Article details: 2016-0100	
Title	Retrospective Cross-Sectional Study Investigating Factors of Diagnostic and Referral Intervals for Manitoba Women with Epithelial Ovarian Cancer: Manitoba Ovarian Cancer Outcomes (MOCO) study group
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Reviewer 1	Dr. Prafull Ghatage
Institution	Gynecologic Oncology, University of Calgary, Calgary, Alta.
General comments (author response in bold)	Interesting paper; however, it would add strength to this paper if there was a table comparing ER and non-ER patients with reference to differences Stage, Histology,survival,age aside from presentation. **We have replaced table 1 with this recommendation.**
Reviewer 2	Dr. James Bentley
Institution	Department of Obstetrics and Gynecology, Dalhousie University, Halifax NS
General comments (author response in bold)	This retrospective review of referral and diagnosis provides useful information. 1. At no point in the discussion of referral pathways was the role of the generalist OB Gyn noted. This deserves a mention even if it was not a factor, it would be nice to know for resource planning which cases were triaged in some way by a generalist? **This information was added to Line 143: "21% had an interaction with an Obstetrician/Gynecologist during their diagnostic interval"** 2. I noted that there were 601 cases and in the results section it says that in total 469 had an initial diagnosis made +/- confirmed by histology. However in table 1 all 601 have a histotype classification. Can you clarify this? **The 469 patients were diagnosed by histology. The remaining patients did not have final confirmation and were treated based on cytology. This was clarified in line 134-137: "Subsequent diagnostic confirmation by histology was seen in an additional 182 cases, yielding 469 patients (78.04%) overall with diagnosis confirmed on histology, the remaining patients were not confirmed by final histology, and were treated based on cytology alone."**
Reviewer 3	Dr. V.L. Allgar
Institution	HYMS/Health Sciences, York University, Toronto, Ont.
General comments (author response in bold)	1. Date of suspicion was recorded as first point of contact with a health care provider with symptoms of EOC, or where there was incidental finding of EOC. This doesn't include patient delay e.g. patient recognition of suspicion prior to first contact. **We absolutely agree with this statement and is an operational definition. We decided to balance the benefits of patient recall with definitive medical records data. The data prior to presentation is not available. We have included this as a clarified limitation in our paper (Line 225-231)** 2. There are no univariate statistical tests of each factor with time from suspicion to diagnosis (page 6, para 2). E.g. factors in Table 1 **Due to table size and page limitations, the Univariate analysis was excluded. We have now included it as supplemental tables 1-5.** 3. The median diagnostic interval for an ER patient was 7 days versus 55 days for non-ER patients, this is not surprising but was it statistically significant? **This value was included in the figures, but not included in the text. We have corrected this and added the p value in line 156.** 4. The paper then focuses on comparing ER patient versus non-ER patients. Whilst the analysis is appropriate, this should be reflected in the objectives of the paper and in the title. There should be a descriptive table with the variables split by ER - non ER and univariate analyses. **The variables for ER vs non-ER have been adjusted as outlined above (see revised Table 1). ER status was not the initial objective of the study, and was found to be a significant variable on analysis. The discussion about ER status is extended because of the substantial difference noted in patient outcome and time-to-diagnosis.**
Reviewer 4	Prof. Richard D. Neal
Institution	Institute of Health Sciences, University of Leeds, Leeds, England
General comments (author response in bold)	Introduction 1. Much important and relevant literature, including the findings of two systematic reviews, is not included. This includes:

- Smith EM, Anderson B (1985) The effects of symptoms and delay in seeking diagnosis on stage of disease at diagnosis among women with cancers of the ovary. Cancer 56: 2727–2732.
- Tokuda Y, Chinen K, Obara H, Joishy SK (2009) Intervals between symptom onset and clinical presentation in cancer patients. Intern Med 48: 899–905.
- Fruchter RG, Boyce J (1981) Delays in diagnosis and stage of disease in gynecologic cancer. Cancer Detect Prev 4: 481–486.
- Menczer J (2000) Diagnosis and treatment delay in gynaecological malignancies: does it affect outcome? Int J Gynecol Cancer 10: 89–94.
- Menczer J, Chetrit A, Sadetzki S (2009) The effect of symptom duration in epithelial ovarian
- Robinson KM, Christensen KB, Ottesen B, Krasnik A (2012) Diagnostic delay, quality of life and patient satisfaction among women diagnosed with endometrial or ovarian cancer: a nationwide Danish study. Qual Life Res 21: 1519–1525.
- Neal RD, Tharmanathan P, France B, Din NU, Cotton S, Fallon-Ferguson J, Hamilton W, Hendry A, Hendry M, Lewis R, Macleod U, Mitchell ED, Pickett M, Rai T, Shaw K, Stuart N, Tørring ML, Wilkinson C, Williams B, Williams N, Emery J. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. British Journal of Cancer 2015, 1–16 doi: 10.1038/bjc.2015.48

This feels like a major omission, and one that has prevented them from framing their study in an appropriate context.

The main objective of our study was to identify various factors affecting the diagnostic and referral intervals. We have clarified the definitions to be consistent with the literature as noted above. Please see the comments below for question 2.

All of the suggested studies have been reviewed and information that was felt to be relevant was added to our discussion (Line 196-231)

2. Furthermore some of these older studies are of poor quality and there is much to learn from more recent studies (albeit in other cancers) that have examined time intervals to diagnosis and their association with clinical outcomes, and using methods that avoid some of the bias and confounding that these studies are open too. Examples of these include:

- Elit L, O'Leary E, Pond G, Seow H (2013) Impact of wait times on survival for women with uterine cancer. J Clin Oncol 51: 67.
- Gobbi PG, Bergonzi M, Comelli M, Villano L, Pozzoli D, Vanoli A, Dionigi P (2013) The prognostic role of time to diagnosis and presenting symptoms in patients with pancreatic cancer. Cancer Epidemiol 37: 186–190.
- Murchie P, Raja EA, Brewster DH, Campbell NC, Ritchie LD, Robertson R, Samuel L, Gray N, Lee AJ (2014) Time from presentation in primary care to treatment of symptomatic colorectal cancer: effect on disease stage and survival. Br J Cancer 111: 461–469.
- Tørring ML, Frydenberg M, Hamilton W, Hansen RP, Lautrup MD, Vedsted P (2012) Diagnostic interval and mortality in colorectal cancer: U-shaped association demonstrated for three different datasets. J Clin Epidemiol 65: 669–678.
- Tørring ML, Frydenberg M, Hansen RP, Olesen F, Vedsted P (2013) Evidence of increasing mortality with longer diagnostic intervals for five common cancers: a cohort study in primary care. Eur J Cancer 49(9): 2187–2198.

As a consequence the study that is reported here is open to biases and consequences, and therefore its findings must be interpreted with great caution, and do not take forwards our understanding of this issue.

We respect and appreciate the reviewer's comments as such we have refined the definition of time-to-diagnosis, as: "Date of first presentation was recorded as first point of contact with a health care provider with symptoms of EOC, or where there was incidental finding of EOC. Date of referral encounter was recorded as the initial GynOnc appointment. Diagnostic interval was defined as the time from date of first presentation to diagnosis and the referral interval was defined as the date of first presentation to initial GynOnc visit." Line 104-110, and have quoted the Weller and Neal papers to refine the definitions used and be more consistent with the literature. While not using the same language our definition is consistent with the definition of T7 and T8 in Neal et. al. British Journal of Cancer 2015.

We also analyzed what was considered T9 in the Neal et al. (2015) paper and found that in our population this was highly correlated to T7 and T8, and therefore no

	further description was provided (lines 157-159) **The above noted trials were not referenced in our paper because we felt that the relevance from other cancers does not directly translate to the challenges posed in ovarian cancer diagnosis. For example, both colorectal and endometrial cancers present with more obvious symptoms with earlier stage disease.** **We agree that this study is open to bias, as are all retrospective chart reviews. We have expanded the limitations section to better delineate these limitation (line 222-231). To reduce bias we avoided patient recall and supplemented the chart data with administrative health care data from the provincial health database including physician claims and hospital administrative data (line 100-108), which added expanded time compared to the chart alone data, increasing accuracy. To be more comprehensive we analyzed diagnostic, referral and treatment intervals to assure that all were correlated and not another source of bias.** 3. There is also a consensus statement on the design and reporting of studies on early cancer diagnosis: Weller D, Vedsted P, Rubin G, Walter F, Emery J, Scott S, Campbell C, Andersen RS, Hamilton W, Olesen F, Rose P, Nafees S, van Rijswijk E, Muth C, Beyer M, Neal RD. The Aarhus Statement: Improving design and reporting of studies on early cancer diagnosis. BJC 2012,106:1262-1267. DOI 10.1038/bjc.2012.68. Whilst it is not a necessity of this journal for authors to report their work in line with this, it does mean that their definitions are not in keeping with other recently published literature. **Given the above changes, we are now compliant with the Aarhus definitions and have revised the limitations statement in this study. We have also clarified our definitions of date of first contact, date of diagnosis and date of death. We have also clarified that our study is a combined "audit/database analysis" as outlined in the Weller paper (line 219).** Key examples of text in the manuscript that reflect the difficulties with this paper include: 4. The statement in the abstract 'ER patients and those with shorter diagnostic intervals… ' (albeit wrongly defined) …' had significantly poorer survival. Of course they will, have but not as a cause of the shorter diagnostic interval. **This statement has been removed in the revised manuscript.** 5. 'Data extracted from patient charts…' – these are open to all manner of biases (as outlined in the Weller paper above) **We agree with this statement and have expanded on this in the limitations.** 6. 'Date of suspicion' is almost impossible to define from records and has no validity as a construct. **Date of suspicion was defined incorrectly and has been revised as date of first presentation.** 7. In the analysis, many of the factors interact with each other – no attempt appears to have been made to adjust for these **Interaction terms have now been tested, and we have found a significant interaction for the analysis in Table 4.**