Author’s response to reviews

Title: Worse survival in breast cancer in elderly may not be due to underutilization of medical procedures as observed upon changing healthcare system in Poland

Authors:
Janusz Kocik (jkocik@cmkp.edu.pl)
Małgorzata Pajączek (malgorzata.pajaczek@gmail.com)
Tomasz Kryczka (kryczka.tomasz@gmail.com)

Version: 1 Date: 20 Mar 2019

Author’s response to reviews:

Dear Editor,

Let me thoroughly address the issues raised by the distinguished reviewers in hope that it would help the publication of this report.

Reviewer 1 specific comments:

Reviewer:
Many readers will only read the abstract so it should contain enough information to make your point. This abstract is missing data and supporting statistics.

Answer:
This is a good point. Then we moved key statistics to the abstract in a revised manuscript.

Reviewer:
Is healthcare budgeting, funding, or spending the issue?

Answer:
Low budgeting of healthcare was referred continuously as a reason of lower outcomes in Poland. You may find such observation or conclusion by Polish co-authors in the article cited by us:

In fact, we show that it was still despite progress in funding.

However, in our paper we also raise the question about the appropriateness of this reasoning.

Reviewer:

On page 5, the sentence that spans lines 24-29 needs to be rephrased because the direction of association seems incorrect.

Answer:

The sentence:

‘Proliferation is slow and there is higher frequency of Grade 1 tumor, wider prevalence of favorable prognostic hormone receptors expression and lower probability of HER expression that is associated with poor survival (6).’

was changed to:

Proliferation is slow and there is higher frequency of Grade 1 tumor, wider prevalence of favorable prognostic hormone receptors expression and lower probability of HER expression, the latest associated with poor survival (6).

Reviewer:

In the methods section, better definition of variables is needed. This is particularly true for treatment variables.

Answer:

The aim of this study was not the assessment or evaluation of efficacy of specific treatment modalities that were used in clinical approach. In this paper we wanted to highlight the human factor and the health care system limitations that caused our slight disappointment in outcome of older patients. Therefore, we did not use any additional variables despite the general ones
described in the paper. In fact, more specific issues addressed by the Reviewer in the next questions:

‘How was type of surgery defined?

Was radiation after BCS and radiation completion included?

Did you track dose and completion of chemotherapy course?

How was appropriate use of chemotherapy and endocrine therapy defined?

Was there any information about adherence to endocrine therapy?’

Go out of the scope of this paper and their presentation in the article would not add any valuable information concerning the main subject.

Reviewer:

How was use of chemotherapy defined?

Answer:

Numbers of visits for chemotherapy – outpatient or inpatient – were shown in the paper. The record in National Health Fund Register is based on International Classification of Diseases ICD-10 coding, code Z51.1 Cycles of chemotherapy. The other modalities are coded accordingly. The details demanded by reviewer are not available. Their collection would require cohort observational study on a population sample that was not the intention of this study.

Reviewer:

Why was the mortality/incidence ratio chosen?

Answer:

MIR is generally used as a high-level comparative measure to identify inequities in cancer outcomes. MIR is more accurate survival indicator than the relative survival factor, especially if we want to compare the outcomes in different populations (e.g. different countries, different health care systems, different health care funding and even different age groups, and etc...). It is simple indicator, which is very important as in some countries genuine survival data related to treatment procedures or type of neoplasm - are not available. In addition, MIR has adequate literature on its confidence as it is often used for research on international or intergroup
disparities in cancer survival. Then, keeping in mind that the presentation of our results in the simple form as above (MIR) could easier initiate the discussion in the scientific journals, we mostly focused on this parameter in our article.

Reviewer:
Is it pertinent to comparing outcomes by age?

Answer:
This measure is definitely used as an indicator of cancer management outcomes also comparing groups by age, as shown in e.g.:


Reviewer:
Since treatment standards vary over time, is the MIR appropriate for studying treatment patterns?

Answer:
Since survival is relatively long, subjects that succumb due to breast cancer in a time period have been treated differently that are those that fall ill in this period. Nevertheless, the period under observation was relatively too short to warrant a change in treatment standards that influence survival. Incidence rose steadily in observed period in both study populations despite no new prophylactic measures was introduced. We compared both study populations in the same time period so all patients had chance to be subject to the same measures that influence incidence and mortality. The mortality-to-incidence ratio (MIR) is a novel measure that can evaluate the cancer mortality in relation to incidence; it serves as a proxy for 1-survival and appears to be a fairly accurate simple predictor of 5-year survival rates. I. a. the MIR has proved useful for identifying disparities in cancer screening and treatment for colorectal cancer1.


Reviewer:
The results section is missing a description of the study population.

Answer:
In the Results section we add a sentence describing study population, after the first sentence in the paragraph:

The study population encompasses most probably all patients that were diagnosed with breast cancer in the specified period of time, between 2010 and 2015 that were subjects to any kind of treatment both hospitalized and ambulatory and/or observation in outpatient setting.

Also in a section discussing limitations the phrase has been added:

Despite of census type of data that allow us to take a look at course of treatment of whole breast cancer population we have been not able to study qualitative details of pharmacological regimes, radiotherapy intensity and surgery extent likely to be modified and individualized in patients older and with low performance. We inferred on possible disparities only using the number of specific procedures not their range or variety. We discuss process outcomes that may be in relation to survival but the estimate may be too rough.

Reviewer:
The results section also needs to include statistical comparisons and significance levels.

Answer:
There were added two additional sentences in the section ‘Materials and Methods’:

Results of statistical tests were recognized as significant with probability of difference between variables (p) below 0.05. In the case of stronger statistical significance, the p value was included in the Results section.’

Reviewer:
The discussion should focus on the findings of the study and how they compare to those of other studies.

Answer:
This is exactly what we have aimed at. The bibliography consists of 28 positions and 18 of them are directly related to concerns of possible hesitation influence on breast cancer survival in elderly. The dominating view is that restriction in treatment are harmful but there are also studies that decrease in aggressiveness of treatment is neutral to outcome. We have discussed this issue
from different points of view. Since views are polarized it required broader introduction of a reader.

Reviewer:
Supporting reference is needed for the 1st sentence of the 2nd paragraph in the discussion.

Answer:
The first and second sentence in 2nd paragraph of discussion have been merged and the references to 2nd sentence pertain currently to both as it was intended from the beginning.

Reviewer:
Supporting reference is needed for the sentence that spans lines 36-38 on page 11.

Answer:
The sentence referred has been merged with the one following it, so now a reference to second sentence refers to both, as it was intended from the beginning. In fact both sentences refer to the same publication.

Reviewer:
The discussion is missing discussion of strengths and weaknesses of the work.

Answer:
The section on limitations has been added

Reviewer:
The conclusion on page 13 are not supported by the data.

Answer:
We aimed at the conclusion that that process outcomes, as number of visits and procedures do not translate directly in change of survival, especially in vulnerable groups. In case of Poland considerable rise of funding in short time, resulting in opportunity to attend unsatisfied demand on services from possibly neglected population of elderly breast cancer patients has not been
translated in survival rise. We claim that other subtle variables influence survival and need additional attention. We are sure that data type and presentation warrant such conclusion.

The above has been added to Conclusions to further clear up our view

Reviewer 2 specific comments:

Reviewer:

Title: Antineoplastic 'under-utilization' is different from 'undertreatment,' hence, the topic should be modified to indicate 'may not associate with procedure under-utilization.' The current paper does not provide adequate evidence on adequate or under-treatment.

Answer:

We conquer the reviewer view and propose to change and abbreviate the title to:

“Worse survival in breast cancer in elderly may not be due to under-utilization of medical procedures as observed upon changing healthcare funding in Poland”

Reviewer has the point because we often meet the situation in clinical practice when the patient has access to the treatment modalities but further treatment is not warranted. Then, so-called ‘under-utilization’ simply becomes ‘undertreatment’. This is what we could hardly show with a kind of data we have in our registries.

We used the term ‘undertreatment’ in the title of this paper, because the differences in survival of younger and older patients is commonly seen as the result of limitations to the diagnostic and/or therapeutic procedures, which often appears to be a problem related to non-adequate funding.

In fact, we show that worse outcome of 65+ patients may be not related to funding limitations, but probably – and this subject should be further explored - due to inadequate readiness of healthcare system to reorganize and refine comprehensive care in elderly.

Reviewer:

Abstract: There are two copies of Abstract slightly different in descriptions. Please unifying them into a single copy.

Answer:

We apologize for a mistake. The abstracts were unified in the current version of paper.
Reviewer:

Page 8, Line 41 to 49: More medical comorbidities in the older patients would result in higher outpatient visits when compared to younger patients.

Answer:

Yes, it was one of our explanations given in this fragment of text when discussing possible reasons for slightly higher number of visits in elderly. Please note that these are outpatient visits in oncology centers so most probably associated with cancer issues. The utilization of other healthcare services by cancer patients were not studies.

Reviewer:

Page 11, Line 21 to 53: These sentences are entirely out of scope because the current paper's results did not investigate any portion of them. This reviewer does not think it an excellent way to direct the readers to think these are the answers to explain the results. Moreover, the studies cited were not performed in Poland.

Answer:

Our results have created an opportunity to present ambivalent and not consequent approaches to treatment in elderly patients with breast cancer as per results of different studies. We discussed this phenomenon for different modalities, not only surgery. We cite these papers to highlight the observations reported by others and our results are only an addition to the debate on optimal approach to elderly. We think such wider view will show a reader the complexity of data from cohort, sample based data and supplemented with our, whole population based, observations. Therefore we claim the references discussed are relevant to recognition of the problem.

Reviewer:

Table 1. Actual numbers should be demonstrated side by side between 65- and 65+ women.

Answer:

We present actual numbers in supplemental material files.

We made the table as simple as possible, considering that the statistical analysis concerns the data from 2010 to 2015 for two groups of patients (65+ and 65-). The table contains 6 main variables. If we add data from 2010 to 2015 (6 numbers for 65+ and 6 numbers for 65-), we receive 12 numbers per one variable (eg. ‘outpatients visits’). Multiplying by 6 variables – we receive 72 numbers that would be added to the columns with ‘p’ results and ‘Procedures’. These
numbers would veil the main purpose of the table (comparison of procedures). In fact, the numbers would not add any additional information to the results of the study and would have no influence on the discussion.

Reviewer:

Table 2. Keep decimal under three. Please do not use coma for the decimal point. Use a dot (full stop). In the footnote of this Table, please add information on how to interpret the correlations, any cut-off?

Answer:
The table was changed according to comments of the reviewer. Short instruction on interpretation is added

Reviewer:

Fig. 1: age-standardized incidence and mortality, not aged-related.

Answer:
Change in the description of Fig. 1 was introduced to the text, as suggested.

Reviewer:

Fig. 5: the curves for the outpatient chemotherapy cannot be discerned owing to very similar (or even genuinely similar) colors. The term 'Administrative changes' is not clear enough for readers.

Answer:
Appropriate changes were introduced in the Fig. 5, as suggested by the Reviewer.

Hopefully these explanations will help to decide positively about publication of this report

Sincerely,

Janusz Kocik and Tomasz Kryczka