The risk of overtreatment in localized prostate cancer has become a subject of paramount importance and is one of the major reasons behind some of the negative perceptions of screening. Although treatment today has less morbidity than in the past, there is still significant risk associated with all available treatment options. To dissociate screening from treatment, the concepts of watchful waiting (WW) and active surveillance (AS) have gained widespread attention and appeal.

The concept of WW implies that patients are followed up without intervention until symptoms manifest or clinical or metastatic progression becomes apparent. The concept of WW has become less attractive, especially for younger patients, given that a large randomized clinical trial demonstrated that radical prostatectomy significantly improved metastasis-free and overall survival compared with WW.

A compromise between WW and immediate intervention has given rise to the concept of AS. Given the low risk of 10-year cancer-specific mortality, AS has become a recommended option for selected patients diagnosed with apparently low-risk cancer. Low-risk disease is generally defined as Gleason grade 6 cancers with prostate-specific antigen (PSA) findings below 10 ng/mL and nothing more than clinical T2a disease on digital rectal examination (DRE). The subclassification of very-low-risk cancer is defined as 2 or fewer positive biopsy findings with less than 50% of any core being cancerous. These cases are often defined as Gleason grade 6 cancers with prostate-specific antigen (PSA) findings below 10 ng/mL and nothing more than clinical T2a disease on digital rectal examination (DRE).

Whether we can safely expand the concept of AS to some patients with intermediate-risk prostate cancers has become a subject of interest to both physicians and patients. The study in this issue of JAMA Oncology by Ralston et al compares low-risk to favorable intermediate-risk prostate cancer and shows that brachytherapy was equally effective, with a very low risk of mortality, in both groups. According to the authors, the findings suggest that some intermediate-risk patients may actu-
ally be good candidates for AS. This suggestion is interesting but requires careful reflection.

It is true that in the past 10 years there has been a certain degree of grade migration, where Gleason grade 3 cancers are sometimes reclassified to grade 4. This may suggest that historical studies showing very low progression of grade 3 cancers might in fact have included favorable-looking grade 4 disease by today’s standards. However, it is clear that the duration of follow-up of the cohort in the study by Raldow et al is short in terms of prostate cancer timelines. It is also important to note that the authors are reviewing outcomes of patients who were treated rather than observed. The authors concede that they cannot be sure whether the results obtained would have been the same if the patients had been under AS. This reality, combined with the risk of undergrading and understaging documented Gleason grade 4 cancers, makes AS risky, to be undertaken with extreme caution.

There is also evidence from studies such as PIVOT and other cohorts suggesting that patients with intermediate-risk prostate cancer have worse outcomes under AS. The large ProtecT study will hopefully help answer some of these questions and help identify the profile of patients that can be safely managed with active surveillance.

Another important factor that may reduce the generalizability of the results reported by Raldow et al is pathology expertise. Studies have shown that there is significant cancer upgrading when pathologic findings of non-prostate experts are reexamined by prostate experts.

So what will it take for physicians and patients to be more comfortable with AS? Obviously, a better understanding of the biology of the cancer at hand would be very helpful. Efforts in that area are being made with the use of magnetic resonance imaging as well as the search for reliable tissue, serum, and urine biomarkers to help stratify disease. These are the areas where we need to focus our research efforts because simply repeating biopsies has its share of inconvenience and limitations even beyond the alarming increase in the risk of sepsis.

So what can we learn from this study by Raldow et al? One of the most important findings is that favorable intermediate-risk cancers can be very well controlled with brachytherapy. This is very worthwhile information. What about expanding the indications for AS? Although I am a urologist who has been practicing active surveillance for most of my low-risk patients for many years, I suggest that we continue to be very cautious, and extremely selective, in offering AS to patients with any features of intermediate-risk prostate cancer.