Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The American Journal of Surgery xxx (xxxx) xxx

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

A systematic review and meta-analysis of surgery delays and survival in breast, lung and colon cancers: Implication for surgical triage during the COVID-19 pandemic

Brett A. Johnson [a, b, *], Anthony C. Waddimba [c, d], Gerald O. Ogola [d, e], James W. Fleshman Jr. [f], John T. Preskitt [b]

[a] College of Medicine, Texas A&M Health Science Center, Dallas Campus, Texas, United States
[b] Division of Surgical Oncology, Department of Surgery, Baylor University Medical Center, Dallas, TX, United States
[c] Health Systems Science, Department of Surgery, Baylor University Medical Center, Dallas, TX, United States
[d] Baylor Scott and White Research Institute, Dallas, TX, United States
[e] Biostatistics, Department of Surgery, Baylor University Medical Center, Dallas, TX, United States
[f] Division of Colon and Rectal Surgery, Department of Surgery, Baylor University Medical Center, Dallas, TX, United States

ARTICLE INFO

Article history:
Received 12 November 2020
Received in revised form
2 December 2020
Accepted 6 December 2020

Keywords:
COVID-19
Cancer
Breast
Lung
Colon
Surgery

ABSTRACT

Background: Thousands of cancer surgeries were delayed during the peak of the COVID-19 pandemic. This study examines if surgical delays impact survival for breast, lung and colon cancers.
Methods: PubMed/MEDLINE, EMBASE, Cochrane Library and Web of Science were searched. Articles evaluating the relationship between delays in surgery and overall survival (OS), disease-free survival (DFS) or cancer-specific survival (CSS) were included.
Results: Of the 14,422 articles screened, 25 were included in the review and 18 (totaling 2,533,355 patients) were pooled for meta-analyses. Delaying surgery for 12 weeks may decrease OS in breast (HR 1.46, 95%CI 1.28–1.65), lung (HR 1.04, 95%CI 1.02–1.06) and colon (HR 1.24, 95%CI 1.12–1.38) cancers. When breast cancers were analyzed by stage, OS was decreased in stages I (HR 1.27, 95%CI 1.16–1.40) and II (HR 1.13, 95%CI 1.02–1.24) but not in stage III (HR 1.20, 95%CI 0.94–1.53).
Conclusion: Delaying breast, lung and colon cancer surgeries during the COVID-19 pandemic may decrease survival.

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has indirectly threatened the health of thousands of cancer patients by disrupting their treatment schedules.[1] To conserve resources and limit the spread of the virus, many hospitals were forced to delay elective surgeries.[2,3] Nearly 38% of cancer surgeries are estimated to have been canceled worldwide during the 12-week peak of the pandemic.[4] During this time numerous professional associations[5–7] published guidelines for triaging cancer cases. The speed at which these were created provided rapidly needed guidance to individual healthcare institutions, given that triaging of cancer surgeries in the United States (U.S.) is not a common practice.[8] However, the need for immediate guidance also limited the amount of anticipatory research that could occur before issuance of these recommendations. The majority of guidelines were based on the opinions of a small panel of experts, which resulted in discordance between recommendations.[9] Therefore, it is imperative to adduce sufficient medical evidence to update and strengthen guidelines in preparation for future waves of COVID-19.

Few reviews and meta-analyses have examined the relationship between delays in surgery and survival for breast, lung and colon cancers. A meta-analysis[10] published in 1999 reported a 3 month delay in treatment for breast cancer was associated with a 12% lower rate of survival. That review did not examine delays in surgery alone but instead included all initial treatment modalities. A 2007 meta-analysis[11] found delays in surgery for colorectal cancers

* Corresponding author. Baylor Scott & White Surgical Oncology Specialists, 3410 Worth St, Ste 235, Dallas, TX, 7524, United States.
E-mail addresses: brett.Johnson@bswhealth.org (B.A. Johnson), anthony.waddimba@bswhealth.org (A.C. Waddimba), gerald.ogola@bswhealth.org (G.O. Ogola), james.fleshman@bswhealth.org (J.W. Fleshman), john.preskitt@bswhealth.org (J.T. Preskitt).

https://doi.org/10.1016/j.amjsurg.2020.12.015
0002-9610/

did not worsen survival, however, the interpretation of these results is limited since colon and rectal cancers were not evaluated separate. A systematic review[12] from 2018 examined the relationship between time-to-surgery (TTS) for colon cancer and outcomes, however no meta-analysis was performed. Two reviews[13,14] evaluated treatment delays in lung cancer, but neither examined surgery-specific delays.

Although numerous studies have examined the impact that increasing TTS has on survival in cancer patients, there is no evidence-based standard that can serve as an empirical benchmark for when a cancer surgery should be considered delayed. This leads to inconsistent results between studies and potential confusion in efforts to determine the true impact of delaying surgery. We addressed this gap in the literature by conducting a systematic review and meta-analysis, whose primary objective was to evaluate if delaying surgery by 12 weeks impacts survival for breast, lung, and colon cancers.

Materials and methods

Protocol and search strategy

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[15] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[16] guidelines. Structured searches of the PubMed/MEDLINE, EMBASE, Cochrane Library and Web of Science databases were conducted (April 2020) to identify relevant articles. The defined search strategy, available in Appendix A, yielded a preliminary collection of articles. Filters were used to limit results to English language and full-text papers published prior to April 1, 2020. Abstracts and full-texts of articles with relevant titles were reviewed. Additionally, references of included publications were examined to identify studies not captured in the preliminary search.

Eligibility criteria and study selection

Assessment of eligibility was conducted independently by the first author (B.A.J.) and studies in question were further evaluated by a second reviewer (A.C.W). Eligible studies fulfilled the following inclusion criteria: (1) the majority of the sample population diagnosed with invasive ductal or lobular breast cancer, non-small cell lung cancer or adenocarcinoma of the colon; (2) surgery was the initial treatment; (3) surgical delays analyzed separate from all other treatment delays; (4) TTS interval clearly defined as diagnosis to surgery; and (5) appropriate reporting of outcomes (discussed below). To minimize the effect of confounding variables between comparison groups, only studies which fulfilled the following additional criteria were included in the meta-analyses: (1) relevant prognostic factors identified; and (2) published findings incorporated multivariate risk adjustment for relevant prognostic factors or balanced such covariates between comparison groups.[17]

Studies were excluded for any of the following: (1) abstracts only and review articles; (2) sample sizes <100; (3) non-invasive tumors included in analysis; (4) the majority of the patient population analyzed had metastatic (stage IV) disease; (5) multiple cancer types included in analysis; or (6) duplicate study populations.

Study quality

Included studies were evaluated using the Newcastle-Ottawa Scale (NOS) which identifies the quality of nonrandomized studies. The scale ranges from 0 to 9 with a score of $\geq$7 indicating a high quality study.[18] Descriptions of the categories used to evaluate each study are in Appendix A.

Summary measures and data collection

The primary endpoint was overall survival (OS). Secondary endpoints included cancer-specific survival (CSS) and disease-free survival (DFS). For inclusion into this paper, outcomes must be reported as hazard ratios (HRs), odds ratios (ORs), risk ratios (RRs) or as p-values. Studies that reported HRs with 95% CIs for OS were considered for inclusion in the meta-analyses. Additional variables extracted from individual studies included: years of diagnosis of sample population; country study took place; source of data; inclusion criteria; sample sizes; mean/median TTS; mean/median follow-up, ages of sample population; any adjuvant therapy received; and prognostic factors controlled for.

Statistical analysis and bias assessment

HRs were converted to represent a 12-week delay in surgery and then pooled using the method described in prior meta-analyses.[19–22] A random-effects model was fitted given the prospect of moderate to high heterogeneity.[23] Heterogeneity was quantified by calculating $I^2$and a sensitivity analysis further evaluated the impact each study had on the overall heterogeneity.[24–26] Publication bias was assessed via visual inspection of funnel plots and the Egger's regression test for analyses with 10 or more studies.[27] Statistical significance was defined as a p-value <0.05 and all tests were 2-sided. Statistical analyses were performed using SAS® software version 9.4 (SAS, Inc., Cary, NC) and R® software version 3.6.0 (R Development Core Team, Vienna, Austria).

Results

After 14,422 publications were screened, a total of 186 abstracts/full texts were evaluated. Ultimately, 25 observational studies met inclusion criteria for the review, of which 18 studies, consisting of 2,533,355 patients, met inclusion criteria for meta-analysis. Of the seven studies excluded from the meta-analyses, six[28–33] did not report HRs and/or 95% CIs for OS and one[34] contributed an overall weight of <0.0%. The inclusion process is illustrated by the flow diagram in Appendix A.

Years of publication of included studies ranged from 2002 to 2020 and sample sizes ranged from 398 to 683,604 patients. A total of 23 studies examined OS, 5 examined DFS and 5 examined CSS. A summary of findings from each study is listed in Table 1 and further study characteristics are available in Appendix A.

The mean score on the Newcastle-Ottawa Scale was 7.8 for all included studies and 7.9 for only the studies included in the meta-analyses. Among the studies included in the meta-analyses, 10 did not have an average follow-up of at least 5 years, 3 did not control for tumor stage and 3 had sample populations not representative of the total population at risk. Little to no asymmetry was observed in the funnel plots for lung and colon cancers, indicating a low risk of publication bias. Although minor asymmetry existed on the breast cancer funnel plot, the value for Egger's test was 0.11, indicating non-significant asymmetry. Detailed results of the Newcastle-Ottawa Scale and the funnel plots are available in Appendix A.

Breast Cancer

OS was reported in twelve breast cancer studies; including eleven analyses of non-stage specific (multiple stage) disease[29,35–44]; four of stage I only disease[39,41,42,45]; four of stage II only disease[39,41,42,45]; and three of stage III only disease.[39,41,42]

Table 1
Summary of findings from 25 studies included in the systematic review.

Source	Site	Outcomes measured	Patient No.	Stage(s)	TTS Comparison Groups (Days)	Raw[a] HR	95% CI	p-value
Khorana et al, 2019	Breast	OS	683,604	I	1-42 vs 43-180	**1.017**	**1.014–1.020**	**<0.001**
			387,198	II		**1.006**	**1.003–1.009**	**<0.001**
	Lung		193,058	I	1-42 vs 43-180	**1.024**	**1.022–1.026**	**<0.001**
			49,386	II		**1.017**	**1.014–1.021**	**<0.001**
Shin et al, 2013	Breast	OS	1946	I-III	1-28 vs 29-56	1.33	0.77–2.31	NR
					1-28 vs 57-84	0.77	0.30–1.97	NR
					1-28 vs 85-365	1.91	0.42–1.48	NR
	Lung		398	I-II	1-28 vs 29-56	1.05	0.67–1.65	NR
					1-28 vs 57-84	0.65	0.28–1.48	NR
					1-28 vs 85-365	0.79	0.42–1.48	NR
Yun et al, 2012	Breast	OS	29,047	I-IV	1-31 vs ≥ 32	**1.59**	**1.37–1.84**	NR
	Lung		9094		1-37 vs ≥ 38	**1.13**	**1.02–1.25**	NR
	Colon		21,379		1-31 vs ≥ 32	1.10	1.00–1.21	NR
Mateo et al, 2020	Breast	OS	351,087	I-III	Each 30-day delay	**1.104**	**1.08–1.13**	**<0.001**
Ho et al, 2020	Breast	OS	7930	I-III	1-30 vs 31-60	**1.23**	**1.08–1.40**	**0.002**
					1-30 vs 61-90	**1.38**	**1.04–1.83**	**0.030**
					1-30 vs 91-180	**1.68**	**1.15–2.46**	**0.007**
		CSS			1-30 vs 31-60	1.12	0.95–1.32	0.19
					1-30 vs 61-90	1.06	0.72–1.56	0.77
					1-30 vs 91-180	1.55	0.98–2.45	0.06
Eaglehouse et al, 2019	Breast	OS	9699	I-III	1-21 vs 22-35	0.97	0.78–1.21	**0.04**
					1-21 vs 36-365	**1.30**	**1.04–1.61**	
			5033	I	1-21 vs 22-35	1.14	0.73–1.77	**0.03**
					1-21 vs 36-365	**1.67**	**1.11–2.52**	
			3735	II	1-21 vs 22-35	0.92	0.68–1.25	0.39
					1-21 vs 36-365	1.24	0.90–1.71	
			901	III	1-21 vs 22-35	1.21	0.75–1.95	0.77
					1-21 vs 36-365	1.24	0.75–2.04	
Erickson et al, 2018	Breast	OS	7017	I-III	Each 1-day delay	**1.011**	**1.006–1.016**	**<0.001**
Mansfield et al., 2017	Breast	DFS	1131	I	22-42 vs 43-63	0.576	0.320–1.034	0.07
			835	II		1.202	0.723–1.997	0.48
Bleicher et al, 2016	Breast	OS[b]	94,544	I-III	Each 30-day delay	**1.09**	**1.06–1.13**	**<0.001**
		CSS[b]			Each 60-day delay	**1.26**	**1.02–1.54**	**0.03**
		OS[b]	NR	I	Each 30-day delay	**1.13**	**1.08–1.18**	**<0.001**
		CSS[b]			Each 60-day delay	**1.84**	**1.10–3.07**	**0.02**
		OS[b]	NR	II	Each 30-day delay	**1.06**	**1.01–1.11**	**0.01**
		CSS[b]			Each 60-day delay	1.03	0.83–1.28	0.80
		OS[b]	NR	III	Each 30-day delay	1.06	0.97–1.16	0.17
		CSS[b]			Each 60-day delay	1.04	0.82–1.33	0.74
		OS[c]	115,790	I-III	Each 30-day delay	**1.10**	**1.07–1.13**	**<0.001**
			NR	I		**1.16**	**1.12–1.21**	**<0.001**
			NR	II		**1.09**	**1.05–1.13**	**<0.001**
			NR	III		1.01	0.96–1.07	0.64
Polverini et al, 2016	Breast	OS	420,792	I-III	1-27 vs 28-55	0.98	0.96–1.00	0.07
					1-27 vs 56-83	1.03	0.99–1.06	0.11
					1-27 vs 84-182	**1.14**	**1.09–1.20**	**<0.001**
			NR	I	1-27 vs 56-83	**1.07**	**1.02–1.13**	NR
					1-27 vs 84-182	**1.19**	**1.11–1.28**	NR
			NR	II	1-27 vs 84-182	**1.16**	**1.08–1.25**	NR
			NR	III	1-27 vs 84-182	NR	NR	NS
Yoo et al., 2016	Breast	OS	1702	I-III	1-29 vs ≥ 30	NR	NR	0.95
		DFS				1.109	0.782–1.572	0.56
Smith et al, 2013	Breast	OS	4143	I-IV	1-13 vs 14-27	0.96	0.65–1.42	**0.03**
					1-13 vs 28-41	1.11	0.69–1.78	
					1-13 vs 42+	**1.82**	**1.21–2.74**	
Redaniel et al, 2013	Breast	OS	5389	I-II	25-38 vs 39-62	1.09	0.93–1.29	NR
Vujovic et al., 2009	Breast	DFS	397	I-III	1-83 vs ≥ 84	NR	NR	**0.04**
		CSS				NR	NR	**0.006**
Huang et al., 2020[d]	Lung	OS	561	I	1-21 vs ≥ 22	**2.031**	**1.041–3.963**	**0.04**
Yang et al, 2017	Lung	OS	4984	I	1-38 vs ≥ 39	**1.13**	**1.02–1.25**	**0.02**
Samson et al., 2015	Lung	OS	27,022	I	1-55 vs ≥ 56	NR	NR	**<0.001**
Aragoneses et al., 2002	Lung	OS	1082	I-II	1-20 vs 21-40	0.9[e]	0.7–1.1	0.56
					1-20 vs 41-60	1.0[e]	0.8–1.3	0.71
					1-20 vs 61-154	1.0[e]	0.7–1.4	0.73
Grass et al, 2020	Colon	OS	118,504	I-III	Each 14-day delay	**1.06**	**1.05–1.07**	**<0.001**
Bagaria et al, 2018	Colon	OS	4685	I-III	1-7 vs 8-14	1.02	0.92–1.14	0.7
					1-7 vs 15-21	1.03	0.90–1.17	0.68
					1-7 vs 22-28	1.05	0.89–1.23	0.59
					1-7 vs 29-35	1.12	0.92–1.36	0.25
					1-7 vs 36-42	1.14	0.89–1.46	0.31
					1-7 vs 43-49	1.11	0.79–1.56	0.54
					1-7 vs 50-63	1.17	0.86–1.60	0.32
					1-7 vs 63-84	1.07	0.73–1.57	0.73

(*continued on next page*)

Table 1 (*continued*)

Source	Site	Outcomes measured	Patient No.	Stage(s)	TTS Comparison Groups (Days)	Raw[a] HR	95% CI	p-value
					1-7 vs 85+	**1.47**	**1.02–2.11**	**0.04**
Flemming et al, 2017	Colon	OS	4326	I-IV	1-55 vs ≥ 56	1.07	0.91–1.24	0.42
		CSS				0.82	0.66–1.03	0.83
Wanis et al, 2017	Colon	OS	908	I-III	1-30 vs ≥ 31	0.823	0.627–1.081	0.17
		DFS				0.886	0.611–1.283	0.52
Amri et al., 2014	Colon	OS	741	I-IV	Each quartile delay[f]	0.91	NR	0.24
		DFS				0.95	NR	0.47
Simunovic et al, 2009	Colon	OS	7989	I-IV	1-14 vs 15-28	1.0	0.9–1.1	0.74
					1-14 vs 29-42	1.0	0.9–1.1	0.76
					1-14 vs 43-120	**1.2**	**1.1–1.3**	**0.003**
		CSS			1-14 vs 15-28	0.9	0.8–1.0	0.21
					1-14 vs 29-42	0.9	0.7–1.0	0.08
					1-14 vs 43-120	1.0	0.8–1.1	0.63
Iversen et al, 2009	Colon	OS	458	I-IV	1-29 vs ≥ 30	0.84	0.62–1.13	NR

TTS, time-to-surgery; HR, hazard ratio; CI, confidence interval; NR, not report; NS, non-significant; OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival.
Studies expressed in **bold** indicate inclusion in the meta-analysis.
HRs; 95% CIs; p-values expressed in **bold** indicate statistical significance.
Empty cells indicate the text above applies for the row.
[a] Hazard ratios as reported in each individual study.
[b] Analysis of SEER-Medicare dataset.
[c] Analysis of NCDB dataset.
[d] Excluded from meta-analysis because study contributed an overall weight of <0.0% to final pooled analysis.
[e] Expressed in terms of relative risk.
[f] Quartile ranges include days 1–13; 14–23; 24–37; 38-798.

Sample sizes ranged from 1702 to 420,792 with a mean of 176,657 patients. Increasing TTS was associated with a decreased OS in 9/11 non-stage specific studies, 4/4 stage I only studies, 3/4 stage II only studies, and 0/3 stage III only studies.

Results of the meta-analysis for non-stage specific breast cancers are illustrated as a forest plot in Fig. 1. The results suggest a delay in surgery of 12 weeks is associated with decreased OS (HR 1.46, 95%CI 1.28–1.65, I^2 86%). Results of the stage-specific breast cancer meta-analyses are illustrated as forest plots in Fig. 2. The results suggest a delay in surgery of 12 weeks is associated with decreased OS for stages I (HR 1.27, 95%CI 1.16–1.40, I^2 97%) and II (HR 1.13, 95%CI 1.02–1.24, I^2 89%) diseases but not for stage III (HR 1.20, 95%CI 0.94–1.53, I^2 63%) disease.

The sensitivity analysis for studies of non-stage specific breast cancers indicates excluding Polverini et al.[42] decreases overall heterogeneity from I^2 = 86% to 77% and increases the overall HR [95% CI] from 1.46 [1.28–1.65] to 1.52 [1.35–1.71]. For stage I only all studies were found to contribute equally to overall heterogeneity. For stage II only studies excluding Khorana et al.[45] decreases overall heterogeneity from I^2 = 89% to 44% and increases the overall HR [95% CI] from 1.13 [1.02–1.24] to 1.17 [1.08–1.27]. For stage III only studies excluding Eaglehouse et al.[39] decreases overall heterogeneity from I^2 = 63% to 0% and the overall HR remains insignificant.

Lung Cancer

OS was reported in seven lung cancer studies; including three analyses of non-stage specific (multiple stages) disease[32,35,36]; four of stage I only disease[31,34,45,46]; and one of stage II only disease.[45] Sample sizes ranged from 398 to 242,444 with a mean of 40,798 patients. Increasing TTS was associated with decreased OS in 1/3 non-stage specific studies, 4/4 stage I only studies, and 1/1 stage II only studies.

Results of the meta-analysis for lung cancer are illustrated as a

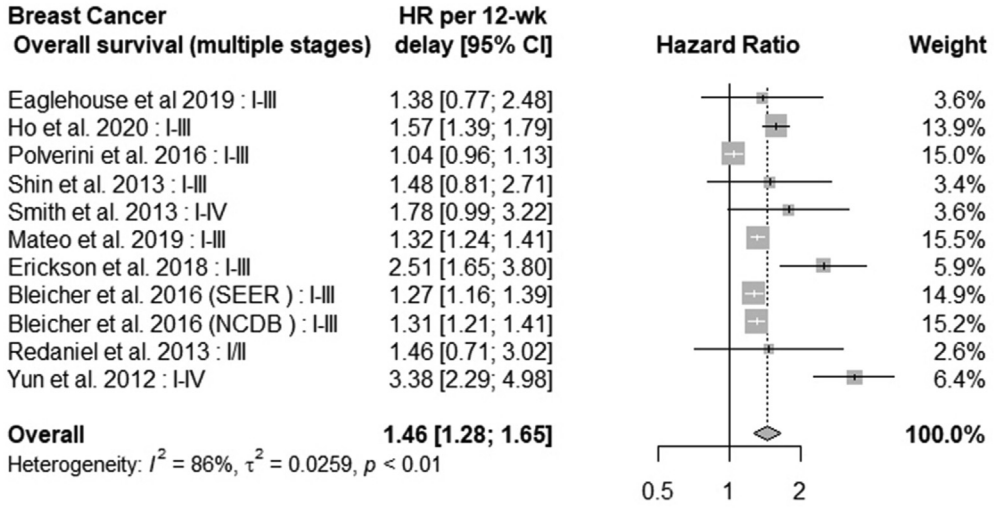

Fig. 1. Meta-analysis of the estimated hazard ratio for overall survival for a delay in surgery of 12 Weeks among patients with breast cancer.

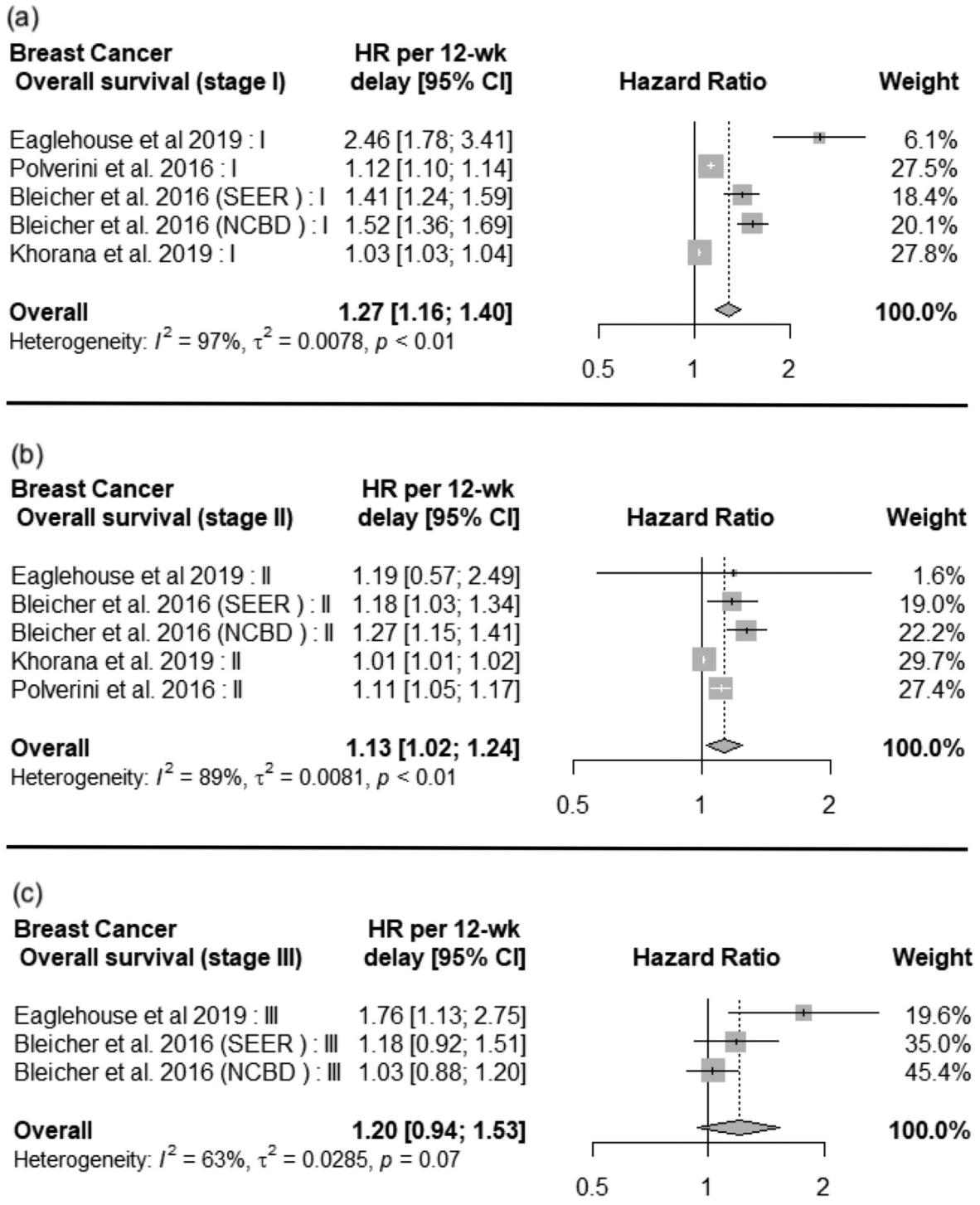

Fig. 2. Stage-specific meta-analyses of the estimated hazard ratios for overall survival for a delay in surgery of 12 Weeks among patients with breast cancer.

forest plot in Fig. 3. The results suggest a delay in surgery of 12 weeks is associated with decreased OS (HR 1.04, 95%CI 1.02–1.06, I^2 84%). Too few HRs were reported to perform meaningful stage-specific analyses. In the sensitivity analysis for lung cancer all studies were found to contribute equally to overall heterogeneity.

Colon Cancer

OS was reported in 8 colon cancer studies[33,36,47–52] and all analyses were of non-stage specific (multiple stages) disease. Sample sizes ranged from 458 to 118,504 with a mean of 19,874 patients. Increasing TTS was associated with decreased OS in 3/8 studies.

Results of the meta-analysis for colon cancer are illustrated as a forest plot in Fig. 4. The results suggest a delay in surgery of 12 weeks is associated with decreased OS (HR 1.24, 95%CI, 1.12–1.38, I^2 71%).

The sensitivity analysis for studies of colon cancer indicates excluding Grass et al.[47] decreases overall heterogeneity from

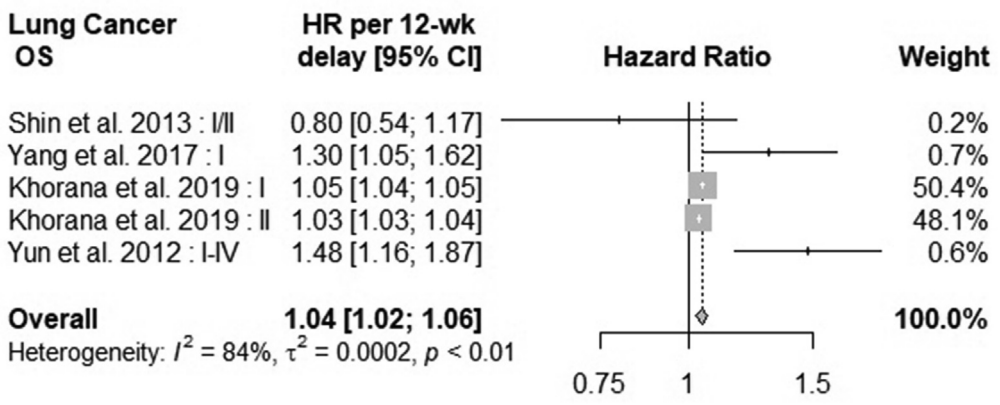

Fig. 3. Meta-analysis of the estimated hazard ratio for overall survival for a delay in surgery of 12 Weeks among patients with lung cancer.

I^2 = 71% to 40% and decreases the overall HR [95% CI] from 1.24 [1.12−1.38] to 1.18 [1.06−1.33].

Discussion

The lack of evidence-based standards for what is considered a delay in cancer surgery has led to inconsistent study designs and few attempts at synthesizing data between studies. By converting HRs to a common 12-week delay in surgery, for the first time we were able to pool findings from studies evaluating surgical delays and survival in breast, lung and colon cancers. The results of the meta-analyses indicate a surgical delay of 12 weeks is associated with decreased overall survival in these three cancer types. Results from the stage-specific analyses for breast cancer suggest delaying surgery by 12 weeks decreases overall survival for stage I and II diseases but not stage III disease. Findings from this study should be utilized to empirically strengthen and modify existing triage guidelines in preparation for future waves of COVID-19.

The pooled HR for breast cancer was the largest among the three cancer types examined, which may indicate survival in these patients is especially sensitive to surgical delays. The stage-specific analyses performed for breast cancer are of particular interest since COVID-19 triage guidelines differ by tumor stage. Most guidelines recommend delaying early-stage breast cancers and to instead consider neoadjuvant treatment with chemotherapy or endocrine therapy. However, our results suggest these cancers are most impacted by delays in surgery. Although alternative treatments exist, it is important to consider that under normal circumstances chemotherapy is not given for many early-stage (especially stage I) breast cancers.[53] While the current literature does suggest endocrine therapy can safely be utilized in the neoadjuvant setting, the appropriate patient population and the exact treatment regimen are not yet well defined.[54] For stage III, the impact of surgical delays trended toward worse survival, however, significance was not reached. Compared to stages I/II, it is possible delaying surgery for stage III disease has a negligible impact on survival since these patients already experience significantly poorer outcomes from their 'delay' in diagnosis. Therefore, our results suggest surgeries for stage III breast cancers should be delayed prior to stages I/II during future waves of COVID-19. If delays for stages I/II become necessary, surgeries should first be delayed for patients who likely would receive adjuvant chemotherapy under normal circumstances, given the well-established efficacy of neoadjuvant chemotherapy.

The pooled HR for lung cancer suggests a delay in surgery of 12 weeks is associated with a slight decrease in overall survival. It is noteworthy that 4/5 of the studies in our analysis included only stage I and/or II diseases. While this limits the comparability of the

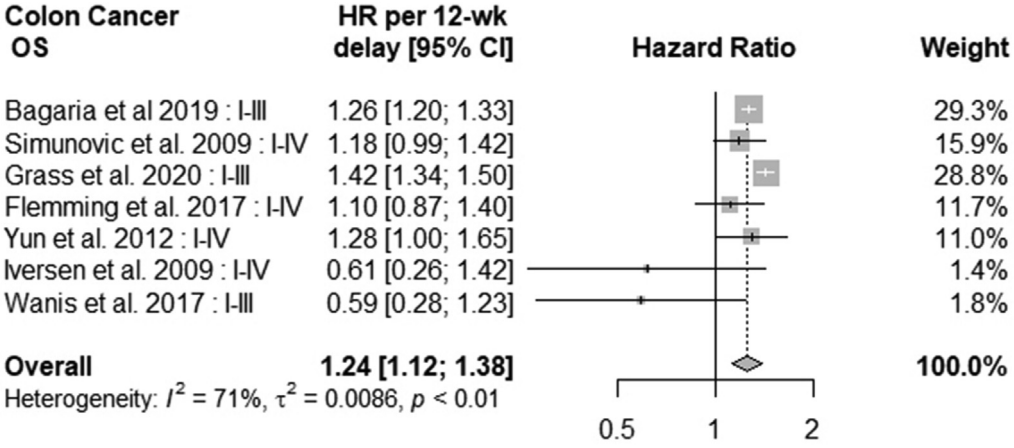

Fig. 4. Meta-analysis of the estimated hazard ratio for overall survival for a delay in surgery of 12 Weeks among patients with colon cancer.
Legend (Figs. 1, 2, 3, 4) The size of the boxes represents the weight the study has in the overall analysis; the black lines coming off of each box represent the 95% confidence intervals of the study; confidence interval lines that cross the line of no effect indicate results are not significant; the center of the diamond(s) represents the overall HR and the edges represent the 95% confidence interval; Abbreviations: OS, overall survival; HR, hazard ration; CI, confidence interval.

results to the triage recommendations for stage III disease, our analysis suggest early-stage lung cancers are sensitive to delays in surgery. Many of the guidelines recommend delaying small and early stage lung cancers and to consider alternative non-surgical treatments such as stereotactic ablative radiotherapy, cryotherapy or radiofrequency ablation.[5,7] However, curative surgery is often the single treatment for early-stage lung cancer[53] and the efficacy of alternative treatments has been shown to be inconsistent.[55–57] Our results suggest if delaying surgery for stages I/II lung cancers becomes necessary during future waves of COVID-19 it should be done with caution and rescheduled for the earliest possible date.

The pooled HR for colon cancer suggests a delay in surgery of 12 weeks is associated with decreased overall survival. Most triage guidelines discourage delaying curative-intent surgery for colon cancer, which our findings support.[5,6] If it becomes necessary to delay surgery for colon cancer during future waves of COVID-19 our results suggest that it should be done with extreme caution and rescheduled for the earliest possible date.

Limitations

The most substantial limitation to this paper is the heterogeneity found between pooled studies, most notably for breast and lung cancers. However, results of the meta-analyses remained similar following the sensitivity analyses. Second, since individual studies did not compare consistent TTS lengths, it was necessary to standardize each time interval in order to compare findings. To accomplish this, we relied on the assumption a log-linear relationship exists between the effect of TTS and OS. Third, even though the overall assessment of quality indicates the inclusion of high-quality studies, there were numerous studies which did not control for stage and/or did not have an appropriate length of follow-up. Fourth, only full-text articles in English were included which may cause publication bias, although the funnel plots/Egger's test indicate the risk for bias was low. The decision to only include full-text articles was made after a cursory reading of seemingly relevant abstracts revealed that upon their full-text reviews, studies often fell short of our strict inclusion criteria.[58] Lastly, our analysis is limited to non-randomized observational studies, however, the prospect of randomizing cancer patients to different categories of surgical delays is unlikely due to the ethical implications.

Conclusion

The results of the meta-analyses suggest a delay in surgery of 12 weeks is associated with decreased overall survival in breast (especially for stage I and II), lung and colon cancers. Triage guidelines for cancer surgeries during the COVID-19 pandemic should take into consideration the emerging medical evidence adduced by this and other similar studies. Future research would benefit from the synchronization of study designs, implementation of a constant TTS interval and use of similar TTS comparison groups in order to improve comparability of findings. To help better guide surgical triage recommendations during future waves of COVID-19, studies should further evaluate which stages and subtypes are most impacted by delays in surgery in these and other cancer types.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.amjsurg.2020.12.015.

Author contributions

Study concept and design – Johnson, Preskitt, Fleshman, Waddimba. Acquisition of data – Johnson, Waddimba, Ogola. Analysis and interpretation of data – All authors. Drafting of manuscript – Johnson, Waddimba, Preskitt, Fleshman. Critical revision of the manuscript for intellectual content – All authors. Final approval of version to be published – All authors. Accountable for all aspects of the work – Johnson.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures

Mr. Johnson, Dr. Waddimba, Dr. Ogola, Dr. Fleshman and Dr. Preskitt do not have proprietary or commercial interest in any product mentioned or concept discussed in this article to report.

References

1. Blumenthal D, Fowler EJ, Abrams M, Collins SR. Covid-19 — implications for the health care system. *N Engl J Med*. 2020;383(15):1483–1488. https://doi.org/10.1056/NEJMsb2021088.
2. *COVID-19: Recommendations for Management of Elective Surgical Procedures*. 2020.
3. *CMS Releases Recommendations on Adult Elective Surgeries, Non-essential Medical, Surgical, and Dental Procedures during COVID-19 Response*. 2020.
4. Negopdiev D, Collaborative C, Hoste E. Elective surgery cancellations due to the COVID-19 pandemic: global predictive modelling to inform surgical recovery plans. *Br J Surg*. 2020;107(11):1440–1449.
5. COVID-19. *Elective Case Triage Guidelines for Surgical Care*; 2020 [cited 2020 May 1]; Available from: https://www.facs.org/covid-19/clinical-guidance/elective-case.
6. Bartlett DL, Howe JR, Chang G, et al. Management of cancer surgery cases during the COVID-19 pandemic: considerations. *Ann Surg Oncol*. 2020 Jun;27(6):1717–1720. PubMed PMID: 32270420. Pubmed Central PMCID: PMC7141488. Epub 2020/04/10.
7. Thoracic Surgery Outcomes Research Network I, Antonoff M, Backhus L, et al. COVID-19 guidance for triage of operations for thoracic malignancies: a consensus statement from thoracic surgery outcomes research network. *Ann Thorac Surg*. 2020 Apr 4;160(2):601–605. PubMed PMID: 32278755. Pubmed Central PMCID: PMC7146713. Epub 2020/04/13.
8. Stahel PF. How to risk-stratify elective surgery during the COVID-19 pandemic? *Patient Saf Surg*. 2020;14:8. PubMed PMID: 32288785. eng.
9. Garg PK, Kaul P, Choudhary D, et al. Discordance of COVID-19 guidelines for patients with cancer: a systematic review. *J Surg Oncol*. 2020;122(4):579–593.
10. Richards MA, Westcombe AM, Love SB, et al. Influence of delay on survival in patients with breast cancer: a systematic review. *Lancet*. 1999;353(9159):1119–1126, 1999/04/03/.
11. Ramos M, Esteva M, Cabeza E, et al. Relationship of diagnostic and therapeutic delay with survival in colorectal cancer: a review. *European journal of cancer*. 2007;43(17):2467–2478.
12. Hansen CH, Gögenur M, Madsen MT, Gögenur I. The effect of time from diagnosis to surgery on oncological outcomes in patients undergoing surgery for colon cancer: a systematic review. *Eur J Surg Oncol*. 2018;44(10):1479–1485.
13. Malalasekera A, Nahm S, Blinman PL, et al. How long is too long? A scoping review of health system delays in lung cancer. *Eur Respir Rev*. 2018 Sep 30;27(149). PubMed PMID: 30158277. Epub 2018/08/31. eng.
14. Neal RD, Tharmanathan P, France B, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. *Br J Canc*. 2015 Mar 31;112(Suppl 1):S92–S107. PubMed PMID: 25734382. Pubmed Central PMCID: PMC4385982. Epub 2015/03/04. eng.
15. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7), e1000097.
16. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *Jama*. 2000;283(15):2008–2012.
17. Simunovic N, Sprague S, Bhandari M. Methodological issues in systematic reviews and meta-analyses of observational studies in orthopaedic research. *JBJS*. 2009;91(Supplement_3):87–94.
18. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European journal of epidemiology*. 2010;25(9):603–605.
19. Biagi JJ, Raphael MJ, Mackillop WJ, et al. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic

review and meta-analysis. *Jama*. 2011 Jun 8;305(22):2335–2342. PubMed PMID: 21642686. Epub 2011/06/07. eng.
20. Yu K-D, Huang S, Zhang J-X, et al. Association between delayed initiation of adjuvant CMF or anthracycline-based chemotherapy and survival in breast cancer: a systematic review and meta-analysis. *BMC Canc*. 2013;13(1):240.
21. Zhan Q-H, Fu J-Q, Fu F-M, et al. Survival and time to initiation of adjuvant chemotherapy among breast cancer patients: a systematic review and meta-analysis. *Oncotarget*. 2018;9(2):2739.
22. Boyne DJ, Cuthbert CA, O'Sullivan DE, et al. Association between adjuvant chemotherapy duration and survival among patients with stage II and III colon cancer: a systematic review and meta-analysis. *JAMA Network Open*. 2019;2(5), e194154.
23. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials*. 2015;45:139–145.
24. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. Lippincott Williams & Wilkins; 2008.
25. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Bmj*. 2003 Sep 6;327(7414):557–560. PubMed PMID: 12958120. Pubmed Central PMCID: PMC192859. Epub 2003/09/06. eng.
26. Patsopoulos NA, Evangelou E, Ioannidis JP. Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. *Int J Epidemiol*. 2008;37(5):1148–1157.
27. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj*. 1997;315(7109):629–634.
28. Mansfield SA, Abdel-Rasoul M, Terando AM, Agnese DM. Timing of breast cancer surgery-how much does it matter? *Breast J*. 2017 Jul;23(4):444–451. PubMed PMID: 28117507. Epub 2017/01/25.
29. Yoo TK, Han W, Moon HG, et al. Delay of treatment initiation does not adversely affect survival outcome in breast cancer. *Cancer Res Treat*. 2016 Jul;48(3):962–969. PubMed PMID: 26511801. Pubmed Central PMCID: PMC4946375. Epub 2015/10/30.
30. Vujovic O, Yu E, Cherian A, et al. Effect of interval to definitive breast surgery on clinical presentation and survival in early-stage invasive breast cancer. *Int J Radiat Oncol Biol Phys*. 2009 Nov 1;75(3):771–774. PubMed PMID: 19304404. Epub 2009/03/24.
31. Samson P, Patel A, Garrett T, 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 Jun;99(6):1906–1912. discussion 13. PubMed PMID: 25890663. Pubmed Central PMCID: PMC4458152. Epub 2015/04/22.
32. Aragoneses FG, Moreno N, Leon P, et al. Influence of delays on survival in the surgical treatment of bronchogenic carcinoma. *Lung Canc*. 2002 2002/04/01/;36(1):59–63.
33. Amri R, Bordeianou LG, Sylla P, Berger DL. Treatment delay in surgically-treated colon cancer: does it affect outcomes? *Ann Surg Oncol*. 2014 Nov;21(12):3909–3916. PubMed PMID: 24849522. Epub 2014/05/23.
34. Huang C-S, Hsu P-K, Chen C-K, et al. Delayed surgery after histologic or radiologic-diagnosed clinical stage I lung adenocarcinoma. *J Thorac Dis*. 2020;12(3):615.
35. Shin DW, Cho J, Kim SY, et al. Delay to curative surgery greater than 12 weeks is associated with increased mortality in patients with colorectal and breast cancer but not lung or thyroid cancer. *Ann Surg Oncol*. 2013 Aug;20(8):2468–2476. PubMed PMID: 23529782. Epub 2013/03/27.
36. Yun YH, Kim YA, Min YH, et al. The influence of hospital volume and surgical treatment delay on long-term survival after cancer surgery. *Ann Oncol*. 2012 Oct;23(10):2731–2737. PubMed PMID: 22553194. Epub 2012/05/04.
37. Mateo AM, Mazor AM, Obeid E, et al. Time to surgery and the impact of delay in the non-neoadjuvant setting on triple-negative breast cancers and other phenotypes. *Ann Surg Oncol*. 2020 May;27(5):1679–1692. PubMed PMID: 31712923. Pubmed Central PMCID: PMC7145740. Epub 2019/11/13.
38. Ho PJ, Cook AR, Binte Mohamed Ri NK, et al. Impact of delayed treatment in women diagnosed with breast cancer: a population-based study. *Cancer medicine*. 2020;9(7):2435–2444.
39. Eaglehouse YL, Georg MW, Shriver CD, Zhu K. Time-to-surgery and overall survival after breast cancer diagnosis in a universal health system. *Breast Canc Res Treat*. 2019;178(2):441–450.
40. Eriksson L, Bergh J, Humphreys K, et al. Time from breast cancer diagnosis to therapeutic surgery and breast cancer prognosis: a population-based cohort study. *Int J Canc*. 2018 Sep 1;143(5):1093–1104. PubMed PMID: 29603736. Epub 2018/04/01.
41. Bleicher RJ, Ruth K, Sigurdson ER, et al. Time to surgery and breast cancer survival in the United States. *JAMA Oncol*. 2016 Mar;2(3):330–339. PubMed PMID: 26659430. Pubmed Central PMCID: PMC4788555. Epub 2015/12/15.
42. Polverini AC, Nelson RA, Marcinkowski E, et al. Time to treatment: measuring quality breast cancer care. *Ann Surg Oncol*. 2016 Oct;23(10):3392–3402. PubMed PMID: 27503492. Epub 2016/08/10.
43. Smith EC, Ziogas A, Anton-Culver H. Delay in surgical treatment and survival after breast cancer diagnosis in young women by race/ethnicity. *JAMA Surg*. 2013 Jun;148(6):516–523. PubMed PMID: 23615681. Epub 2013/04/26.
44. Redaniel MT, Martin RM, Cawthorn S, et al. The association of waiting times from diagnosis to surgery with survival in women with localised breast cancer in England. *Br J Canc*. 2013 Jul 9;109(1):42–49. PubMed PMID: 23799851. Pubmed Central PMCID: PMC3708566. Epub 2013/06/27.
45. Khorana AA, Tullio K, Elson P, et al. Time to initial cancer treatment in the United States and association with survival over time: an observational study. *PloS One*. 2019;14(3), e0213209. PubMed PMID: 30822350. Pubmed Central PMCID: PMC6396925. Epub 2019/03/02.
46. Yang CJ, Wang H, Kumar A, et al. Impact of timing of lobectomy on survival for clinical stage IA lung squamous cell carcinoma. *Chest*. 2017 Dec;152(6):1239–1250. PubMed PMID: 28800867. Epub 2017/08/13.
47. Grass F, Behm KT, Duchalais E, et al. Impact of delay to surgery on survival in stage I-III colon cancer. *Eur J Surg Oncol*. 2020 Mar;46(3):455–461. PubMed PMID: 31806516. Epub 2019/12/07.
48. Bagaria SP, Heckman MG, Diehl NN, et al. Delay to colectomy and survival for patients diagnosed with colon cancer. *J Invest Surg*. 2018;32(4):350–357. https://doi.org/10.1080/08941939.2017.1421732.
49. Flemming JA, Nanji S, Wei X, et al. Association between the time to surgery and survival among patients with colon cancer: a population-based study. *Eur J Surg Oncol*. 2017 Aug;43(8):1447–1455. PubMed PMID: 28528190. Epub 2017/05/22.
50. Wanis KN, Patel SV, Brackstone M. Do moderate surgical treatment delays influence survival in colon cancer? *Dis Colon Rectum*. 2017;60(12):1241–1249.
51. Simunovic M, Rempel E, Theriault ME, et al. Influence of delays to nonemergent colon cancer surgery on operative mortality, disease-specific survival and overall survival. *Can J Surg*. 2009 Aug;52(4):E79–E86. PubMed PMID: 19680502. Pubmed Central PMCID: PMC2724831. Epub 2009/08/15.
52. Iversen LH, Antonsen S, Laurberg S, Lautrup MD. Therapeutic delay reduces survival of rectal cancer but not of colonic cancer. *Br J Surg*. 2009 Oct;96(10):1183–1189. PubMed PMID: 19787765. Epub 2009/09/30.
53. National Cancer Data Base. Benchmark Reports [database on the Internet] http://oliver.facs.org/BMPub/; 2020 [cited May 1, 2020]. Available from:.
54. Spring LM, Gupta A, Reynolds KL, et al. Neoadjuvant endocrine therapy for estrogen receptor-positive breast cancer: a systematic review and meta-analysis. *JAMA oncology*. 2016;2(11):1477–1486. PubMed PMID: 27367583. eng.
55. Cao C, Wang D, Chung C, et al. A systematic review and meta-analysis of stereotactic body radiation therapy versus surgery for patients with non–small cell lung cancer. *J Thorac Cardiovasc Surg*. 2019;157(1):362–373. e8.
56. Khorfan R, Kruser TJ, Coughlin JM, et al. Survival of primary sbrt compared to surgery for operable stage i/ii non-small cell lung cancer. *Ann Thorac Surg*. 2020;110(1):228–234.
57. Zappa C, Mousa SA. Non-small cell lung cancer: current treatment and future advances. *Transl Lung Cancer Res*. 2016;5(3):288.
58. Higgins JP, Ramsay C, Reeves BC, et al. Issues relating to study design and risk of bias when including non-randomized studies in systematic reviews on the effects of interventions. *Res Synth Methods*. 2013;4(1):12–25.