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LETTER TO THE EDITOR

What's wrong with the status quo? Plenty

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Dear Editor:

The International Anal Neoplasia Society (www.iansociety.org) is composed of clinicians, scientists, and advocates committed to better understanding the pathogenesis, diagnosis, treatment, and prevention of anal neoplasia with the ultimate goal of preventing anal cancer [1]. We are always interested in new research that helps us with our mission and read with interest the paper by Tomassi et al. describing their results of anal cancer incidence in patients treated within the Kaiser Permanente Southern California healthcare system [2]. We believe a more appropriate title for this paper might be "What's wrong with the status quo?"

The authors collected data on over 5 million patients who had a least 1 year of "active membership" in the system between January 2005 and December 2015. Patients were evaluated with visual "inspection of the perineum, digital rectal examination, and anoscopy at interval times ranging from 3 to12 months (shorter interval if symptomatic or dysplastic and longer if asymptomatic)." [2] Only patients with symptomatic or "grossly abnormal lesions" were treated. Patients were stratified into those with increased risk for anal cancer (HIV infection, prior HPV-related anal or gynecologic disease) and those with no obvious risk factor. After a mean of 5.4 years, 452 incident anal cancers were identified with only ¼ being stage 1 and 41% being stage 3 or 4. The authors report that the incidence of anal cancer per 100,000 person years overall was 1.3, 28.8 in HIV-infected individuals and 191.5 in individuals with prior anal dysplasia. Overall mortality after a mean of 3.3 years from cancer diagnosis was 35.2% [2]. The authors conclude that expectant management addressing only gross or symptomatic disease "is safe and effective even in high-risk patients" [2].

We could not disagree more. Anal cancer is one of the few cancers in the USA that rather than decreasing is actually increasing at over 2% per year for the past 10 years, with increasing mortality as well [3]. Perhaps expectant management as proposed by Tomassi et al. and others from the San Diego area is a contributing factor [2, 4]. The data presented is also strikingly different from other large population-based series. The incidence of anal cancer in HIV-infected patients as reported of only 28.8/100,000 person years is much lower than the 50.7/100,000 person years as determined in a much larger population-based study of almost 450,000 HIV-infected individuals in the USA [5]. Recently, Lee et al. examined rates of progression to anal cancer in individuals with a diagnosis of anal intraepithelial neoplasia grade 3 from the SEER database and found 19% developed anal cancer within a mean of 2.7 years whereas Tomassi et al. found that only 1.06% progressed over a longer follow-up. Huge differences.

So how can Tomassi et al. report lower rates of anal cancer compared to other published data [2]? Perhaps the answer lies in what is not presented. It is clear that this is a large series of over 5 million patients, but are these really patients undergoing expectant management or are they just enrolled in the health plan for at least 1 year? How often were they seen or were they seen at all? Do all patients really have anoscopy and digital examination at least yearly if not more often? What about patients only seen for acute illness like influenza, back pain, and so many other ailments? Do they really get anoscopy and digital examination? Do these individuals inflate the denominator muddying results? Patients with symptomatic and grossly evident disease were treated—how many did that effect and prevent progression? And what about the men versus the women with HIV, or HIV-uninfected MSM who are considered at risk for anal cancer? Surely these data points are available in the medical record, should have been analyzed, and could clearly impact progression rates.

We also do not share the authors' conclusions that a progression of 193.3 per 100,000 person years in individuals with high-grade dysplasia is insignificant. The incidence of

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prostate cancer in men is only 112.6 per 100,000 person years [6]! Who better to screen with high-resolution anoscopy and treat than those that you have already identified as having a much higher risk of progression than the general population. How good could the follow-up really be when only ¼ of patients with anal cancer were stage 1? Tomassi et al. also adopt the mantra that treating anal high-grade dysplasia is fraught with morbidity including stricture, incontinence, and "defecatory dysfunction" [2]. Tomassi et al. specifically site a paper by Watson et al. as showing high rates of fecal incontinence. It is unclear if these patients received any treatment other than biopsy or if they underwent wide local excision for perianal disease which we do not advocate [2, 7]. No recent large series of HRA-targeted destruction of HSIL have found significant morbidity [8–11]. Moreover, a recent series comparing expectant management with targeted destruction did not find any stricture or incontinence and there was significantly higher clearance of HSIL in the treatment group [12].

We do not have all the answers, but we do not agree that the status quo of expectant management waiting for cancer to develop is the ideal. True HSIL recurrence after treatment is high but rates of progression to cancer are lower compared to series of expectant management [2, 4, 8–10]. Multiple treatments are often required, but over time, recurrence diminishes. Would anyone choose chemotherapy and radiation over targeted HSIL destruction before cancer develops? Until a large prospective trial (ANCHOR Study, ClinicalTrials.gov number NCT02135419) results are known, we believe that more can be done than just watching and waiting for cancer to develop. Why settle for ¾ of patients with large or metastatic cancers? Why is a 35% mortality rate acceptable? Stating that these rates are comparable to the rest of California does not mean it is ideal—it just means that most patients in the state are also treated with expectant management. We need better screening tools and better treatments. Please join us in our quest to better understand how to diagnose and treat anal neoplasia to prevent cancer instead of trying to validate a status quo that clearly is not working.

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