Pathological Outcomes of Candidates for Active Surveillance of Prostate Cancer

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Abbreviations and Acronyms

DRE = digital rectal examination

ECE = extracapsular extension

PSA = prostate specific antigen

PSAD = prostate specific antigen density

RP = radical prostatectomy

SVI = seminal vesicle involvement

TRUS = transrectal ultrasound

UCSF = University of California, San Francisco

UODB = urological oncology database

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Purpose: Active surveillance of prostate cancer has emerged as a viable treatment option for men with features of low risk disease. Five prospective studies have enrolled patients for active surveillance with varying inclusion criteria. We evaluated the pathological outcomes of men meeting published criteria for active surveillance who elected immediate radical prostatectomy to assess the risk of under grading and under staging in candidates for active surveillance.

Materials and Methods: Data were extracted from our institutional urological oncology database for all men who underwent radical prostatectomy between 1996 and 2007. The primary outcome was pathological up staging, defined as the occurrence of extracapsular extension or seminal vesicle involvement. Pathological upgrading was identified as a secondary outcome. We determined the proportion of men who would have qualified for each published active surveillance study and the respective rates of upgrading and up staging in each group.

Results: We identified 1,097 men who underwent radical prostatectomy with a mean age of 59 years. Overall 28% of the men experienced a Gleason upgrade, 21% had extracapsular extension and 11% had seminal vesicle involvement. In men qualifying based on published active surveillance inclusion criteria, rates of upgrading varied between 23% and 35%, the incidence of extracapsular extension ranged from 7% to 19% and seminal vesicle involvement ranged from 2% to 9%.

Conclusions: Varying entry criteria for active surveillance show different rates of adverse pathological features at radical prostatectomy. Predictably fewer men met the more stringent criteria but these men had a lower incidence of seminal vesicle involvement and extracapsular extension. Such data can be used to advise men of the risks of active surveillance.

Key Words: prostatic neoplasms, patient selection, neoplasm staging, pathology

DESPITE advances in treatments and screening efforts, prostate cancer remains the second leading cause of cancer related mortality in American men with 186,000 new cases and 28,600 deaths projected in 2008.[1] Widespread use of screening tools for prostate cancer has led to the detection of a higher proportion of low risk lesions, the majority of which are still definitively treated with surgery or radiation.[2–4] Treatment decisions are complicated by the inability to predict which lesions will remain indolent and which will become clinically significant during a man's lifetime. This has raised concern regarding overtreatment of low risk lesions and em-

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phasizes the need for new prognostic tumor markers and more accurate identification of candidates for active surveillance. Currently approximately 10% of men diagnosed with low risk prostate cancer pursue active surveillance for initial treatment of their disease.[2] The use of active surveillance has started to increase again after an apparent nadir of 6.2% in 2000 as more published studies better describe clinically low risk lesions.[2,5,6]

Five recent prospective cohort studies used varying inclusion criteria for active surveillance but generally included maximum Gleason sum, PSA, number of positive biopsy cores, percent of single core involvement and clinical staging.[7–11] Many of these criteria are based on a model developed by Epstein et al in 1994, in which men with PSAD 0.15 ng/ml or less, Gleason grade 6 or less, less than 3 positive biopsy cores and no biopsy core with more than 50% involvement were shown to likely have insignificant disease at radical prostatectomy, defined as tumor volume less than 0.5 cc, no Gleason pattern 4 or 5 and organ confined.[6] Surveillance methods of men selecting delayed treatment also varied significantly but usually included PSA, DRE, TRUS and re-biopsy at a range of intervals.[7–11] These studies resulted in 14% to 35% of patients progressing from active surveillance to definitive treatment for varying reasons (table 1).[7–11]

The variations in inclusion criteria of these studies demonstrate the uncertainty surrounding which cutoffs of clinical prostate cancer characteristics best prognosticate low risk disease. We examine the inclusion criteria for active surveillance used in 5 leading prospective studies and apply these criteria to men who instead underwent immediate RP. We determined the safety of enrollment practices in active surveillance and identified the prevalence of under staging and under grading, thereby exposing some men to the potential risk of delayed, less effective treatment.

MATERIALS AND METHODS

Data were extracted from the UCSF institutional UODB for all men undergoing RP for primary treatment of prostate cancer. Men were included in the study if they underwent RP within 6 months of initial diagnosis between 1996 and 2007, received no other types of primary treatment, and had complete clinical data including PSA, PSAD, prostate biopsy with 6 or more cores, and preoperative and postoperative tumor staging and grading. Based on preoperative disease characteristics (PSA, PSAD, Gleason sum, clinical stage and biopsy results by core) we determined whether these men would have met inclusion criteria for any of the 5 identified prospective active surveillance studies. We defined up staging as any occurrence of extracapsular extension or seminal vesicle involvement in the prostatectomy specimen. ECE represents stage pT3a and SVI represents stage pT3b based on the 2002 American Joint Committee on Cancer update.[12] We defined upgrading as any increase in Gleason sum from biopsy to surgery to a sum of at least 7, without differentiating between 3 + 4 and 4 + 3 disease. We recognize that Gleason 7, especially Gleason 3 + 4, may still qualify for active surveillance according to certain criteria but chose to use a single consistent definition of upgrading for this study.

Table 1. *Prospective studies enrolling patients in active surveillance programs*

References	Institution	No. Pts	Mean Age	Inclusion Criteria	Surveillance Protocol	Mean Yrs Followup	% Treated
Loblaw et al[10]	University of Toronto	423	67	Gleason 3 + 4 or less, PSA 15 ng/ml or less, stage T1–T2, 3 or less pos biopsy cores, 50% or less single core involvement	PSA, re-biopsy after 1 yr then every 3 yrs	4.6	35
Hardie et al[9]	Royal Marsden	80	71	Gleason 7 or less, stage T1–T2, PSA 20 ng/ml or less	DRE, PSA every 3–6 mos then every 6 mos	3.5	14
Carter et al[8]	Johns Hopkins Medical Institution	407	66	Gleason 6 or less, no pattern 4 or 5, PSAD 0.15 or less, stage T1, 2 or less pos biopsy cores, 50% or less single core involvement	DRE, PSA every 6 mos biopsy every 12 mos	3.4	25
Dall'Era et al[7]	UCSF	312	63	Gleason 6 or less, PSA 10 ng/ml or less, stage T1–T2, 1/3 or less pos biopsy cores, 50% or less single core involvement	DRE, PSA every 3 mos TRUS every 9–12 mos, biopsy after 1 yr then every 1–2 yrs	3	21
Patel et al[11]	Memorial Sloan-Kettering Cancer Center	88	65.3	Gleason 7 or less, stage T1–T2	DRE, PSA every 3 mos for 1 yr then every 6 mos, re-biopsy at 6 mos	4.6	35