Response to K Gaertner and M.Frass

Dear all,

thank you for your response to my comments on your paper [1] addressing some of my points. Of course I understand that we should keep to English on behalf of the corresponding author AD Kaye. My English got a little bit rusty over the past years, but I hope it is sufficient to make myself understood.

Thanks for your confirmation that the times given in your paper are based on the time of diagnosis. As for MRCC and MSARC even without deeper knowledge of oncology I figured that when these indications are named as 'metastatic...' then the time of diagnosis and time zero for survival would be the time when the occurrence of metastases was detected. But as long as these two points in time coincide, then patients #18, #19 and #24 were dead by a couple of months when they started their homeopathic treatment. Especially patient #19 must have been in a pretty poor condition undertaking her first session 97 months after diagnosis (of MSARC I presume) but having survived (the same diagnosis I presume) 52 months only. Must have been an eerie experience to discuss health matters with a person deceased for 45 months. Maybe you should put some light into this matter.

Although you did clarify some points on the nature of your data, you did not address my major issue, namely that the reported benefit of the adjuvant homeopathic treatment may largely be a statistical artifact only. And may just as well be a result of the different approaches in the treatment your patients received compared to what is reported in the literature you use as control data. Okay, you did address this issue in a few sentences in your duscussion section - but not very deeply so. It may very well be overlooked by someone who is impressed by the magnitude of the benefit of a few sugar pills.

Maybe I was not clear enough in my recent comments, so I will elaborate on my points.

Of course it is a sensible thing to do to start a preliminary study prior to launching a full fledged PCT, but as you published your results, especially as in Fig. 2 and Table 4, these tend to be used by homeopaths to advertise the power of homeopathic treatments. So these data are bound to receive much more attention and get much more significance than other preliminary studies. That is why I feel, that if my points are correct, then there should be some steps taken to correct what has been published.

GBM-data

To shed some more light on my point let us consider your data for GBM in some detail.

The piece of literature you compare your data to is the paper of Stupp et al. from 2009 [2]. There the patients were treated either with standard radio therapy or radiotherapy with adjuvant application of temozolomide. I could verify from your table 4, that your control data are taken from the Kaplan-Meier-Plot in Fig. 2 of said paper, especially the blue line summarizing the combined therapy.

Your subgroup consists of seven patients, five of them underwent surgery together with chemo- and radiotherapy. This additional surgery may or may not have some impact on survival time, I am not in the position to judge. But I would guess that it had, if not, what was the reason why it was performed in the first place? So if the homeopathy patients really showed a longer survival time, if they did at all (see below), then this might well at least in part be attributed to the additional surgery that the control group did not receive.

Your inclusion criteria have it, that the patients of the homeopathy group must have participated in a homeopathic treatment - which is understood, of course - that took some time to complete. So your data do not include participants with short survival times while your control data do. This gives rise to statistical artifacts as follows.

For simplicity I just take the median patient of your data to represent the whole subgroup. This is patient #4 who started homeopathic treatment four months after his/her diagnosis.

Inclusion criteria have it, that at least three homeopathic sessions must be completed, which according to your paper takes another four to six months to do. So we can assume that patient #4 survived nine months to qualify for inclusion. The population in the control data did start at point 0 and within the first nine months 25 % did die as given by the blue line in Fig. 2 in [2]. So 100 % of the homeopathic group consist (on average) of members of these 75 % of the original population that did survive nine months. Consequently, the proper survival ratio to compare to is the number of patients that survived one year vs. the number of patients that did survive nine months. So to get the comparative annual survival rates there has to be some scaling applied, by the factor of 100/75 to be exact. The one year survival rate to compare to is not 60 % but 60 percentage-points from 75

percentage-points which yields 80 %. For the other data see table 1.

The expected median survival time for the homeopathy group then is the point in time when half of its number is expected to have died. This is at half of 75 % having survived nine months resulting in 37.5 % of the total population. The Kaplan-Meier-Plot yields 18.7 months starting with the patient's diagnosis. For a compilation of my results see table 1.

	Original paper [1] (Table 4)		Reprocessed	
Survival	Expected	Achieved	Expected	Achieved
One year	60 %	85.7 %	80 %	85.7 %
Two years	27.2 %	28.5 %	36.2 %	28.5 %
Three years	16 %	28.6 %	21.3 %	28.5 %
Medium	14.6 months	19 months	18.7 months	19 months

Table 1: Comparison original results to reprocessed results for glioblastoma

For the indication of glioblastoma the benefit of the adjunct treatment, namely the reported improved survival in all four categories, proves to be an artifact. Adjusting the control data for the cutoff of short time survivals, two years ratio and medium survival time are what is to be expected, the advantage in one year and three year survival ratio is rather small and may well be attributed to the small sample size in [1] - even if we do not take the effects of additional surgery into account.

PC-data

The data for pancreatic cancer seem to prove the artificial nature of the benefit even more, though I had to make some assumptions that might result in some adjustments of my figures.

Gaertner uses a paper published in 2012 by Boyd et al. [3] to define control data. The authors there give four different Kaplan-Meier-Plots for their findings out of which I presume Fig. 2 to be the one in question. This seems corroborated by the median survival time of 6.6 months quoted there and in Table 4 of the Gaertner-paper. But unfortunately, the data Gaertner used as comparisons for the annual survival data do not fit in. In fact, I could not identify any of the Kaplan-Meier-Plots to yield 8 % and 5.8 % for one and two year survival rate respectively, neither could I identify the source, where 22 months expected survival for non-stage-IV patients could be derived from. But lacking better data, I

stick to Fig. 2 of [3].

For one out of the eight patients in the PC-group there are no data about the start of his homeopathic treatment, so I dropped this patient from my evaluation (which apparently Gaertner did, too).

The median with regard to the beginning of her homeopathic treatment is patient #43, who started six months after her diagnosis and met the inclusion criteria after an additional 5 months. At that point in time survival is only 31.4 % as measured from the Kaplan-Meier-Plot, but she proved to be one of these just by still being present. These remaining patients have a median expected survival time when half of them will probably have died. So their median survival time is given by the survival time of 15.7 % which is 19.8 months.

For the reassessment of the one and two year survival rates I took the one and two year readings from this Kaplan-Meier-Plot and rescaled them by the factor of 100/31.4.

	original paper (Table 4)		reprocessed	
Survival	expected	achieved	expected	achieved
one year	8 %	87.5 %	28.8 / 31.4 = 91.7 %	5/6 = 83.3%
two years	5.8 %	37.5 %	12.1 / 31.4 = 38.5 %	2/6 = 33.3 %
three years	no data	12.5 %	no data	0/7 = 0 %
median	6.6 months	17.5 months	19.8 months	19 months

Table 2: Comparison of original results to reprocessed results for pancreas cancer. Please note, patient is #42 dropped completely and patient #40 joined in year three only.

The striking benefit of the adjuvant homeopathic treatment reported by Gaertner et al., apparently giving the patients an advantage of a prolonged median survival of a factor of nearly 3 - simply does not exist. In fact the patients seem to fare about what is to be expected, that is of course skipping the point that three out of the seven patients included in my reevaluation had a much better prognosis of 22 months.

Other data

For CCC the impact of a reanalysis seems not that strong, but the patients reported on by Knüppel et

al. [4] seem to have received chemotherapy alone, whereas for the patients analysed by Gaertner two out of five had additional surgery and one had additional radiotherapy. The impact of this is not discussed.

For the other indications I could not find Kaplan-Meier-Plots in the referenced papers. But I guess the authors will find other data to do a proper comparison.

Discussion and conclusion

As far as I can see, in three out of three indications that I could review, there are either discrepancies in the treatments the patients received - where the ones considered in the study received the more complex treatment - and / or the reported advantage of prolonged survival did result from a wrong approach in comparing statistics. I dare say, much of this will be present in the other data as well. My evaluation is of course just done as a hands on approach and a more detailed scrutiny may bring some small changes to my figures. But I guess that these would not reverse my findings.

So Gaertner's et al. Fig. 2 and Tab. 4 contain results that are too optimistic and not justified by the data. Of course, this is a pilot study with a RCT or other paper to follow and the results will have to stand a much more rigorous test. You might be inclined to say, so what, just let's wait and see.

But this is a course of action or better non-action that is unacceptable. Homeopaths are used to utilize pilot studies only to corroborate their claims. In a recent meta-analysis [5] 8 out of 21 studies included were pilot studies, out of the three studies evaluated to contain 'valid results' two were pilot studies. So in the field of homeopathy, pilot studies are very commonly considered evidence. And therefore there is a need to have the data corrected. Gaertner et al. properly state that their findings cannot prove, if homeopathy was more or less helpful in the improvement - but these things tend to be overlooked by readers and patients. Homeopathy was applied and depending on the indication, survival could be three times longer than without. That is the main message - and who cares what did the trick if not homeopathy.

And to my experience, the results of Gaertner are being used to push homeopathy as a powerful and effective treatment for cancer and proving the homeopathic claims in general. I first came across this paper when a homeopathic practitioner used Fig. 2 as evidence that the homeopathic cancer treatment he was advertising was scientifically tested and proved. Even Michael Frass himself

presented the same graph in a meeting of homeopaths taking place in Berlin in Feb. 2015 - just with the same claim, that homeopathy is an effective treatment, even for cancer. And this might be misleading for patients - or for practitioners treating or advising patients.

So I think the authors should check my reanalysis and if they find my points to the mark, then they should take appropriate steps to have the published data corrected. The editors will know how to best handle this matter. I would prefer that the authors themselves take the action - but not too far in the future, say within the next month, I would begin to compile a review article and submit it for publication.

Schopfheim / Germany Dr. Norbert Aust
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