Peer-review

This mini-review which is about the application of NDV in the treatment of CRC needs some corrections. In the Conclusion section, the authors concluded that the strategy of NDV anti-CRC therapy has been widely explored. Actually, as they mentioned, only one phase II and one small phase III study from a single center were published (ref #78 & #79). In the trial published by Schulze et al in 2009 (ref #79), total 50 patients were randomised to the adjuvant vaccination (n=25 pts) with ATV-NDV or control (no treatment) group (n=25 pts). All patients were curatively resected for CRC liver metastasis before randomization. In the total patient group, no differences in the primary and secondary end-points were detected. Only a subgroup analysis revealed a significant OS advantage for vaccinated colon cancer patients (n=13 pts!). These data are not enough to draw a conclusion. On the other hand, again in the Conclusion section, authors conclude that NDV is associated with fewer side effects and higher safety than chemotherapy or radiotherapy. However, there is not any published comparative trial in the literature! This conclusion is not acceptable without any evidence. In the Table 1, there is a typing error: ref #79 after Schirrmacher et al should be #82. Except these statements, this mini-review is worth to publish. The topic that is current situation of the treatment with NDV in CRC is highly attractive for readers and figures are excellent.

First of all, thanks for your affirmation of this manuscript. I will reply to your comments as follows.

1- Some of the references included in the manuscript can answer this question. An article *Ockert D, Schirrmacher V, Beck N, Stoelben E, Ahlert T, Flechtenmacher J, Hagmiiller E, Buchcik R, Nagel M, Saeger HD. Newcastle disease virus-infected intact autologous tumor cell vaccine for adjuvant active specifc immunotherapy of resected colorectal carcinoma. Clin Cancer Res 1996; 2: 21–28 [PMID: 9816085]* is also a phase II clinical trial of ATV-NDV for colorectal cancer, but the text is related to the comparison of BCG, so it is not included in the manuscript. In addition, a phase III clinical trial (ref#80) is added to the paper, and the clinical sample size is 567 patients. This study reported 335 patients with colorectal cancer who received stage I-IV ATV-NDV. 310 patients received autologous tumor cell vaccine after surgery, and another 25 stage IV patients who received ATV-NDV only, 257 patients who underwent surgery only. The average survival period was 5.13 years (resection alone group 4.15 years), the median survival period was over 7 years (resection alone group 4.46 years). The 1-year survival rate was 96 % for 25 patients treated with NDV immunotherapy. After NDV vaccine immunotherapy, the number of NK cell increased and immune function imporved obviously.For more rigorous expression, "The extensive preclinical data and data from clinical trials with oncolytic NDV clearly reveal its efficacy for CRC." has been changed to "The multiple preclinical data and data from clinical trials with oncolytic NDV clearly reveal its Efficacy for CRC."

2-In order to be more accurate, the original has been changed to "The experimental group received 6 doses of ATV-NDV, and after approximately 10 years of follow-up, although no differences in primary and secondary endpoints were detected in the total patient group, the experimental subgroup (13 patients with colon cancer) showed significant advantages in terms of overall survival. The vaccination appeared to help prolong overall survival and metastasis-free survival".

3-In an article *Huang C, Fan XH, Jiang YH, et al. Anti-tumor effect of Newcastle disease virus strain D817 against nude mouse xenografts of human colon carcinoma. Zhonghua Zhong Liu Za Zhi. 2009, 31(7):490-4. [PMID: 19950694](Actually a Chinese article)*, the authors used NDV D817 strain to research its inhibitory effect on human colon cancer xenografts in nude mice. At the same time, PBS and fluorouracil (5-Fu) were used as controls. The results showed that NDV D817 was moderate hepatocyte edema in each dose group. However, hepatic steatosis was observed in 1/3 nude mice in the 5-Fu group. It is indicated that the toxic and side effects of NDV on tumor-bearing nude mice are relatively small. When a virus was detected in nude mice, only the presence of the virus was detected in the tumor tissue, and no virus was detected in the blood supernatant and other important organs in the body, further indicating that the NDV D817 strain is safe for biological treatment. Because it is a Chinese article, and it is a mouse experiment, it is not included in the article. No direct comparison between NDV and radiotherapy has been found. So for the sake of rigor, this sentence has been deleted in the original text.

4-Thank you for your correction, which has been revised in the manuscript.

Reviewer #2: The structure of manuscript is in keeping with the common required criteria. The topic of the work is very actual, because despite the surgical treatment and chemotherapy for colorectal cancer, the majority of colorectal cancer patients die due to liver or lung metastasis or recurrence. Therefore, there is an urgent need to find more effective treatment strategies to reduce their mortality. Newcastle disease virus can selectively infect tumor cells and can also improve the ability of Newcastle disease virus to resist colorectal cancer by constructing an autologous tumor vaccine. Authors described molecular biological characteristics of Newcastle disease virus, the oncolytic mechanism of Newcastle disease virus, and the possibilities in the treatment of colorectal cancer in vitro and clinical application of the Newcastle disease virus against colorectal cancer patients. Work is clearly legible, brings summarizes new knowledges. The citations are actual and their format respect usual standards. The conclusion reflects the author´s knowledges and these can be accepted. However, more research is needed to determine the preclinical and clinical effects of Newcastle disease virus to verify its safety and efficacy in colorectal cancer therapy. I recommend the manuscript to be published.

First of all, thanks for your affirmation of this manuscript. I will reply to your comments as follows.

At present, the oncolytic effect of Newcastle disease virus on colorectal cancer has been confirmed by in vitro experiments and tumor-bearing mouse models (Ref #55#66#67#68#69#70#71#72). The initial treatment results have also been obtained by some Phase I-IV clinical trials (Ref #75#76#77#78#79#80#82#83). Based on the success of these experiments, more NDV will be used in the treatment of colorectal cancer in the future. At the same time, oncolytic virus immunotherapy and combination therapy may be more conducive to the treatment of colorectal cancer, which of course requires more clinical trials to verify.