The Use of Bronchoscopy During the Coronavirus Disease 2019 Pandemic

CHEST/AABIP Guideline and Expert Panel Report

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Search strategy, PICO Question #1

Search Strategy

1. “Coronavirus AND bronchoscopy”
2. “COVID-19 and bronchoscopy”
3. “covid19 or COVID19 or COVID-19 AND powered air purifying respirator”
4. “covid19 or COVID19 or COVID-19 AND personal protective equipment”
5. “Coronavirus AND personal protective equipment”
6. “Coronavirus AND powered air purifying respirator”
7. “coronavirus AND N95”
8. “Covid19 or COVID19 or COVID-19 AND N95”
9. “Coronavirus or covid19 or COVID19 AND face shield”

PRISMA Diagram, PICO question #1

Records identified through database searching (n=167)

Records after duplicates removed, then screened by title (n=16)

Records excluded based on title or duplicates (n=151)

Records screened by abstract (n=16)

Records excluded based on abstract (n=13)

Records screened based on full text review (n=3)

Records excluded based on full text review (n=3)

Studies included in quantitative synthesis (n=0)

• Articles not available in English (n=1)
• Not addressing COVID-19 (n=1)
• Not addressing bronchoscopy (n=1)
Search strategy, PICO Question #2

<table>
<thead>
<tr>
<th>Search Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. “COVID-19 AND Diagnostic Specimen Collection”</td>
</tr>
<tr>
<td>2. “COVID-19 AND Nasal pharyngeal or oral swabs”</td>
</tr>
<tr>
<td>4. “COVID-19 test AND tracheal aspirate”</td>
</tr>
<tr>
<td>5. “COVID-19 test AND non-bronch Bal, Blind Bronchial sampling”</td>
</tr>
<tr>
<td>9. “H1N1 AND Risk of Aerosolization in Respiratory Procedures”</td>
</tr>
<tr>
<td>10. “Aerosol Generating procedures AND risk of transmission to health care workers”</td>
</tr>
</tbody>
</table>

PRISMA Diagram, PICO question #2

[Diagram showing the search strategy flow, from records identified through database searching, to records excluded based on full text review, and studies included in quantitative synthesis, along with reasons for exclusion such as: articles not available in English (n=1), review articles and opinions (n=13), single case report (n=0), lack of comparator group (n=4).]
Search strategy, PICO Question #3

Search Strategy

1. "COVID-19 AND N95"
2. "COVID-19 AND Surgical Mask"
3. "COVID-19 Protection of Health Care Workers"
4. "COVID-19 Asymptomatic patients"

PRISMA Diagram, PICO question #3

[Diagram showing the process of record selection and exclusion based on search strategy and full-text review criteria.]
Search strategy, PICO Question #4

Search Strategy

1. “COVID-19 AND community transmission”
2. “COVID-19 AND asymptomatic”
3. “COVID-19 AND bronchoscopy”
4. “COVID-19 test AND community transmission”
5. “COVID-19 test AND asymptomatic”
6. “COVID-19 test AND bronchoscopy”

PRISMA Diagram, PICO question #4

Records identified through database searching (n=53)
Records after duplicates removed, then screened by title (n=49)
Records excluded based on title (n=20)
Records screened by abstract (n=29)
Records excluded based on abstract (n=4)
Records screened based on full text review (n=25)
Studies included in quantitative synthesis (n=0)

Full-text articles excluded based on full text review (n=25)
- Articles not available in English (n=8)
- Review articles and opinions (n=9)
- Single case report (n=2)
- Lack of comparator group (n=6)
Search strategy, PICO Question #5

Search Strategy

1. Lung cancer AND treatment AND delay

PRISMA Diagram, PICO question #5

Records identified through database searching (n=1,557) using Pubmed: (Lung cancer) AND (treatment) AND (Delay)

Records after duplicates removed, eligible for screening by title (n=1,557)

Records after title screening removed, eligible for screening by abstract (n=76)

Records excluded based on title (n=1,481)

Records after abstract screening, eligible for full manuscript review (n=18)

Records excluded based on abstract (n=48)

Studies included in quantitative synthesis (n=13)
**Search strategy, PICO Question #6**

### Search Strategy

1. “COVID-19 AND viral shedding”
2. “COVID-19 AND transmission period”
3. “COVID-19 AND convalescence”
4. “COVID-19 AND bronchoscopy”

### PRISMA Diagram, PICO question #6

- Records identified through database searching (n=96)
  - Records after duplicates removed, then screened by title (n=90)
    - Records screened by abstract (n=39)
    - Records excluded based on title (n=51)
      - Records excluded based on abstract (n=15)
        - Records included in quantitative analysis (n=0)
          
          Full-text articles excluded based on full text review (n=24)
          - Articles not available in English (n=11)
          - Review articles and opinions (n=5)
          - Single case report (n=1)
          - Lack of comparator group (n=7)
Impact of Delay of Care on Lung Cancer Survival: Evidence review and methodologic considerations

The available evidence is often conflicting regarding the relationship between timeliness of care and outcome. Paradoxically, multiple studies reported that more timely care was associated with worse outcomes. These paradoxical results can be partly explained by residual confounding by indication. Essentially, patients with more-advanced or aggressive disease, as well as those presenting with critical complications of cancer (e.g., brain metastasis with altered mental status and impending herniation) are both more likely to receive timely care and less likely to survive than patients with less-advanced disease.

Many studies adjusted for cancer stage, either using multivariable models or by constructing different models for different stages. However, many did not consider that the impact of delay in care might vary by stage. Importantly, one study by Abrao did demonstrate a statistically significant interaction between stage, time to treatment, and survival time. Patients with stage II disease with delayed treatment had an increased risk of death (HR 3.08, p=0.04) while stage IV patients with delayed treatment had a decreased risk of death (HR 0.48, p<0.001).

Similarly, a study by Gomez used SEER-Medicare data to assess the impact of timely treatment (≤ 35 days from diagnosis to treatment) vs. delayed (>35 days). The investigators stratified patients based on disease stage and used separate models for each group. This method is effective when there is effect-measure modification (i.e., interaction) between stage, time to treatment, and survival. Like Abrao, they found that in patients with local disease, timely treatment was associated with decreased risk of death (HR 0.86, p<0.001). In patients with distant metastatic disease timely treatment was associated with increased risk of death (HR 1.35, p<0.001) during the first year, but this changed over time and after one year of survival early treatment became protective (HR 0.86, p=0.04).

Nadpara also used SEER-Medicare data to analyze survival stratified by stage and timely treatment but instead used the British Thoracic Society and RAND corporation definitions for timely care. Treatment delay was associated with a non-statistically significant difference in survival in early stage disease (3-year survival: timely vs. delayed stage I: 62% vs. 58%; stage II: 40% vs. 37%). In advanced disease treatment delay was associated with a statistically significant improvement in survival (3-year survival: timely vs. delayed stage III: 17% vs. 22%; stage IV: 4% vs. 9%). The findings from these three studies are consistent with possible confounding by indication for stage III and IV patients, with more
severely ill advanced stage patients being treated more rapidly while less severely ill patients wait, resulting in the observed effect measure modification.4,5,11

However, there is conflicting data. In a West Virginia Cancer Registry-Medicare study also by Nadpara, adjusted lung cancer mortality risk using a multivariable Cox model was decreased in patients receiving delayed care as opposed to timely care (HR 0.75, p<0.05).1 The authors state that stratified analysis by lung cancer type and stage failed to demonstrate any benefit for timely care, although the data are not shown in the report. Other studies that included multiple stages did not evaluate for effect measure modification and this may in part explain the conflicting and paradoxical findings.6,16

Several studies evaluated only patients undergoing surgical treatment.3,9,19-21 Three found no association between timeliness and survival.19-21 However, these results might have been biased toward the null by the exclusion of patients who did not undergo surgery because they had more-advanced disease caused by longer delays. A study by Yang and colleagues focusing solely on surgically treated squamous cell patients did find evidence of effect, depending on the length of the delay.3 In a study of 4,984 patients with squamous cell carcinoma undergoing surgical resection, patients who had surgery 38 days or more after diagnosis had worse 5-year survival than patients with earlier surgery.

Many studies suffered from two major problems. The first is the failure to adjust properly for changes in disease stage that resulted from delays in care. Even studies that stratified on stage suffer from this problem – specifically that a delay in care might result in a higher disease stage that was subsequently identified. If this higher stage was identified (e.g. by EBUS) then a patient who advanced in stage during the delay interval would be compared to patients who had a higher stage of disease to begin with but who had timely care. This in turn leads to paradox. For example, a patient with stage II disease has a delay in care and becomes stage III. At the time of surgery, single station N2 disease is identified, so the patient is now stage IIIA. This patient is compared to other stage IIIA patients. However, this patient is truly very early in their lifecycle of IIIA disease because they have just converted from stage II. The other patients with stage III disease represent a distribution from early to late within their stage IIIA lifecycle and will metastasize sooner, being further along in the process. Compared to other stage IIIA patients, this originally stage II patient with delayed care who now has stage IIIA disease really does have a survival advantage. It is not that delay of care is leading to a better outcome, but rather that delay of care is leading us to use a faulty comparator (i.e. stage III disease patients rather than a stage II patient).

The other methodologic issue is the origin of time. In many but not all of the studies cited, survival time is measured from the first day of treatment until death, although in some studies time zero is not clearly specified.5,6,9,16,18,22 But the proper origin of time is really time from symptoms or radiographic identification. Why? Consider two patients each with the same 0.5 cm lung nodule at time zero. Patient A
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elects for immediate surgery while patient B elects serial CT scans. Patient A survives three years from the time of surgery. Patient B undergoes surgery in one year when the nodule demonstrates growth and survives for two more years. If we measure survival from time of surgery patient A did better. However, in reality patient B lived just as long and probably had less disability, having the benefit of delaying surgery for a year. The proper origin of time for studies of delay in time-to-treatment is from initial radiographic identification or symptoms as opposed to time of treatment. If the origin of time is time of treatment, it introduces systematic bias that can lead to overestimating the benefit of early treatment. Similarly, depending on the population studied, even using time from tissue diagnosis (as opposed to radiographic nodule identification) may be problematic, since it would lead to the same type of bias. Methodologically, this makes estimating the impact of delays in diagnosis and treatment difficult.

Additional indirect support comes from studies of patients undergoing screening in Japan. Patients that did not follow up promptly had lower median survival which correlated with larger tumor size. A similar study found that patients undergoing chest radiography for screening who had a delay in lung cancer diagnosis of > 4 months from their initial abnormality had decreased survival. However, it is not clear in these reports whether time zero for survival analysis was the time of nodule identification (i.e. correct method) or time of treatment (i.e. biased method). The survival curves do not separate that much, such that a two- or three-month lead time bias introduced by choosing the wrong time zero (earlier treatment leading to more lead time) might account for much of the observed difference in survival. Conversely, if we evaluated survival from time of radiographic identification, it is likely that the survival curves would be more similar.

The best indirect proof of concept that delay may be harmful is the NLST which demonstrated a 20% reduction in lung cancer related mortality. This constitutes indirect evidence, because the population in the NLST was different than the population being addressed in this question. The NLST cohort consisted of high-risk patients without a known or suspected lung cancer. The NLST is really a study of interventions to identify nodules earlier, not a study of earlier treatment of nodules that have already been identified. However, the underlying concept of earlier treatment being better in patients with known or suspected disease is probably sound, although the magnitude of the effect probably varies significantly with clinical stage and cannot be precisely estimated from the data.
References:


*Online supplements are not copyedited prior to posting and the author(s) take full responsibility for the accuracy of all data.*


# e-Appendix 3- Evidence table for PICO question 5

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Impact of time delay on survival</th>
<th>Comments</th>
<th>Time zero definition used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonzalez-Barcala F, et al. 1</td>
<td>307</td>
<td>Decreased risk</td>
<td></td>
<td>Time from treatment implied but not specified</td>
</tr>
<tr>
<td>Yang CJ, et al. 2</td>
<td>4984</td>
<td>Increased risk</td>
<td>Surgical patients with squamous cell</td>
<td>Date of diagnosis</td>
</tr>
<tr>
<td>Vinod SK, et al. 3</td>
<td>1729</td>
<td>No effect</td>
<td></td>
<td>Not specified</td>
</tr>
<tr>
<td>Kanarek NF, et al. 4</td>
<td>174</td>
<td>Increased risk</td>
<td>Surgical patients</td>
<td>Time from first surgery</td>
</tr>
<tr>
<td>Gomez DR, et al. 5</td>
<td>28732</td>
<td>Increased risk in local disease, No effect in regional disease, decreased risk in distant disease within one year, increased risk after one year</td>
<td>Treatment? Implied but not explicit in online supplement</td>
<td></td>
</tr>
<tr>
<td>Samson P, et al. 6</td>
<td>27022</td>
<td>Increases risk in stage I patients</td>
<td>Surgical patients</td>
<td>not specified if it is diagnosis or treatment</td>
</tr>
<tr>
<td>Abrao FC, et al. 7</td>
<td>359</td>
<td>Increased risk in stage II patients; decreased risk in stage IV</td>
<td></td>
<td>Treatment start</td>
</tr>
<tr>
<td>Radzikowska E, et al. 8</td>
<td>3479</td>
<td>No effect</td>
<td>Small cell</td>
<td>Treatment time</td>
</tr>
<tr>
<td>Živković D, et al. 9</td>
<td>206</td>
<td>No effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadpara PA, et al. 10</td>
<td>1924</td>
<td>No effect</td>
<td>date of diagnosis</td>
<td></td>
</tr>
<tr>
<td>Nadpara PA, et al. 11</td>
<td>48850</td>
<td>Decreased risk in stage III and IV patients</td>
<td>date of diagnosis</td>
<td></td>
</tr>
<tr>
<td>Alanen V, et al. 12</td>
<td>221</td>
<td>Decreased risk</td>
<td>histologic dx if available, otherwise radiologic</td>
<td></td>
</tr>
<tr>
<td>Khorana AA, et al. 13</td>
<td>363863</td>
<td>Increases risk in stage I and II lung cancer</td>
<td>Treatment start</td>
<td></td>
</tr>
</tbody>
</table>
References


