Conflicts of interest: The authors have nothing to disclose.

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Re: Long-term Rate of Mesh Sling Removal Following Midurethral Mesh Sling Insertion Among Women With Stress Urinary Incontinence

Gurol-Urganci I, Geary RS, Mamza JB, et al

JAMA 2018;320:1659-69

Experts' summary:

Stress urinary incontinence (SUI) is a highly prevalent condition with a significant effect on quality of life for nearly one-third of adult women. A midurethral sling (MUS) remains the most common surgical treatment for SUI. This study examines long-term mesh removal rates following MUS insertion using a national population-based retrospective cohort. Conducted in England, the study included Hospital Episode Statistics (HES) data, which capture records for all inpatient admissions to National Health Service (NHS) hospitals. The authors found that of the 95 057 women who had an MUS inserted between 2006 and 2015, nearly two-thirds were retropubic cases (the remainder were obturator). The rate of sling removal was 3.3% at 9 yr, and was lower in the transobturator than in the retropubic group. The rate of reoperation for SUI was 4.5% at 9 yr, and the rate of any reoperation (removal + reoperation for SUI) was 6.9% at 9 yr.

Experts' comments:

The authors address an important question on a scale much larger than in prior studies. With access to data for inpatient admissions at all NHS hospitals in England, they were able to capture a large portion of the national population to give clinicians a sense of what happens in the long term after mesh slings are placed in women for SUI. Their reported reoperation rates are low, with a mesh removal rate at 1 yr of only 1.4%, which increased to only 3.3% at 9 yr. When the rates of mesh removal are combined with reoperation for SUI, they increased to only 2.6% at 1 yr and 6.9% at 9 yr. These reoperation rates are lower than those previously reported by Funk et al. [1] in a study of more than 150 000 women in the USA, in which the 9-yr cumulative incidence of repeat surgery following any SUI surgery 14.5%, with a sling-specific reoperation rate of 13%. The reoperation rates for MUS published in this new study are lower than those previously reported by Funk et al for several SUI procedures, including bulking agents, needle suspensions, Burch, and MUS.

This study is retrospective and unfortunately there is no information provided regarding overall complications following MUS, as only reoperations are identified. Therefore, patients requiring treatment for de novo overactive bladder, dyspareunia, mesh extrusion/erosion, and other complications that were not managed via surgical excision were not identified in the study. Furthermore, other details regarding mesh excision (total vs partial vs incision alone), while differentiated, are not clearly defined.

Despite some of these significant limitations, the authors provide important information for clinicians and their patients considering surgery for SUI (overall favorable reoperation rates following MUS) on a very contentious topic at a very critical juncture.

Conflicts of interest: The authors have nothing to disclose.

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Re: Genomic Differences Between "Primary" and "Secondary" Muscle-invasive Bladder Cancer as a Basis for Disparate Outcomes to Cisplatin-based Neoadjuvant Chemotherapy

Pietzak EJ, Zabor EC, Bagrodia A, et al

Eur Urol 2019;75:231–39

Experts' summary:

The authors investigated whether patients with non-muscle-invasive bladder cancer (NMIBC) who experience progression to muscle-invasive bladder cancer ("secondary" MIBC) differ in clinical outcome and chemosensitivity compared to patients presenting with "primary" MIBC [1]. A retrospective analysis of clinical data from an MIBC patient cohort was performed (clinical stage T2–4aN0M0 disease, ≥3 cycles of neoadjuvant chemotherapy [NAC]). Pathologic response at radical cystectomy (RC) was defined as ≤pT1N0. Pathologic response was lower in patients with secondary MIBC on both univariate (26% vs 45%; $p = 0.02$) and multivariable analyses (odds ratio 0.4, 95% confidence interval 0.18–0.84; $p = 0.02$). Moreover, secondary MIBC was associated with worse recurrence-free survival ($p < 0.007$) and overall survival ($p = 0.048$). Next, they showed that of the somatic genomic alterations in genes implicated in platinum-based chemotherapy response in MIBC (*ERCC2*, *ATM*, *FANCC*, and *RB1*), only *ERCC2* mutations account for this difference in clinical outcome and chemosensitivity between primary and secondary MIBC [2,3]. *ERCC2* missense mutations were enriched in primary versus secondary MIBC (11% vs 1.8%; $p = 0.044$) and findings validated in an independent prospective cohort confirmed enriched *ERCC2* mutations in primary versus secondary MIBC tumors (17.1% vs 0%; $p = 0.033$).

The authors conclude that upfront RC or enrollment in clinical trials should be considered for patients with secondary MIBC because of the marginal clinical benefit of NAC.

Experts' comments:

This study highlights the current overall weakness of biomarkers in predicting response to NAC. As a surrogate, the authors suggest using secondary MIBC to identify patients who might benefit from upfront RC or could be considered for clinical trials. Prior studies have already demonstrated worse clinical outcomes for secondary compared to primary MIBC [4]. Up to now, this worse outcome was explained by secondary MIBC patients having received multiple ineffective bacillus Calmette-Guérin (BCG) instillations, leading to a delay in RC. This is the first study to demonstrate that secondary MIBC patients have a lower response to NAC than primary MIBC patients, and that this could be caused by a difference in genomic make-up of the tumors. Importantly, the authors showed few *ERCC2* mutations in secondary MIBC. Despite the retrospective nature of this study, these interesting findings raise the question of whether resistance to NAC in secondary MIBC is an intrinsic tumor feature or is acquired during treatment with BCG (treatment selection of clones resistant to subsequent NAC). Since our molecular insights are still quite limited, to answer this question, additional studies profiling NMIBC patients at a high risk of developing progression are urgently needed to elucidate the genomic landscape of these tumors [5].

Conflicts of interest: The authors have nothing to disclose.

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