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Reviewer A

Reviewer A Comment 1: I appreciate the effort of the work presented. This study examined the association between diagnosis-to-treatment time interval and survival for early stage lung cancer in relation to each histologic subtype. I think there are two major problems, and a major revision of manuscript is needed.
First, it must be statistically examined whether the method of calculating the P value of COX analysis divided into three groups is appropriate. Isn't it necessary to divide it into three complicated groups?

Responses: We thank the reviewer for this comment. To examine the effect of timely treatment, how to define the timely treatment is critical. The guidelines on lung cancer timely treatment are inconsistent and these recommendations are largely based on expert opinions with limited evidence. Previous studies defined the timely treatment differently (based on different guidelines, or from other studies, or median interval in the study populations), which we think is one of the reasons for inconsistent findings on the survival effect from timely treatment of lung cancer. In our study, as we examined the survival effect of timely surgery for different lung cancer histologic subtypes, using only one single cutoff point to define the timely treatment could conceal the true association (the optimal cutoff point of timely surgery could vary by histologic subtype). We tried to maximize the information we can present from the data.

1. First of all, we examined the timeliness of the surgery in an ordinal format (with ONE categorical variable: ≥3 months, 2-<3 months, 1-<2 months, and <1 month, using <1 month as reference group) to evaluate the dose-dependent effect from the delayed surgery. We expected to see the longer interval between diagnosis and surgery was associated with worse survival (hazard ratios increased as the time interval increased), and we did find the dose-dependent pattern for all lung cancer subtypes combined, adenocarcinoma, and squamous or epidermoid carcinoma. For example, for adenocarcinoma, receiving surgery in 1-2 months from diagnosis was associated with 1.10 times (95% CI: 1.02-1.19) the hazard, 2-3 months was associated with 1.11 times (95% CI: 1.01-1.22) the hazard, and ≥3 months was associated with 1.29 times (95% CI: 1.16-1.44) the hazard of cancer-specific death, compared to receiving surgery within 1 month from tumor diagnosis. For these subtypes, any delay in surgery should be avoided and the surgery within 1 month from diagnosis is the optimal time interval.
2. Several subtypes did not show dose-dependent effects from the above analyses for two reasons: 1) there is no dose-dependent association (longer delay, worse survival) between delayed surgery and survival, in contrast, there could be a threshold in the effect of delayed surgery (defined by one cut-off point); 2) the sample size was small, which can be exacerbated by classification into four groups (with multi-categorical variables as in the above analyses) and reduce the statistical power. To overcome these challenges, we then examined the timely surgery in the binary format (with THREE

binary variables: ≥1 vs. <1 month, ≥2 vs. < 2 months, ≥3 vs. <3 months) to identify the optimal cut-off point of timely surgery for each subtype. We did find that for large cell carcinoma, 3 months could be the optimal cut-off point to define the timely surgery (no significant results were found when using 1 or 2 months as cut-off point), but 1 or 2 months for bronchioloalveolar carcinoma. This can be important evidence for future confirmatory studies.

3. From statistical perspective, hazard ratio and P-value were calculated for each individual analysis. Multivariable Cox proportional hazard models can treat both multi-categorical predictors and binary predictors and yield P-value for each comparison (1,2). Hazard ratios and P-values were unbiased.
4. However, we agreed with the reviewer and acknowledged that we conducted multiple comparisons in the analyses which could inflate the type I error. We did not adjust for multiple comparisons for three reasons: 1) whether multiple comparison adjustment is necessary is still under debate and many research showed that multiple comparison adjustment is not needed, especially for the pre-defined hypothesis testing (3-5); 2) the analyses were conducted in each individual subtype (different subpopulations), which can be considered as different family of analyses (familywise type I error rate was not inflated much); 3) in addition to P-value, the changes in the point estimate of hazard ratios can show the survival effect from delayed surgery, especially the dose-dependent effect, which indicates that the null hypothesis (no association between delayed surgery and survival) was not true.

References:

1. *Cox, D. R.; Oakes, D. (1984). Analysis of Survival Data. New York: Chapman & Hall. ISBN 978-0412244902.*
2. *Kalbfleisch , J.D.; Prentice R.L. (1980). The statistical analysis of failure time data. John Wiley & Sons, Inc., New York, 1980. ISBN 0-471-05519-0.*
3. *Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology (Cambridge, Mass). 1990;1(1):43-6.*
4. *Anderson, N. H. (2014).* Empirical direction in design and analysis. *New York, NY: Routledge.*
5. *Stangor, C. (2015).* Research methods for the behavioral sciences *(5th ed.). Stamford, CT: Cengage.*

Reviewer A Comment 2: Next, it covers an awfully long period of 12 years. During that time, the progress of cancer treatment has been remarkable, and I think it may be preferable to study the DFS rather than the OS. In addition, the period, for example, former period (2004-2009) and latter period (2010-2015), should be added to the analysis.

Responses: We thank the reviewer for this comment. We agree with the reviewer that disease free survival can be a better outcome than cancer-specific and overall survival, as it is a more proximal outcome to reflect treatment effects. However, since SEER does not actively collect disease recurrence, disease free survival was not available in the SEER database. SEER conducts passive data linkage with National Death Index to obtain survival status and the

underlying cause of death. Thus, cancer-specific survival and overall survival were the only outcomes we can use in the analyses.

In addition, we agree with the reviewer that the long study period could be a potential confounder. We added the study period (2004-2009 vs. 2010-2015) as a covariate in the analyses. The main findings remained the same. We revised the methods and results (including all tables, figures, and text) section accordingly. The revised tables and figures are not shown here because of the limited space, please see the revised manuscript.

Changes in the text:

Covariates included age at diagnosis (<50, 50-59, 60-69, ≥70 years), sex, race (white, other), marital status (married, single or divorced or separated or widowed or unmarried or domestic partner, unknown), tumor size (AJCC tumor size T1, T2), grade (well differentiated, moderately differentiated, poorly differentiated or undifferentiated, unknown), histologic subtype, surgery type (resection of one lobe or bilobectomy, lobectomy or bilobectomy with dissection of lymph nodes or pneumonectomy), chemotherapy (yes, no or unknown), radiation therapy (yes, no or unknown), and study period (2004-2009, 2010-2015).

Reviewer B

The authors analyze time to surgical treatment since diagnosis for Stage I/IIA NSCLC and found that this could impact on survival especially in certain subtypes like adenoca. squamous and brnchioloalveolar.

The study is interesting and paves the way for timely treatment in case of diagnosis of early stage NSCLC. I have minor comments:

Reviewer B Comment 1: page 6, line 129: is this VII Edition? please specify

Response: We thank the reviewer for the comment. The AJCC 6th Edition was used in 2004-2009 and AJCC 7th Edition was used in 2010-2015 in the SEER database. We revised the manuscript accordingly.

Changes in the text:

In this study, patients diagnosed with the American Joint Committee on Cancer (AJCC) stage I-IIA lung cancer during 2004 and 2015 (AJCC 6th Edition used for 2004-2009 cases and AJCC 7th Edition used for 2010-2015 cases) were identified from the SEER database, including data from 18 cancer registries.

Reviewer B Comment 2: were all patients radically resected (negative margins?) please specify in the methods

Response: We thank the reviewer for the comment. All patients included in this analysis were diagnosed with stage I-IIA, lymph node negative lung cancer and received surgery of lobectomy, bilobectomy or pneumonectomy. However, since SEER data do not include information on marginal status, we were not able to define whether patients had negative margins from surgery.

Reviewer B Comment 3: Some IB pus (e.g. ethose with T 4-5 cm) and most stage IIA patients could have received adjuvant chemotherapy which might have had an impact on patient survival. However, data on adjuvant chemotherapy is unknown. If this is the case, please acknowledge in the discussion as a potential limitation

Response: We thank the reviewer for the comment. We agree with the reviewer that chemotherapy utilization and radiation therapy utilization could be confounders in the association under investigation. The reason we did not include these two variables in the previous analyses was that for these two variables, no treatment and treatment unknown were grouped together in the original database. We were not able to differentiate patients who did not use chemotherapy or radiation therapy from patients whose chemotherapy or radiation therapy status was unknown. In this revision, we added these two variables as covariates in the multivariable models, the findings remained very similar (most of the changes in hazard ratios were on the number of hundredths). We also addressed the grouping issue of these two variables as a limitation. We revised the Methods, Results (including all tables, figures, and text), and Discussion sections accordingly. The revised the Results section (including tables and figures) is not shown here because of the limited space, please see the revised manuscript.

Changes in the text:

Covariates included age at diagnosis (<50, 50-59, 60-69, ≥70 years), sex, race (white, other), marital status (married, single or divorced or separated or widowed or unmarried or domestic partner, unknown), tumor size (AJCC tumor size T1, T2), grade (well differentiated, moderately differentiated, poorly differentiated or undifferentiated, unknown), histologic subtype, surgery type (resection of one lobe or bilobectomy, lobectomy or bilobectomy with dissection of lymph nodes or pneumonectomy), chemotherapy (yes, no or unknown), radiation therapy (yes, no or unknown), and study period (2004-2009, 2010-2015).

Thirdly, for the variables of chemotherapy utilization and radiation therapy utilization, no treatment and treatment unknown were grouped together. This is an inherent limitation of cancer registry data.

Reviewer B Comment 4: Nice work, focuses on an interesting and often neglected aspect

Response: We appreciate the reviewer for the time and effort reviewing this article!

Reviewer C

Reviewer C Comment 1: This manuscript evaluates the time from diagnosis to surgery by histology for early stage lung cancer. There is very little information on this in the published literature so it is novel and of interest to readers.

Response: We appreciate the reviewer for the time and effort reviewing this article!

Major comments.

Reviewer C Comment 2: Throughout the paper the interval mentioned time from diagnosis to treatment. The treatment in this manuscript is only surgery, other treatments are not considered, so the word 'treatment' should be replaced with 'surgery' to show that it is the time from 'diagnosis to surgery' which is what is being studied. It is misleading to say treatment as this could incorporate radiotherapy and systemic therapy.

Response: We thank the reviewer for the comment. In the initial version of the manuscript, we used 'time interval between diagnosis and initial treatment' as the exposure variable, because this was the original variable in the SEER database. However, as suggested by several reviewers, because the study population we selected was stage I&IIA patients who received definitive surgery, and the only treatment we evaluated was surgery, we changed the exposure variable as 'diagnosis-to-surgery interval' (instead of 'diagnosis-to-initial treatment interval). For this purpose, we additionally excluded the patients who received radiation prior to surgery or had unknown sequence between surgery and radiation (N=437, out of 41,049 patients in the original sample). We redid the analyses but the findings and conclusions remained the same. We revised the Methods section to specify the process we conducted to ensure that the selected patients were highly likely to receive surgery as the initial treatment (text changes as below), we revised the Introduction section with a focus on the surgery (instead of any treatment) (text changes as below), we revised the Discussion section by adding the previous research on survival effect of timely surgery (text changes as below), we acknowledged the limitation of using 'diagnosis-to-initial treatment interval' as a substitute for 'diagnosis-to-surgery interval' (text changes as below), we updated the Results section (text changes not shown here because of limited space), and we edited the whole manuscript by emphasizing the surgery as the main exposure (replacing treatment with surgery in many places, text changes not shown here because of limited space).

Changes in the text:

Methods section:

The primary exposure variable was the time interval between tumor diagnosis and surgery. The original variable in the SEER database was the interval between tumor diagnosis and treatment initiation (in months). We used this variable to approximate the interval between tumor diagnosis and surgery, as the initial treatment was highly likely to be surgery in this selected patient population. Three inclusion/exclusion criteria were applied to ensure the selected population receiving surgery as the initial treatment: 1) we included stage I-IIA lung cancer patients, for whom the recommended initial treatment is surgery if the cancer is operable (both NSCLC and SCLC) (7,8); 2) we included only the patients who received a definitive surgery (lobectomy, bilobectomy, or pneumonectomy); and 3) we excluded the patients whose radiation therapy was given before the surgery or before/after the surgery and the patients whose sequence between radiation and surgery was unknown. In other words, stage I-IIA lung cancer patients who received surgery and the surgery was the only treatment or prior to radiation were included in the analyses, thus, we used the time interval between diagnosis and treatment initiation as a substitute for the time interval between diagnosis and surgery.

Introduction section:

Although surgery is the initial treatment recommended to the operable diseases (7,8), the major clinical guidelines on the timing of lung cancer surgery are inconsistent. Rand Corporation recommended lung cancer surgery within 6 weeks from diagnosis in 2000 and did not update the guidelines since then (9). American College of Chest Physicians (ACCP) recommended surgery within 4-8 weeks of referral in 2003 guidelines (10), but in its most recent guidelines from 2013, only 'interventions to improve timeliness should be developed locally by addressing barriers to providing timely care that are specific to the local setting' was recommended (11). British Thoracic Surgery (BTS) suggested a maximum of 8 weeks from respiratory specialist consultation to surgery in 1998 (12), however, no specific recommendations on the timing of treatment was provided in its 2019 guidelines (13). Danish Lung Cancer Group and Registry recommended less than 14 days from diagnosis to treatment (14).

Discussion section:

Among the studies focusing on the effect of timely surgery, two studies using National Cancer Data Base (NCDB) reported higher likelihood of pathologic upstaging and worse survival associated with delayed surgical resection among stage I NSCLC patients (25,26), which is consistent with our findings. One study reported 4% increased hazard of death for every one week delay to surgery among stage I & II community diagnosed NSCLC patients (36). Two studies analyzing stage I & II NSCLC patients from single institution did not find significant association between delayed surgical resection and survival, for which the small sample size could be the reason (29,37).

Despite strengths, our study is also subjected to limitations. First of all, the exact date of surgery was not available in the original dataset. The time interval between the diagnosis and treatment initiation was used to approximate the diagnosis-to-surgery interval. Although we believe this approximation was appropriate as surgery was highly likely to be the initial treatment in the study population, future studies with exact surgery date are needed to confirm the findings.

Reviewer C Comment 3: It would be useful to add some specific results in the results section of the abstract rather than just stating the overall results in descriptive form ie hazard ratios, p values etc. What are the main findings and for which histological subtypes. Which cancers did timeliness impact on significantly and which did not.

Response: We thank the reviewer for the suggestion. The only reason that we were not able to report hazard ratios and P-values is the word limit for the abstract. With the most essential contents in 'Background', 'Methods', 'Results', and 'Conclusions' sections, the current abstract has already reached the word limit required by the journal (350 words, abbreviations are not allowed), there is really no space for the hazard ratios and P-values in the abstract, especially given that 1) we examined all lung cancer subtypes combined and seven individual subtypes (8 subpopulations); 2) we examined the effect of delayed surgery in both categorical format and

binary format (6 hazard ratios for each subpopulation for each outcome); 3) we examined two outcomes (cancer-specific survival and overall survival). So even to report the results for one single subtype, there were 12 hazard ratios and P-values (we had to report at least a few hazard ratios even if we do not present all the 12 hazard ratios and P-values; and it was better to describe a few subtypes if we decide to do so). We did report the main findings, including the subtypes of which there is association between delayed surgery and survival, of which there is dose-dependent effect from delayed surgery, and of which no association was detected. We additionally added the effect size (about 20-40% increased risk) in the abstract. We hope the summary in the abstract can guide the readers to get more detailed information in the tables.

Changes in the text:

Delayed surgery was associated with worse cancer-specific and overall survival for all lung cancers, adenocarcinoma, squamous or epidermoid, bronchioloalveolar, and large cell carcinoma (20%-40% increased risk). Dose-dependent effects were observed in all lung cancers, adenocarcinoma, and squamous and epidermoid carcinoma (longer delay, worse survival). No significant association between surgery delay and survival was observed in adenosquamous, carcinoid, and small cell carcinoma.

Reviewer C Comment 4: Discussion – There are a number of referenced studies for timeliness of care. Please discuss whether which stages of lung cancer were included, which histologies (NSCLC vs SCLC vs all) and whether all treatments or selected treatments were included. The different study populations and treatment may explain some of these differences. The same comments apply to the 2 previous SEER studies, what treatment was included in these analyses? The references to other timeliness studies are limited. Please see Vinod SK et al Lung Cancer 2017; 112: 16-24. This population based study on timeliness has a table summarizing other relevant literature. http://dx.doi.org/10.1016/j.lungcan.2017.07.032. The discussion is wordy at times and could be separated into more paragraphs.

Response: We thank the reviewer for the suggestion and sharing the literature! For each study we compared in the Discussion section, we added the details on stage, cancer subtype, and treatment type in the manuscript (text changes as below). As there are intensive literature on the survival effect of timely treatment, we originally focused on the studies published after 2010. In this revision, we conducted an intensive literature review, updated the references, and provided discussion about other studies focusing on timely surgery. We also cited the paper the reviewer suggested (Vinod SK et al, Does timeliness of care in non-small cell lung cancer impact on survival? Lung Cancer. 2017). In addition, we separated the Discussion section into more paragraphs.

Changes in the text:

There were two studies using the SEER-Medicare dataset examining the consequences of delayed care on lung cancer survival. Both studies examined the survival effect of the time interval from diagnosis to any treatment initiation among all stage lung cancer patients. One study evaluated NSCLC patients from 2004-2007 and found that diagnosis-to-treatment interval ≤35 days is associated with better survival among patients with localized disease, which

is similar with our findings (34). Another study analyzed 2002-2007 NSCLC and SCLC patients but found a paradoxical association between timely treatment and overall survival (32). Compared to these two studies, we used more contemporary data of curative patients and focused on the effect of timely surgery, i.e., stage I & IIA patients who received definitive surgery. The more restricted study population can explain the higher prevalence of delayed treatment in our study (34% of patients receiving treatment within 1 month from diagnosis in our study vs. higher than 60% of patients receiving timely care in the other two studies), as both early stage and receiving surgery are the risk factors of delayed treatment (32, 35). Among the studies focusing on the effect of timely surgery, two studies using National Cancer Data Base (NCDB) reported higher likelihood of pathologic upstaging and worse survival associated with delayed surgical resection among stage I NSCLC patients (25, 26), which is consistent with our findings. One study reported 4% increased hazard of death for every one week delay to surgery among stage I & II community diagnosed NSCLC patients (36). Two studies analyzing stage I & II NSCLC patients from single institution did not find significant association between delayed surgical resection and survival, for which the small sample size could be the reason (29,37).

One previous study analyzing a patient population with clinical stage IA lung squamous cell carcinoma from National Cancer Data Base, reported 36% of patients receiving surgery within 30 days from diagnosis and 11%-13% increased risk of all-cause mortality associated with delayed surgery, which is very similar with our findings for squamous cell carcinoma (10%-20% increased risk) (36).

Another recent study analyzing 286 propensity score matched clinical stage I lung adenocarcinoma patients found that delayed surgery (>21 days from histologic diagnosis to surgery) is associated with two-fold risk of all-cause mortality (HR = 2.03, P = 0.038), which is higher than 10%-36% increased risk in our adenocarcinoma patients.

Minor comments

Reviewer C Comment 5: Title – Suggest changing to 'Diagnosis-to-surgery interval and survival for different histologies of Stage I-IIA lung cancer'

Response: We thank the reviewer for the comment. The title was changed as suggested.

Reviewer C Comment 6: Line 56 – delete the word 'about' in front of the numbers.

Response: We thank the reviewer for the comment. If deleting the word 'about', the sentence will start with a number, which is not appropriate. Thus, we revised the sentence accordingly.

Changes in the text:

The proportion of patients receiving treatment <1 month, 1-<2 months, 2-<3 months, and ≥3 months from diagnosis were 34.1%, 33.9%, 19.8%, and 12.1%, respectively.

Reviewer C Comment 7: Lines 98-112. The introduction is quite long. This section about

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different histologies could be summarized. There is no need to describe the cell appearance etc. Just summarise frequency of common histologies and their doubling times. Important to state that surgery is the main treatment for early stage NSCLC but not for SCLC where chemotherapy is the main treatment (+/- surgery or radiotherapy for early stage).

Response: We thank the reviewer for the suggestion. We reviewed the NCCN guidelines regarding lung cancer treatment recommendations, and summarized it in the Introduction section. In brief, for early stage lung cancer, no matter NSCLC or SCLC, if operable, surgery is the recommended initial treatment. However, majority of SCLC is inoperable, for which chemotherapy sequential or concurrent with radiation therapy is recommended (these patients not included in the analyses). In addition, we shortened the descriptions about the histologic subtypes, keeping only the key information in the Introduction section.

Changes in the text:

Generally, two broad classes of lung cancer are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is a group of several histologies, representing about 85% of all lung cancer cases. The recommended initial treatment for early stage NSCLC is surgery (7). SCLC has a higher tumor growth rate and worse prognosis than NSCLC (15). Surgical resection is also recommended to operable SCLC, however, most SCLC has spread at diagnosis, for which the mainstay treatment is chemotherapy (8). In the past two decades, more attention has been paid to the histologic subtypes (16). For example, adenocarcinoma is the most common histology of lung cancer, representing almost half of lung cancer cases (17). Squamous cell carcinoma accounts for about 30% of NSCLC, which has a shorter doubling time, lower sensitivity to targeted therapy, and poorer survival than adenocarcinoma (18,19). Other histologic subtypes, such as bronchioloalveolar carcinoma and carcinoid carcinoma, are rare but usually well-differentiated and have high survival rates if resected at an early stage (20,21).

Reviewer C Comment 8: Line 129 – Which version of AJCC staging was used?

Response: We thank the reviewer for the comment. The AJCC 6th Edition was used in 2004-2009 and AJCC 7th Edition was used in 2010-2015 in the SEER database. We revised the manuscript accordingly.

Changes in the text:

In this study, patients diagnosed with the American Joint Committee on Cancer (AJCC) stage I-IIA lung cancer during 2004 and 2015 (AJCC 6th Edition used for 2004-2009 cases and AJCC 7th Edition used for 2010-2015 cases) were identified from the SEER database, including data from 18 cancer registries.

Reviewer C Comment 9: Line 162 – What about having pneumonectomy as a separate group for surgery?

Response: We thank the reviewer for the comment. We tried to classify the patients receiving

pneumonectomy as a separate group in the reanalysis, however, we found that the frequency of pneumonectomy recipients was only 2.33% (947 patients) among total population. The sample size will decrease and be not sufficient for multivariable analysis for each histologic subtype, especially the less frequent subtypes. The reason of small proportion of pneumonectomy could be that only stage I-IIA patients were eligible and included in the study, among whom the disease was limited and too extensive surgery was not needed. Thus, we did not categorize pneumonectomy as a separate group of surgery in the final analysis.

Reviewer C Comment 10: Line 184,187 – delete the word 'about'.

Response: We thank the reviewer for the comment. If deleting the word 'about', the sentences will start with a number, which is not appropriate. Thus, we revised the sentences as below:

Changes in the text:
During the follow-up, 39.9% of the patients died from any causes, while 23.3% of the patients died from cancer-specific causes.

The proportion of the patients receiving treatment <1 month, 1-<2 months, 2-<3 months, and ≥3 months from diagnosis were 34.1%, 33.9%, 19.8%, and 12.1%, respectively (Table 1).

Reviewer C Comment 11: Table 1 – Suggest reporting numbers to 1 decimal point and then reporting these figures in the manuscript to be exact and avoid the word 'about'.

Response: We thank the reviewer for the suggestion. The numbers in Table 1 were modified to 1 decimal point and the word 'about' in the manuscript was removed or rephrased.

Reviewer C Comment 12: Table 1 – How many patients had a diagnosis to treatment time = 0 days ie the histological confirmation of cancer was made at time of surgery? Should these patients be excluded from this analysis of timeliness because of confounding?

Response: We thank the reviewer for the comment. To keep confidentiality, the time interval between diagnosis and treatment was coded by month, not by day, in the SEER database. Thus, we were not able to exclude the patients with diagnosis-to-surgery time interval of 0 day. However, we included only the patients who received lobectomy, bilobectomy, or pneumonectomy, who were most likely to have the tumor diagnosis prior to the surgery. Patients who had tumor diagnosed during surgery were more likely to receive less extensive surgery, such as local tumor destruction or excision, who were excluded from the analysis.

Reviewer C Comment 13: Line 241-243 – The reported results for large cell ca do not match up with the results in Table 2 where there are no statistically significant findings for large cell.

Response: We thank the reviewer for the comment. We double checked the numbers in the table and in the text, actually both agreed with each other. In the text, we were NOT reporting the hazard ratio of ≥3 months vs. <1 month from multi-categorical analysis, which was 1.38

(0.90-2.13) and not significant. Instead, we were reporting the hazard ratio of ≥3 months vs. <3 months from binary analysis, which was 1.59 (1.06-2.38) and significant. Both can be found in Table 2.

However, as we updated the analyses and the tables, in the text, we used the updated number as below:

For large cell carcinoma, >3 month from diagnosis to treatment was associated with significant worse survival (HR: 1.63; 95% CI: 1.09-2.44) than <3 months interval, controlling for covariates.

Reviewer C Comment 14: Lines 65, 263 – 'dose response' is not the correct term to use for analysis of time to treatment versus survival. Better to simply say that 'increased time from diagnosis to surgery was associated with poor survival in adenocarcinoma and squamous/epidermoid carcinoma.'

Response: We thank the reviewer for the comment. We searched the literature and found that 'dose-dependent' can be a better term to describe the linear association between timely surgery and better survival. If using the sentence suggested by the reviewer 'increased time from diagnosis to surgery was associated with poor survival in adenocarcinoma and squamous/epidermoid carcinoma', it could be hard for the readers to differentiate the linear association (dose-dependent, P-value for trend significant) and non-linear association (single cutoff-point identified, P-value significant). We revised 'dose-response' into 'dose-dependent', and we added more clarifications of dose-dependent effects in the manuscript.

Changes in the text:

Methods section:

The time interval between tumor diagnosis and surgery was examined in a multi-categorical format: less than 1 month (<1 month), 1 month or longer but less than 2 months (1-<2 months), 2 months or longer but less than 3 months (2-<3 months), 3 months or longer (≥3 months). With multi-categorical variables, potential dose-dependent effect (longer delay, worse survival) can be detected by the trend analyses. Furthermore, to detect any non-linear associations (no trend for the worse survival associated with the increased time interval, but delay beyond a single cut-off point in the interval associated with worse survival) and maintain the sample size in multivariable analyses, especially for the less frequent histologic subtypes, a secondary exposure variable of the diagnosis-to-surgery interval was examined in a binary format: ≥1 vs. <1 month, ≥2 vs. <2 months, and ≥3 vs. <3 months.

Discussion section:

The strong dose-dependent effect from delayed surgery was detected in patients with adenocarcinoma and squamous or epidermoid carcinoma (longer delay, worse survival).

Secondly, while most previous studies defined the delayed treatment into a single binary variable, we investigated the delayed treatment in both multi-categorical and binary format. By comparing the survival of patients receiving surgery 1-<2 months, 2-<3 months, and ≥3 months to <1 month and providing P value for trend, we can evaluate the dose-dependent

effect from delayed treatment, which can provide stronger evidence on the association. By using 1 month, 2 months, and 3 months as cutoff points to generate three binary variables, we have higher chance to identify the most appropriate interval for timely surgery for each histologic subtype.

Reviewer C Comment 15: Line 282 – Change to 'early stage disease treated with surgery' to specify your exact study population

Response: We thank the reviewer for the comment. The manuscript was revised accordingly.

Changes in the text:
In our study, we focused on the early stage disease treated with surgery and stratified the sample by histologic subtype to control the confounding and effect modification from stage and histology.

Reviewer C Comment 16: Line 354 – Other limitations are not accounting for the patients performance status. Both poor performance status and comorbidities may delay time to surgery if other conditions have to be optimized prior to surgery, but they may also be associated with poorer survival in their own right although less likely to impact on CSS.

Response: We thank the reviewer for the comment. We agree with the reviewer that patient's comorbidities and performance status can be confounders in the association between timely treatment and survival. However, data on comorbidities and performance status was not available. Thus, we acknowledged this as a limitation in the Discussion section.

Changes in the text:
Another limitation is the lack of information on patient's comorbidity and performance status, which can be important confounders of timely care. We alleviated the confounding effect from comorbidity and performance status by including only patients who received surgery and using cancer-specific survival as an outcome. Patients with severe comorbid conditions or poor performance status who were not eligible for surgery were excluded in the analysis. Cancer-specific survival is less likely to be confounded by other health conditions and comorbidities.

Reviewer C Comment 17: Line 368 – please change to 'our findings support the initiation of surgery within 1 month from diagnosis in patients with Stage I-IIA lung cancer' ie be specific. The way the sentence is written leaves it open to interpretation to other treatment modalities not evaluated in this study. The conclusion of the abstract should also be specifically worded.

Response: We thank the reviewer for the comment. The sentences were revised in both the Abstract section and the Discussion section.

Changes in the text:
Our findings support the guidelines of receiving surgery within 1 month from tumor diagnosis

in patients with stage I-IIA lung cancer.

Reviewer D

Thank you for the opportunity to review the paper titled 'Timely treatment and survival for stage I-IIA lung cancer with different histologic subtype.' by Lu Zhang et al. The paper presents conclusions of an epidemiological study of timely surgery after histopathological diagnosis of various subtypes of lung cancer. It regards an interesting aspect of treatment efficacy in delayed surgery.

In the reviewer belief, the paper provides an educational message and should be published with minor changes / comments regarding following aspects:

Reviewer D Comment 1: The nomenclature of the manuscript is not clear and not consistent. In the sentence "However, there is a lack of consensus on the impact of timely care on lung cancer survival and the major clinical guidelines on the timing of lung cancer treatment are inconsistent." the authors refer to a surgery. This should be more precise, as "care" or "treatment" can refer to radiotherapy, chemotherapy or best-supportive care. Authors indicate that there is a lack of evidence of delayed treatment onset in lung cancer treatment by citing Hanna et al (1) article. The cited review refers to two studies on non-small cell lung cancer (NSCLC) showing no significant benefit of timely surgery and two other studies of timing of onset of adjuvant chemotherapy (Salazar et al., Booth et al.). Is this a scope of the paper and if yes, how would the authors comment on other published articles showing conflicting results of different timing of adjuvant chemotherapy onset after lung cancer surgery by Ramsden et al., Salazar et al., Booth et al., Wang et al. and Szejniuk et al. (2-6)?

Response: We thank the reviewer for the comment. In the initial version of the manuscript, we used 'time interval between diagnosis and initial treatment' as the exposure variable, because it was the original variable in the SEER database. However, as suggested by several reviewers, because the study population we selected was stage I&IIA patients who received definitive surgery, and the only treatment we evaluated was surgery, we changed the exposure variable as 'diagnosis-to-surgery interval' (instead of 'diagnosis-to-initial treatment interval). For this purpose, we additionally excluded the patients who received radiation prior to surgery or had unknown sequence between surgery and radiation (N=437, out of 41,049 patients in the original sample). We redid the analyses but the findings and conclusions remained the same. We revised the Methods section to specify the process we conducted to ensure that the selected patients were highly likely to receive surgery as the initial treatment (text changes as below), we revised the Introduction section with a focus on the surgery (instead of any treatment) (text changes as below), we revised the Discussion section by adding the previous research on survival effect of timely surgery (text changes as below), we acknowledged the limitation of using 'diagnosis-to-initial treatment interval' as a substitute for 'diagnosis-to-surgery interval' (text changes as below), we updated the Results section (text changes not shown here because of limited space), and we edited the whole manuscript by emphasizing the surgery as the main exposure

(replacing treatment with surgery in many places, text changes not shown here because of limited space).

There were many studies evaluating the survival effects of timely lung cancer care, we focused on the studies published after 2010 in the initial version of the manuscript. As a response to this comment, we conducted an intensive literature review on the research examining survival effects of timely surgery and discussed these studies in the Discussion section (text changes as below). As the timely radiation and chemotherapy were not our focus, we did not discuss these two papers in the Discussion section.

Changes in the text:

Methods section:

The primary exposure variable was the time interval between tumor diagnosis and surgery. The original variable in the SEER database was the interval between tumor diagnosis and treatment initiation (in months). We used this variable to approximate the interval between tumor diagnosis and surgery, as the initial treatment in this selected patient population is highly likely to be surgery. Three procedures were conducted to ensure the selected population receiving surgery as the initial treatment: 1) we included stage I-IIA lung cancer patients, for whom the recommended initial treatment is surgery if the cancer is operable (both NSCLC and SCLC) (7,8); 2) we included only the patients who received a definitive surgery (lobectomy, bilobectomy, or pneumonectomy); and 3) we excluded the patients whose radiation therapy was given before the surgery or before/after the surgery and the patients whose sequence between radiation and surgery was unknown. In other words, stage I-IIA lung cancer patients who received surgery and the surgery was the only treatment or prior to radiation was included in the analyses, thus, we used the time interval between diagnosis and treatment initiation as a substitute for the time interval between diagnosis and surgery.

Introduction section:

Although surgery is the initial treatment recommended to the operable diseases (7,8), the major clinical guidelines on the timing of lung cancer surgery are inconsistent. Rand Corporation recommended lung cancer surgery within 6 weeks from diagnosis in 2000 and did not update the guidelines since then (9). American College of Chest Physicians (ACCP) recommended surgery within 4-8 weeks of referral in 2003 guidelines (10), but in its most recent guidelines from 2013, only 'interventions to improve timeliness should be developed locally by addressing barriers to providing timely care that are specific to the local setting' was recommended (11). British Thoracic Surgery (BTS) suggested a maximum of 8 weeks from respiratory specialist consultation to surgery in 1998 (12), however, no specific recommendations on the timing of treatment was provided in its 2019 guidelines (13). Danish Lung Cancer Group and Registry recommended less than 14 days from diagnosis to treatment (14).

Discussion section:

Among the studies focusing the effect of timely surgery, two studies using National Cancer Data Base (NCDB) reported higher likelihood of pathologic upstaging and worse survival

associated with delayed surgical resection among stage I NSCLC patients (25,26), which is consistent with our findings. One study reported 4% increased hazard of death for every one week delay to surgery among stage I&II community diagnosed NSCLC patients (36). Two studies analyzing stage I&II NSCLC patients from single institution did not find significant association between delayed surgical resection and survival, for which the small sample size could be the reason (29,37).

Despite strengths, our study is also subjected to limitations. First of all, the exact date of surgery was not available in the original dataset. The time interval between the diagnosis and the initial treatment initiation was used to approximate the diagnosis-to-surgery interval. Although we believe this approximation was appropriate as surgery was highly likely to be used as the initial treatment in the study population, future studies with exact surgery date are needed to confirm the findings.

Reviewer D Comment 2: How was the lung cancer staging established and was it based on the 7th or the 6th TNM edition?

Response: We thank the reviewer for the comment. The AJCC 6th Edition was used in 2004-2009 and AJCC 7th Edition was used in 2010-2015 in the SEER database. We revised the manuscript accordingly.

Changes in the text:
In this study, patients diagnosed with the American Joint Committee on Cancer (AJCC) stage I-IIA lung cancer during 2004 and 2015 (AJCC 6th Edition used for 2004-2009 cases and AJCC 7th Edition used for 2010-2015 cases) were identified from the SEER database, including data from 18 cancer registries.

Reviewer D Comment 3: Was the histopathological diagnosis discussed with pathologists regarding the changes in the diagnosis of bronchoalveolar subtype (7)?

Response: We thank the reviewer for the comment. As our cases were from 2004-2015, we believe that most recent changes in the diagnosis of bronchioloalveolar carcinoma were not reflected in our sample.

Reviewer D Comment 4: How would authors explain the lack of significant association between better survival and early surgery for adenosquamous carcinoma, carcinoid carcinoma, and small cell carcinoma?

Response: We thank the reviewer for the comment. We think the sample size could be the first reason for not detecting significant association for these subtypes. Previous studies using national sample (with much larger sample size) (1,2) tended to find significant association between timely surgery and improved survival compared to studies using smaller sample from single institution (3,4). Beyond the sample size, each subtype actually showed different pattern in the survival effect of timely surgery. For adenosquamous carcinoma which has a faster tumor

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growth rate than adenocarcinoma, the point estimate of hazard ratios showed that 1 month could be the optimal cutoff point to define timely surgery, as the patients receiving surgery later than 1 month showed similar survival patterns. For carcinoid carcinoma which has very slow growth rate and good prognosis, point estimate of hazard ratios showed that 3 months was more likely to be the optimal cutoff point, which echoed the fact of slow growth rate of this subtype and indicated the surgery within 3 months from diagnosis does not affect survival. Small cell carcinoma could have different story. Majority (≥90%) of small cell carcinomas are not operable at diagnosis, thus the small cell carcinoma selected in this study (which was operable at diagnosis) may not fully represent the characteristics of this subtype. The small cell carcinoma included in this study could have slower tumor growth rate and better survival compared to typical small cell carcinoma which has spread at diagnosis, thus the effect of timely surgery was not significant. Future studies with larger sample size and more detailed information on other treatment (especially chemotherapy which is the mainstay treatment for small cell carcinoma) are needed to examine the effect of timely treatment for small cell carcinoma.

References:

1. Samson P, Patel A, Garrett T, Crabtree T, Kreisel D, Krupnick AS, et al. Effects of Delayed Surgical Resection on Short-Term and Long-Term Outcomes in Clinical Stage I Non-Small Cell Lung Cancer. Ann Thorac Surg. 2015;99(6):1906-12; discussion 13.
2. Bott MJ, Patel AP, Crabtree TD, Colditz GA, Kreisel D, Krupnick AS, et al. Pathologic Upstaging in Patients Undergoing Resection for Stage I Non-Small Cell Lung Cancer: Are There Modifiable Predictors? Ann Thorac Surg. 2015;100(6):2048-53.
3. Aragoneses FG, Moreno N, Leon P, Fontan EG, Folque E. Influence of delays on survival in the surgical treatment of bronchogenic carcinoma. Lung Cancer. 2002;36(1):59-63.
4. Quarterman RL, McMillan A, Ratcliffe MB, Block MI. Effect of preoperative delay on prognosis for patients with early stage non-small cell lung cancer. The Journal of thoracic and cardiovascular surgery. 2003;125(1):108-13; discussion 13-4.

Reviewer D Comment 5: The small cell lung cancer (SCLC) is normally not treated with surgery. Do authors investigated if the stages of SCLC were higher than for the rest of the cohort and can explain the lack of benefit of early surgery? SCLC is characterized by a rapid cancer cell growth. Biologically, early surgery should increase the survival. Please comment on that.

Response: We thank the reviewer for the comment. As we included only stage I&IIA patients, we found that stage II cases accounted for 42.3%, 54.7%, 34.4%, 60.0%, 54.1%, 37.2%, and 41.6% for adenocarcinoma, squamous or epidermoid carcinoma, bronchioloalveolar carcinoma, large cell carcinoma, adenosquamous carcinoma, carcinoid carcinoma, and SCLC patients, respectively. SCLC did not have higher frequency of stage II diseases than other subtypes. As there were only 377 SCLC patients, we believe small sample size could be a reason for not detecting any significant association. In addition, as in our response to the last comment, we think the operable SCLC (selected in this study) may not fully represent the characteristics of typical SCLC. We were not able to investigate why early surgery was not associated with SCLC

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survival benefit in this study. Futures studies with larger sample size and more detailed information on other treatment, especially chemotherapy, is needed to decipher the survival effect of timely treatment for SCLC.

Reviewer D Comment 6: Do authors believe that their results can influence a clinical practice and motivate for earlier surgery?

Response: We thank the reviewer for the comment. Yes, given the inconsistent findings from the previous research, we do believe our results can emphasize the clinical importance of early surgery. The detected dose-dependent effects (longer delay, worse survival) especially highlight the necessity of early surgery.

Reviewer D Comment 7: The manuscript presents results of a retrospective study without data of patient comorbidity. How possible is it, according to authors, that delayed surgery was a result of patient comorbidity and pre-operative time needed for surgery preparation (such as poorly regulated diabetes of COPD)?

Response: We thank the reviewer for the comment. We agree with the reviewer that comorbidity can be a potential confounder in the association between timely surgery and survival. However we think the adjustment of comorbidity will not substantially change the conclusions for three reasons: 1) in the previous studies, comorbidity did not explain much of the association between timely surgery and survival; 2) in our study, we included only the patients who underwent definitive surgery, thus, those who had severe comorbid conditions and were too fragile for surgery were excluded from the analysis; 3) we used cancer-specific survival as one of the outcomes, which could be less likely to be influenced by the comorbidity, and the findings on cancer-specific survival and overall survival were similar. However, we acknowledge this is a limitation of our study and made the following changes in the Discussion section.

Changes in the text:

The second limitation is the lack of information on patient's comorbidity and performance status, which can be important confounders of timely surgery. We alleviated the confounding effect from comorbidity and performance status by including only patients who received surgery and using cancer-specific survival as an outcome. Patients with severe comorbid conditions or poor performance status who were not eligible for surgery were excluded in the analysis. Cancer-specific survival is less likely to be confounded by other health conditions and comorbidities.

References:

1. Samson P, Patel A, Garrett T, Crabtree T, Kreisel D, Krupnick AS, et al. Effects of Delayed Surgical Resection on Short-Term and Long-Term Outcomes in Clinical Stage I Non-Small Cell Lung Cancer. Ann Thorac Surg. 2015;99(6):1906-12; discussion 13.
2. Bott MJ, Patel AP, Crabtree TD, Colditz GA, Kreisel D, Krupnick AS, et al. Pathologic Upstaging in Patients Undergoing Resection for Stage I Non-Small Cell Lung Cancer:

Are There Modifiable Predictors? Ann Thorac Surg. 2015;100(6):2048-53.

Reviewer D Comment 8: Was there any impact of the type of surgery on survival in the cohort? Do patients treated with lobectomy received earlier surgery compared to other patients?

Response: We thank the reviewer for the comment. In our data, 36.0% of patients receiving lobectomy or bilobectomy, compared to 33.7% of patients receiving more extensive surgery (lobectomy or bilobectomy with dissection of lymph nodes or pneumonectomy), undertook surgery within 1 month, but the frequency of receiving surgery in 2-<3 or ≥3 months from diagnosis were very similar in the two patient groups (19.1% vs. 19.9%, 12.2% vs. 12.1%, Table 1). Thus, patients receiving less extensive surgery did have shorter diagnosis-to-surgery interval (<1 month). However, as surgery type was controlled in the multivariable analyses, we believe the adjusted hazard ratios already took the effects from surgery type into account.

Reviewer D Comment 9: In summary, the clinical significance of the paper should be more emphasized and future efforts to earlier surgery highlighted. The nature of the problem is the organizational structure and possibilities for early surgery rather than lack of interest to timely operation. Please comment more on that aspect.

Response: We thank the reviewer for the suggestion. We added the following paragraph in the Discussion section.

Changes in the text:

Our findings emphasize the clinical importance of timely care for lung cancer, which has been considered as a practice gap (40). In addition to survival benefit, timely care can relieve patients' stress and anxiety, and improve quality of life. However, multiple diagnostic tests and consultations could make the timely lung cancer management challenging. Previous studies examined the effects of nurse-led care coordination (41), multidisciplinary clinics via telemedicine (42), and outpatient diagnostic process (43, 44) to shorten the time to active treatment. More recent studies proposed the target time window to improve timely care (34, 36). Based on these findings, how to overcome the institutional challenges to provide timely management is a priority for lung cancer care.

References from reviewer:

1. Hanna TP, King WD, Thibodeau S, Jalink M, Paulin GA, Harvey-Jones E, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. Bmj. 2020;371:m4087
2. K. Ramsden, J. Laskin, C. Ho, Adjuvant chemotherapy in resected stage II non-small cell lung cancer: evaluating the impact of dose intensity and time to treatment, Clin Oncol 27 (7) (2015) 394–400.
3. M. Salazar, J. Rosen, Z. Wang, et al., Association of delayed adjuvant chemotherapy with survival after lung cancer surgery, JAMA Oncol 3 (5) (2017) 610–619.
4. C.M. Booth, F.A. Shepherd, Y. Peng, et al., Time to adjuvant chemotherapy and survival in non-small cell lung cancer: a population-based study, Cancer 119 (6) (2013) 1243–1250.
5. B.Y. Wang, J.Y. Huang, W.H. Hung, et al., Impact on survival on interval between surgery

and adjuvant chemotherapy in completely resected stage IB-IIIA Lung cancer, PLoS ONE 11 (11) (2016) 1–10.

6. W.M. Szejniuk, M. Cekala, M. Bøgsted, et al. Adjuvant platinum-based chemotherapy in non-small cell lung cancer: The role of relative dose-intensity and treatment delay, Can Treat Res Commun. 2021 Jan 22;27:100318.

7. K. Rebanta et al. Bronchoalveolar Cancer. https://www.ncbi.nlm.nih.gov/books/NBK513281/