ANCHOR Trial Results Are In: So Where Do We Go From Here?

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See "Incidence rate and risk factors for anal squamous cell carcinoma in a cohort of people living with HIV from 2004 to 2017: implementation of a screening program," by Guisado et al. on page 28.

I have been waiting a long time to say this: the ANCHOR trial shows that treating anal high-grade dysplasia (HSIL) significantly reduced the incidence of anal squamous cell carcinoma (ASCC) when compared with close monitoring alone! For those of you who do not know, the ANCHOR trial (https://www.clinicaltrials.gov NCT 02135419) randomly assigned 4446 people living with HIV (PLWHIV) to either HSIL treatment (most often high-resolution anoscopy (HRA)-guided ablative therapy) or active monitoring.[1] All participants received HRA at least every 6 months, and those in the treatment arm with recurrent HSIL were re-treated, whereas those undergoing active monitoring were watched closely with HRA and yearly biopsy to check for progression to ASCC. Although the results are being readied for peer-reviewed publication, we can say that anal HSIL treatment significantly reduced the incidence of ASCC.

I know I often harangue clinicians about the importance of screening for and treating HSIL to prevent anal cancer, whereas others take aim at my arguments by suggesting that the data did not yet support this approach.[2,3] While we debated, ASCC incidence increased as did mortality. Deshmukh et al[4] utilized the US Cancer Statistics data set that combines data from multiple national registries covering 99% of the US population to elucidate trends in ASCC incidence and mortality between 2001 and 2015 (mortality to 2016). They reported that ASCC incidence increased 2.7%/y with the highest increase in those ≥50 years. Anal squamous cell carcinoma mortality also increased 3.1%/y, again highest in those ≥50 years. Consistent with increased mortality was an increase over time in advanced stage diagnosis that tripled for men and doubled for women, a fact borne out by 2 recent series from colorectal surgeons reporting on expectant management.[4–6]

As an ANCHOR trial principal investigator, I did not know whether HSIL treatment would, in fact, prevent cancer until September 2021. Until that time, I looked to my own research and the literature for evidence from others for signs that treatment is effective. I read with great interest the article from Guisado et al[7] reporting on the incidence and risk factors for ASCC in their cohort of PLWHIV receiving care at the infectious diseases unit in Seville, Spain. Besides the large number of participants followed (3878 with 40.8% men who have sex with men (MSM)) over 29,228 person-years (py), the cohort was also unique in that MSM were offered entry into a screening and treating anal neoplasia (SCAN) program beginning in 2010. Those entering SCAN underwent HSIL screening with anal cytology, HRA, and targeted HSIL ablation. Thus, those choosing to enter SCAN made up an HSIL screening and treatment cohort, whereas all others remained in the follow-up group. Twenty ASCCs were identified, all male patients (11 MSM) including 4 MSM in the SCAN group.[7]

The ASCC incident rate (IR) for the entire cohort was 63.9/100,000 py, and the incidence rate ratio comparing 2011 to 2017 with 2004 to 2010 was 3.15 ($p<0.001$) illustrating the increase in cancer over time. When looking at just MSM, the ASCC IR was 103.6/100,000 py. For all others, the ASCC IR was 48.4/100,000 py.[7] Guisado et al found that those with a lower level of education, 36 to 49 years of age, smokers, MSM, with lower $CD4^+$ counts, who did not achieve immune reconstitution or with symptomatic

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HIV-related disease, were at significantly increased risk for ASCC.[7]

In 2011 when SCAN began, 897 MSM entered, accumulating 4181 py of follow-up, whereas 1457 MSM remained in the follow-up cohort with 2892 py of follow-up. Four participants in SCAN developed ASCC, but 2 had been lost to follow up for 1 and 5 years.[7] Two presented with T1 and 2 with T2 lesions without evidence of metastatic disease. In contrast, 16 participants in the follow-up group developed cancer and only one had a T1 lesion and 2 had T2 lesions (one with nodal metastasis). Two participants presented with distant metastasis. Anal squamous cell carcinoma incidence rates were approximately 95.7/100,000 py for MSM in SCAN and 201/100,000 py ($p < 0.001$) for those in follow-up. The adjusted incidence rate ratio was 0.3 ($p < 0.001$) for MSM in SCAN compared with those in follow-up ($p < 0.001$). As with the entire study cohort, MSM seen later in the study, without immune reconstitution and having symptomatic HIV-related disease, were significantly more likely to develop ASCC.[7] Lest you think that this study presents data unique to Spain, the authors accurately point out that their reported incidence of ASCC was very similar to that observed in large North American cohorts.[7]

This series is not without limitations.[7] The SCAN and follow-up groups differed demographically in key areas (level of education, symptomatic HIV, only MSM in SCAN), and no women in the series developed ASCC (which is also highly unlikely).[7]

Other recent large series of screening and treatment further support the findings of Guisado et al.[7] Revollo et al[8] followed more than 3000 PLWHIV who were either in a screening and treatment program or a nonscreening group. With 14,595 py of follow-up, they identified 10 ASCC (2 screening and 8 in nonscreening) for a reported incidence of 21.9/100,000 py and 107.0/100,000 py. After propensity score adjustment, screening and treatment offered a significant protective advantage against ASCC over nonscreening with a HR of 0.17 (95% CI, 0.03–0.86).[8] Gaisa et al[9] followed more than 300 PLWHIV with HSIL in a diagnosis and treatment program. Although HSIL recurrence posttreatment was common, they did not report a single case of ASCC. Given progression rates of 1.3% to 1.5%/y reported by others, Gaisa et al probably should have identified 1 or more ASCCs.[6–9]

Although we do not have the hard ANCHOR data yet, these studies of treatment versus observation give us a preview of what to expect. We are at a crossroads; do we advocate screening for and treating of anal HSIL in an effort to stem rising ASCC incidence and mortality, or do we continue to say the evidence is not there yet? I am not naive and know that we must see the actual ANCHOR data before changing practice guidelines. I do know if screening and treatment become the standard of care, it cannot be accomplished without special skill sets and much preparation. High-resolution anoscopy is difficult with a steep learning curve, and many colon and rectal surgeons perform HRA without formal training, potentially leaving patients with a false sense of security that they are HSIL-free simply because an untrained eye failed to identify it.[10] I know we cannot possibly screen everyone for anal HSIL and cancer because it is simply not cost-effective, and too few clinicians are trained in HRA. Nor will screening and HSIL treatment, even in the best of hands, prevent all cancers as Guisado et al and others have shown.[5–7,11,12] We know that ASCC incidence is increasing and again documented by this series.[4–7] We know that mortality is increasing perhaps related to later stage of diagnosis as shown by Guisado et al in the follow-up group as well as in 2 other recent series of expectant management.[4–7] We also know that treating HSIL leads to a higher probability of clearing the disease than betting on de novo regression.[13]

If you do not perform HRA, what can you do? Learn the technique is one obvious answer or enlist the services of a provider who can. It will take a lot of time to gear up successful screening programs, and until then, there are small steps you can take that might help mitigate the continued rise in ASCC and mortality. First and foremost, look for red flags indicating that your patient is at risk. As Guisado et al showed, MSM living with HIV are at greatest risk for cancer, especially if they are ≥50 years, smokers, have symptomatic HIV, and are not immune reconstituted.[7] Arens et al[14] showed that non-Hispanic Black patients and those with prior condyloma were at greater risk of progression in unadjusted analysis. Lee et al[15] showed us that if you surgically remove HSIL and do nothing more, then that patient is also at higher risk for progression to ASCC. If you do not see or feel additional disease in a patient with known HSIL, then refer to someone who can do HRA. Think of condyloma as a marker for human papillomavirus (HPV) infection. If a patient has condyloma, they could very well be coinfected with other more oncogenic HPV types and harbor HSIL. Follow these patients closely. Treat their condyloma and then refer to someone who can perform HRA to rule out coexistent HSIL. When at-risk patients are lost to follow-up, make every effort to engage them in care because those not adhering to surveillance regimens are at greater risk for progression.[7,8,11,12] And last but definitely not least, inquire as to whether your at-risk patients have received the HPV vaccine. The vaccine is now approved by the US Food and Drug Administration for people to age 45 years. Long-term data show that even if you have been infected, vaccinated men experience less recurrent disease after a "washout" period of 2 to 3 years.[16]

In summary, there is much to learn from this excellent work by Guisado et al while we await the final ANCHOR results.[7] Their data are corroborated by other researchers and shed new light on who is most at risk for anal cancer. As an avid reader and reviewer for *Diseases of the Colon & Rectum,* I am so pleased that the authors have submitted

this work to "our" journal and proud that the journal is giving it public voice. Who better to screen for and treat anal HSIL than colon and rectal surgeons? Who better than colon and rectal surgeons to develop new treatment techniques with reduced recurrence? Who better to teach and advance screening techniques than colon and rectal surgeons? We encounter at-risk patients every day. Let this research be a guide to help us help our at-risk patients as we prepare for the full ANCHOR results and hopefully improved anal cancer prevention. We are once again at a crossroads with 2 paths diverging; one toward screening and treatment and one toward monitoring. I think the signs are increasingly pointing in one direction. Follow us.

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