APM ANNALS OF PALLIATIVE MEDICINE
AN OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN PALLIATIVE MEDICINE

Peer Review File

Article Information: http://dx.doi.org/10.21037/apm-20-2439

Reviewer A

Treating elderly patients with cancer is a common problem. Finding the right balance between therapy and unwanted side effects is a major challenge. It is not uncommon for elderly patients in particular to decline the recommended therapy. It is all the more important to answer the question why these patients reject these recommendations, This article tries to work out predictive factors that are associated with a rejection of therapy.

Introduction

The introduction is very similar to the cited review [3] Puts MT, Tapscott B, Fitch M et al. A systematic review of factors influencing older adults' decision to accept or decline cancer treatment. Cancer Treat Rev 2015; 41 (2): 197-215 at. For example, one sentence is completely identical. Line 42: “It is estimated that 42% of all incident cases and….”.

R- Dear Reviewer, thank you very much for all the comments and suggestions made, which were taken into consideration.
We have modified our text as advised (see Page 2, line 33-37)

Results

The article describes only socio-demographic factors, types of intervention and clinical characteristics, that are associated with rejection of therapy.

Attention can be paid to these factors, but unfortunately they cannot be changed.

In this respect, the scientific relevance for me is relatively low, although the actual question is very interesting.

The meaningfulness of the article should therefore be enhanced with further analyzes or in the discussion.

1.) Since only socio-demographic and clinical characteristics could be worked out, the

question arises, what is the difference to younger patients who refuse a therapy recommendation.

2.) What are the wishes or goals of the elderly patient and do they agree with the wishes of the practitioner? Perhaps then it turns out that the rejection of therapy is not a failure at all, but simply does not correspond to the wishes of the older patient.

3.) Many of the studies listed also assessed survival with regard to the rejection or acceptance of the therapy recommendation. It would be interesting to what extent the rejection of a therapy has an explicit influence on the survival of older patients, given their already limited life expectancy.

R- 1) We added some data about the difference to younger patients on the discussion topic (see page 25, line-275-280)

R-2) The vast majority of studies found about this issue were quantitative and retrospective from large databases (See page 22 -line 203-205, and page 26, line- 303-305). Nonetheless, we described some reasons behind the treatment refusal found in the qualitative study of this review (see page 23- line 242-253).

R- 3) We added some data about the impact on survival of older patients who refused treatment in the Results- table 1 (see page 7, line 170), and in the discussion topic (see page 25 , line 286-291)

Discussion

The discussion jumps from one topic to another and then picks up the same topic again later. So it is difficult for the reader to follow the discussion.

Would it be possible to structure the content of the discussion better?

R- Yes, we did it. Thank you for the suggestion. At 1st paragraph: aspects related with elderly and refusal treatment; 2nd paragraph- discussion about the mainly results found in the review; 3rd – the social-demographic factors; 4th- the clinical factors, 5th, 6th and 7th - the nature of the studies; 8th and 9th - the type of treatment.

References

The number before article 10 is missing.

R- Thank you for advice, we adjusted.

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Reviewer B

This paper is an important work on a major and not sufficiently studied issue: cancer treatment refusal in the elderly.

The rationale and methods are clearly explained, but should integrate a conceptual definition of treatment refusal (or the different possible definition of this concept). As exposed later by the authors, this definition varies according to the different studies (refusal of the most aggressive part of the treatment, such as surgery; or refusal of any treatment, even palliative treatment…). This makes even more necessary a preliminary reflection about the concept of refusal of treatment, especially in older patients : what is exactly refused ? Does the care proposal reflect the standard care proposal in the non elderly patients? Does it already take into account the patient's age? Moreover, is the treatment proposed financially available, or affordable (is it about refusal, or unequal access to healthcare)?

R- Dear Reviewer, thank you very much for all the comments and suggestions made, which were taken into consideration.

In this review, the most studies analyzed was retrospective and descriptive. Unfortunately, the database used in the most of them (the Surveillance Epidemiology and End Results and National Cancer Database) did not provide additional information to explain why elderly refused treatment, most of them showed clinical and demographic characteristics. (see Page 26, line 303-305).

We considered as eligibility criteria the studies that included therapeutic refusal of any cancer treatment, such as surgery, chemotherapy, radiotherapy, as well as curative or palliative treatment, and the studies which included specially the elderly population. We added this in Methods (see on page 3,4- line 75-77)

Regarding the difference related to the younger patients we added some data on discussion topic (see page 25, line-275-280)

I think that the results paragraph could gain in clarity if the authors separated the results of the literature review (the characteristics of the selected studies, 3.1 and 3.3) and the results

regarding the predictive factors of refusal in the elderly.

R- We adjusted the results as required, see page 6 and 7, line 149-169.

The choice to consider together very different clinical situations and therefore potentially very different types of refusal has to be justified (refusal of surgery in early stage treatment or refusal of palliative treatment, for example).

In the same idea, the discussion integrates comments on very different data: quantitative socio-demographic factors, but also more clinical factors, sometimes very subjective as those issued from qualitative studies. The authors should make more clear, since the beginning of the paper and including in the abstract, whether they intend to collect only quantitative predictive factors (that the paragraph "results" suggests), or to review all the factors potentially included in the different studies (that the discussion suggests).

Finally, the appendix is very interesting and some data could be integrated in the discussion, or detailed in the limits of the review : as a matter of fact the huge discrepancy of the studies collected is both a strenght and a weakness of this work, and a very interesting part of it.

R- Due to the scarcity of prospective and qualitative studies, it is difficult to conclude whether the financial question or access to treatments really constituted a predisposition to therapeutic refusal (see Page 23 Line-224-232). Some studies showed association between refusal treatment and social economic status, and it may reflect the difficulty to access health services (page 22, line 204-208)

Our first intention was to analyze the causes of therapeutic refusal, but the studies found for this review signaled much more the sociodemographic and clinical characteristics related to therapeutic refusal than other factors, perhaps due to the nature of the studies, since most of them were descriptive and retrospective and not qualitative studies. Therefore, we decided to emphasize these factors but we argued in the discussion topic some results from the qualitative study included in this review (see page Pg 23 Line- 234-244). Understanding these factors is clinically relevant to health care professionals to enhance treatment adherence, improve outcomes, and provide optimal care considering the patients' profile and values.

We consider all types of interventions because if not, it would limit the review a lot, there are few studies on this issue. But we explained in 2 paragraphs of the discussion the differences taking into account the different types of intervention. (see Page 24 and 25, line 256-268).

Some minor comments :

Line 122 : How many studies integrate a nationwide population? R- 13. See Page 6 Line 135

Line 150 : could you explain what you mean by “even with a poor performance status”? R- We corrected the sentence (Page 7 line 167)

Line 169 : the link with the health insurance could suggest that patients have no financial access to the treatment (more than they refuse it) : as explained above this aspect is of a major importance and has to be better identified, do the studies cited make this point explicit? We added some data about this topic on Page 22 Line 206-208.

Line 226 : do you mean that the better the physician patient communication is, the more frequent are the refusals? This could be counter-intuitive, could you comment? R-These findings were described in the last systematic review (2015) that included some qualitative studies that demonstrated these variables associated with cancer therapy refusal. See page 23, Line 221-224.

Line 254-257 : this sentence is unclear, what is the link between the oral treatments and the fact that more and more older patients will have to face a decision? The decision has to be made whatever the type of treatment is… R- We adjusted this paragraph, thank you for suggestion.