Re: Active Surveillance Magnetic Resonance Imaging Study (ASIST): Results of a Randomized Multicenter Prospective Trial

Klotz L, Loblaw A, Sugar L, et al

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Experts' summary:
ASIST is a randomized, prospective, multicenter trial that evaluated whether adding magnetic resonance imaging (MRI)-fusion targeted biopsies to standard template systematic biopsies in patients on active surveillance (AS) for low-risk prostate cancer more effectively identifies grade reclassification on confirmatory biopsy. Overall, 273 men entering AS with Gleason grade (GG) 1 prostate cancer were randomized to either MRI with targeted + systematic biopsy (n = 137) or systematic biopsy alone (n = 136). The use of MRI-targeted biopsies did not yield higher rates of grade reclassification: upgrading was found in 36/132 men (27%) in the systematic biopsy only arm and 42/127 men (33%) in the MRI with targeted and systematic biopsy arm (p = 0.3). Notably, targeted biopsy missed 7.9% of GG $\geq$2 cancers found on systematic biopsy, and systematic biopsy missed 6.5% of significant cancers found on targeted biopsy. The positive and negative predictive values for MRI for clinically significant cancer in this AS cohort were 23% and 85%, respectively.

Experts' comments:
MRI is increasingly being used as a tool for enrolling and monitoring patients in AS protocols [1,2]. Much of the literature on the utility of MRI in AS, however, is retrospective and based on relatively small study populations [3].

ASIST is the first prospective, randomized trial assessing the performance of MRI and fusion-biopsy compared to standard of care in identifying clinically significant cancer in AS patients. The authors are to be congratulated for their important, high-level, and elegant contribution to the literature. ASIST did not find that MRI with targeted + systematic biopsy was superior for the detection of clinically significant prostate cancer compared to systematic biopsy alone, despite the use of 3-T MRI with an endorectal coil and fusion software. Interestingly, the likelihood of detecting GG $\geq$2 cancer was higher for men with an MRI target (region of interest with a Likert score of 3, 4, or 5), even if the targeted biopsies were negative. This finding might be attributable to a targeting miss despite fusion technology, to MRI inaccuracy, or to a field effect. Experience may play a role, as the positive predictive value (PPV) of a target ranged widely between study sites (8–33%); in addition, the study was designed before the Prostate Imaging-Reporting and Data System (PI-RADS) classification, which could have affected target identification.

In ASIST, 11% (5/45) of patients with a negative MRI had GG $\geq$2 cancers found on systematic biopsy. These outcomes corroborate recent retrospective data showing that targeted biopsies alone are insufficient for surveillance given the low sensitivity and PPV of MRI for detecting higher disease grades in AS populations [4,5]. Together, these data suggest that MRI, standard template systematic biopsies, and targeted biopsies (for men with an MRI target) should all routinely be performed on entering AS.

Like all good clinical trials, ASIST leaves us with as many questions as it answers. For example, how frequently should MRI be used in AS protocols? How often does a de novo target appear during AS? Do targets upgrade over time? And can proposed risk stratification tools that incorporate MRI and other clinical parameters help in subjecting patients to fewer biopsies with reasonable safety [2]? Optimizing the role of prostate imaging during AS remains a fertile area of study.

Conflicts of interest: The authors have nothing to disclose.

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Re: Sunitinib Alone or After Nephrectomy in Metastatic Renal-cell Carcinoma

Méjean A, Ravaud A, Thezenas S, et al

N Engl J Med 2018;379:417–27

Experts' summary:
On the basis of phase 3 clinical trials conducted in the era of IFN systemic therapy, cytoreductive nephrectomy (CN) has become the standard of care for selected patients with metastatic renal cell carcinoma (RCC) and a surgically

resectable primary tumor [1,2]. However, the question remains whether this approach currently applies to patient care in the era of targeted therapies.

In the CARMENA trial, Méjean et al. [3] concluded that sunitinib alone was noninferior to CN followed by sunitinib for patients with low- or intermediate-risk metastatic RCC. Patients with metastatic clear-cell RCC were randomized to sunitinib alone ($n = 224$) or CN followed by sunitinib ($n = 226$). The primary endpoint of overall survival (OS) was assessed using intention to treat (ITT) analysis.

Experts' comments:
The conclusions of this study have been widely questioned given what appear to be major deviations from the assigned treatment plan, potential issues of bias in patient selection, the trial design, and other issues.

For example, 17% of patients in the sunitinib-only arm received delayed nephrectomy, while 7% of patients in the CN + sunitinib arm did not receive CN and 17% never received sunitinib. Why? It might be that the patients studied had higher risk than anticipated. This contention is supported by the fact that the study outcomes were significantly inferior than planned (OS of 18 mo for sunitinib and 14 mo for CN + sunitinib, versus the planed 26 mo). The authors also admit that some potential patients were excluded from participation "at the investigator's discretion" if they had low-risk metastatic disease. In addition, it is widely accepted that deviations from protocol following randomization in ITT/noninferiority trials may cause groups to appear more similar when true treatment differences exist [4].

Much of my academic work has involved clinical trials. I applaud the authors of the CARMENA report for their efforts to answer an important clinical question. However, I believe that their trial is flawed and does not support their contention that CN is of no benefit for patients with metastatic renal cancer. I believe that CN still has a significant role today for patients who are well selected by a team composed of a urologist and a medical oncologist before treatment.

In sum, while the role of CN may continue to evolve as newer and more effective therapies continue to discovered, I believe that the CARMENA trial should not dissuade physicians from currently offering CN to appropriately selected patients.

Conflicts of interest: The author has nothing to disclose.

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Re: The Temporal Association of Robotic Surgical Diffusion with Overtreatment of the Small Renal Mass

Shah PH, Alom MA, Leibovich BC, et al

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Experts' summary:
The authors utilized the National Cancer Data Base to evaluate contemporary practice patterns in the management of small renal masses (SRMs; <4 cm). Some 52 804 patients managed between 2010 and 2014 were analyzed, and trends in the use of active surveillance (AS), ablation, and surgery (robotic, laparoscopic or, open) were assessed overall and for subsets of elderly (>75 yr) and unhealthy (Charlson comorbidity index ≥2) patients. The authors found that surgery remained the primary treatment option (in >70% of patients), despite a small increase in patients managed with AS (from 4.8% to 6%). Moreover, they noted an exponential increase in robotic partial nephrectomy (RPN) and radical nephrectomy (RRN) procedures. This trend was observed in all groups included in the evaluation. On multivariable analysis, year of diagnosis (2014 vs 2010) was associated with higher use of robotic renal surgery versus AS (odds ratio 1.44; $p < 0.001$). The authors conclude that surgical overtreatment of SRM can be attributed to robotic dissemination.

Experts' comments:
While we commend the authors for their work, a closer look at the data might allow a different, and more balanced, interpretation, ultimately avoiding what we believe is a misleading message about the role and impact of robotic surgery in SRM management. The percentage of SRMs managed with "surgery" remained stable over the study period (75% in 2010 vs 74.2% in 2014), with significant increases in RPN (from 19% to 35%) and RRN (from 2.7% to 4.4%) being offset by declines in other "surgical" options (open PN 24% to 15%; laparoscopic PN 8% to 6%; open RN 10% to 5%; and laparoscopic RN 10% to 8%). Thus, from looking at the larger picture we can conclude that implementation of robotic surgery did not translate to overtreatment, but