artifact. In the retrospective study carried out in our cancer specialized hospital, patients were not from the screening population; in China, most CaP cases were revealed by urinary symptoms or bone pain [18], actually those who received TURP as the CAB initiated were following selective indications, otherwise they would just get hormone therapy; on the other hand, many who also experienced BOO did not get TURP. While nonsignificant, those undergoing TURP had a slightly lower PSA level than those that did not, and this may represent a somewhat lower overall tumor burden. Only a prospective study controlling for the amount of systemic disease could determine if this was the reason for the difference. In spite of this concern, our results appear dramatic, given the modest cytoreduction achieved with the TURP. The fact that other patient factors were similar (Table 1) would suggest that the 2 groups are actually reasonably comparable. Ultimately, survival will also be impacted by the treatment regimens for patients who developed HRPC. In general, the increase in survival with those regimens is only on the order of 3 months, but with a few patients realizing more long-term control. Our follow-up is too short to comment definitely on survival, but this will have to be a consideration.

Mechanism underlies the increased response to systemic therapy in metastatic cancer after cytoreductive surgery to the primary tumor is unknown [19]. In metastatic prostate cancer, one possible mechanism is the different androgen microenvironment in and out of the prostate. Previous investigation has found that medical castration reduces tissue androgens by 75% and also reduces the expression of several androgen-regulated genes. However, many androgen-response genes, including the androgen receptor (AR) and PSA, are not suppressed after short-term castration or after 9 months of neoadjuvant ADT. The degree of medical castration based on serum testosterone levels cannot be equated with the thoroughness of androgen ablation in the prostate microenvironment. Standard androgen deprivation does not consistently suppress androgen-dependent gene expression because of higher levels of intraprostatic androgens. Suboptimal suppression of tumoral androgen activity may lead to adaptive cellular changes allowing CaP cell survival in a low androgen environment [20]. Since the primary tumor might be the primordial source of metastatic disease, and newly disseminated cancer cells from the castrated prostate are more probably hormone refractory, destruction of at least part of the CaP by TURP may expose those intact intraprostate cancer cells to lower but more lethal androgen microenvironment due to increased serum exposure. Also, reducing the volume of intraprostatic cancer cells by TURP before they are castration adaptive may reduce the proportion of hormone refractory cells disseminated later.

In our limited number of cases, TURP seemed safe and effective for late stage CaP patients with BOO, as reported by others [1]; however, no matter how minimally invasive the TURP is, especially for those with co-morbidities, it is not always safe because it still needs anesthesia. By now, it is still too early to generalize TURP in a wide range, and TURP should be performed with indication such as bleeding or obstruction in advanced disease until we have more data to confirm the benefit of this kind of interesting treatment by a well controlled prospective study; however, in a selected population, TURP prolonged response to hormone therapy in mHSPC, which showed a tendency to a positive influence on DSS and OS. To date, our preliminary report is the first study regarding response and survival from cytoreductive surgery in mHSPC, and further investigations are warranted.

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