Original Study

Comparison of 11 Active Surveillance Protocols in Contemporary European Men Treated With Radical Prostatectomy

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Abstract

Eleven active surveillance (AS) entry definitions in contemporary European men treated with radical prostatectomy (RP) at Martini-Clinic Prostate Cancer Center were compared. Use of stringent AS entry definitions reduces the number of AS-eligible patients. Moreover, rates of unfavorable pathology at RP as much as triple between most and least stringent AS entry definitions. However, less stringent AS entry definitions result in the lowest AS ineligibility rates, in men without unfavorable pathology.

Background: The aim of this study was to compare 11 active surveillance (AS) protocols in contemporary European men treated with radical prostatectomy (RP) at the Martini-Clinic Prostate Cancer Center. **Patients and Methods:** Analyzed were 3498 RP patients, from 2005 to 2016, who underwent $\geq$ 10 core biopsies and fulfilled at least 1 of 11 examined AS entry definitions. We tested proportions of AS eligibility, ineligibility, presence of primary Gleason 4/5, upstage, and combinations thereof at RP, as well as 5-year biochemical recurrence-free survival (BFS). **Results:** The most and least stringent criteria were very low risk National Comprehensive Cancer Network and Royal Marsden with 18.8% and 96.1% of AS-eligible patients, respectively. Rates of primary Gleason 4/5 at RP, upstaging, or both features, respectively, ranged from 2.3% to 6.7%, 6.1% to 18.2%, and 7.1% to 21.0% for those 2 AS entry definitions. The range of individuals deemed AS-ineligible between the same 2 AS entry definitions, despite not harboring unfavorable pathology (primary Gleason pattern 4/5, upstage, or both), was 80.3% to 3.7%, 78.3% to 3.4%, and 77.8% to 3.4%, respectively. BFS rates showed narrow variability, with a range of 85.9% to 91.8%. **Conclusion:** Use of stringent AS entry definitions reduces the number of AS-eligible patients, which is related to a select range in individual entry parameters. Moreover, rates of unfavorable pathology at RP as much as tripled between most and least stringent AS entry definitions. However, less stringent AS entry definitions result in the lowest AS-ineligibility rates, in men without unfavorable pathology. BFS rates were virtually invariably high. Clinicians should know differences in key parameters underlying each AS entry definition, associated effect on rates of eligibility, and potential misclassification of individuals.

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Introduction

Active surveillance (AS) represents a treatment modality that is highly recommended in many patients,[1] on the basis of the protracted natural history of prostate cancer (PCa)[2-5] and on its favorable effect on quality of life,[6,7] as well as lower cost compared with other modalities.[8] Currently, there are several criteria to identify patients, in whom AS could be considered. Of those, 11 AS entry definitions have been widely endorsed in practice guidelines, clinical research, and/or clinical practice.[9-20]

Despite their popularity, no contemporary assessment of their performance with respect to resulting pathological grade, stage, and/or rates of biochemical recurrence (BCR) after definitive treatment has been reported, especially in contemporary European patients. Moreover, there is great variability between different AS entry criteria definitions. For example, maximum prostate-specific antigen (PSA) values for inclusion might range from $\leq$ 10 ng/mL[10,13,14] to $\leq$ 15 ng/mL.[9] Similarly, the number of allowed positive biopsy cores might range from 1 to 2, or $>$ 2 depending on the AS entry definition. In consequence, very wide differences in the proportions of patients that are deemed AS-eligible might ensue and might translate into a wide range of pathological characteristics and/or might yield a wide spectrum of BCR survival-free rates (BFS).[21]

On the basis of these considerations, we hypothesized that important differences in performance characteristics might be associated with different AS entry definitions. These in turn might undermine the ability of select AS criteria to correctly identify patients with grade and/or stage that is amenable to AS and might result in misclassification. To test the pathological characteristics, as well as BFS in AS candidates, we relied on radical prostatectomy (RP) pathology as gold standard. For purpose of analyses, we relied on most contemporary European patients, who were treated with RP between 2005 and 2016.

Patients and Methods

Between January 2005 and March 2016, 16,159 consecutive patients were treated with either open or robot-assisted RP for PCa at the Martini-Clinic Prostate Cancer Center, Hamburg, Germany.[22] All patients underwent transrectal ultrasound (TRUS)-guided $\geq$ 10 core biopsies and fulfilled the requirements of at least 1 AS entry definition (Table 1). Biopsy interpretation was performed by local pathologists. For purpose of head-to-head analyses, inclusion criteria required availability of variables required in all 11 tested AS entry definitions: clinical tumor stage, PSA (AxSYM; Abbott Diagnostics, Abbott Park, IL), TRUS-derived PSA density (PSAD), biopsy Gleason grade, as well as number and percentage of positive biopsy cores. Neoadjuvant therapy or missing clinicopathological characteristics represented exclusions. The final study cohort included 3498 PCa patients (21.6%). All data were prospectively recorded in an institutional review board-approved database.

All RP specimens were processed and examined by dedicated uropathologists.[23] Grading was performed according to the Gleason system. Dissected pelvic lymph nodes and periprostatic fibrofatty tissue were separately submitted for standard histopathological evaluation. BCR was defined as $\geq$ 2 consecutive measures of PSA $\geq$ 0.2 ng/mL.[24]

Statistical Analyses

We examined 11 AS entry definitions. Within the study cohort, patients were classified according to eligibility of these criteria, which are presented in Table 1.[9-18] The tested AS entry definitions consisted of low-risk and very low-risk National Comprehensive Cancer Network (NCCN),[19] European Association of Urology (EAU),[20] the European Randomized Study of Screening for Prostate Cancer, Prostate Cancer Research International: Active Surveillance (PRIAS),[25] Johns Hopkins University School of Medicine (Johns Hopkins),[11] University of Miami (Miami),[15] Memorial Sloan Kettering Cancer Center (MSKCC),[14] University of California, San Francisco (UCSF),[13] the conservative and extended University of Toronto criteria (Toronto and Toronto extended),[12] and finally, Royal Marsden Hospital (Royal Marsden).[9]

For each AS entry definition, 4 pathological characteristics were tested: (1) presence of any primary Gleason pattern 4/5 at RP pathology; (2) rate of any upgrade[26]; (3) pathologically unfavorable upstage, defined as the presence of $\geq$ pT3 tumor stage and/or lymph node metastases at RP pathology; and (4) rate of combined upstage and presence of primary Gleason pattern 4/5. Analyses were repeated in 411 patients who had $\geq$ 2 biopsy sessions to emulate follow-up repeat biopsy in AS patients.

Moreover, we calculated the proportion of AS-ineligible patients according to the 11 tested AS entry definitions, specifically, among those with absence of the 4 examined pathological characteristics described previously. Finally, we examined the rate of BFS at 5 years after RP.

Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges (IQRs) were included for continuously coded variables. BFS rates for the respective AS entry definitions at 5 years were calculated with the Kaplan–Meier method. All tests were 2-sided with P values $<$ .05 to indicate statistical significance. Analyses were performed using the statistical package R, version 3.2.2 (R Foundation for Statistical Computing).

Results

Baseline characteristics of the 3498 patients who were deemed AS-eligible according to at least 1 of 11 tested AS entry definitions are presented in Table 2. The median age was 64.2 years (IQR, 58.9-68.3). T1c clinical stage was most prevalent (n = 3076; 87.9%). Specifically, 2982 patients (85.3%) had PSA value $<$ 10 ng/mL, and 1803 (51.5%) and 2519 patients (72.0%) had respective PSAD values of $<$ 0.15 or $<$ 0.20. Among the study cohort, 2148 (61.4%) and 1350 (38.6%) patients were diagnosed with biopsy Gleason grade 3 + 3 and 3 + 4, respectively. Overall, 1024 (29.3%), 873 (25.0%), and 1601 (45.8%) patients had respectively, 1, 2, or 3 positive biopsy cores. Maximum tumor involvement per biopsy core up to 50% and up to 20% was recorded in 2844 (81.3%) and 1893 patients (54.1%), respectively.

On the basis of the number of patients who were AS-eligible, the most and least stringent AS criteria were the very low-risk criteria of the NCCN, which defined 658 patients (18.8%) as AS-eligible, and Royal Marsden criteria, which in turn defined 3363 patients (96.1%) as AS-eligible, respectively. There was considerable overlap between the different definitions of AS entry criteria (Table 1). For example, the Toronto AS entry definitions entirely overlapped with those of UCSF, MSKCC, and Miami.

Pathological tumor characteristics stratified according to 11 AS definitions are shown in Table 3. The rates of upgrade to primary Gleason pattern 4/5 invariably remained below 7%, with a narrow