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## Reply to J.J. Tosoian et al

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## Reply to J.J. Tosoian et al

Potential overtreatment of prostate cancer has increased the use of active surveillance (AS).<sup>1</sup> We agree with Tosoian and Carter<sup>2</sup> that variable inclusion criteria used in previous studies<sup>3</sup> and the lack of mature randomized data mean that there is uncertainty in identifying the ideal patient population to receive AS. We would like to confirm that the endorsed Cancer Care Ontario (CCO) guideline<sup>4</sup> applied a quality assessment of the included studies, and this was taken into consideration during our evaluation. The original CCO guideline did not include any strength-of-recommendation ratings, and none were added according to ASCO endorsement methodology.

For low-risk cancer, there is a lack of compelling evidence showing that immediate treatment improves overall survival. The SPCG-4 (Scandinavian Prostate Cancer Group Trial Number 4) trial<sup>5</sup> randomly assigned patients to watchful waiting versus radical prostatectomy and found a nonsignificant 3.8% mortality reduction for low-risk patients in the prostatectomy group with a median follow-up of > 13 years. However, it is not clear whether this difference applies to screening-detected patients, and whether AS differs from watchful waiting. A more contemporary randomized trial showed no survival benefit from radical prostatectomy versus observation in low-risk patients through at least 12 years of follow-up.<sup>6</sup>

We agree that more research is needed to identify the ideal patient group for AS. The ASCO endorsement acknowledges and provides qualifying statements regarding patient characteristics such as age, race, and volume of disease and acknowledges that treatment decisions should be made in consideration of the individual patient. To date, there are no data suggesting that any patient characteristics (including patients classified as very-low risk v low risk by the National Comprehensive Cancer Network) indicate a need for immediate treatment of low-risk patients. Indeed, recent evidence suggests rates of upgrading and upstaging were comparable in black and white men with low-risk prostate cancer.<sup>7</sup> Two of the largest, most mature AS studies had the broadest inclusion criteria and both included patients with intermediate-risk disease. To date, these studies have demonstrated low rates of metastases and cancer-related mortality with 50% to 63.5% of patients remaining untreated at 10 years.<sup>8,9</sup> Many of these patients were recruited before the introduction of the International Society of Urological Pathology modified Gleason grading system in 2005, with studies suggesting that up to one third of Gleason 3+3 tumors would now be classified as Gleason 3+4.<sup>10,11</sup> Furthermore, biopsies now increasingly include greater numbers of cores coupled with multiparametric staging using magnetic resonance imaging scans, which has led to grade and stage migration, suggesting that these results reflect worst-case scenarios. If

it is demonstrated that very-low-risk versus low-risk patients have different long-term survival outcomes after AS, this can inform future clinical practice and guidelines, but until data become available, we feel that the ASCO endorsement<sup>12</sup> with the described acknowledgment of patient heterogeneity best summarizes currently available evidence.

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Disclosures provided by the authors are available with this article at [www.jco.org](http://www.jco.org).

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