Infectious Agents and Cancer

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Optimizing timing for elective surgery in cancer patients following COVID-19 infection; a post-pandemic analysis

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Abstract

Introduction The COVID-19 pandemic introduced challenges including delaying elective surgery. For cancer patients, reducing delays is preferred to prevent unfavorable outcomes. there is a lack of consensus regarding the optimal timing of elective surgery following a SARS-CoV-2. This study aimed to find the optimal time to elective surgery to minimize 30-day postoperative morbidity and mortality.

Methods This is a retrospective chart review of all adult patients who underwent elective surgery with a confirmed preoperative COVID-19 diagnosis between September 2020 and April 2023. Patients' elective surgeries delays were examined to determine the optimal time to surgery in terms of postoperative complications. Analysis was controlled for age, ASA score, comorbidities, and smoking status.

Results 358 records examined, 94.7% had delayed surgery and 5.3% had cancelled surgery. The optimal time to surgery was ≥ 17 days to minimize postoperative pulmonary complications [OR: 0.299, $p = 0.048$], other postoperative complications [OR: 0.459, $p = 0.01$], and a decrease in length of hospital stay. In multivariate analysis, the only significant predictors for postoperative complications were time to surgery; surgery ≥ 17 days after diagnosis had better postoperative outcomes [$p < 0.001$], and COVID-19 symptoms status [$p = 0.019$].

Conclusion The best time to surgery in this cohort is at least 17 days (or a range of 2–3 weeks) for optimal results. Further research is needed to investigate the effect of such delays on oncological outcomes in this cohort.

Keywords COVID-19, Postoperative complications, Cancer, Delay in surgery, Time to surgery

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Introduction

The COVID-19 pandemic introduced new challenges to healthcare globally. In addition to burdening hospitals and healthcare centers [1, 2], it added a new variable to consider when treating patients. Delaying elective surgery due to an active SARS-CoV-2 infection is one of the new variables introduced by the pandemic [3]. Patients with active preoperative SARS-CoV-2 infection are at a higher risk of developing postoperative pulmonary complications (PPC) [4, 5]. Delaying surgery due to an active COVID-19 infection can potentially reduce PPC, postoperative surgical complications, and 30-day mortality [6].

While delays in elective surgery due to active respiratory infections have existed pre-pandemic, there is limited evidence regarding the optimal timing of elective surgery following a SARS-CoV-2 infection. Different guidelines suggest a delay of anywhere from 2 weeks to 12 weeks following infection [3, 4]. The American Society of Anesthesiologists recommends delaying surgery until patients have demonstrated recovery from COVID-19 (*COVID-19 and elective surgery* 2023) [7]. However, this time is different for each individual and offers a minimum safety window but not an optimal time of surgery. Additionally, this introduces challenges in assessing and determining recovery as well as managing operating room lists. With the variability of determined safety windows, multiple studies drew different optimal times to surgery. Kovoor et al. recommend 8–12-week delay post COVID-19 diagnosis [8], whereas a study conducted by Bryant et al. found that there was a 1% reduction in risk of developing postoperative complications for every 10 day delay [9]. Another study found that patients operated on within 6 weeks of a COVID-19 diagnosis were at an increased risk of 30-day postoperative mortality and 30-day postoperative pulmonary complications [10].

For cancer patients, minimizing surgical delay is preferred to prevent disease progression or worsening outcomes [11, 12]. However, it is paramount to minimize the risk of postoperative complications. Thus, determining optimal timing of surgery after COVID-19 infection in this population is essential.

The aim of this study is to determine the optimal timing of surgery for cancer patients with an active preoperative COVID-19 infection to minimize PPC, postoperative surgical complications, and 30-day mortality.

Methods

A retrospective chart review was utilized in this study. A census sample was used which included all adult who were scheduled for elective surgery at King Hussein Cancer Center between September 2020 and April 2023, whose surgeries were delayed due to a confirmed COVID-19 diagnosis by PCR or rapid antigen test. A delay in elective surgery was used to determine the optimal time to surgery in terms of postoperative outcomes. Pediatric patients, patients and patients who had non-elective surgeries were excluded.

The primary outcomes were postoperative complications within 30-days, including postoperative pulmonary complications, mortality, reoperation, readmission, and length of hospital stay. Postoperative complications up to 30 days post-surgery were considered and defined as any deviation from the normal expected postoperative course. Postoperative pulmonary complications were defined as respiratory infection, respiratory failure, pleural effusion, atelectasis, pneumothorax, and aspiration pneumonitis. The length of stay was measured from the date of surgery to the date of discharge. 30-day mortality, readmission or reoperation was only included if it was directly related to the surgery.

Secondary outcomes were the effect of COVID-19 waves. Qaqish et al. described the first wave spanning from September 2020 to January 2021, marked by the initial variants namely (B.1.1.312 and B.1.36.10) [13]. We defined wave 2 as any infection after January 2021, encompassing all other variants that are considered by Qaqish et al. as fast spreading including the Delta, UK, and Omicron variants.

The study used R software version 4.2.1 to analyze data. Descriptive statistics were used to describe demographic and clinicopathological characteristics. Inferential statistics included independent T-Test for continuous data and a Chi-Squared Test for categorical data to detect differences between individuals who developed complications and those who did not. Variables that demonstrated significant differences in the univariate analysis between the two groups were integrated into a multivariable regression. An ROC curve was used to determine the optimal time to surgery to minimize the aforementioned outcomes. The significance level was set at $p < 0.05$.

Results

A total of 358 adult patients, whose elective surgeries were delayed due to a confirmed COVID-19 diagnosis, were included in the study, these patients were identified through a retrospective chart review conducted at the KHCC during the study period. The mean age was 51.5 years (± 14.7). The cohort included 58.9% females and 41.1% males. 102 patients (28.5%) were active smokers. Comorbidities were present in 201 patients (56.1%), with 18 (5.0%) having a history of pulmonary comorbidities prior to surgery. The most common cancers were breast cancer ($n = 108$, 30.2%), GI cancer ($n = 71$, 19.8%), and hematological cancer ($n = 52$, 14.5%).

Regarding COVID-19 vaccination, 45.8% patients were vaccinated at the time of surgery. More than half of patients (54.8%) were symptomatic at the time of COVID-19 diagnosis, with most reported symptom

being fatigue. Of the 358 records examined, 97.2% were diagnosed using PCR, and 2.8% were diagnosed using rapid antigen test. Notably, 19 procedures (5.3%) were canceled due to a positive COVID-19 test at the time of surgery, and 94.7% had delayed surgery. Clinicodemographic characteristics are presented in Table 1.

Of the 358 patients, 339 patients underwent surgery and were included in this analysis. Table 1 compares patients with postoperative complications to those without; there was no statistically significant difference in age between the two groups ($p = 0.72$). Gender distribution was also comparable between the two groups ($p = 0.84$). Additionally, there was no statistically significant difference in the presence of preexisting pulmonary conditions (4% and 5% of patients respectively, $p = 0.85$). Similarly, no significant differences were found for smoking status ($p = 0.93$).

Vaccinated individuals had a shorter time to surgery compared to unvaccinated individuals (mean 11.7 vs. 20.3 days respectively, $p < 0.001$). Although there were more postoperative complications among vaccinated individuals compared to unvaccinated individuals (24.4% vs. 21.9% respectively), the difference was not statistically significant ($p = 0.59$).

In terms of COVID-19 waves, 134 patients who underwent procedures were in first wave, postoperative complications were reported in 23 procedures (17.2%), whereas 205 procedures performed in the second wave, with a postoperative complication rate of 26.8% ($p = 0.039$). The average time to surgery for wave 1 was 41.3 days, however for wave 2 it was 26.7 days to surgery from a positive COVID-19 test.

Additionally, patients who were symptomatic at the time of COVID-19 diagnosis were more likely to develop postoperative complications than those who were not (27.3% vs. 17.8% respectively, $p = 0.04$).

Table 2 highlights the frequency of different complications and Clavien-Dindo classification. The most frequent complication was SSI (29.5%), followed by PPC (24.4%). The majority of complications were Grade II (53.85%), indicating moderate severity requiring pharmacological intervention. Minor complications (Grade I) accounted for 17.95%, while severe complications requiring surgical, endoscopic, or radiological intervention (Grade IIIa and IIIb) comprised 19.23%. There were no Grade IV complications (life-threatening with organ dysfunction), and mortality (Grade V) was reported in 8.97% of cases. The findings highlight that most complications were of mild to moderate severity, with a smaller proportion of major complications and mortality.

Using the ROC model, a cutoff point of 17 days was determined as the optimal time to surgery after a positive COVID-19 test (AUC = 0.643). Based on these results, we evaluated the time to surgery using this cutoff, to correlate with postoperative complications.

The overall postoperative complications were lower in the ≥ 17-day group (OR = 0.36, $P < 0.001$). Specifically, the ≥ 17-day group had fewer pulmonary complications (OR = 0.27, $p = 0.007$) and surgical site infections (OR = 0.32, $p = 0.01$). Similarly, 30-day reoperation rate was lower in this group (OR = 0.30, $p = 0.03$). Moreover, the ≥ 17-day group had a lower length of hospital stay (LOS average: 2.46 days vs. 6.4-day, $p < 0.001$). 30-day postoperative mortality and 30-day re-admission were lower in the ≥ 17-day group, but were not significant ($p = 0.129$, $p = 0.168$, respectively). (Fig. 1)

Significant factors (17-day cutoff, wave and symptoms at time of diagnosis) were analyzed in a multivariable binomial logistic regression model. In the multivariate analysis, the only significant predictors of postoperative complications were time to surgery and being symptomatic during COVID-19 infection. Patients who underwent surgery more than or equal to 17 days after a positive COVID-19 test had a lower likelihood of developing postoperative complications (OR 0.39, $p = 0.002$). The COVID-19 wave was not an independent predictor of postoperative outcomes ($p = 0.188$) (Table 3).

Discussion

The study aimed to determine the optimal time to surgery after a confirmed COVID-19 infection by correlating the time from COVID-19 diagnosis to surgery with postoperative outcomes. Our results show that the risk of pulmonary complications, surgical site infections, and reoperations is decreased when surgery is delayed for or more than or equal to 17 days following a COVID-19 diagnosis. This is aligned with earlier studies that report increased risks of postoperative complications shortly after COVID-19 infection [6, 10, 14, 15]. Despite being paramount for controlling COVID-19, the timing to surgery had a stronger independent impact on postoperative outcomes than vaccination status.

Another study by Dai et al. also found that the postoperative complications in patients who underwent colorectal cancer surgery had a significantly higher risk of postoperative complications compared to the control group (26.3% vs. 8.4% respectively; OR 3.87, $p = 0.001$), with pneumonia being the most frequent complication recorded, occurring in 15.8% of COVID-19 patients, and sepsis reported in 7% of patients [16]. Similarly, our study found pulmonary complications in 24.4% of cases, surgical site infections and readmissions were both at 29.5%, and postoperative complications were seen in 23%. Furthermore, compared to patients who waited more than or equal to 17 days for surgery, patients who had surgery before 17 days after COVID-19 had higher incidence of complications.

Table 1 Comparison between patients who underwent surgery and developed postoperative complications versus those who did not (*N* = 339)

Variable	Level	Total Cohort *N* (%)	Postoperative Complications = No (*N* = 261, 77%)		Postoperative Complications = Yes (*N* = 78, 23%)		*P* value
			Frequency	(%)	Frequency	(%)	
Age	Mean	51.5	51.3		52		0.72
	Median	52	51		51.5		
	SD	14.56	14.6		14.4		
	Range (Max - Min)	69 (89 – 20)	69 (89 – 20)		66 (86 – 20)		
Sex	Female	201 (59.29%)	154	76.62%	47	23.38%	0.84
	Male	138 (40.71%)	107	77.54%	31	22.46%	
Smoking Status	EX	28 (8.26%)	21	75.00%	7	25.00%	0.93
	No	211 (62.24%)	162	76.78%	49	23.22%	
	Yes	100 (29.5%)	78	78.00%	22	22.00%	
Preoperative Comorbidity	No	149 (43.95%)	119	79.87%	30	20.13%	0.27
	Yes	190 (56.05%)	142	74.74%	48	25.26%	
Number of Comorbidity	1	87 (25.66%)	64	73.56%	23	26.44%	0.56
	2	59 (17.4%)	47	79.66%	12	20.34%	
	3	33 (9.73%)	24	72.73%	9	27.27%	
	> 3	11 (3.24%)	7	63.64%	4	36.36%	
Type of Comorbidity							
Hypertension	No	227 (66.96%)	175	77.09%	52	22.91%	0.9
	Yes	112 (33.04%)	86	76.79%	26	23.21%	
Diabetes	No	270 (79.65%)	209	77.41%	61	22.59%	0.72
	Yes	69 (20.35%)	52	75.36%	17	24.64%	
Cardiac Comorbidity	No	313 (92.33%)	242	77.32%	71	22.68%	0.62
	Yes	26 (7.67%)	19	73.08%	7	26.92%	
Pulmonary Comorbidity	No	323 (95.28%)	249	77.09%	74	22.91%	0.85
	Yes	16 (4.72%)	12	75.00%	4	25.00%	
Renal Comorbidity	No	327 (96.46%)	255	77.98%	72	22.02%	0.35
	Yes	12 (3.54%)	6	50.00%	6	50.00%	
Other	No	225 (66.37%)	177	78.67%	48	21.33%	0.3
	Yes	114 (33.63%)	84	73.68%	30	26.32%	
Type of cancer	Breast Cancer	104 (30.68%)	85	81.73%	19	18.27%	0.06
	Connective tumors	17 (5.01%)	10	58.82%	7	41.18%	
	GI cancer	66 (19.47%)	51	77.27%	15	22.73%	
	Gynecology	15 (4.42%)	9	60.00%	6	40.00%	
	Head & Neck	24 (7.08%)	20	83.33%	4	16.67%	
	Hematology	49 (14.45%)	36	73.47%	13	26.53%	
	Neurosurgery	12 (3.54%)	6	50.00%	6	50.00%	
	Urology	41 (12.09%)	36	87.80%	5	12.20%	
	Other	11 (3.24%)	8	72.73%	3	27.27%	
Metastatic Disease	No	264 (77.88%)	203	76.89%	61	23.11%	0.94
	Yes	75 (22.12%)	58	77.33%	17	22.67%	
Neoadjuvant Therapy	No	166 (48.97%)	133	80.12%	33	19.88%	0.37
	Yes	173 (51.03%)	128	73.99%	45	26.01%	
Type of Neoadjuvant Therapy	RTx	11 (3.24%)	7	63.64%	4	36.36%	0.39
	CTx	124 (36.58%)	91	73.39%	33	26.61%	
	CRTx	38 (11.21%)	30	78.95%	8	21.05%	
Vaccine	No	183 (53.98%)	143	78.14%	40	21.86%	0.59
	Yes	156 (46.02%)	118	75.64%	38	24.36%	
COVID Waves	Wave 1	134 (39.53%)	111	42.50%	23	39.50%	0.039
	Wave 2	205 (60.47%)	150	57.50%	55	60.50%	
Symptomatic	No	152 (44.84%)	125	82.24%	27	17.76%	**0.039**
	Yes	187 (55.16%)	136	72.73%	51	27.27%	

Table 1 (continued)

Variable	Level	Total Cohort *N* (%)	Postoperative Complications = No (*N* = 261, 77%)		Postoperative Complications = Yes (*N* = 78, 23%)		*P* value
			Frequency	(%)	Frequency	(%)	
Delay Periods (Between COVID-19 and Surgery)	Less than 2 weeks	56.0 (16.5%)	29	11.1%	27	34.6%	**< 0.001**
	From 2 to 3 weeks	49.0 (14.5%)	44	16.9%	5	6.4%	
	More than 3 weeks	234.0 (69.0%)	188	72%	46	59%	
ASA	1	12 (3.54%)	10	83.33%	2	16.67%	0.27
	2	301 (88.79%)	231	76.74%	70	23.26%	
	3	23 (6.78%)	19	82.61%	4	17.39%	
	4	3 (0.88%)	1	33.33%	2	66.67%	
Grade of surgery	Major	156 (46.02%)	113	72.44%	43	27.56%	0.18
	Medium	97 (28.61%)	78	80.41%	19	19.59%	
	Minor	86 (25.37%)	70	81.40%	16	18.60%	
Length Of Stay (Days)	Mean (SD)	3.3 (7.8)	2.1 (3.6)		7.3 (14.1)		< 0.0001
	Range	0–99	0–37		0–99		

Table 2 Rate and types of postoperative complications

Variable	Level	*N* (%)
postoperative complications	No	78 (23.01%)
	Yes	261 (76.99%)
Percent of complication types Out of the overall complications		
Pulmonary After Surgery		19 (24.36%)
SSI		23 (29.49%)
VTE		4 (5.13%)
AKI		7 (8.97%)
Cardiac After Surgery		4 (5.13%)
Sepsis		5 (6.41%)
UTI		5 (6.41%)
30-Days Mortality Post-Op		7 (8.97%)
30-Days Readmission		23 (29.49%)
30-Days Reoperation		13 (16.67%)
Frequency and distribution of complications according to Clavien-Dindo classification		
I		14 (17.95%)
II		42 (53.85%)
IIIa		2 (2.56%)
IIIb		13 (16.67%)
IV		0 (0%)
V		7 (8.97%)

In an ambidirectional cohort study conducted by Ranganathan et al. on 348 cancer patients who underwent surgery within a median of 45 days (7 weeks) post COVID-19 diagnosis, it was found that the severity of COVID-19 (mild vs. moderate) and the timing of surgery within 7 weeks of a COVID-19 diagnosis did not significantly affect postoperative complications or mortality (OR 1.95, $p = 0.32$; OR 0.61, $p = 0.10$, respectively) [17]. In contrast, our study findings indicate that patients who underwent surgery before 17 days had significantly higher rates of postoperative complications, including reoperation, pulmonary complications, and longer length of stay. This emphasizes that a waiting period of at least 17 days post COVID-19 infection is associated with improved postoperative outcomes, particularly in terms of postoperative complications. The contradiction between our study and Ranganathan et al.'s study could be related to a longer cutoff used (45 days vs. 17 days), variations in patient demographics and COVID-19 severity, which was not part of our study. One notable variation between our studies is that we used a statistically determined cutoff point whereas they used a median, leading to the difference in results.

In a nationwide cohort study by Ju et al., which included 99,555 cancer patients in South Korea, 30,933 (31.1%) had a preoperative COVID-19 diagnosis [18]. According to their findings, patients who had surgery within two weeks after COVID-19 infection had much higher 30-day death rates (adjusted OR 1.47, 95% CI 1.02–2.12, $p = 0.038$), and 90-day mortality showed comparable patterns. Furthermore, complete vaccination had a significant association with a decrease in both 30-day postoperative mortality (OR 0.38, $p < 0.001$) and 90-day postoperative mortality (OR 0.39, $p < 0.001$). Takeuchi et al. conducted another study on the timing of surgery following COVID-19 infection. They found that patients who underwent surgery within four weeks of being infected with COVID-19 had a higher risk of postoperative complications (OR 1.57, $p = 0.095$), with pneumonia being the most common (OR 2.31, 95%, $p = 0.071$) than patients who underwent surgery more than four weeks after COVID-19 diagnosis [19]. Both studies are consistent with our results, which point to a greater risk of complications after surgery within a short interval after a COVID-19 diagnosis, especially within the 17-day window that we determined. Our study found no significant differences in postoperative complications between vaccinated and unvaccinated patients. This may be due to some patients being treated before the vaccine rollout and the use of different vaccine types with varying efficacies. Notably, vaccinated patients had a shorter time

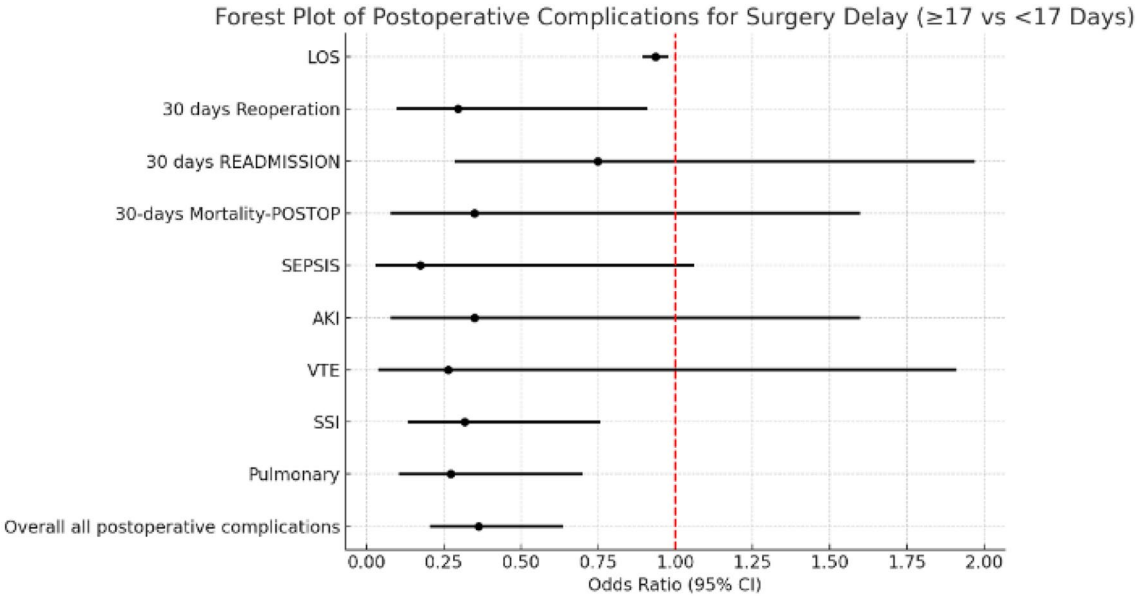

Fig. 1 Odds ratio for postoperative complications for the two groups (the reference group being those with less than a 17-day delay)

Table 3 Multivariable analysis of postoperative complications

Predictor	Estimate	SE	Z	*p*	Odds ratio	95% Confidence Interval	
						Lower	Upper
Intercept	-1.14	0.399	-2.86	0.004	0.32	0.146	0.699
Wave:							
Wave 2– Wave 1	0.391	0.297	1.32	0.188	1.479	0.826	2.648
Two group:							
≥ 17– <17	-0.941	0.305	-3.08	0.002	0.39	0.214	0.71
Symptomatic:							
Yes– No	0.647	0.277	2.34	0.019	1.91	1.11	3.288

Note. Estimates represent the log odds of "post-op complication = Yes" vs. "post-op complication = No"

to surgery, which could have contributed to their higher complication rates in our study.

As reported by Nepogodiev et al., A prospective cohort study of 19,684 patients with perioperative SARS-CoV-2 infection (December 2021 to February 2022) found that mortality and 30-day postoperative pulmonary complications significantly decreased compared to the first COVID-19 wave [20]. Conversely, we observed that postoperative outcomes were better in wave 1 than in wave 2, although this trend dissolved in multivariable analysis. This suggests that the initially favorable outcomes in wave 1 were due to patients having a longer time between COVID-19 infection and surgery compared to those in wave 2. It should also be noted that wave 2 had more comorbidities, more neoadjuvant chemotherapy compared to wave 1.

These results highlight the significance of scheduling surgery following COVID-19 infection, and more investigations are required to fully comprehend the impact of COVID-19 vaccine on surgical outcomes.

The strengths of our study include a large sample size of cancer patients; inclusion of varied elective surgery specialties following COVID-19 infection, and the application of a well-defined cutoff date of 17 days following infection, enables us to make strong inferences on the influence of surgical timing on postoperative outcomes. On the other hand, the study's limitations stem from a single-center setting and retrospective methodology. Furthermore, the severity of COVID-19 was not taken into consideration in our investigation, which would have allowed for a more precise analysis of postoperative outcomes, the absence of long-term follow-up is another limitation. Future studies should focus on stratifying patients by cancer type and surgery complexity to provide more tailored recommendations, also studies should investigate the long-term consequences of varied time intervals between COVID-19 infection and surgery, encompassing COVID-19 infection severity. In addition, larger, multi-center cohort studies are required to validate our results and evaluate the effect of vaccination

status on postoperative outcomes following COVID-19 infection.

Conclusion

Identifying and addressing risk factors for postoperative complications is crucial for improving health outcomes. The COVID-19 pandemic shifted the medical focus to its risks and associations with outcomes. This study emphasizes the importance of timing of surgery in cancer patients after a COVID-19 diagnosis. Our findings indicate that delaying surgery for at least 17 days, or 2–3 weeks post-infection, significantly reduces complications, underscoring the need to consider elective surgery timing to minimize adverse events.

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Author contributions
M.A., Y.S., and O.A. contributed to the conceptualization of the study, writing of the manuscript, and interpretation of the analysis. R.K. participated in all aspects of the study except conceptualization, including data collection, analysis, manuscript writing, and final review. L.A., A.M., F.A., and Y.S. were responsible for data collection, manuscript review, and editing. All authors contributed to the final review and approved the manuscript for submission. Y.S was responsible for data analysis.

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Data availability
Data AvailabilityThe datasets analyzed during the current study are available upon reasonable request from thecorresponding author. Due to privacy concerns associated with patient data, the datasets are not publiclyavailable.

Declarations

Ethics approval and consent to participate
This retrospective chart review study was performed in accordance with the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of King Hussein Cancer Center (Approval No: 21 khcc 169). Due to the retrospective nature of the study, informed consent from individual participants was not required. All patient data was anonymized to ensure confidentiality.

Consent for publication
As this study involves retrospective data and does not include individual data or images that could identify participants, consent for publication was not required.

Competing interests
The authors declare no competing interests.

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