Oncologic Outcomes Following Robot-Assisted Radical Prostatectomy for Clinical T3 Prostate Disease

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ABSTRACT **Background:** Little is known about oncologic outcomes following robot-assisted-radical-prostatectomy (RALP) for clinical T3 (cT3) prostate cancer.

Objectives: To investigate oncologic outcomes of patients with cT3 prostate cancer treated by RALP.

Methods: Medical records of patients who underwent RALP from 2010 to 2018 were retrieved.

cT3 cases were reviewed. Demographic and pre/postoperative pathology data were analyzed. Patients were followed in 3–6 month intervals with repeat PSA analyses. Adjuvant/salvage treatments were monitored. Biochemical recurrence (BCR) meant PSA levels of ⩾ 0.2 ng/ml.

Results: Seventy-nine patients met inclusion criteria. Median age at surgery was 64 years. Preoperative PSA level was 7.14 ng/dl, median prostate weight was 54 grams, and 23 cases (29.1%) were down-staged to pathological stage T2. Positive surgical margin rate was 42%. Five patients were lost to follow-up. Median follow-up time for the remaining 74 patients was 24 months. Postoperative relapse in PSA levels occurred in 31 patients (42%), and BCR in 28 (38%). Median time to BCR was 9 months. The overall 5-year BCR-free survival rate was 61%. Predicting factors for BCR were age (hazard-ratio [HR] 0.85, 95% confidence interval [95%CI] 0.74–0.97, $P = 0.017$) and prostate weight (HR 1.04, 95%CI 1.01–1.08, $P = 0.021$). Twenty-six patients (35%) received adjuvant/salvage treatments. Three patients died from metastatic prostate cancer 31, 52, and 78 months post-surgery. Another patient died 6 months post-surgery of unknown reasons. The 5-year cancer-specific survival rate was 92%.

Conclusions: RALP is an oncologic effective procedure for cT3 prostate cancer. Adjuvant/salvage treatment is needed to achieve optimal disease-control.

IMAJ 2021; 23: 111–115

KEY WORDS: oncologic outcomes, prostate cancer; clinical T3, robot-assisted radical prostatectomy

Radical prostatectomy (RP) has long been considered the ultimate remedy for men diagnosed with localized prostate cancer (clinical T1/T2 [cT1/T2]). The optimal surgical option for those with locally advanced disease (clinical T3 [cT3]), however, remains undetermined.

Early open radical prostatectomy case series have focused on cT3 cases in an attempt to provide a conclusive answer [1-4], with numbers varying between 100 and 843 cases and a median follow-up of 30–171 months. Researchers have reported 3–10 year biochemical recurrence (BCR)-free survival rates varying between 40%–45% [1-3], a 10-year clinical recurrence-free survival of 76% [2], and a 20-year local recurrence-free survival of 76% [4].

Recent data published on 13,856 patients with 695 radical prostatectomy cases conducted between 1992–2009 and 1989–1999, respectively [5,6], concluded that there is an advantage for RP over watchful waiting in men with cT3 disease who have long life expectancy [6].

Moreover, RP combined with adjuvant radiotherapy (RT) carried a lower risk of cancer-specific death and improved overall survival compared with RT and hormonal treatment (HT) [5].

The impact of laparoscopic RP for cT3 prostate cancer was explored in one study on 492 cases in which the reported 10-year cancer-specific mortality-free survival was 97.4% [7].

The introduction of the da-Vinci® Robotic System (Intuitive Surgical, Sunnyvale, CA, USA) and its validation in RP cases [8] has led to a tremendous shift worldwide towards a robot-assisted radical prostatectomy (RALP) approach. In fact, the vast majority of RP cases are now being performed robotically.

Reports of the oncologic impact of this widespread application of RALP for cT3 prostate cancer, however, are sparse and little is known about its oncologic outcome. We documented the short term oncologic outcomes of cT3 cases treated by the RALP approach in our institution.

PATIENTS AND METHODS

PATIENT POPULATION

Following approval by our institutional review board (Sheba Medical Center IRB, approval #SMC-10-8243) we reviewed a prospective registry database of all patients who underwent RALP between January 2010 and December 2018 at our medical center. Informed consent was waived by the local committee.

We retrieved patient demographic and medical data, as well as intra- and postoperative details on the operations that had been performed by four surgeons. Patient age, body mass index

(BMI), preoperative clinical T3 (PSA) level, and biopsy Gleason score were recorded. Each study patient had a minimum of 12-core biopsy and a documented tumor volume.

The surgical cases were defined as cT3 according to the findings on preoperative digital rectal examinations (DRE) or multiparametric magnetic resonance imaging (mp-MRI) studies that were reviewed by a single radiologist (OP) who confirmed extraprostatic extension of malignancy with or without seminal vesicle involvement. In the absence of a mp-MRI, the DRE was taken as positive for cT3 provided other preoperative imaging methods (e.g., PET/CT GA68 *prostate-specific membrane antigen*, computerized tomographic scan, or bone scan) ruled out local spread or distant metastases.

Patients who had received HT, neo-adjuvant chemotherapy, or RT prior to surgery were excluded from the study. Patients who had enhancing lymph nodes on PET/CT or distant metastases elsewhere were also excluded from the study.

STUDY DESIGN

RALP was performed by means of the da-Vinci Si® Surgical System, implementing a 6-port trans-peritoneal approach as described in detail elsewhere [9]. Pelvic lymph node dissection (i.e., obturator, external, and internal iliac nodes) was performed for patients with a biopsy Gleason score of 7(4+3)–10 or a preoperative PSA level > 10 ng/ml.

Prostate weight, pathological stage, and Gleason score, as well as surgical margin status were recorded and analyzed as well.

All pathologic specimens were reviewed and interpreted by a single pathologist (EF). Pathologic assessment was carried out as described in detail elsewhere [10].

FOLLOW-UP

The study patients were followed in our outpatient clinic in 3–6 month intervals with repeat serum PSA level acquisition. The adjuvant treatment and follow-up visits of cases referred to our institutional oncology service were monitored. BCR was defined as serum PSA levels of ≥ 0.2 ng/ml in at least two consecutive blood tests or a single measurement of ≥ 0.2 ng/ml with previously detected PSA.

STATISTICAL ANALYSIS

Statistical analysis was performed using univariate and multivariable logistic regression analyses to determine features associated with positive surgical margins. Survival was estimated using the Kaplan-Meier method and compared with the log-rank test. Cox proportional hazard regression models were used to evaluate predictors of PSA relapse, controlling for clinical and pathologic variables. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). Data are given as median/interquartile range (IQR) unless otherwise specified. A *P* value < 0.05 was considered statistically significant.

RESULTS

Seventy-nine patients met the inclusion criteria and their data were included in the final statistical analysis. The median age at surgery was 64 years (IQR 59–68), the median BMI was 28 (25.6–30.5), and the preoperative PSA level was 7.14 ng/dl (5.2–11.6). The median final prostate weight was 54 grams (43–73). Twenty-three of the 79 cT3 cases (29.1%) were down-staged to pathological stage T2 (pT2).

The cT3 cases and the corresponding pT2 cases per year are detailed in Table 1. Table 1 also shows the preoperative biopsy Gleason scores as well as the pathological Gleason scores, grades, and surgical margin status.

Univariate analysis determined that age, preoperative PSA, and pathologic Gleason score were independent predictors of positive surgical margins. On multivariate analysis, only the pre-operative serum PSA level remained associated with surgi-

Table 1. Pre- and postoperative pathologic characteristics for cT3 cases

Variables, n	N=79				
Biopsy Gleason Score (%)					
6(3+3)	25 (31.6)				
7(3+4)	28 (35.4)				
7(4+3)	11 (13.9)				
›8	13 (16.4)				
Missing	2 (2.5)				
Pathologic Gleason Score (%)					
6(3+3)	10 (12.7)				
7(3+4)	23 (29.1)				
7(4+3)	31 (39.2)				
›8	15 (19)				
Pathologic stage (%)					
T2	23 (29.1)				
T3a	45 (57)				
T3b	11 (13.9)				
N+	3 (3.8)				
Positive surgical margins (%)		Apex	Posterior/ postero-lateral	Base/ bladder neck	Mid
Total	33 (42)	25 (75%)	15 (45%)	5 (15%)	1 (3%)
pT2	5 (21.7)*	6	0	0	0
pT3a	22 (49)*	13	11	3	0
pT3b	6 (54.5)*	6	4	2	1

*Percentage was calculated by dividing the number of positive margins of each pathologic stage by the total number of that stage
cT3 = clinical T3

Table 2. Postoperative PSA level relapse and corresponding adjuvant/salvage treatments

Postoperative relapsed PSA levels	N=31 (42%)
Consecutive increase in post-operative PSA level, (PSA < 0.2 ng/ml)	n=3
	Lost to follow up: 1
	Spontaneous remission: 1
	Adjuvant RT: 1
Postoperative PSA level failed to decrease < 0.2 ng/ml 6 weeks post-surgery	n=9
	Lost to follow-up: 2
	Adjuvant RT: 4
	Adjuvant HT + chemotherapy: 1
	Adjuvant RT + HT + chemotherapy: 2
Consecutive increase in postoperative PSA level (PSA ⩾ 0.2 ng/ml)	n=19
	Salvage RT: 13
	Salvage RT + HT: 2
	Salvage RT + HT + chemotherapy: 1
	Salvage HT + chemotherapy: 1
	Lost to follow-up: 2

HT=hormonal therapy, RT=radiotherapy, PSA = prostate-specific antigen

Table 3. Relapsed postoperative PSA level in accordance with pathologic stage and Gleason score

Relapsed postoperative PSA level	N=31
Pathologic stage (%)*	
T2	5 (29)
T3a	18 (43)
T3b	8 (73)
Pathologic Gleason score (%)*	
6 (3 + 3)	3 (33)
7 (3 + 4)	1 (4.7)
7 (4+ 3)	15 (51.7)
⩾ 8	10 (66.6)

*Percentage was calculated by dividing the number of elevated PSA levels for each pathologic stage/Gleason score by its total number in a cohort of 74 patients
PSA = prostate-specific antigen

cal margin status (hazard ratio [HR] 1.1, 95% confidence interval [95%CI] 1.01–1.2, $P = 0.036$).

Five patients were lost to follow-up after surgery. The median follow-up time for the remaining 74 study patients was 24 months (12–51).

A postoperative relapse in PSA levels was detected in 31 of the 74 (42%) patients. A consecutive PSA level relapse was recorded in three patients, although the final level did not exceed 0.2 ng/ml. In another nine patients, the PSA level failed to reach below 0.2 ng/ml post-surgery (BCR = 0 months).

The PSA level dropped to zero 6 weeks post-surgery in 19 patients (25.6%); however, it steadily increased thereafter beyond the threshold of 0.2 ng/ml. The median time to BCR in that group was 24 months (9–36).BCR was detected in a total of 28 patients (38%) with a median time to BCR of 9 months (0–27). Predictive factors for BCR included age (HR 0.85, 95%CI 0.74–0.97, $P = 0.017$) and prostate weight (HR 1.04, 95%CI 1.01–1.08, $P = 0.021$). There were no differences between pathological stages T2 and T3 or stages T3a and T3b with regard to BCR.

The 5-year BCR-free survival rate was 61%.Relapse of the PSA level and the corresponding adjuvant treatment are detailed in Table 2. Overall, nine patients (12.1%) received adjuvant treatment of any kind, and one of them received adjuvant RT due to final pathological grade and stage without PSA relapse. Seventeen patients (23%) underwent salvage treatment of any kind due to BCR. The relapsed PSA levels according to pathological stage and Gleason score are listed in Table 3.

Four patients died during the 8 years of follow-up, and three of the deaths were from metastatic prostate cancer at 31, 52, and 78 months post-surgery. Another patient died 6 months post-surgery of unknown reason. All four deceased patients had a pathological Gleason score of 9, and all but one had pathological T3b disease. The remaining patient had pathological T3a disease. The overall 5-year cancer-specific survival (CSS) for our patient cohort was 92%.

DISCUSSION

The da-Vinci® surgical system gained popularity worldwide due to the 3-dimensional, × 12 magnified imaging of the surgical field it provides, as well as the increased dexterity, maneuverability, and precision obtained by incorporating the EndoWrist® technology into the robotic device.

Due to its complexity, RALP became the prototype of robotic surgery in humans, and has left traditional open surgery far in its wake.

The critics cautioned that the lack of haptic feedback as well as the learning curves will adversely affect the oncological outcomes, caveats that dampened the enthusiasm and caused the urologic community to carefully select their candidates for RALP. Consequently, most publications in the English literature refer to cT1/T2 robotic cases.

In one study that addressed the long-term BCR-free survival rates in patients treated with RALP for localized prostate cancer [11], the median follow-up was 67.5 months and the mean time to BCR was 83.8 months. The BCR-free survival rates were based on the pathological Gleason score and stage, and the study

Table 4. Publications on oncological outcomes for clinical T3 (cT3) prostate cancer treated with robot-assisted radical prostatectomy

First author, year	Adjuvant/salvage treatment	N	cT3 (%)	Median follow-up (IQR)	Median time to BCR (IQR)	BCR-free survival (%)
Sooriakumaran 2012 [15]	Excluded from study	904	28 (3.1)	6.3 years* (5.6–7.2)	2.3 years (1–3.7)	84.8
Gandaglia 2017 [16]	58.5%	94	94 (100)	23.5 months (18.7–27.3)		3 years (63.3)
Kumar 2017 [17]	–	5300	975 (18.4)	38.1 months* (mean)	8.9-21.1 months (mean)	3 years (48.5–92.1 for pT3 disease)
Menon 2010 [18]	–	1384	32 (2.3)	5 years* (3.1–5.8)	20.4 months	3,5,7 years (78.2,72, 67.5for high-risk disease)

BCR = biochemical recurrence, IQR = interquartile range
*Relates to all clinical stages

concluded that RALP was an oncologically effective procedure. Thereafter, several large case series concluded that RALP is a safe and oncologically effective procedure even in the setting of high-risk disease [12-14].

There are currently only four studies in the literature that report oncological outcomes for cT3 disease following RALP [15-18], and only one that fully addressed the oncologic aspect of cT3 disease treated by RALP [16]. The findings of these four studies are summarized in Table 4.

Although the overall percentage of cT3 cases and the total numbers are small, the time to BCR is approximately 2 years over a follow-up period of 2–6 years, similar to our current study findings.

Encouraged by preliminary studies that concluded that RALP may be an effective procedure in cases of high-risk disease [15-18], this method of treatment was adopted in 2010 for cT3 cases, with the understanding that there was a high likelihood for the need for adjuvant/salvage treatment thereafter.

In our series, postoperative relapse in PSA levels was detected in 29 of the 74 study patients (39.2%), and BCR was observed in 21 patients (28.4%). Twenty-six of these 74 patients (35%) required some kind of adjuvant/salvage treatment, which is a smaller proportion compared with the 58.5% reported by Gandaglia and associates [16].

The independent predictors of BCR cited in earlier studies were as follows: preoperative PSA levels [15-17], biopsy Gleason score [18], postoperative persistently elevated PSA levels (> 0.1 ng/ml) [17], pathologic Gleason scores [15-18], pathologic stages [15,16], and the presence of positive surgical margins [16,17].

Contrary to the values cited by Kumar and colleagues [17], our results did not indicate that there was a higher likelihood of persistently postoperatively elevated PSA levels (> 0.1 ng/ml) for cT3 cases. Moreover, we found, for what we believe to be the first time, that age and prostate weight may serve as independent factors for BCR in cT3 cases.

Our BCR-free survival rate of 61% and our CSS rate of 92% correlate with those reported by Gandaglia et al. [16] (63.3% and 95.8%, respectively).

LIMITATIONS

Some limitations of our study include the relatively small number of patients with a cT3 disease, the relatively short follow-up period, its retrospective nature, and the inability to compare the outcome of RALP treatment to that of open RP for matched cases of cT3.

Notwithstanding, the findings of the present study further validate the effectiveness of RALP for cT3 cases and support earlier studies that pointed on surgical treatment as an effective tool for the treatment of prostate cancer [5,6].

It should, however, be considered that there is a high likelihood that an adjuvant or salvage treatment will eventually be required to achieve an optimal level of disease control in cases of cT3 that underwent RALP.

CONCLUSIONS

RALP is an oncologically effective procedure for cT3 prostate cancer. There is a high likelihood that an adjuvant/salvage treatment will eventually be needed to achieve optimal disease control.

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Capsule

Diversity of *KIRs* in invasive breast cancer patients and healthy controls along with the clinical significance in ER/PR/HER2+ patients

Killer cell immunoglobulin-like receptors (KIR) consists of activating and inhibitory genes are essential for natural killer cell education. To determine the association of *KIR*s with susceptibility to invasive breast cancer (BC), genotyping of 16 *KIR*s was performed by sequence-specific primers-polymerase chain reaction in 226 confirmed cases of BC with defined estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2) status and 226 healthy controls (CNs). **Larki** et al. observed a lower frequency of *2DL1* and *2DS4del* along with increased frequency of *2DS4fl* in cases compared to CNs. Further analysis revealed a higher frequency of *KIR2DL2*, *2DS1, 2DS2,3DS1* in ER+ cases, *2DL2*, *2DL5* in PR+ and *2DL1* in HER2+ cases compared to CNs. The detrimental role of KIR2DS4fl was observed in ER+ and PR+ cases whereas 2DS4del confers protection against ER+, PR+, and HER2+ cases. The authors noted the predisposing role of Bx genotype, *KIR2DS1, 2DS2, 2DS5, 2DL2, 2DL5* for lymphatic invasion in ER+ cases along with a higher rate of lymph node metastasis (LNM) in carriers of Bx genotype and *KIR2DS1* in ER+ cases. The authors suggest a link between B haplotype associated genes with the increased risk of lymphatic invasion and LNM, particularly in ER+ cases of BC.

Genes & Immunity 2020; 21: 380
Eitan Israeli

Capsule

Precision therapy for immune tolerance

Autoimmune diseases, such as multiple sclerosis (MS), result from a breach of immunological self-tolerance and tissue damage by autoreactive T lymphocytes. Current treatments can cause systemic immune suppression and side effects such as increased risk of infections. **Krienke** and associates designed a messenger RNA vaccine strategy that lacks adjuvant activity and delivers MS autoantigens into lymphoid dendritic cells. This approach expands a distinct type of antigen-specific effector regulatory T cell that suppresses autoreactivity against targeted autoantigens and promotes bystander suppression of autoreactive T cells against other myelin-specific autoantigens. In mouse models of MS, the vaccine delayed the onset and reduced the severity of established disease without showing overt symptoms of general immune suppression.

Science 202; 371: 145
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