Author’s response to reviews

Title: Prognostic factors for survival after bronchoscopic intervention in patients with airway obstruction due to primary pulmonary malignancy

Authors:

Bo-Guen Kim (kbg1q2w3e@gmail.com)
Beomsu Shin (bsshin83@gmail.com)
Boksoon Chang (meera.chang@gmail.com)
Hojoong Kim (hjk3425@skku.edu)
Byeong-Ho Jeong (myacousticlung@gmail.com)

Version: 1 Date: 26 Jan 2020

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Reviewer 1
This is a clinical, retrospective study that evaluated the clinical outcomes and prognostic factors of bronchoscopic interventions in 224 patients with MCAO due to primary pulmonary malignancy from 2004 to 2017 at a University Hospital. A multivariable Cox proportional hazard regression analysis was used to identify independent prognostic factors associated with survival after the first bronchoscopic intervention. The authors observed that among 224 patients, 191 (85.3%) were males, and the median age was 63 years. The most common histological type of malignancy was squamous cell carcinoma (71.0%). Technical success was achieved in 93.7% of patients. Acute complications and procedure-related death occurred in 15.6% and 1.3% of patients, respectively. The median survival time was 7.0 months, and survival rates at one year and two years were 39.7% and 28.3%, respectively. Poor survival was associated with underlying chronic pulmonary disease, poor performance status, extended lesion, extrinsic or mixed lesion, and MCAO due to disease progression and not receiving adjuvant treatment after bronchoscopic intervention.

Specific Comments;
C1. Did the authors observe any difference among patients with tracheal, main bronchial and lobar bronchial lesions regarding the prognosis?
R1. Thank you for your suggestion. The locations of the lesions are detailed in Table 2. After site of lesion was newly classified into 4 categories (tracheal lesion [n = 44], main bronchial lesion [n = 102], lobar bronchial lesion [n = 27], and extended lesions [n = 51]), multivariate Cox regression analysis was additionally performed as previous Table 4. When tracheal lesion was a reference category, there was no category with statistical significance in univariate Cox regression analysis (main bronchus = HR 1.205, 95% CI 0.777-1.870, P = 0.405; lobar bronchus = HR 0.677, 95% CI 0.405-1.131, P = 0.136; and extended lesions = HR 1.079, 95% CI 0.657-1.771, P = 0.765). Furthermore, newly categorized variable for site of lesion was excluded from the final multivariate Cox regression with backward stepwise selection model. So, we think ‘single or extended lesion’ is more important to
assess the prognosis.

C2. Did the authors have information about relapsing stenosis in their patients?
R2. Thank you for the important suggestion. We already had an information about the restenosis as a chronic complication. We apologize for unintentionally not including the data about restenosis in Table 3. During the study period, a total of 20 restenosis cases occurred. We added this information in Table 3 and the Results section (line 198-199, page 10).

Reviewer 2
C1. I suggest that the authors add some information regarding the type of sedation and time of sedation this is also an essential factor
R1. Thank you for your suggestion to improve the quality of our paper. As described in the Methods section, all interventional bronchoscopy were performed with rigid bronchoscopy under general anesthesia. The procedure time was median 35 (IQR, 28-45) min. We added this information in Table 3 and the Results section (line 182, page 10).

Reviewer 3
C1. Thank you for this valuable manuscript. It can be published in this actual forma, but it would be nice that you could add the comparison tumor types, intervention choice and complication rates of early and late phase patients
R1. Thank you for your interest in our paper and for the helpful comments. We already performed the trend test for patients’ characteristics, treatment modalities, and clinical outcomes through the study period. When the study period was divided into early (2004-2009), intermediate (2010-2013), and recent (2014-2017) phases, proportions of adenocarcinoma in the tumor histological types have increased from 10% (8/77) to 20% (13/64) to 23% (19/83, P for trend = 0.041), respectively. In treatment modalities, silicone stents have been more used (35% [27/77] to 50% [32/64] to 65% [54/83], P for trend < 0.001), but use of laser (36% [28/77] to 41% [26/64] to 20% [17/83], P for trend = 0.029) and ballooning (16% [12/77] to 11% [7/64] to 5% [4/83], P for trend = 0.025) have decreased. Of the clinical outcomes, there was no statistically significant change in technical failure rates, but rates of excessive bleeding have decreased from 10% (8/77) to 6% (4/64) to 2% (2/83, P for trend = 0.038).
We are currently analyzing and studying on a comparison of patients’ characteristics, treatment modalities, and clinical outcomes according to the time periods in patients with benign airway stenosis and malignant obstruction. If you’ll kindly excuse me, it will be difficult to add this information in this revised version.

Reviewer 4
C1. The authors present a single center experience with interventional pulmonary management of central airway obstruction due to respiratory malignancies. The article is clearly written and the data well organized. Overall the conclusions are supported by the data and are similar to the findings in many previously published manuscripts. My primary concern with the manuscript is the level of detail provided about the patient cohort. There is no data about smoking history, or if the patients are active smokers.
R1. Thank you for your interest in our paper and for the helpful comments. We added the information for smoking history in the Results section (line 165-166, page 9) and Table 1.

C2. I suspect that active smoking, and a more extensive smoking history effects outcomes in these
patients and is an important risk factor to consider.

R2. We totally agree with your opinion that smoking history can be associated with survival. So, we reanalyzed the multivariate Cox regression after adding smoking history. However, smoking history did not affect the final results of multivariate Cox regression analysis. We added this information in the Table 4.

Of 32 references in our paper, 16 papers are the original articles on malignant airway obstruction (Ref 7, 9, 10, 12, 13, 14, 15, 16, 17, 21, 24, 25, 27, 28, 30, and 32; ref 14 and ref 27 are same cohort). Of these 16 papers, only 5 papers reported the smoking history (current or prior use = 872/1115 [78.2%] [14,27]; smoker = 10/30 [33%] [15]; current = 10/58 [17%], former = 25/58 [43%], never = 23/58 [40%] [16]; smoker = 5/72 [7%], ex-smoker = 44/72 [61%], never = 23/72 [32%] [28]). In addition, only two studies analyzed the association between smoking history and survival in patients with malignant central airway obstruction, and they reported there was no statistical association [15,28].

C3. In addition, the comorbidities presented in this population are surprisingly low compared with most groups of presumably heavy tobacco users that have previously been published. The authors should address this issue as to how it may affect their results compared with other populations who may have a higher burden of physiologic compromise.

R3. According to the largest multicenter cohort study for patients with malignant central airway obstruction (AQuIRE study, N = 1115) [14,27], asthma, COPD, cardiovascular disease, diabetes, and chronic kidney disease were 5%, 30%, 51%, 16%, and 1.5%, respectively. In our study, proportion of diabetes (13.8%) and chronic kidney disease (2.2%) were similar to AQuIRE study.

We reported the proportion of congestive heart disease was 6.7%, which is far difference from 51% for cardiovascular disease in AQuIRE study. We think it may be caused that we included only patients with congestive heart disease, not including hypertension, arrhythmia, or vascular disorder.

We reported the proportion of chronic pulmonary disease (not dividing into asthma and COPD) was 20%, which is far lower than 5% and 30% for asthma and COPD, respectively, in AQuIRE study. We think it is the limitation of this study nature of retrospective chart review. AQuIRE study was a prospectively collected cohort study for interventional pulmonology, so the information for pulmonary disease such as asthma and COPD may be more clearly collected than our study.

Finally, the effect of comorbidities may not be properly assessed on the prognosis in this study. We added this information in the Discussion section (line 288-292, page 14).