Reviewer's report

Title: Survival analysis of patients with invasive extramammary Paget disease: implications of anatomic sites

Version: 0 Date: 27 Aug 2017

Reviewer: Tien-Anh N Tran

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Survival analysis of patients with invasive extramammary Paget disease: implications of anatomic sites

BCAN-D-17-01348

This is an interesting study on the survival of patients with extramammary Paget disease. The authors analyzed SEER data from 1973 to 2013 of extramammary Paget disease. The study should add valuable information to the literature on this rare disease. However, some revisions are required to help the readers better understand the study.

1) First of all, I have some questions about the anatomic sites as defined by the authors in the methods:

To me, labial is part of the vulva and should be combined with vulva as one category and not with vagina. From an anatomic standpoint, the labia minora and majora are part of the vulva. Histologically, the labia are lined by keratinizing squamous epithelium which therefore should be considered as part of the skin in the vulvar area. The vagina on the other hand is lined by non-keratinizing squamous epithelium and hence considered a type of mucosa. Therefore, the patients should reanalyze the data, combining vulva/labial in one group and compared with the vaginal group. I can imagine that the vaginal group has a worse outcome compared to the vulvar group because vaginal EMPD is more difficult to detect clinically due to the more "internal" location and therefore probably manifested clinically at a later clinical stage. I believe vulvar and labial should be grouped together unless the authors have other reasons to separate vulvar from labial groups. In that case, the authors should clarify their reasoning in the methods.

Another group of the study is "skin". I'm not quite sure what the authors mean by skin because vulva and labial are also skin. Therefore, the authors should define the skin group anatomically. What parts of the body comprise the skin group.

The last group is "Other". It appears that the authors mean the anal and perianal areas as other. If so, the authors should clarify that in the methods.
2) One of the conclusion of the study is that patients who underwent radiation therapy had an overall poorer outcome. This conclusion might be misleading in my view as the authors did not elaborate the underlying reason for this negative effect of radiation on invasive EMPD although the authors cited Tolia et al study (Ref 22) that appeared to support a role of radiation in advanced invasive EMPD. In my opinion, the authors should analyze whether patient who received radiation therapy in their study had a more advanced clinical stage or worse clinical disease compared to the patients who did not receive radiation. Was radiation used only in patients who could not be treated merely with surgery and therefore a sign that these patients had advanced disease? This conclusion might be interpreted by the readers that radiation had a bad side effects on patients with invasive EMPD (or a risk factor as the authors stated in the first paragraph of the discussion) instead that it was actually used in advanced invasive EMPD where surgery could not locally control the disease and therefore portends a bad outcome for the patients, just due to the aggressive nature of the cases, independent from radiation therapy.

3) I'm not completely clear with the definition of "secondary malignancy" in the study. Do the authors mean a malignant process in the gastrointestinal, gynecological, or genitourinary tracts that cause EMPD as "secondary malignancy"? Or a malignant process at a distant site such as lungs or some other sites? If the authors meant an adenocarcinoma of the GI, GYN, or GU tract that spread to the vulvar or perianal areas as "secondary malignancies". I believe in those cases the EMPD is secondary while the adenocarcinoma in the GI, GYN, and GU is the primary malignancy. To me, primary EMPD should include only cases primarily arising from the skin (probably from anogenital mammary-like glands of the skin) without any adenocarcinoma in the GI, GYN, and GU tracts.

4) Discussion Part, Concurrent malignancy: The authors should better define what concurrent malignancy means? What secondary malignancy means? I find this part quite confusing.

5) Some minor concerns regarding the studies include:

a) Background Paragraph 1, Line 7-8: "invasive EMPD is found in men and women and may occur somewhat more frequently in women".

My understanding is EMPD is significantly more common in women than men, as also supported by the results of this study (34 % in male vs. 66% in female).

b) Background Paragraph 1, Line 8-10: "The most common anatomic sites at which EMPD may arise are the vulva, including the vagina or labia as part of the vulva, and penis or scrotum and perianal region."
As stated above, labia are part of vulva, but the vagina should not be considered as part of the vulva.

c) Background Paragraph 1, Line 10-12: "Historically, the incidence rates for EMPD have generally been highest for the vulva anatomic site except for a higher incidence of primary skin EMPD in 1978, 1979 and 1994."

Again, what is the definition of "primary skin". What are the body parts that contribute "primary skin"?

d) "About 100% of mammary PD is associated with underlying breast cancer":

Should change into: Almost all cases of PD are associated with underlying breast cancer.

e) Background Paragraph 3, Line 4-8: "The prognosis for EMPD is also worsened by the presence of a concurrent malignancy, with survival rates as high as 46% when underlying malignancy is present, and an 18% survival rate without underlying malignancy."

Discrepancies in the data. Please check reference for correct data.

f) Background Paragraph 3, Line 9-10 "it is clinically critical to differentiate between the two using a panel of appropriate receptors"

It should be a panel of appropriate immunohistochemical antibodies. Receptors alone are not enough to determine the primary sites of EMPD.

g) Background paragraph 3, Line 13-15 "In addition, most studies of EMPD have been conducted in male case series or larger male-only populations and less is known about EMPD in females."

Need references to support this claim.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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