Reviewer comments: 2013-0017	
Title	Stage, treatment and outcomes for patients with breast cancer in British Columbia in 2002: a population-based cohort study
Authors	Ashley Davidson MD, Stephen Chia MD, Robert Olson MD, Alan Nichol MD, Caroline Speers BA, Andy J. Coldman PhD, Chris Bajdik PhD, Ryan Woods MSc, Scott Tyldesley MD
Reviewer 1	Waseem Sharieff MD PhD
Institution	McMaster University, Hamilton Ont.; Staff Radiation Oncologist, Cape Breton Cancer Centre, Sydney NS
General comments	The authors used registry databases in British Columbia to report patient and tumor characteristics, screening and treatment utilization and overall and disease specific survival of breast cancer patients. They compared the utilization and survival rates to published ideal rates and US and European registry data. I have the following comments: Strengths This is a large case series with 10 years of follow up. Weaknesses Introduction The introduction lacks a focus and jumps from one idea to another. The authors mention disparity within and across populations, which is not a subject of investigation in this paper. They have previously published their data to show variation in screening and treatment utilization by community size. Introduction section should identify gaps in knowledge and the objectives of the paper should be to fill in those gaps. Objectives 1. Describe patient characteristics, stage distribution, stage specific treatment utilization and outcomes. 2. Compare BC data with literature. I am not sure how much stage distribution is of value in current times of risk profiling and sentinel node biopsies. Z11 and MA20 trials have made significant impact on breast cancer treatment. This paper does not reflect on these changing patterns. Ideally comparison between BC and other data should be made with individual patient level data in hand. If access to those data is not available, the authors may use meta-analysis approach. Methods The authors should describe what information is available in each data source. How were they recorded and how different sources were linked to obtain patient specific information. They should also mention if any of the outcomes were adjudicated. How was breast cancer specific survival defined? What statistical methods were used to summarize the data to meet the first objective? What methods were used to meet the second objective? Results The authors have tried to explain the results as they report them. Results should be explained in the discussion section. The two paragraphs on page 8 should be moved to the discussion section. The authors report confidence intervals of 5 and 10 year survival. They should mention in the method section how these were computed. Figure 1. consider a pie chart instead of bar chart. Figure 2 & 3. Sensoring is shown in figure 3 and not in figure 2. Why? Please report no. at risk at each time point. Table 1. This is too dense. I am not sure whether there is any added value by showing a breakdown by stage. For example, how would stage influence margin status in treatment decision? Table 2: It might be more appropriate to discuss these in the discussion section rather than reporting them as results. Table 3: what is the significance of these benchmarks by stage? If any, the authors should mention it in the methods section. Otherwise omit the benchmarks. Most centers would aim to radiate within 12 weeks post operatively unless the patient is receiving chemotherapy. Table 4: same as for Table 2. Tables 5a/b: same as above. The authors report rates of screen attendees. Can they stratify survival outcomes by screen attendees and non-attendees? Interpretation This section should focus on the results, what they mean and how they compare with other reports. The authors should also mention limitations. The major ones are lack of toxicity data and quality of life measures. The authors initially stated that BC has one of the best breast cancer survival rates.

	However, they conclude that BC rates are comparable to other regions of the world. Are they rejecting that hypothesis? Minor comments Page 3 line 7, please change relative survival rate to overall survival. Page 3 line 58-6¬0, please change 'for free' to 'at no cost to patient'. Nothing is for free. It is tax payers money.
Reviewer 2	Alice Dragomir MSc PhD
Institution	Surgery/Urology, McGill University, Montréal, Que.
General comments	General comments: The manuscript ''Population-based stage, treatment and outcomes for patients diagnosed with breast cancer in British Columbia in 2002" is a descriptive study of a cohort of 2,927 women diagnosed in 2002 with breast cancer. The data are extracted from the BC Cancer Registry and linked to BC Cancer Agency (BCCA) radiotherapy records and BCCA pharmacy data repository. Clinical information for women referred to the BCCA was extracted from the Breast Cancer Outcomes Unit (BCOU), whereas for all the other cases this information was derived from the registry pathology records. Breast cancer screening is available through the Screening Mammography Program of BC (SMPBC). Over 50% of women included in the study cohort were attendees of the SMPBC. The primary objective of this study was to describe the patient characteristics, stage distribution and stage-specific treatment utilization. The second objective was to compare the stage distribution and survival by stage for breast cancer patients in BC to published international reports. My specific comments about this manuscript include the following: Major concerns 1. There are several important clinical data on a patient level other than the breast cancer stage which were collected for the study cohort. I am wondering why the authors have not considered appropriate to use these well-known prognostic factors in multivariate analysis. In general, descriptive studies provide limited information. In contrast, a valuable information will be to understand what are the factors predicting a treatment-specific utilization other than the stage of the disease. 2. (page 7 and Table 3) The treatment utilization is limited to 4 categories: initial surgery, radiation therapy, chemotherapy and hormonal therapy. Important information will be to give details on the type of each treatment. It will be interesting to know if for example, the type of chemotherapy will change with increase in cancer stage. 3. In addition, many of patients receive combination of treatments, but this information is not provided. Again, it will be interesting to understand the use of treatment combinations by cancer stage. 4. The cohort study consists exclusively from incident cases identified in 2002, which limits the description of stage, treatment utilization and outcomes to this specific year. Since then, important progresses have been done for breast cancer treatment, and its management has probably changed. A better knowledge of the current treatment pathway will be valuable. Including incident case from 2001 to 2013 will allow a better understanding of both current treatment utilization, and treatment trend over this period. 5. Overall and disease-specific survivals were exclusively estimated by Kaplan-Meier analysis. In general, Kaplan-Meier is used for survival data as preliminary analysis; this provides an unadjusted rate of event in time. As probability of dying is age-dependent and age groups vary across breast cancer stages, the overall survival needs to be adjusted at least for this factor. Example (Table 1): percentage of women 70 years and older : 24% in stage 0, 32% in stage I, 29% in stage II, 30% in stage III and 39% in stage IV. I suggest the Cox proportional hazard model will be most appropriate to account for potential confounders variables and to adjust for possible prognosis factors. 6. Concerning the comparison of survival by stage for breast cancer patients in BC to published international reports, I would say that this is provided only with US data (SEER, ref 18, page 5A). Concerning the comparison with other countries (table 5B), this has limited value since survival is dependent on disease stage distribution. Stage distribution can vary across countries, and for that, it is required for an adequate comparison. 7. Being a participant to SMPBC seems to impact breast cancer stage at diagnosis. Are there any other patients' characteristics or treatment characteristics that are different between attendees of the SMPBC and non-attendees? Minor comments 1. Abstract: the abbreviation BCSS was not defined. 2. Table 4: HT: BCCA 61% vs ideal (22) 64% does not concord with the ''Endocrine therapy use in BC, however, exceeds the published ideal rate for all stages (22).'' (page 8 (29-31) and with ''Use of endocrine therapy in BC exceeds calculated ideal utilization rates.'' (page 10 (12-14)). 3. Page 8 (36-38) the sentence does not fit to this place.
Author response	**Reviewer 1 comments:**

	"Introduction 1. The introduction lacks a focus and jumps from one idea to another. The authors mention disparity within and across populations, which is not a subject of investigation in this paper. They have previously published their data to show variation in screening and treatment utilization by community size. Introduction section should identify gaps in knowledge and the objectives of the paper should be to fill in those gaps." **These comments were also made be the editor, and have been addressed as outlined above.** "2. I am not sure how much stage distribution is of value in current times of risk profiling and sentinel node biopsies. Z11 and MA20 trials have made significant impact on breast cancer treatment. This paper does not reflect on these changing patterns." **We acknowledge that this paper, which is largely about long term survival, does not address outcomes related to recent study results and the implications to current practice and the potential changes in long term outcomes that they may imply. We have acknowledged this limitation in the interpretation section. We respectively disagree with reviewer that stage is not important, neither in 2002, nor in 2013. This opinion is well supported by the AJCC and UICC, and our own results demonstate that stage, at least for patients diagnosed in 2002, was highly prognostic (note that stage was very highly significant prognostic factor on multivariate analysis).** 3. "Ideally comparison between BC and other data should be made with individual patient level data in hand. If access to those data is not available, the authors may use meta-analysis approach." **We agree that ideally individual patient data should be used for meta-analysis. We were not doing a meta-analysis, just comparing our results to the literature to provide context of the results. We have removed the tables that compared our results to the literature in the results section of our paper, and have put them in the interpretation section as suggested.** "Methods 4. The authors should describe what information is available in each data source. How were they recorded and how different sources were linked to obtain patient specific information." **We have clarified the information avaialble in all data sources and how they are linked on page 3 of the methods.** 5. "They should also mention if any of the outcomes were adjudicated." **We have clarified this on page 3 paragraph 1 of the methods.** 6. "How was breast cancer specific survival defined?" **We have clarified this on page 3, paragraph 1 of the methods.** 7. "What statistical methods were used to summarize the data to meet the first objective?" **The methods are descriptive in terms of the case mix, this is clarified on page 4 and 5 of the methods. The survival outcomes were described as actuarial outcomes using the Kaplan Meier method, and outcomes in realtkon to prognositic and treatment factors were described using a multivarate Cox model, The later was added at the editors request as outlined above. This is clarified on page 5, paragraph 1 in the methods section.** 8. "What methods were used to meet the second objective?" **As per the editors comments, we have removed the second objective.** "Results 9. The authors have tried to explain the results as they report them. Results should be explained in the discussion section." **We have removed interpretations from the results section, amnd moved them to the appropriate sections of the interpretation section**. 10. "The two paragraphs on page 8 should be moved to the discussion section."

	We have moved these as suggested. 11. "The authors report confidence intervals of 5 and 10 year survival. They should mention in the method section how these were computed." **We have clarified how this was calculated on page 5 of the methods section.** 12. "Figure 1. consider a pie chart instead of bar chart. [Editor's note: Figure 1 can be deleted, as the data are adequately explained in the results section and in the corresponding table.]" **We have deleted this as per Editors recommentation.** 13. "Figure 2 & 3. Sensoring is shown in figure 3 and not in figure 2. Why? Please report no. at risk at each time point." **Cencoring marks are shown on both figures. However, since all patients were diagnosed in 2002, and all surival data is complete for overall surivval outcome, the cencoring marks only appear for patients still alive in 2011, and therefore only on the far right side of the figure. We have added the numbers at risk to to bottom of figures 2 and 3 (now called figures 1 and 2, as original figure 1 was deleted at editor's request).** 14. "Table 1. This is too dense. I am not sure whether there is any added value by showing a breakdown by stage. For example, how would stage influence margin status in treatment decision?" **Margin status effects the decision to perform further surgery in stage I and II breast cancer, and low margin positive rate is an indicator of better quality local therapy. We felt readers would want the content shown to interpret the findings within there own context.** 15. "Table 2: It might be more appropriate to discuss these in the discussion section rather than reporting them as results." **We agree the comparison of stage to SEER is better described in the discussion section. We have made this change.** 16. "Table 3: what is the significance of these benchmarks by stage? If any, the authors should mention it in the methods section. Otherwise omit the benchmarks. Most centers would aim to radiate within 12 weeks post operatively unless the patient is receiving chemotherapy." **The significance of these benchmarks by stage gives a reference for the use of treatment in relation to the indications in each stage. This allows the reader to understand the use of each modality within each stage, which a facilitates a deeper interpretation of how the survival outcomes were acheived. We have clarified this in the methods on page 5 as suggested. We agree that the timing of RT use depends on the use of chemotherapy, and radiotherapy and hormone therapy rates within a year of diagnosis allow for the sequencing of radiotherapy and hormone therapy after chemotherapy in a single metric. These metrics have been used in the literature elsewhere.** 17. "Table 4: same as for Table 2." **We have made this change.** 18. "Tables 5a/b: same as above". **We have removed these tables as suggested by the editor, and instead make reference to the comarison in the interpretation section.** 19. "The authors report rates of screen attendees. Can they stratify survival outcomes by screen attendees and non-attendees?" **We have added a survival analysis stratified by screen attendees as requested, but caution againsts over interpretation of this due to known lead and length time biases inherent with screening. We have added the analysis to the methods and results sections as requested. See page 7 paragraph 2 of results, and paragraph 1 page 8 in the interpretation section.** Interpretation 20. "This section should focus on the results, what they mean and how they compare

with other reports. The authors should also mention limitations. The major ones are lack of toxicity data and quality of life measures."

We have acknowledged these limitations in the interpretation section.

21. "The authors initially stated that BC has one of the best breast cancer survival rates. However, they conclude that BC rates are comparable to other regions of the world. Are they rejecting that hypothesis?"

The editors made a similar comment. We have toned down the language in this regard as suggested, as it was not the main intent to test this hypothesis.

Minor comments
22. "Page 3 line 7, please change relative survival rate to overall survival. "

Done.

23."Page 3 line 58-6¬0, please change 'for free' to 'at no cost to patient'. Nothing is for free. It is tax payers money."

Done.

Reviewer: 2
Comments to the Author

My specific comments about this manuscript include the following:

Major concerns
1. "There are several important clinical data on a patient level other than the breast cancer stage which were collected for the study cohort. I am wondering why the authors have not considered appropriate to use these well-known prognostic factors in multivariate analysis. In general, descriptive studies provide limited information. In contrast, a valuable information will be to understand what are the factors predicting a treatment-specific utilization other than the stage of the disease."

This point was also raised by the editor summary, and we have added a multivariate analysis with the other known prognostic factors.

2. "(page 7 and Table 3) The treatment utilization is limited to 4 categories: initial surgery, radiation therapy, chemotherapy and hormonal therapy. Important information will be to give details on the type of each treatment. It will be interesting to know if for example, the type of chemotherapy will change with increase in cancer stage."

The two reviewers had conflicting advice about making the tables more or less dense. We agree that there is a limit to how much information can be conveyed in one table and one paper. We have elected not to further expand of contract the tables in this manuscript, but will consider expanding the detail on utilizaiton within specific subgroups in a further publication more focused on that issue.

3. In addition, many of patients receive combination of treatments, but this information is not provided. Again, it will be interesting to understand the use of treatment combinations by cancer stage.

We agree there are lots of potentially intersting fuerther studies that could be pursued using this data. Again, we note that the two reviewers had conflicting advice about making the tables more or less dense. We agree that there is a limit to how much information can be conveyed in one table and one paper. We have elected not to further expand of contract the tables in this manuscript, but will consider expanding the detail on utilizaiton within specific subgroups in a further publication more focused on the issue of details of treatment combinations within specific subgroups, but felt is was beyond the scope of the current manuscript.

4. "The cohort study consists exclusively from incident cases identified in 2002, which limits the description of stage, treatment utilization and outcomes to this specific year. Since then, important progresses have been done for breast cancer treatment, and its management has probably changed. A better knowledge of the current treatment pathway will be valuable. Including incident case from 2001 to 2013 will allow a better understanding of both current treatment utilization, and treatment trend over this period."

We agree that it would be ideal to have multiple years with such data, but the

	complete data was only available for 2002. This has been clarified in the manuscipt, and was also addressed in our response to the editors comment number 1. 5. "Overall and disease-specific survivals were exclusively estimated by Kaplan-Meier analysis. In general, Kaplan-Meier is used for survival data as preliminary analysis; this provides an unadjusted rate of event in time. As probability of dying is age-dependent and age groups vary across breast cancer stages, the overall survival needs to be adjusted at least for this factor. Example (Table 1): percentage of women 70 years and older : 24% in stage 0, 32% in stage I, 29% in stage II, 30% in stage III and 39% in stage IV. I suggest the Cox proportional hazard model will be most appropriate to account for potential confounders variables and to adjust for possible prognosis factors." **We have added a Cox model to the manuscript as sugggested, and have incluced age in the model as well as major availalbe prognostic factors and treatment factors.** 6. "Concerning the comparison of survival by stage for breast cancer patients in BC to published international reports, I would say that this is provided only with US data (SEER, ref 18, page 5A). Concerning the comparison with other countries (table 5B), this has limited value since survival is dependent on disease stage distribution. Stage distribution can vary across countries, and for that, it is required for an adequate comparison." **The issue of table 5a and b were dealt with earlier in relation to the editors comments. As this was not the main focus of the paper, we have removed the comparison form the objective, methods and table 5a and b, and put the comparative information in the interpretation as suggested earlier.** 7. "Being a participant to SMPBC seems to impact breast cancer stage at diagnosis. Are there any other patients' characteristics or treatment characteristics that are different between attendees of the SMPBC and non-attendees?" **Yes there are significant biases associated wtih screen attendees that correlate with risk factors and outcome. We have alluded to this in the results section, that outcomes in relation to screen groups should be interpreted with caution due to potential biases related to lead and length time associated with screening.** Minor comments 8. "Abstract: the abbreviation BCSS was not defined". **We have added the definition of BCSS in the abstact.** 9. "Table 4: HT: BCCA 61% vs ideal (22) 64% does not concord with the ''Endocrine therapy use in BC, however, exceeds the published ideal rate for all stages (22).'' (page 8 (29-31) and with ''Use of endocrine therapy in BC exceeds calculated ideal utilization rates.'' (page 10 (12-14))." There was an error in the original table 4. **We have corrected this, so the information is no longer contradictory. We have reworded the infomation in the interpretation section to make this clearer as well.** 10. "Page 8 (36-38) the sentence does not fit to this place." **We agree, and have moved this to relevant section of the interpretation section.**