

Analysis of outcome following robotic assisted radical prostatectomy for patients with high risk prostate cancer as per D'Amico classification

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ABSTRACT

Introduction: Prognosis of prostate cancer depends on the risk stratification. D'Amico classification, the most commonly used risk stratification method is based on three factors, i.e., prostate specific antigen (PSA), Gleason grade and clinical stage. The impact of presence of multiple risk factors on prognosis after radical prostatectomy has not been studied in Indian patients. We analyzed the outcome of patients with high-risk disease undergoing robotic-assisted radical prostatectomy (RARP), as per D'Amico classification.

Materials and Methods: Our study is a review of the data of all patients with high-risk prostate cancer who underwent RARP between July 2010 and January 2015. Preoperative, perioperative and outcome data were analyzed for patients with high-risk disease as per D'Amico classification.

Results: Of 227 patients who underwent RARP, 90 (39.6%) were in the high-risk group. PSA > 20 ng/ml was the most common risk factor, present in 50 (55.6%) patients. All three risk factors were present in 3 patients, and single risk factor was present in 65 patients. Nine (10%) patients had lymphnode involvement, 18 (20%) had positive margin, and 38 (41.1%) had extraprostatic extension (EPE). Among these adverse outcomes, only EPE showed significant association with multiplicity of risk factors. At 12 months, 27.8% had biochemical recurrence (BCR). 92% of patients were continent at 12 months.

Conclusion: About 92% of patients with high-risk disease were continent at 12 months, whereas less than one-third of the patients had BCR. EPE was the only outcome associated with multiplicity of risk factors. Adjuvant treatment is not required in two-thirds of patients.

Key words: Carcinoma prostate, high risk, multiplicity of factors, outcome, robotic-assisted radical prostatectomy

INTRODUCTION

Prostate cancer is the most common nonskin cancer affecting men.^[1] Prostate-specific antigen (PSA) level, tumor grade, and clinical stage determine the prognosis.^[2] This disease has a wide spectrum ranging from the very low PSA, low-grade impalpable disease to the very high PSA, high grade locally advanced disease. Treatment too varies from active surveillance

to radical prostatectomy/radiotherapy, hormone therapy or chemotherapy depending on the disease severity.^[3,4] Various classifications are used to objectively evaluate the risk of morbidity. Patients are classified into low, intermediate, and high risk on based on PSA, Gleason grade, and clinical stage. In addition, a few risk stratification tools use age in addition. D'Amico's is the most commonly used, validated and cited risk stratification for prostate cancer.^[5]

We have previously published data on continence outcomes after robotic-assisted radical prostatectomy (RARP) from our cohort of subjects.^[6,7] In this study, we analyzed the

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outcome of patients with high-risk prostate cancer (as per the D'Amico classification) from the same cohort with some additional cases.

MATERIALS AND METHODS

We reviewed the data of 90 patients of high-risk prostate cancer stratified as per D'Amico classification^[2] who underwent RARP between July 2010 and January 2015. Demographic characteristics, preoperative oncological work up, perioperative data, and postoperative outcome were analyzed.

RARP was performed by two consultants with robotic surgery proficiency, with a da Vinci, Si system. Anterior approach or posterior approach was used, depending on the preference of the surgeon. Bilateral pelvic lymphadenectomy was done in all cases. Unilateral/bilateral standard nerve-sparing surgery was done as per pathology. Cystogram was obtained and catheter was removed between postoperative days 7 to 14. Patients were followed up with serum PSA after 1 month, 3 months, 6 months, and then 6 monthly. Continence status depending on the pad usage was also determined. Patients using no pads or a safety liner were considered to be continent. Additional requirement of adjuvant therapy was documented. The primary endpoint of the study is biochemical recurrence (BCR). BCR was defined as PSA > 0.2 ng/ml. Patients who were given adjuvant hormonal therapy due to lymphnode positive status or lost to follow-up were considered as biochemical failure. We analyzed the overall pathological and oncological outcomes and also a difference in the outcome depending on the risk factors present. Chi-square test was used to find the significance of the difference.

RESULTS

During the period between July 2010 and March 2015, 227 patients underwent RARP. Ninety (39.6%) patients among them had high-risk disease. The mean follow-up was 14.9 months ranging from 3 months to 56 months. The mean age of the patients with the high-risk disease was 64.8 years, and the mean body mass index was 25.7. On analysis of the high-risk criteria, PSA was more than 20 in 50 patients, Gleason 8 or above in 30 patients and T2c in 38 patients.

The distribution of risk factors is shown in Figure 1. All the three risk factors were present in 3 (3.3%) patients. Two risk factors were present in 22 (24.4%) patients and a single risk factor in 65 (72.2%) patients. If we consider the individual risk factors, PSA > 20 ng/ml was found in 50 (55.6%) and cT2c, and high-grade disease was seen in 38 (42.2%) and 30 (33.3%) patients respectively.

The median estimated blood loss was 150 ml ranging from 50 ml to 1500 ml. One patient required blood transfusion.

Four patients had Clavien Grade 1 complications and two patients had Clavien 2 complications. Overall complication rate was 5.5%. No patient had Clavien Grade 3 or more complications. The median mean postoperative duration of stay was 2.5 days (2–7 days).

8.9% of patients were continent on catheter removal, 83.4% and 92.6% at 3 months and 1 year, respectively.

The final histopathology is given in Table 1. One of the patients had a final histopathology of pT0. He had PSA 21, Gleason 6, and cT1c disease. In nine patients, the final histopathology was downgraded to Gleason 7 or 6. Among them, one had PSA 22 ng/ml and one had cT2c. The rest six patients would have been intermediate or low-risk disease, but for the high grade in a preoperative core biopsy. In a subset analysis, all these patients had localized disease with negative margin and no BCR.

Mean number of lymphnodes removed were 12.9 (2–27). Lymphnode positive disease was seen in 9 (10%) patients. Positive margin is seen in 18 (20%) and extraprostatic extension (EPE) in 38 (41.1%) patients. Table 2 gives the subset analysis of the risk factors and pathological outcome. None of the three factors group had positive lymphnode or positive margin. Multiplicity of risk factors was a significant contributor for EPE. Ninety (50%) of the patients with EPE had BCR. BCR as such was not significantly associated with multiplicity of risk factors.

31 (34.4%) patients, received adjuvant/additional therapy. Patients with T3b disease or T3a with positive margin were offered adjuvant radiotherapy. Radiotherapy alone was given for 10 patients. Fifteen received hormonal treatment and six received combination treatment. Patients who had BCR were offered hormonal therapy.

Five patients were lost to follow-up. Twenty-seven (29.7%) had BCR over a median follow-up of 14.9 months. BCR at

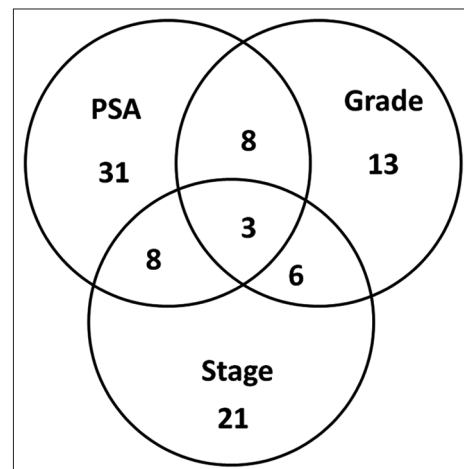


Figure 1: Distribution of high risk factors in the patients

Table 1: Final histopathology of the high risk patients

Pathology	Number
T0N0	1
T2aN0	4
T2bN0	3
T2cN0	33
T2cN1	2
T3aN0	16
T3aN1	2
T3bN0	24
T3bN1	5
Total	90

Table 2: Subset analysis of multiplicity of risk factors and outcome

Outcome	Three factors	Two factors	One factor	P
Lymphnode positive	0/3	3/22	6/65	0.74
Margin positive	0/3	5/22	13/65	0.65
Extra prostatic extension	3/3	15/22	29/65	0.04
BCR at 3 months	0/3	6/22	9/65	0.25
BCR – overall	1/3	11/22	15/65	0.06

BCR=Biochemical recurrence

3 months was 15.5%, and at 12 months it was 27.8%. Of the 60 patients with no BCR, 1 had received combined therapy and 8 received radiation therapy (RT).

Two (2.2%) patients died during the study period. One patient was hormone refractory with liver metastasis and started on chemotherapy and died due to chemotherapy-related cardiomyopathy. The other patient died due to unrelated causes.

DISCUSSION

Prognosis of carcinoma prostate depends on the risk status of the patient.^[2] High-risk group patients are found to have increased BCR and incontinence rates.^[2] This is mainly to the higher pathological stage and aggressive disease. The presence of either of the high-risk factors viz. PSA > 20 ng/ml, Gleason Grade 8 or more and clinical stage T2c constitutes high risk. However, the significance of single versus multiple risk factors is controversial. Many studies suggest that the multiplicity of risk factors affects the prognosis adversely.^[8-10] No such study is available on Indian patients.

The overall number of high-risk cases from 1990 to 2007 by CaPSURE database is 31.2%.^[11] There has been a decreasing trend with the proportion falling from 43.5% between 1990 and 1994 to 24% between 2004 and 2007. This is probably due to earlier detection by PSA screening. In India, most

patients present with locally advanced or metastatic disease due to lack of awareness and late presentation. Even those, presenting with localized disease and amenable to radical prostatectomy, are in the high-risk group.^[12] In our study, we found 34.4% of high-risk patients.

Gleason grade is the common high-risk factor in many studies – ranging from 29.7% to 74.1%.^[13-17] In our series, PSA was the common factor contributing to high-risk stratification (55.6%). Gleason grade was the least common factor, in 33.3% of patients. According to CAPSURE database, 50.8%, 61.5%, and 21.9% had high PSA, Higher grade, and higher stage respectively.^[11] Comparatively, our patients had a higher PSA and higher stage disease than the grade.

Cooperberg *et al.* reported that 23.5% of patients presented with more than one risk factor. In our study, we had 27.7% with more than one risk factor. The mean blood loss and postoperative stay are comparable to the other series.^[11]

Significantly, of 13 patients who had high-risk disease on Gleason grade alone preoperatively, 6 were downgraded to lower Gleason grade in final histopathology. Gleason grade migration has been reported in the literature.^[9,18,19] None of these six patients had BCR on follow-up. The difference in the preoperative and postoperative biopsies could be due to inter-observer variation or very small focus of high-grade disease. Downgrading suggests that some patients may have actually been intermediate or low-risk strata in the first instance. This gives credence to the fact that radical prostatectomy provides the best complete specimen for assessing the disease and should be offered to even the high-risk patients. This prevents unnecessary adjuvant treatments.^[18]

Overall 92% of the patients were continent at 12 months follow-up. The overall continence rate among high-risk groups varies from 84% to 96% in various study groups.^[5] Our rate is comparable with these results. This gives credence to the fact that high-risk group alone does not predispose to incontinence. Our patients had an intermediate time frame follow-up. Some patients who underwent RT postoperatively may have poorer continence outcome later. This needs to be analyzed with further long follow-up.

Ten percent lymphnode positivity and higher positive margin rates indicate that these patients may be in need of additional treatment later. Most likely need adjuvant treatment. Forty-one percent had extraprostatic disease including 30% with seminal vesicle invasion. It shows that many patients have the locally advanced disease and need multimodality treatment, including radiotherapy, for the management of high-risk prostate cancer. Most of the series on high-risk prostate cancer with a large sample size have similar results.^[5]

Gandaglia *et al.* had postulated that the high-risk group undergoing RARP had a higher incidence of complications.^[5,20] In our series, none of the patients had Clavien 3 or more complications.

Many series report the use of adjuvant therapy in high-risk patients undergoing RARP.^[5] At a mean follow-up of 14.9 months, 31 patients (34.4%) of patients had received adjuvant therapy. Among them, 16 patients had received radiotherapy with or without hormonal therapy. Twenty-one patients (23.3%) received some form of hormonal therapy. BCR rates ranged from 15.5% to 27.8% at 3 months and 12 months, respectively. The previous series report a range between 9% and 26% for BCR at 12 months.^[5] At 3 years, it is round 55% in a study by Connolly *et al.*^[9] Most of the patients with BCR were started on hormonal therapy. Two patients had hormone refractory disease on follow-up, and one patient died due to complications of chemotherapy. As a converse analysis 59 (65.6%) patients did not require any adjuvant therapy at an intermediate follow-up of 14.9 months.

Three factors, PSA >20 ng/ml, Grade 8 or above and cT2c stage are used for risk stratification. Very few studies discuss the additive effects of multiple risk factors on the prognosis.^[8-10] They reported poorer outcome in the presence of multiple factors. We calculated the contribution of multiplicity of risk factors in the final outcome. The details are given in the table. We found that only three patients had all the three risk factors [Table 2].

We found no significant difference in the lymph node positivity and positive surgical margin rates between those with single or multiple factors. EPE was significantly high in those with multiple factors. BCR showed a trend towards multiple factor involvement ($P = 0.06$).

D'Amico classification is commonly used for risk stratification in prostate cancer. All the three risk factors may be present only in few cases. Individual risk factors may have different outcomes, and all patients cannot be put in one basket. Both radical prostatectomy and combined hormonal and radiotherapy are preferred treatments for high-risk prostate cancer. With radical prostatectomy as a treatment option, adjuvant hormonal therapy can be done away with in 60% of patients. Additional few parameters such as PSA kinetics, better characterization of core biopsy, blood and tissue biomarkers and incorporation of magnetic resonance imaging findings may help in better stratification of the high-risk group. This will help in optimization of treatment with a minimal requirement of adjuvant treatment.

CONCLUSION

Our series is the largest on the outcome of high-risk carcinoma prostate patients in the Indian population, undergoing

radical prostatectomy. High PSA level is the most common high-risk factor. EPE is the only pathological outcome affected by the presence of multiple risk factors. Continence rate of more than 90% can be achieved in high-risk patients. Adjuvant treatment may not be required in two-thirds of these patients. Better parameters of classification are required for precise stratification of high-risk prostate cancer.

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Conflicts of interest

There are no conflicts of interest.

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