Author's response to reviews

Title: Should extragonadal germ cell tumors be included in studies of families with testicular germ cell tumors?

Authors:

Rodrigo Guindalini (rodrigoscg@usp.br)
Edite P Oliveira (edite.oliveira@hsl.org.br)
Marina CM Silvino (masilvino85@gmail.com)
Paulo Marcelo Hoff (paulo.hoff@icesp.org.br)
Bernardo Garicochea (bgarico@terra.com.br)

Version: 2 Date: 9 January 2013

Author's response to reviews: see over
Jan 9, 2013

*Hereditary Cancer in Clinical Practice*

Dear Editor,

We thank the Reviewers for their comments and suggestions, which were very useful in guiding our revisions. All suggested modifications were incorporated into our manuscript, and we hope that we have adequately addressed the Reviewers’ concerns and that the manuscript is now acceptable for publication in the *Hereditary Cancer in Clinical Practice*. Please find below a point-by-point response to all of the Reviewers’ comments and a list of the changes made to the manuscript.

Cordially,

Rodrigo Guindalini, MD

PhD student (cancer genetics)

Visiting Scholar at University of Chicago – The Center for Clinical Cancer Genetics
Reviewer 1 – Comment 1) Given that the title of the article poses the question of screening for relatives of individuals with extragonadal germ cell tumor (GCT), it would be important to summarize the status of testicular screening and the current practice regarding screening for relatives of individuals with testicular GCT, to help put the discussion in context.

Answer: We would like to thank the Reviewer for the pertinent suggestion. We have summarized the status of testicular screening and the current practice regarding screening for high-risk individuals in the Background section, as highlighted below.

Page 3, line 23: “The establishment of a universal screening program using testicular palpation (clinical or patient self-examination) or serum biomarker for healthy young patients lacks clinical evidence. And, although some risk factors for TGCT are well known, effectiveness of high-risk patients screening is controversial. Recent systematic review did not detect published randomized clinical trials comparing screening versus no screening for testicular cancer. On the basis of uncertain benefits and some likelihood of harms, US Preventive Services Task Force and the American Academy of Family Physicians discourage screening. But others, such as the American Cancer Society and the European Association of Urology, recommend different approaches: testicular examination to be part of a periodic cancer-related checkup and self-testicular examination for individuals with clinical risk factors, respectively.”

Reviewer 1 – Comment 2) In the Background section, the authors stated that “The omission of extragonadal tumors in the published reports may have contributed to the underestimation of the importance of the hereditary factor of germ cell tumors and hindered the development of strategies for screening and follow-up of FTGCT”. Are
there any estimates of the proportion of extragonadal GCT that occurs in the familial setting? Please elaborate or provide more data to support this statement. Likewise, the statement “based on the present case report we could hypothesize if the exclusion of extragonadal germ cell tumors from FTGCT studies may exert a negative influence on the advances of the knowledge regarding the underlying common genetic mechanisms of germ cell tumors” seems to suggest that extragonadal GTC accounts for a significant proportion of familial GCT, an assumption that cannot be made based on one case report.

Answer: We appreciate the Reviewer’s comments and apologize if our Background section was not sufficiently detailed. Given that the familial association of gonadal and extragonadal germ cell tumors has not yet been established, we totally agree that one case report is not enough to make a strong assumption. However, we consider that, using "careful" and “conservative” words, the present report may be important to raise this question for the research community and hopefully contribute to advances of the field. In an attempt to make this point clearer in the text, we have modified the sentences, as described below:

Page 4, line 10: All reports of family inheritance focused exclusively in isolated germ cell tumors of testis\textsuperscript{4,6,7} and the estimation of the contribution of extragonadal germ cell tumor in the familial setting is not known. Therefore, the omission of extragonadal tumors in the published reports may have contributed to the underestimation of the importance of the hereditary factor of germ cell tumors, especially when there is a presence of an affected twin.

Page 5, line 10: “In this sense, although the familial association of gonadal and extragonadal germ cell tumors has not yet been established, based on the present
case report it is possible to question if the exclusion of extragonadal germ cell tumors from FTGCT studies may exert a negative influence on the advances of the knowledge regarding the underlying common genetic mechanisms of germ cell tumors.

Page 5, line 25: We believe that future research on the association of testicular and extragonadal germ cell tumors in the familial setting may provide new insights and discoveries in the field and, hopefully, help on the design of strategies for prevention, screening and follow-up of families with germ cell tumors, especially when there is a presence of an affected twin.”

Reviewer 1 – Comment 3) Please consider revising the title of the article. “Is there a need to screen for testicular germ cell tumor in relatives of patient with extragonadal germ cell tumor?” seems to suggest that a) relatives of individuals with extragonadal GCT are at such increased risk of testicular GCT that screening is indicated; and b) there exists a standard for testicular GCT screening. The first point cannot be supported with one case report, and the article does not at all discuss the current state of testicular GCT screening.

Answer: We thank the Reviewer for this important comment. We agree that he Title deserved adequacy and modified it, as suggested. The Title now is: “Should extragonadal germ cell tumor be included in studies of families with testicular germ cell tumors?” Moreover, in order to adjust the abstract to the new title, additional changes have been made: Page 2, line 12: “Nevertheless, information about the occurrence of TGCT in relatives of patients with extragonadal germ cell tumor is limited.”