Family history in patients who would have been candidates for active surveillance

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Introduction: *It is unknown whether a family history of prostate cancer confers additional risk among men who are candidates for active surveillance (AS).*

Materials and methods: *Using a prospectively maintained database of men who underwent radical prostatectomy (RP) (2010- 2018), candidates for AS were identified according to the expanded criteria. Pathological upgrading was defined as a pathologic Gleason score (pGS) of 3+4 or higher for patients with a biopsy GS of 3+3 and a pGS of 4+3 or higher for patients with a biopsy GS of 3+4. Major upgrading was defined as a pGS of 4+4 or higher. The $\chi 2$ test was used for comparisons.*

Results: *Of 1,320 men who were candidates for AS, 288 (21.8%) had a family history of prostate cancer. There were no differences in terms of the age, number of positive cores, or number of patients with a GS of 7 between the two groups. Pathological upgrading was observed in 61.1% of the total cohort, with no difference observed between the two groups (60.7% versus 62.5%; $p = 0.5$).*

Conclusion: *In men who are eligible for AS according to the expanded criteria, a family history of prostate cancer does not appear to be associated with adverse pathology at RP.*

Key Words: active surveillance, family history, prostate cancer

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Introduction

In 2011, the United State Preventive Services Task Force (USPSTF) had issued a grade D against prostate-specific antigen (PSA) screening, due to the risks

of overdiagnosis and overtreatment.[1] Despite the controversial recommendation and eventual change to a grade C recommendation, the one concern that has had universal support was the overtreatment of low risk disease. Henceforth, the guidelines from major urology and cancer associations have been emphasizing on the role of active surveillance (AS) in the management algorithm of low-risk prostate cancer.[2,3] These recommendations have led AS to become the preferred initial management of low risk prostate cancer, as observed in several contemporary registries.[4,5]

Identifying ideal candidates for AS with low risk of metastasis has been an issue of debate among the urology community; consequently, there are around thirteen AS criteria described in the literature. These selection criteria have been mainly based on the following: tumor stage, PSA level, PSA density, number of positive cores, percentage of cancer in prostate cores, and Gleason grading.[6] Some studies have suggested that select intermediate risk patients may be safely included in an AS protocol, but prognostic risk factors and long-term outcomes are not well characterized.[6]

Although national guidelines consider the presence of a family history of prostate cancer as a trigger for screening at a younger age,[2,3] there is no benefit of additional screening for men with a family history of prostate cancer, and no association with AS outcomes.[7,8] However, these studies only included low risk or very low risk prostate cancer.[8] As broader inclusion criteria for AS has been considered given the low metastatic risk of Gleason 6 prostate cancer, the role of family history of prostate cancer in the selection of men for AS based on expanded criteria remains unclear.[9]

To elucidate the role of family history of prostate cancer in selecting men for AS based on the expanded criteria, we performed a study to evaluate the association of family history of prostate cancer with adverse pathological findings on radical prostatectomy (RP) following RP in patients who would have been candidates for AS based on expanded criteria.

Materials and methods

Using a prospectively maintained database of men who underwent robot-assisted RP by a single surgeon between January 2010 and December 2018, we identified patients who would have been candidates AS by the expanded criteria. The cohort was further subdivided based on the presence of a family history of prostate cancer. Family history of prostate cancer was defined if a first-degree relative diagnosed with prostate cancer at any age. We excluded patients who had no information about their biological family (n = 70), received focal therapy (n = 2), were diagnosed with prostatic tissue obtained from transurethral resection (n = 3), and had missing data regarding the number of positive cores (n = 20). Of note, the majority of the patients had their biopsy outside our institution.

The "expanded" AS criteria included clinical stage less than T3, PSA of 10 ng/mL or less, and Gleason 3 + 3 diseases or less. If the age was greater than 70, the criteria include Gleason 3 + 4 or less, and PSA < 15 ng/mL.[11,12] Bilateral pelvic lymphadenectomy was performed in 26% of the patients; the decision to perform lymphadenectomy was based on the PSA value, biopsy Gleason Score, and clinical stage.[13]

Outcomes

The primary endpoint was identifying adverse pathological features at RP specimen, namely the presence of extraprostatic extension, seminal vesicle invasion, and pathologic upgrading. Pathologic upgrading as described by Turner II et al, was defined as the presence of primary or secondary Gleason 4 or higher for patients with biopsy Gleason 3 + 3, and pathologic primary Gleason 4 or higher for patients with biopsy Gleason 3 + 4. Major upgrading was defined as pathologic Gleason 4+4 or higher.[14]

Statistical analysis

Baseline characteristics, pathological variables were abstracted from the institutional database. Categorical variables were compared between two groups using chi-square, while continuous variables were compared between two groups using t-test. Statistical analysis was completed with SPSS, version 25.

Results

Of 1,320 men who were candidates for AS by the expanded criteria, 288 (21.8%) had a family history of prostate cancer. Mean PSA was lower in men with a family history of prostate cancer as compared to men without a family history of prostate cancer (4.5 versus 4.9, p = 0.002). There were no differences in the age at presentation, race, body mass index (BMI), number of positive cores, maximum percentage of cancer in a single biopsy core, number of patients with Gleason 7 between the two groups, Table 1.

At prostatectomy, positive margin rate was similar in both groups (18.5% versus 14.9%, p = 0.169). There

TABLE 1. **Demographic, clinical, and prostate biopsy characteristics in men with and without family history of prostate cancer who met the expanded criteria for active surveillance**

Expanded criteria	Total cohort	No Fhx of prostate cancer	+ve Fhx of prostate cancer	p value
	1,320	**1,032**	**288**	
Age mean SD	59.7 ± 7.3	59.9 ± 7.3	59 ± 7.4	0.065
Age categorical				0.13
< 50	102 (7.7%)	71 (6.9%)	31 (10.7%)	
50-59	563 (42.7%)	445 (43.1%)	118 (41%)	
60-69	528 (40%)	412 (40%)	116 (40.3%)	
≥ 70	127 (9.6%)	104 (10%)	23 (8%)	
Preop PSA (mean SD)	4.8 ± 2	4.9 ± 2	4.5 ± 2	0.002
Race				0.11
White	1169 (88.5%)	915 (88.6%)	254 (88.2%)	
African American	103 (7.8%)	79 (7.7%)	24 (8.3%)	
Other	48 (3.7%)	38 (3.7%)	10 (3.5%)	
BMI (mean SD)	28.1 ± 4.62	28.2 ± 4.6	27.9 ± 4.5	0.32
Biopsy Gleason score				0.46
3+3	1264 (95.8%)	986 (95.5%)	278 (96.5%)	
3+4	56 (4.2%)	46 (4.5%)	10 (3.5%)	
Clinical stage				0.26
T1c	1094 (82.9%)	863 (83.6%)	231 (80%)	
T2a	218 (16.5%)	162 (15.7%)	56 (19.4%)	
T2b-c	8 (0.6%)	7 (0.7%)	1 (0.6%)	
Number of positive cores				0.8
1	491(37.2%)	384 (37.2%)	107 (37.1)	
2	318 (24.1%)	246 (23.8%)	72 (25%)	
3	209 (15.8%)	161 (15.6%)	48 (16.7%)	
4	130 (9.8%)	103 (10%)	27 (9.4%)	
5	76 (5.8%)	64 (6.3%)	12 (4.2%)	
6 or more	96 (7.3%)	74 (7.1%)	22 (7.7%)	
Percentage of core positive, %,median [IQR]	20 [8-40]	20 [8-41]	20 [10-40]	0.4
Maximum percentage of cancer in a single core				0.31
< 5	92 (7%)	68 (6.6%)	24 (8.3%)	
5-25	632 (47.9%)	487 (47.2%)	145 (50.3%)	
25-50	383 (29%)	302 (29.3%)	81 (28.1%)	
> 50	213 (16.1%)	175 (16.9%)	38 (13.2%)	
Number of biopsy cores				0.67
6-11	61 (4.6%)	49 (4.7%)	12 (4.2%)	
12+	1259 (95.4)	983 (95.3%)	276 (95.8%)	

Fhx = family history; PSA = prostate-specific antigen; BMI = body mass index

was no difference in the number of patients with non-confined disease between the two groups (12.8% versus16.7%, p = 0.11). Pathological upgrading was observed in 61.1% of the total cohort, with no statistical difference observed between the two groups (60.7% versus 62.5%, p = 0.5), Table 2.

TABLE 2. **Radical prostatectomy findings in patients with and without family history of prostate cancer who met the expanded criteria for active surveillance**

Expanded criteria	Total cohort 1,320	No family history of prostate cancer 1,032	Family history of prostate cancer 288	p value
Extraprostatic extension	184 (13.9%)	152 (14.7%)	32 (11.1%)	0.11
Seminal vesicle involvement	25 (1.9%)	20 (1.9%)	5 (1.7%)	0.82
Pathological Gleason score				0.7
6	476 (36.1%)	374 (36.3%)	102 (35.4%)	
3+4=7	753 (57%)	586 (56.8%)	168 (58.3%)	
4+3=7	79 (6%)	61 (5.9%)	17 (5.9%)	
8-10	12 (0.9%)	11 (1%)	1 (0.4%)	
Upgrading	807 (61.1%)	627 (60.7%)	180 (62.5%)	0.5
Major upgrading	12 (0.9%)	11 (1%)	1 (0.4%)	0.27
Positive margin	234 (17.7)	191(18.5%)	43 (14.9%)	0.169
Lymph node invasion	0/1320	0/1032	0/288	> 0.5

Discussion

Family history of prostate cancer was reported in 21% of this cohort. We found that the presence of family history of prostate cancer in men who would have been eligible for AS and underwent robot-assisted RP had no association with adverse pathologic findings at prostatectomy.

Despite the guideline recommendation for earlier prostate cancer screening for men with family history of prostate cancer, the association of family history of prostate cancer with outcomes has been inconsistent.[2,3] The Finnish Prostate Cancer Screening Trial demonstrated no benefit of additional screening for men with a family history of prostate cancer. Moreover, several retrospective studies in the PSA era showed the minimal impact of family history of prostate cancer on prostate cancer aggressiveness and prognosis.[15-19] In the current study, the presence of a family history of prostate cancer in men who met expanded criteria for AS was not associated with an increase in the likelihood of pathological upgrading. These findings suggest the presence of a family history of prostate cancer of prostate cancer in men might have a minimal role in identifying those men at highest risk for pathological upgrading. The results from our study are in-line with the findings of the systematic review by Telang et al which included patients with low volume disease.[8]

On the other hand, underlying genetic factors affecting prostate cancer behavior in individuals with familial prostate cancer may still be important in determining individual prognosis at later disease stage.[20] For instance, the National Comprehensive Cancer Network (NCCN) recommend genetic testing for men with low to intermediate risk who have young age of diagnosis or a family history suggestive of hereditary breast/ovarian cancer syndrome or Lynch syndrome.[20] Recently, the NCCN Prostate Cancer Guidelines (version 1.2019) endorse assessing the status of BRCA mutation and other prostate cancer gene status in the discussion of AS in early-stage prostate cancer.[21]

Several groups studied the association between the presence of family history of prostate cancer and different clinic-pathological characteristics in men with locally advanced prostate cancer. Matikainen *et al* found no association between family history of prostate cancer and age at diagnosis, PSA value, and Gleason score,[22] although the Finnish Prostate Cancer Screening Trial found higher PSA concentration among patients with family history of prostate cancer. The authors of this trial had noticed that PSA performance in terms of specificity and sensitivity was slightly inferior in those with a family history of prostate cancer.[7] In this study with extended criteria for AS, there was no association between family history of prostate cancer and age at diagnosis, biopsy, and final Gleason score; however, the PSA level was slightly lower in patients with family history of prostate cancer. This might reflect the real-world practice in which men with a family history of prostate cancer would be aggressively screened by their provider.[22]

Anxiety may serve as a major barrier to participation in AS. Only a few studies looked at the association between the presence of family history of prostate cancer and anxiety. For example, Marzouk et al found no association between family history of prostate cancer and prostate cancer-specific anxiety measured using MAX-PC (Memorial Anxiety Scale for Prostate Cancer).[23] Tan et al reported that family history of prostate cancer did not increase prostate cancer-specific anxiety; however, it was associated with increased generalized anxiety measured using HADS (Hospital Anxiety and Depression Scale).[24] Kinsella and colleagues identified family history of prostate cancer as a potential patient-related factor that might act as a barrier for selecting AS as treatment choice for low-risk prostate cancer.[6] The results from our study might help the physicians during counseling to mitigate the impact of family history of prostate cancer on final pathology upgrading at time of prostatectomy, in an attempt to normalize anxiety at the initial encounter which is likely will improve patient adherence to AS.[25]

Despite the novelty of our study, here are some notable limitations. First, reporting the presence of family history of prostate cancer depends on patient ability to recall this information; therefore, we could not exclude recall bias in our study. Second, African American patients were underrepresented in this cohort, and this might be related to the referral pattern. Third, all these patients were eligible for AS based on the initial biopsy results and did not undergo a confirmatory biopsy. Also, most of the biopsies were done outside our institution, and this might explain the high rate of final upgrading at the final pathology in this cohort. Nevertheless, this may help in the generalizability of our findings to patients undergoing biopsies outside center of excellence. In addition, the effect of the presence of family history of prostate cancer on the screening intensity, and threshold for biopsy could not be assessed in our data, which might lead to selection bias. Finally, formal genetic counseling was offered for a very selected cases; however, the recent practice in our institution is complying with the recent recommendations of NCCN for genetic testing which is offering genetic testing for all men with metastatic prostate cancer and for men with prostate cancer with a Gleason score seven or higher and one close relative with ovarian, pancreatic, metastatic prostate, or early-onset breast cancer (younger than age 50); two close relatives with breast or prostate cancer at any age; or Ashkenazi Jewish ancestry.[20]

Up to our knowledge, our study is the first that assessed the impact of family history of prostate cancer in men who would have been eligible for AS based on expanded criteria on pathological upgrading. The finding from this study should be viewed as a continuum of the efforts to optimize counseling for men with prostate cancer. □

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