Original Article

Time to surgery in thoracic cancers and prioritization during COVID-19: a systematic review

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Background: Coronavirus disease 2019 (COVID-19) has overwhelmed hospital resources worldwide, requiring widespread cancellation of non-emergency operations, including lung and esophageal cancer operations. In the United States, while hospitals begin to increase surgical volume and tackle the backlog of cases, the specter of a "second wave," with a potential vaccine months to years away, highlights the ongoing need to triage cases based upon the risk of surgical delay. We synthesize the available literature on time to surgery and its impact on outcomes along with a critical appraisal of the released triage guidelines in the United States.

Methods: We performed a systematic literature review using PubMed according to preferred reporting items for systematic reviews and meta-analyses guidelines evaluating relevant literature from the past 15 years.

Results: Out of 679 screened abstracts, 12 studies investigating time to surgery in lung cancer were included. In stage I–II lung cancer, delayed resection beyond 6 to 8 weeks is consistently associated with lower survival. No identified evidence justifies a 2 cm cutoff for immediate versus delayed surgery. For stage IIIa lung cancer, time to surgery greater than 6 weeks after neoadjuvant therapy is similarly associated with worse survival. For esophageal cancer, 254 abstracts were screened and 23 studies were included. Minimal literature addresses primary esophagectomy, but time to surgery over 8 weeks is associated with lower survival. In the neoadjuvant setting, longer time to surgery is associated with increased pathologic complete response, but also decreased survival. The optimal window for esophagectomy following neoadjuvant therapy is 6 to 8 weeks.

Conclusions: In the setting of the COVID-19 pandemic, timely resection of lung and esophageal cancer should be prioritized whenever possible based upon local resources and disease-burden.

Keywords: Time to surgery; lung cancer; esophageal cancer; surgical delay; cancer outcomes

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Introduction

Coronavirus disease 2019 (COVID-19) continues to strain global health systems with exponential spread and high morbidity. Parts of the United States were overwhelmed with the need to ration ventilators and other hospital resources. In order to maximize hospital capacity, the Centers for Disease Control and Prevention released interim guidance in March 2020 recommending rescheduling of elective surgical procedures and moving elective urgent procedures to the outpatient setting when

possible (1). The American College of Surgeons (ACS) subsequently echoed these recommendations and published specialty-specific guidelines to triage elective surgical cases in accordance with local conditions (2). As COVID-19 cases continue to escalate in the United States with over two million cases and one-hundred thousand deaths as of June 2020, elective surgical volume has plummeted—including for cancer operations. While states have begun to reopen and resume elective procedures, a large backlog of surgical cases requires ongoing prioritization and an impending "second wave" will continue to constrain surgical capacity.

For many forms of cancer, surgical resection remains the cornerstone and often first step of curative therapy. Delayed resection may result in further tumor growth, invasion, and metastasis. However, the effects of time to surgery for many cancers have not been well characterized and the "acceptable" wait time prior to worsened outcomes is unclear. Beyond oncologic outcomes, the formidable combination of a cancer diagnosis with delayed surgery creates immense mental and physical challenges for our patients. In the setting of unprecedented hospital strain expected to continue for at least months combined with the glut of accumulated cases needing to be scheduled, it is critical to understand which operations should be prioritized and which can be delayed with minimal risk. The Thoracic Surgery Outcomes Research Network published detailed guidance for lung and esophageal cancer that takes into account hospital resources, urgency of procedure, and potential alternative management strategies. Phase I comprises largely maintained hospital resources and minimal burden from COVID-19, while phases II and III represent significant burden and all surgical procedures are delayed except for conditions threatening survival within days or hours, respectively (3). No previous systematic review has evaluated the impact of time to surgery in lung cancer or in primarily-resected esophageal cancer.

We seek to synthesize the available data on time to surgery and its impact on outcomes in adult patients, in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-analyses (PRISMA) checklist, providing an evidence-based approach to prioritization of lung and esophageal cancer surgery during the COVID-19 pandemic, along with a critical appraisal of the released guidelines.

Methods

Identification of studies

This systematic review follows the PRISMA checklist (available at http://dx.doi.org/10.21037/jtd-20-2400) (4). We identified studies that evaluated time to surgery with oncologic outcomes. The PubMed database was searched from January 1, 2005 to March 23, 2020 according to the predefined search strategy; specific search terms are below: ((“lobectomy” OR “lung resection” OR “pulmonary resection”) AND (“delay” OR “time to surgery” OR “time-to-surgery” OR “timing” OR “time to treatment” OR “time-to-treatment”)) OR (“lung cancer” AND “surgery” AND (“time to surgery” OR “time-to-surgery” OR “timing” OR “delay”)); ((“esophagectomy” OR “esophageal resection”) AND (“delay” OR “time to surgery” OR “time-to-surgery” OR “timing” OR “time to treatment” OR “time-to-treatment”)) OR (“esophageal cancer” AND “surgery” AND (“Time to surgery” OR “time-to-surgery” OR “timing” OR “delay”)).

For each cancer, two authors independently and in duplicate conducted an electronic literature search, screening of eligible records, review of potentially relevant complete articles, and evaluation for inclusion. The reference lists of all included studies were hand-searched for additionally potentially relevant articles.

Study inclusion and data extraction

Studies were eligible for inclusion if they evaluated the effect of time to surgery on pathologic upstaging or response, disease-free survival, or overall survival. Studies were excluded if they did not separate patients who received surgical treatment from other treatments, if they were not written in English, or if they included patients under 18. The following data were extracted using a predefined extraction form: first author, publication year, study design, number of patients, patient population, neoadjuvant therapy, age, matching/multivariate analysis, outcome measure, time to surgery groups, length of follow up, and summary findings. When given, odds ratios or hazard ratios were extracted.

Assessment of quality and bias

Levels of evidence were assigned according to the Oxford Centre for Evidence-Based Medicine (5). We utilized the Newcastle-Ottawa Scale to evaluate potential bias for observational studies. Ranging from zero to nine, the scale evaluates patient selection, comparability of patient populations, and outcome assessment (6). Both the level of evidence and the Newcastle-Ottawa Scale were assessed

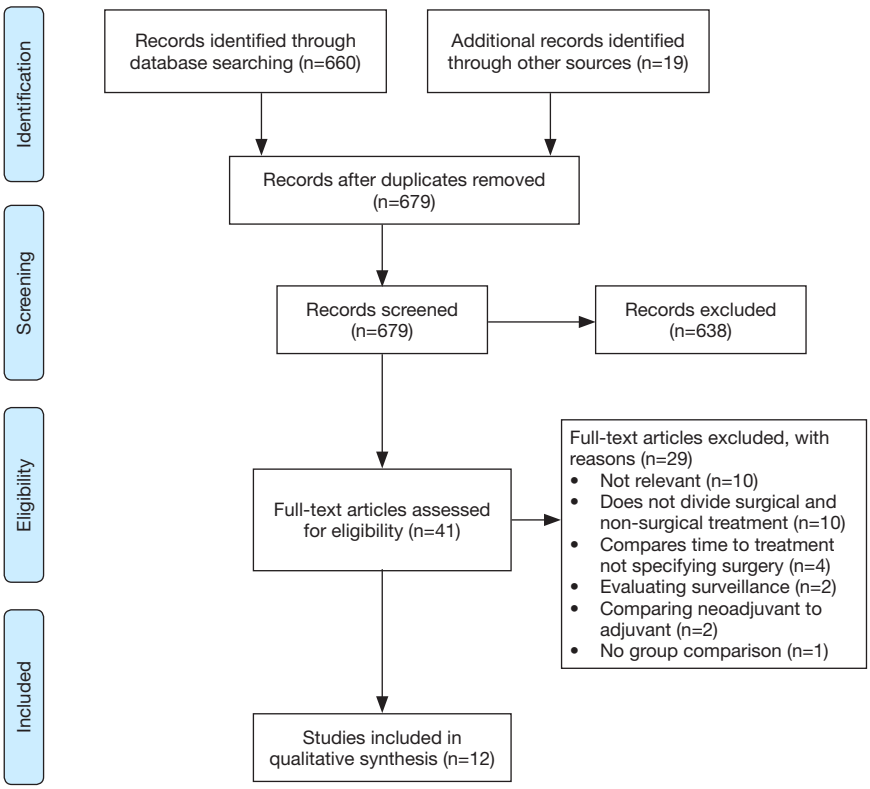

Figure 1 Inclusion flow diagram for time to surgery in lung cancer.

independently by two reviewers and disagreements were resolved through discussion.

Results

Lung cancer

A total of 679 abstracts were identified from the search strategy, with 660 from PubMed and an additional 19 abstracts identified through reference list review. A total of 41 full text articles were evaluated and 12 papers met the criteria to evaluate whether surgical delay affects outcomes in lung cancer (*Figure 1*). Extracted data for included studies are found in *Table 1*. Included studies predominantly involved early (stage I–II) non-small cell lung cancer (NSCLC), with two papers including all stages of disease and two specifically focusing on Stage IIIa. Nine studies evaluated primary resection, while three papers focused on surgery after neoadjuvant chemoradiotherapy. Most studies evaluated overall survival, two investigated overall survival and upstaging, and four only studied upstaging. All studies were retrospective cohort studies, with a combination of national database use and single-institution experiences. Most studies evaluated time to surgery greater than 4 to 8 weeks, with four studies evaluating a period greater than three months.

Three large studies evaluated stage I NSCLC utilizing the National Cancer Database (NCDB), demonstrating increased upstaging and worse survival with increasing time to surgery (7,15,17). Bott *et al.* found that time to surgery greater than 8 weeks was associated with pathologic upstaging (OR 1.10, 95% CI: 1.03–1.16) (7). Samson *et al.* evaluated the same population with propensity matching, demonstrating that surgical delay over 8 weeks is associated with pathologic upstaging (P=0.002) although the absolute difference was small (pathologic stage over 1, 16.6% *vs.* 18.3%, P=0.002). Further, they found that surgical delay was associated with increased 30-day mortality (2.4% *vs.* 2.9%, P=0.01) and decreased overall survival (69.2 *vs.* 57.7 months). Finally, Yang *et al.* specifically evaluated stage Ia patients finding a time to surgery greater than 38 days was associated with decreased five-year survival (HR 1.13,

Table 1 Summary of included studies for lung cancer

Study	Level of evidence	Quality score	Number	Population	Age (years)	Outcome measure	Time to surgery/ delay groups	Follow up	Worse outcome	Summary finding
Bott *et al.*, 2015 (7)	2b	8	55,653	Stage I NSCLC	68.1±10.0	Upstaging	±8 weeks	NS	Yes	Upstaging: >8 weeks OR 1.10 (1.03–1.16)
Coughlin *et al.*, 2015 (8)	2b	7	222	Stage I or II NSCLC	Mean 64–69 depending on group	Upstaging, OS	<1, ≥1–2, ≥2–3, ≥3–4 months	Stage I: 30±11 months; Stage II: 26±13 months	Yes	Upstaging: no difference; OS: Stage I ND, Stage II: ≥2–3 months *vs.* <1 HR 3.6 (1.09–12.09)
Gao *et al.*, 2016 (9)	2b	8	1,623	T1–3N2 NSCLC with nCRT	Mean 60.3–61.2 depending on TTS	OS	0–3, >3 to ≤6, >6 to ≤9, >9 to ≤ 12 weeks	NS: 5-year survival	Yes	OS: 0–3 weeks ref; >3–6 weeks, HR 1.26 (0.94–1.67); >6–9 weeks, HR 1.33 (1.01–1.76); >9–12 weeks, HR 1.02 (1.01–1.02)
Kanarek *et al.*, 2014 (10)	2b	8	174	Stage I–II NSCLC	NS: 61%>65	OS	±6 weeks	>3 years	Yes	OS: each additional week: HR 1.05 (1.01–1.09)
Liberman *et al.*, 2006 (11)	2b	5	256	Stage I–IV NSCLC	Mean 65.3 (SD 10.2)	Upstaging	Continuous variable	None	No	Symptoms to surgery: OR 1.00 (0.999–1.001); surgeon to surgery: OR 1.00 (0.997–1.002)
Maiga *et al.*, 2017 (11)	2b	7	265	Suspected lung cancer with resection	Median 66 (range, 60–72)	Upstaging	≤60, >60 days	None	No	Upstaging: ≤60 *vs.* >60 days, 22% *vs.* 30% (P=0.278)
Marulli *et al.*, 2018 (12)	2b	8	231	NSCLC cT1–3N0	Median 68 (IQR 62–74)	Upstaging	PET/CT to surgery <31, 31–60, >60 days	None	No	Nodal upstaging: no association with TTS (P=0.470)
Odell *et al.*, 2019 (13)	2b	6	240,680	NSCLC pN1-2 with nCRT	NS	OS	±120 days	NS	Yes	OS: <120 days ref; >120 days HR 1.17 (1.07–1.27)
Rice *et al.*, 2020 (14)	2b	8	5,946	NSCLC stage IIIa with nCRT	Median 63 (range, 56–69)	OS	<77, 77–114, >114 days	NS: 3-year survival	Yes	OS: <77 days ref; 77–114 days, HR 1.073 (0.964–1.195); >114 days, HR 1.25 (1.103–1.416)
Samson *et al.*, 2016 (15)	2b	9	55,653	NSCLC stage I	Mean 68.8, SD: 9.8	Upstaging, OS	±8 weeks	NS	Yes	Upstaging: <8 *vs.* ≥8 weeks, 16.6% *vs.* 18.3% (P<0.001); OS: <8 *vs.* ≥8 weeks, 69.2 *vs.* 57.7 months (P<0.001)
Shin *et al.*, 2013 (16)	2b	6	398	Locoregional NSCLC	Mean 63.5, SD: 8.7	OS	≤1, >1 to 4, >4 to 8, >12 weeks	Median 4.7 years	No	OS: >1–4 weeks ref; <1 week, HR 1.13 (0.77–1.66); >4–8 weeks, HR 1.05 (0.67–1.65); >8–12 weeks, HR 0.65 (0.28–1.48); >12 weeks, HR 0.79 (0.42–1.48)
Yang *et al.*, 2017 (17)	2b	8	4,984	NSCLC stage IA	Median 70 (IQR 64–76)	OS	±37 days	Median 32 months	Yes	OS: >37 days HR 1.13 (1.02–1.25)

HR, hazard ratio; IQR, interquartile range; nCRT, neoadjuvant chemoradiotherapy; NSCLC, non-squamous cell lung cancer; NS, not stated; OR, odds ratio; OS, overall survival; ref, reference group; TTS, time to surgery;

95% CI: 1.02–1.25) (17).

Several single institution studies also evaluated early stage lung cancer. Coughlin *et al.* found in patients with stage I lung cancer, time to surgery up to four months was not associated with upstaging or worse survival, but in patients with stage II lung cancer (n=42) there was increased upstaging and worse survival for time to surgery over 2 months. However, this was an unadjusted analysis with very broad confidence intervals (mortality HR: 3.6, 95% CI: 1.09–12.09) (8). Kanarek *et al.* had similar findings with each additional week to surgery increasing mortality (additional week HR: 1.04, 95% CI: 1.00–1.09), although a delay greater than the predefined six-week cut off did not reach significance (10).

For stage IIIa disease, several studies used the NCDB and found that increased time to surgery after neoadjuvant therapy worsens survival. Gao *et al.* evaluated 1,623 patients and subdivided time to surgery after neoadjuvant chemoradiotherapy into 3-week intervals. Compared to the immediate surgery group (0 to 3 weeks), time to surgery of 6 to 9 weeks was associated with worse overall 5-year survival (30.2% *vs.* 19.6%, HR 1.45, 95% CI: 1.04–2.01). The three to 6-week group trended towards worse overall survival, but this was not significant (30.2% *vs.* 22.6%, HR 1.26, 95% CI: 0.94–1.67) (9). Rice *et al.* divided 5,946 patients into three groups divided by the interquartile range, with a short delay group under 77 days and a long delay group over 114 days after neoadjuvant therapy. Notably, they did not exclude patients who underwent chemotherapy or radiotherapy alone, and more patients in the mid and long delay groups had chemotherapy alone. They found decreased three-year overall survival in patients that surgery was delayed over 114 days compared to patients that underwent surgery within 77 days after neoadjuvant chemoradiotherapy after multivariate adjustment (short 59% *vs.* long 52%, HR 1.25, P=0.0005) (14). Finally, Odell *et al.* investigated compliance with Commission on Cancer lung quality measures, finding that delaying surgery for over 120 days is associated with worse survival (HR 1.17, 95% CI: 1.07–1.27) (13).

Many of the included studies do not specify the maximum length of delay which may impact the outcomes of their studies if patients with very long delays are included. Furthermore, very few papers discuss the reason for delay given inherent limitations in database studies. Of studies that found a worse outcome with surgical delay, those that clearly discussed the length of delay include the following. In Coughlin *et al.*, all of the patients included had surgery within four months for stage I disease, and within three months for stage II disease. For patients with stage I disease, 77% of those with a delay of 3 to 4 months were delayed due to OR availability (8). In Gao *et al.*, delays longer than 12 weeks were not included (9). Kanarek *et al.* reported the upper bound of the 95% CI for referral to surgery as 74 days (10). Samson *et al.* did not provide a maximum delay, but provided the interquartile range for the longer delay group as 64–102 days (15). Similarly, Yang *et al.* stated that 95% of resections occurred within 4 months of diagnosis (17).

Esophageal cancer

In total, 254 abstracts were identified from the search strategy, with 248 from PubMed and an additional six abstracts identified through reference list review. Twenty-seven full papers were reviewed and ultimately 23 papers met the criteria to evaluate whether surgical delay affects outcomes in esophageal cancer (*Figure 2*). Extracted data for included studies are found in *Table 2*. Only four studies evaluated primary esophagectomy with the remainder evaluating surgery after neoadjuvant therapy. All included studies were retrospective cohort studies with one utilizing propensity matching. Several included studies involved multiple centers and many utilized national databases.

Four articles examined time to surgery in primary esophagectomy, with only one study reaching significance. Raman *et al.* used the NCDB to evaluate patients with cT1N0M0 esophageal adenocarcinoma (28). There was no association between time to surgery quartiles and overall survival; however, in continuous modeling time under 50 days was associated with improved survival (HR 0.991, 95% CI: 0.984–0.997) and time to surgery over 100 days was associated with worse survival (HR 1.003, 95% CI: 1.001–1.006) (28). Visser *et al.* (in 2017) utilized the Netherlands Cancer Registry. In the surgery-only subgroup, time to surgery greater than 8 weeks was not significantly associated with pathologic upstaging or worse survival (HR: 1.00, 95% CI: 0.82–1.23) (39). Two small institutional studies were also included, with Visser *et al.* (2016) being the higher quality study. This study suggested worse overall survival with each additional week of delay, also not reaching significance (HR 1.06, 95% CI: 0.99–1.13) (38).

The remainder of the studies investigated time to surgery after neoadjuvant therapy. Only four studies found an association between surgical delay and worse outcome. Three of these were large studies utilizing the

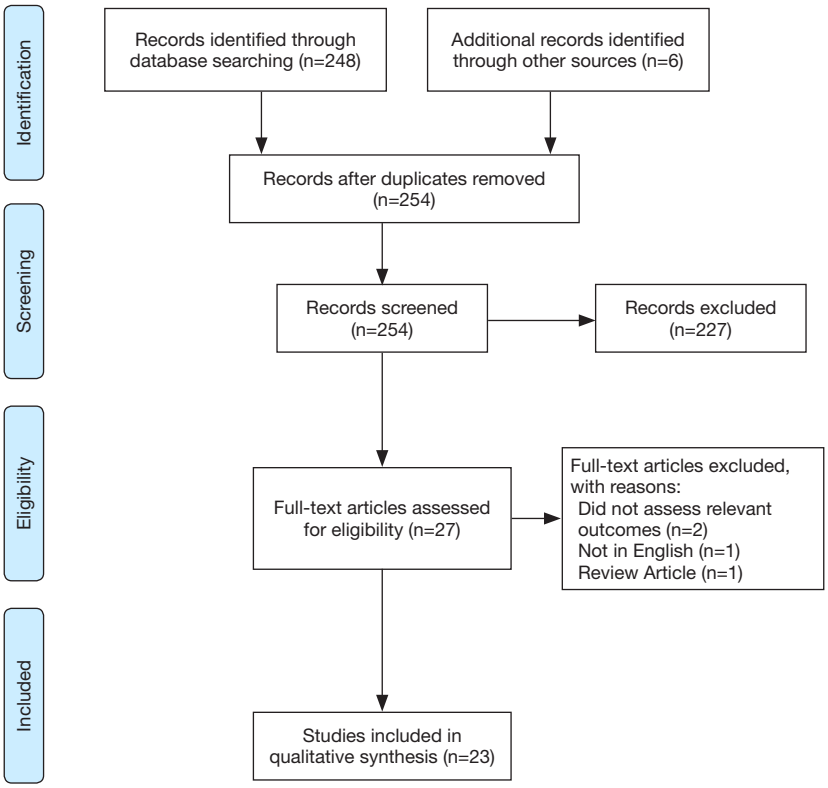

Figure 2 Inclusion flow diagram for time to surgery in esophageal cancer.

NCDB. Ranney *et al.* evaluated patients with stage II or III esophageal adenocarcinoma who underwent neoadjuvant chemoradiotherapy followed by surgery before or after 56 days. While patients in the over 56-day group had greater pathologic downstaging (OR 1.38, 95% CI: 1.02–1.85), they also demonstrated worse overall survival (HR 1.44, 95% CI: 1.22–1.71) (29). Lee *et al.* also used the NCDB but included both adenocarcinoma and squamous cell carcinoma, dividing patients into four-time intervals (40 days or less, 41–50, 51–63, >64). Similarly, a time interval greater than 64 days was associated with greater pathologic complete response (OR 1.53, 95% CI: 1.19–1.98) but worse overall survival (HR 1.16, 95% CI: 1.01–1.33) (27). Franko *et al.* (in 2016) evaluated adenocarcinoma and found that time to surgery over 9 weeks was associated with decreased survival (HR 1.19, 95% CI: 1.03–1.38) (19). The remaining study was Wang *et al.*, who using the Taiwan Cancer Database found that time to surgery over 90 days was associated with worse overall survival, compared to 30–59 days (HR 2.01, 95% CI: 1.14–3.54) (40). Of these studies demonstrating worsened survival with surgical delay, the maximum length of delay was provided in all of them. Ranney *et al.* excluded patients with esophagectomy over 90 days from nCRT (29). Lee *et al.* had a maximum delay of 210 days, but importantly demonstrated worsened survival in the 41–50 and 51–63 days subgroups compared to the reference of 40 days or less–negating the impact of extreme delays on survival (27). Franko *et al.* excluded patients with surgery after 26 weeks (19). Similarly, Wang *et al.* excluded patients with delay over 180 days (40).

The remaining articles did not find an association between surgical delay and worse outcomes in patients receiving neoadjuvant chemotherapy. Of the thirteen studies evaluating pathologic complete response, five showed improvement with delayed resection ranging from 45 days to 13 weeks (23,27,31,32,36). van der Werf *et al.* was a well-designed multicenter retrospective cohort study that included 3,102 patients. They differentiated between esophageal adenocarcinoma and squamous cell carcinoma and examined intervals from under 5 weeks to over 15 weeks. For patients with adenocarcinoma and squamous cell carcinoma, an interval of more than 10 weeks and more than 13 weeks respectively was associated with a higher probability of pathologic complete response. Unfortunately,

Table 2 Summary of included studies for esophageal cancer

Study	Level of evidence	Quality score	Number	Population	Age (years)	Outcome measure	Time to surgery/ delay groups	Follow up	Worse outcome	Summary finding
Chiu *et al.*, 2013 (18)	2b	7	276	Esophagectomy after nCRT	≤8 weeks: 56.8; >8 weeks: 53.5	pCR, OS	±8 weeks	Yes	No	pCR: ≤8 weeks 26%, >8 weeks 20% (P=0.16); OS: ≤8 weeks 29% >8 weeks 23% (P=0.3)
Franko *et al.*, 2016 (19)	2b	8	4,284	Esophagectomy after nCRT	60±9.4	OS	<5, ≥5–7, ≥7–9, ≥9 weeks	41 months	Yes	OS: <5 weeks ref; ≥5–7 weeks HR 1.001 (0.869–1.154); ≥7–9 weeks HR 0.991 (0.856–1.148); ≥9 weeks HR 1.194 (1.032–1.380)
Franko *et al.*, 2018 (20)	2b	8	1,244	Esophagectomy after nCRT	Mean 60.5	OS	Continuous interval	NS: 5-year survival	No	OS: TTS does not affect survival (P=0.769)
Furukawa *et al.*, 2018 (21)	2b	7	134	Esophagectomy after nCRT	NS	DFS, OS	±8 weeks	NS: 5-year survival	No	DFS and OS did not significantly differ between the two groups (P=0.2)
Grotenhuis *et al.*, 2010 (22)	2b	6	491	Primary esophagectomy	Median 65	OS	From symptoms ±3 months; from diagnosis <5, 5–8, >8 weeks	NS: 5-year survival	No	OS: from symptoms ≤3 *vs.* >3 months: 24% *vs.* 29.3% (P=0.10); from diagnosis <5 *vs.* 5–8 *vs.* >8 weeks: 24.7% *vs.* 21.7% *vs.* 32.3% (P=0.12)
Haisley *et al.*, 2016 (23)	2b	8	234	Esophagectomy after nCRT	Median age 64 (IQR 58–70)	pCR, OS	0–42, 43–56, 57–70, 71–84, 85–98, >99 days	NS	No	pCR 85–98 *vs.* 0–42 days: OR 5.46 (1.16–25.68); OS: no difference between groups
Kathiravetpillai *et al.*, 2016 (24)	2b	7	190	cT1–3N0–3M0 with esophagectomy after nCRT	NR	pCR, OS	±8 weeks	NS: 5-year survival	No	pCR: ≤8 *vs.* >8 weeks: 31.1% *vs.* 25.6% (P=0.43); OS: ≤8 *vs.* >8 weeks: 42% *vs.* 37% (P=0.430)
Kim *et al.*, 2012 (25)	2b	6	266	Esophagectomy after nCRT	≤8 weeks mean 57; >8 weeks mean 60	pCR, OS	±8 weeks	Median 55 months	No	pCR: ≤8 *vs.* >8 weeks: 21% *vs.* 22% (P=0.79); OS: ≤8 weeks *vs.* >8 weeks 53 *vs.* 39 months (P=0.23)
Klevebro *et al.*, 2019 (26)	2b	8	643	Esophagectomy after nCRT with esophageal/GEJ cancer	Median: ≤49 days: 64; >49 days: 65	pCR, OS	±49 days	NS: 5-year survival	No	pCR: >49 days: 0.99 (0.64–1.53); OS: >49 days: HR 0.99 (0.79–1.24)

Table 2 (*continued*)

Table 2 (*continued*)

Study	Level of evidence	Quality score	Number	Population	Age (years)	Outcome measure	Time to surgery/ delay groups	Follow up	Worse outcome	Summary finding
Lee *et al.*, 2016 (27)	2b	8	5,393	Esophagectomy after nCRT	Median 62 (range, 20–89)	pCR, OS	≤40, 41–50, 51–63, ≥64 days	NS: 8-year survival	Yes	pCR: ≤41 days: ref; 41–50 days: OR 1.23 (0.95–1.61); 51–63 days: OR 1.42 (1.09–1.84); ≥64 days: OR 1.53 (1.19–1.98); OS: ≤41 days: ref; 41–50 days: HR 0.97 (0.84–1.11); 51–63 days: HR 1.05 (0.91–1.20); ≥64 days: HR 1.16 (1.01–1.33)
Raman *et al.*, 2019 (28)	2b	7	2,495	cT1N0M0 esophageal adenocarcinoma with primary surgery	Median: <50 days: 64; 50–100 days: 66, >100:65	OS	<50, 50–100, >100 days	NS: 5-year survival	Yes	OS: <50 days: HR 0.99 (0.98–1.00); 50–100 days: ref; >100 days: HR 1.00 (1.00–1.01)
Ranney *et al.*, 2017 (29)	2b	7	2,444	Stage II or III with Esophagectomy after nCRT	Median age 61 (IQR: 55–67)	Downstage, OS	±56 days	NS: 5-year survival	Yes	Downstaging: ≥56 days: OR 1.38 (1.02–1.85); OS ≥56 days: HR 1.44 (1.22–1.71)
Ruol *et al.*, 2010 (30)	2b	7	129	Esophagectomy after nCRT	Median 60.4	OS	≤30, 31–60, 61–90 days	NS: 5-year survival	No	OS: 5-year survival ≤30 days: 0%; 31–60 days: 43%; 61–90 days: 35.9% (P=0.13)
Shaikh *et al.*, 2015 (31)	2b	6	88	Esophagectomy after nCRT	61 (range, 36–80)	pCR, OS	26–45, 46–50, 51–63, ≥64 days	Median 87.7 months	No	pCR: ≤45 days ref; 46–50 days: OR 1.75 (0.34–8.95); 51–63 days: OR 2.06 (0.43–9.87); ≥64 days: OR 4.85 (1.11–21.26); OS: no difference in OS between groups (P=0.24)
Shapiro *et al.*, 2014 (32)	2b	7	325	Esophagectomy after nCRT	60 (IQR: 55–67)	pCR, DFS, OS	Continuous interval	NS: 5-year survival	No	pCR: each add. weeks >45 days OR 1.35 (P=0.0004); DFS: each add. weeks HR 0.98 (P=0.620); OS: each add. weeks HR 1.03 (P=0.465)
Singla *et al.*, 2018 (33)	2b	7	226	Esophagectomy after nCRT	Mean 61	pCR, OS	±50 days	Median 52 months	No	OS: ≤50 *vs.* >50 days: 48.9 *vs.* 42.6 months (P=0.73); pCR: ≤50 *vs.* >50 days: 26.9% *vs.* 19% (P=0.24)
Tessier *et al.*, 2014 (34)	2b	7	257	Esophagectomy after nCRT	Median: 59 (range, 38–77)	pCR, OS	±7 weeks	Median 28.4 months	No	pCR: ≥7 weeks: OR 0.8 (0.5–1.4); OS: ≥7 weeks OR 1.0 (0.7–1.4)

Table 2 (*continued*)

Table 2 (*continued*)

Study	Level of evidence	Quality score	Number	Population	Age (years)	Outcome measure	Time to surgery/ delay groups	Follow up	Worse outcome	Summary finding
Tsang *et al.*, 2017 (35)	4	6	107	Esophagectomy after nCRT	Mean ≤64 days: 61; >64 days: 66	pCR, OS	±64 days	NS: 5-year survival	No	pCR ≤64 *vs.* >64 days: 35% *vs.* 24.5% (P=0.23); OS: ≤64 *vs.* >64 days: 61.5% *vs.* 46.2% (P=0.09)
van der Wilk *et al.*, 2018 (36)	2b	8	3,102	Esophagectomy after nCRT	NS	pCR	0–5, 6–7, 8–9 ,10–12, 13–14, >15 weeks	No	No	pCR: >10 *vs.* <5 weeks for adenocarcinoma OR 1.35 (1.00–1.95); >13 *vs.* <5 weeks for squamous cell carcinoma OR 2.86 (1.23–6.65)
van der Wilk *et al.*, 2019 (37)	4	7	98	Esophagectomy after nCRT with pCR, active surveillance *vs.* immediate surgery	Median age: delay: 72; immediate: 70	DFS, OS	Delay: mean 10 months; immediate: mean 3 months	NS: 3-year survival	No	DFS: delayed resection: HR 1.08 (0.44–2.67); OS: delayed resection: HR 0.41 (0.14–1.20)
Visser *et al.*, 2016 (38)	2b	7	137	Primary esophagectomy (subgroup of study)	Mean 64±9.9	DFS, OS	Continuous interval	56 months	No	DFS: TTS HR 1.03 (0.95–1.12); OS: TTS HR 1.06 (0.99–1.13)
Visser *et al.*, 2017 (39)	2b	8	1,250	Primary esophagectomy (subgroup of study)	Mean 65±9.5	Upstaging, OS	≤5, 5–8, ≥8 weeks	Median 78 months	No	Upstaging: No effect; OS: ≤5 weeks: ref; 5–8 weeks: HR 0.92 (0.76–1.13); ≥8 weeks: HR 1.00 (0.76–1.13)
Wang *et al.*, 2015 (40)	2b	6	665	Esophagectomy after nCRT	54±9.4	OS	<30, 30–59, 60–89, >90 days	NS: 3-year survival	Yes	OS: <30 days: HR 1.15 (0.71–1.86); 30–59 days: HR ref; 60–89 days: HR 0.89 (0.57–1.37); ≥90 days: HR 2.01 (1.14–3.54)

NS, not stated; OR, odds ratio; HR, hazard ratio; TTS, time to surgery; DFS, disease-free survival; OS, overall survival; ref, reference group; nCRT, neoadjuvant chemoradiotherapy.

they did not examine overall survival or disease-free survival (36). Franko *et al.* (in 2018) investigated squamous cell carcinoma in the NCDB with time to surgery greater than 9 weeks not associated with worse survival (20). Klevebro *et al.* utilized the Swedish National Register for Esophageal and Gastric Cancer, evaluating patients with time to surgery greater than or less than 49 days. There was no difference in histological response or on overall survival (HR 0.99, 95% CI: 0.79–1.24) (26).

Discussion

Lung cancer

There are no clear guidelines for surgical timing in lung cancer. The National Comprehensive Cancer Network (NCCN) recommends not delaying surgical resection beyond 60 days following completion of clinical staging to prevent upstaging, but does not specify a time from diagnosis to surgery (41). The ACS Commission on Cancer recommends surgery after neoadjuvant chemotherapy occur within 120 days (42). Guidelines for triage of lung cancer surgery during the COVID-19 pandemic highlight different "phases" based upon hospital resources and COVID-19 prevalence. In "Phase I" when capacity is largely preserved, immediate surgery is recommended for solid or predominantly solid lung cancers over 2 cm, node positive cancers, and cancer post neoadjuvant therapy. This is based upon the evaluation of whether survival is "likely to be compromised by surgical delay of 3 months." Cases that are recommended to be deferred include solid nodules or lung cancer under 2 cm, predominantly ground glass nodules or cancers, and tumors with indolent histology (3).

Based upon the accumulated evidence, diagnosed, or suspected stage I and II lung cancer should be resected as soon as possible, and no later than 6 to 8 weeks after diagnosis depending on local conditions. Moderate evidence exists that time to surgery beyond this time increases mortality, with mixed evidence for effect on pathologic upstaging. Importantly, there is no evidence to support a distinction of 2 cm for whether resection of lung cancer should be performed immediately or may be delayed 3 months, as suggested in the ACS guidelines and the Thoracic Surgery Outcomes Research Network guidelines. In the one study specifically evaluating stage Ia lung cancer, a delay over 38 days was associated with worse mortality (17). Even subcentimeter lung cancers are at 10% risk for nodal involvement when solid, highlighting the importance of early resection (43). For stage IIIa lung cancer, evidence consistently shows delayed resection following neoadjuvant therapy is associated with lower survival. Of the included studies, the earliest delay associated with worse survival was greater than 6 weeks (9). These findings support timely resection as stated in the guidelines.

Suspected tumors with low malignant potential, such as suspected adenocarcinoma-in-situ or minimally-invasive adenocarcinoma, could likely be safely deferred with imaging to reassess for progression at three to 6-month intervals, in agreement with the aforementioned guidelines (44). Tumors with ground-glass opacities may also be safely delayed with serial imaging due to their improved prognosis and less aggressive nature. Imaging characteristics—such as consolidation relative to tumor diameter (CTR)—should be used to stratify the risk of aggressive disease and direct clinical decision making in ground-glass opacities on an individualized basis. In a retrospective cohort study, patients with ground-glass opacities with a CTR of 0 had a 4% risk of aggressive cancer, compared to patients with a CTR >25% who had a 70% risk of aggressive cancer (45).

Esophageal cancer

During the COVID-19 pandemic, the ACS and Thoracic Surgery Research Outcomes Network recommend immediate surgery for esophageal cancer stage Ib or greater and esophageal cancer post neoadjuvant therapy, while suggesting endoscopic therapy for amenable early stage Ia/b cancers (3). Esophageal cancer represents an aggressive malignancy and resection typically follows neoadjuvant therapy except in the earliest stage. Fittingly, most of the existing literature evaluates time to surgery following neoadjuvant therapy. In early esophageal cancer, minimal evidence exists regarding the impact of surgical delay on outcomes. The existing evidence suggests that prolonged time to surgery over 8 weeks may results in decreased survival, thus resection should not be delayed when possible.

The data for time to surgery following neoadjuvant therapy are mixed. A recent meta-analysis evaluating optimal time to esophagectomy following neoadjuvant chemoradiation demonstrated that time to surgery greater than seven to 8 weeks improved pathologic complete response (RR 1.13, 95% CI: 1.05–1.21) but decreased overall survival (RR 0.88, 95% CI: 0.82–0.95) (46). Our findings agree with this analysis: some evidence suggests a time to surgery of greater than 6 to 9 weeks following neoadjuvant therapy is associated with lower

survival; however, greater delay improves the likelihood of pathologic complete response. Therefore, the optimal window for surgery after neoadjuvant therapy seems to be approximately 6 to 8 weeks. An important consideration during the COVID-19 pandemic is that there is some evidence of potential equivalence of definitive chemoradiation to trimodality therapy for overall survival, although salvage esophagectomy has increased complication risk (47,48). In the setting of severe resource strain this should be considered.

Considerations during the COVID-19 pandemic

The COVID-19 pandemic presents unique challenges for triage of lung and esophageal surgery. The oncologic considerations–how quickly should we operate before progression and decreased survival–must be weighed among other considerations. Recently published literature investigating outcomes of perioperative COVID-19 infection in an international multicenter cohort study of 1,128 patients demonstrated 23.8% 30-day mortality with 51.2% experiencing pulmonary complications (49). Importantly, COVID-19 infection was only diagnosed preoperatively in 26.1% of patients likely due to the large portion of emergency surgery in this group, although early infection or nosocomial infection postoperatively may also contribute. While many patients underwent emergency surgery and there was no control group, these findings are clearly concerning for high perioperative risk. Thoracic surgery patients undergoing either pulmonary or esophageal resection, who may already be deconditioned from neoadjuvant therapy or from malignancy, have little physiologic reserve for pulmonary complications and COVID-19 infection perioperatively would be devastating. In addition to routine preoperative COVID-19 screening, hospitals must implement strict infection control procedures to minimize the risk of nosocomial infections in this high-risk population.

While some recommendations for managing cancer during the COVID-19 pandemic include consideration of neoadjuvant therapy (instead of primary resection) or extension of neoadjuvant therapy (to delay surgery), this is not without additional risks that are difficult to quantify. In the setting of an overwhelmed hospital system with a high COVID-19 burden, neoadjuvant therapy may allow surgical resection to be delayed with decreased oncologic risk (i.e., the risk of cancer progression or decreased cancer-specific survival) and decreased risk of nosocomial infection in the perioperative period. However, immunosuppression during a pandemic carries the additional risk of infection or severe COVID-19 illness if contracted and neoadjuvant therapy still requires frequent interactions with the healthcare system.

Additional considerations include system-based factors involving the allocation of limited resources. The backlog of delayed surgical procedures is expected to last at least months with a return to normal volume, although additional surges of COVID-19 will continue to impact available resources on a local and regional level. Other high-acuity cancer operations, as well as urgent procedures for benign disease, will compete for scheduling. Furthermore, the risk to the workforce should be minimized. Joint guidelines from the ACS, the American Society of Anesthesiologists, the Association of perioperative Registered Nurses, and the American Hospital Association for reopening provide a roadmap involving assessment of local conditions, COVID-19 testing availability, personal protective equipment availability, considerations for case prioritization, perioperative considerations, and risk-mitigation (50).

The ongoing TERAVOLT study provides the first data regarding outcomes of COVID-19 infection in patients with thoracic malignancies (51). Two hundred consecutive patients presented across 42 institutions in eight countries from March 26, 2020 to April 12, 2020. One-third of these patients died and over one-half (53%) required hospitalization over 8 days. While this is a startlingly high mortality rate—suggesting very poor outcomes for COVID-19 infection in patients with thoracic malignancy—several limitations temper these conclusions and applicability to decision making in a surgically-resectable disease cohort: (I) very limited critical care was provided as only 6% of patients received mechanical ventilation and 9% were admitted to the ICU; (II) 74% of patients had stage IV disease; (III) 59% of patients were enrolled from Italy at the time of peak incidence with severe resource limitations; and (VI) patients were enrolled early in the global pandemic prior to established treatment protocols. Further results from this ongoing study are necessary to make broader conclusions about care of patients with resectable thoracic malignancies during the pandemic.

Limitations

First, the innate limitation of this study is defining the "acceptable" time to surgery and what appropriate outcomes should be considered. When a malignancy is

discovered at an early stage prior to spread, timely surgical resection is often curative. No plausible mechanism would suggest a delayed time to surgery would be beneficial in the absence of other treatment; thus, the goal is to operate prior to progression. However, although cancer is a progressive disease, the progression is not linear. It starts with local invasion and growth prior to spreading elsewhere—to lymph nodes, adjacent organs, or to distant locations. Some cancers, such as prostate cancer and thyroid micropapillary carcinoma, are well known to remain at early stages for years without progression. Other cancers progress rapidly from early stages, such as esophageal and pancreatic cancer. Therefore, while the ideal time to cancer surgery is "without delay", the impact of operating within a certain timeframe likely has a greater impact for more aggressive cancers. Importantly, in the neoadjuvant setting, a longer delay to surgery may allow for improved pathologic response and potentially improved survival.

Second, most studies look at overall survival, disease-free survival, or pathologic staging (either upstaging in the primary setting or downstaging after neoadjuvant therapy). Third, the included literature almost entirely consists of retrospective cohort studies of varying quality, with a combination of large database studies and small institutional studies. Time to surgery cutoffs were chosen arbitrarily in most studies based upon the patient population studied and varied dramatically between studies. Given the significant heterogeneity among patient populations and time to surgery cutoffs, the data could not be meaningfully grouped into a meta-analysis. Fourth, the reasons for delay are not investigated in almost all included studies. If comorbidities or other clinical problems requiring optimization were the source for the delay this may not be appropriately adjusted for. Also, socioeconomic, and other factors that contribute to worse outcomes may also contribute to a longer time to surgery. For every type of cancer, surgeons consistently operate more quickly for more advanced cancers in sicker patients. Even with careful adjustment, it is likely that studies are unable to account for all confounders given their mostly retrospective nature. Fifth, patients with longer surgical delays who progress to unresectable disease may not be accounted for in the studied patient populations. Sixth, our specific search methodology may not have identified all relevant literature as we only evaluated one database, although we did perform a careful citation review of included papers to identify additional relevant literature.

Conclusions

In the setting of the COVID-19 pandemic and unprecedented hospital strain, prioritization of scarce resources becomes critical. While surgical capacity starts to recover in the United States, the accumulated backlog of surgical disease and an impending "second wave" will require ongoing prioritization of operations for the months to come. For patients with operable cancer, the clock is ticking: cancer continues to grow and spread, even in a pandemic. While triage guidelines have been released, no source has previously compiled the available literature on the impact of time to surgery for these malignancies. Moderate evidence demonstrates worsened survival with delayed resection of lung cancer, even in early lung cancer. No evidence justifies a distinction in management of tumors greater than or less than 2 cm. There does not appear to be a "safe delay" for lung cancer and these tumors should be resected promptly. In esophageal cancer, the optimal window for post-neoadjuvant resection appears to be 6 to 8 weeks. Minimal evidence suggests that primary esophagectomy should occur within 8 weeks.

In "Phase I," where hospital resources are largely preserved, resection of lung and esophageal cancer should not be delayed. Once resources are under greater strain, surgeons need to make case-by-case determinations to evaluate the risk of surgical delay, available hospital resources, and the risk to patients from potential nosocomial exposures to determine optimal management. Further, they should consider whether alternative therapies, such as neoadjuvant therapy or endoscopic therapy, might temporize disease progression and extend the safe window to surgery. Ultimately, it is critical that decisions on whether to delay surgery are based upon the available evidence.

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Footnote

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