Gynecologic Oncology 154 (2019) 253–254

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Margins in vulvar cancer: challenges to classical clinicopathologic vulvar recurrence risk factors

Vulvar cancer is a disease for which treatment may carry significant morbidity, but treatment failure causes significant mortality. Despite radical surgery, the risk of local recurrence is significant [1]. Consideration of vulvar recurrence risk factors is imperative, as long-term follow-up from the GROINSS-V-I study demonstrated a significant detriment to disease-specific survival at 10 years in the case of vulvar local recurrence (90.4% vs. 68.7%), whereas previously only nodal control was thought to impact survival [2,3]. Historically, pathologic close margins have been defined as <8mm, which has led to the classic recommendation of surgical margins greater than 1cm [4]. This recommendation has been challenged as retrospective data have emerged supporting the use of smaller resection margins due to an unclear relationship between close tumor resection margins and the risk of local recurrence [5,6].

In this issue of *Gynecologic Oncology*, Grootenhuis and colleagues explore pathologic predictors of local recurrence in vulvar cancer by retrospectively reviewing slides from consecutively treated patients from 2000-2010. While they include classic pathologic factors such as margin status and tumor factors, they also incorporate the presence of premalignant lesions in the margin and in the pathologic specimen. On multivariable analysis, pathologic tumor free margin distance did not predict risk of local recurrence at three different cutoffs (eight, five or three millimeters). Interestingly, the presence of premalignant lesions of both lichen sclerosis (LS) and differentiated vulvar intraepithelial neoplasia (dVIN), either at the resection margin or adjacent to the tumor predicted the risk of local recurrence. For patients with both LS and dVIN at the resection margin, the risk of local recurrence was the highest (76.4% at 10 years after treatment; HR 2.76 with 95% CI 1.62-4.71). Even patients with one or both precursor lesions simply in the pathologic specimen had a significantly increased risk of local recurrence (albeit not to the magnitude seen for patients with precursor lesions at the margin), suggesting that a field cancerization effect may play an important factor role in increasing the risk of local recurrence [7].

The strengths of this study include standardized expert gynecopathologic review and patients treated at a high-volume center known for treatment of vulvar cancer. This study is also the first to quantify the effect of precursor lesions on local recurrence risk using a large series of patients treated consecutively. Given that no margin cutoff could be identified above which the local recurrence risk was decreased, the authors advocate for lowering the recommended surgical margins to three millimeters, though the ideal margin size remains an open question.

This issue includes another retrospective study in which Bedell and colleagues also examine the role of additional treatment for early-stage patients with positive or close surgical margins (<8mm). They did not find a clear improvement in local recurrence-free survival for patients who underwent re-excision or adjuvant vulvar radiation, although the absolute number of patients receiving such additional therapies was small. This study also has the distinction of being one of few to focus on patients with early-stage disease, as the authors point out that most studies examining margin status have included patients with all stages of disease [8].

These studies raise two important considerations regarding clinical recommendations for the treatment and surveillance of vulvar cancer. First, given the significant morbidity associated with radical surgery for vulvar cancer, it is worth questioning practice recommendations which may not reduce the risk of local recurrence. The long-standing recommendation of margins of at least one centimeter translate to a surgery that is disfiguring and disabling. Using smaller margins, if oncologically appropriate, could spare women from treatment-related distress. Second, the identification of premalignant lesions which do predict local recurrence highlights a feature of the disease process which may be actionable and warrants future research. The identification of dVIN may present a pathologic challenge and is an area where education may be needed. Similarly, clinical recognition of this lesion is also important. Grootenhuis and colleagues recommend excision of lesions suspicious for dVIN and reexcision if dVIN is present in the margin.

A key finding of GROINSS-V-I long-term follow-up is that local recurrence impacts disease-specific survival. The corollary to this would appear to be an escalation of treatment to prevent recurrence, such as even larger margins with more extensive surgery, and/or a lower threshold for adjuvant radiation. This is a difficult point to reconcile with some of the findings of these two studies highlighted in this issue of *Gynecologic Oncology*, as they seem to argue for a de-escalation of treatment. However, other findings that are highlighted (such as consideration of new pathologic factors which may more accurately predict which women are at greatest risk of vulvar recurrence) advance the field by illuminating potential avenues for increased efficacy of therapy. The fact that local recurrence risk of vulvar cancer has remained high for the last few decades highlights how vulvar cancer is a disease where improved treatments and updated treatment guidelines are greatly needed. Consideration of any factors which may impact this risk (such as HPV and dVIN) should be incorporated an updated treatment algorithm. Classical teachings in the management of vulvar cancer must be questioned and refined in order to improve outcomes for a disease with significant morbidity and mortality for women worldwide.

https://doi.org/10.1016/j.ygyno.2019.07.007

Conflict of Interest Statement

The authors do not have any conflicts to disclose

Author contribution

Both authors contributed to researching and writing this article

References

[1] N.C. Te Grootenhuis, A.W. Pouwer, G.H. de Bock, H. Hollema, J. Bulten, A.G.J. van der Zee, et al., Prognostic factors for local recurrence of squamous cell carcinoma of the vulva: A systematic review, Gynecol. Oncol. 148 (3) (2018 /03/01) 622–631.
[2] N.C. Te Grootenhuis, A.G. van der Zee, H.C. van Doorn, J. van der Velden, I. Vergote, V. Zanagnolo, et al., Sentinel nodes in vulvar cancer: Long-term follow-up of the GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) I, Gynecol. Oncol. 140 (1) (2016 /01/01) 8–14.
[3] M.H. Oonk, B.M. van Hemel, H. Hollema, J.A. de Hullu, A.C. Ansink, I. Vergote, et al., Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: results from GROINSS-V, a multicentre observational study, Lancet Oncol. 11 (7) (2010 /07/01) 646–652.
[4] J.M. Heaps, Y.S. Fu, F.J. Montz, N.F. Hacker, J.S. Berek, Surgical-pathologic variables predictive of local recurrence in squamous cell carcinoma of the vulva, Gynecol. Oncol. 38 (3) (1990 /09/01) 309–314.
[5] M. Arvas, I. Kahramanoglu, T. Bese, H. Turan, I. Sozen, S. Ilvan, et al., The Role of Pathological Margin Distance and Prognostic Factors After Primary Surgery in Squamous Cell Carcinoma of the Vulva, Int. J. Gynecol. Cancer 28 (3) (2018 Mar) 623–631.
[6] G. Baiocchi, H. Mantoan, L. de Brot, L. Badiglian-Filho, L.Y. Kumagai, C.C. Faloppa, A.A. da Costa, How important is the pathological margin distance in vulvar cancer? Eur. J. Surg. Oncol. 41 (12) (2015 /12/01) 1653–1658.
[7] N.C. Te Grootenhuis, A.W. Pouwer, G.H. de Bock, H. Hollema, J. Bulten, A.G.J. van der Zee, et al., Margin status revisited in vulvar squamous cell carcinoma, Gynecol. Oncol. 154 (2) (2019 /05/18) 262–271.
[8] S.M. Bedell, C. Hedberg, A. Griffin, H. Pearson, A. Wilhite, N. Rubin, B.K. Erickson, Role of adjuvant radiation or re-excision for early stage vulvar squamous cell carcinoma with positive or close surgical margins, Gynecol. Oncol. 154 (2) (2019 /06/03) 272–275.

Sara Dudley MD
Central Maryland Radiation Oncology, Medical Pavilion at Howard County, 10710 Charter Drive, Suite G030, Columbia, MD 21044

Akila Viswanathan MD, MPH
Johns Hopkins Medicine, Department of Radiation Oncology & Molecular Radiation Sciences, The Weinberg Building at the Johns Hopkins Kimmel Cancer Center, 401 North Broadway, Room 1454, Baltimore, MD 21287
Corresponding author.