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REPORTS OF ORIGINAL INVESTIGATIONS

Chemotherapy within 30 days before surgery does not augment postoperative mortality and morbidity

La chimiothérapie dans un délai de 30 jours avant l'intervention chirurgicale n'augmente pas la mortalité et la morbidité postopératoires

Alparslan Turan, MD · Diana Shao · Vafi Salmasi, MD · Hooman Honar, MD · Abdulkadir Atim, MD · Jarrod E. Dalton, MA · Leif Saager, MD · Daniel I. Sessler, MD

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Abstract

Background *Preoperative chemotherapy is frequently given to shrink or decrease the chance of metastasis. However, chemotherapy has well-recognized side effects that may complicate the perioperative period. We therefore tested the hypotheses that chemotherapy within 30 days before cancer surgery is associated with an increased risk of mortality and with a composite of major morbidities within 30 postoperative days.*

Methods *We evaluated 971,455 patients from the American College of Surgeons National Surgical Quality Improvement Program database. Patients were defined as having chemotherapy when they were given any chemotherapy for malignancy within 30 days before surgery. We successfully matched 1,348 pairs of chemotherapy recipients and non-recipients.*

Results *Twenty-one of the 1,348 (1.6%) non-chemotherapy patients died within 30 days after surgery compared with 30 of the 1,348 (2.2%) chemotherapy patients. The odds of mortality were not statistically different between groups based on our logistic regression model [odds ratio (OR) = 1.47; 95% confidence interval (CI) 0.82 to 2.64; P = 0.19]. The most common complication observed was wound infection in 13.1% of non-chemotherapy patients compared with 14.2% of the chemotherapy patients. There was similarly no difference between groups for the collapsed composite of major morbidities [OR = 1.17; 95% CI 0.97 to 1.42; P = 0.09].*

Conclusion *Preoperative use of neoadjuvant chemotherapy in cancer patients undergoing resection surgeries was not associated with a higher rate of early postoperative complications or mortality.*

Résumé

Contexte *La chimiothérapie préopératoire est souvent utilisée pour réduire la taille de métastases ou en diminuer le risque. Cependant, la chimiothérapie entraîne des effets indésirables bien identifiés qui risquent de compliquer la période périopératoire. Nous avons donc testé les hypothèses selon lesquelles la chimiothérapie administrée dans un délai de 30 jours avant une chirurgie oncologique était associée à une augmentation du risque de mortalité et à un ensemble de morbidités majeures survenant dans les 30 premiers jours postopératoires.*

Méthode *Nous avons évalué 971 455 patients de la base de données du Programme national pour l'amélioration de la qualité de la chirurgie de l'American College of*

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A. Turan, MD (✉) · D. Shao · V. Salmasi, MD · H. Honar, MD · A. Atim, MD · L. Saager, MD · D. I. Sessler, MD
Department of Outcomes Research, Cleveland Clinic, 9500 Euclid Avenue, P-77, Cleveland, OH 44195, USA
e-mail: alparslanturan@yahoo.com
URL: www.OR.org

J. E. Dalton, MA
Departments of Quantitative Health Sciences and Outcomes Research, Cleveland Clinic, Cleveland, OH, USA

Surgeons. Les patients étaient considérés avoir eu une chimiothérapie quand ils en avaient reçu une pour tumeur maligne dans les 30 jours précédant l'intervention chirurgicale. Nous avons apparié avec succès 1348 paires de patients (patients ayant reçu une chimiothérapie et patients n'en ayant pas reçu).

Résultats *Parmi les 1348 patients n'ayant pas reçu de chimiothérapie, 21 (1,6 %) sont décédés dans les 30 jours suivant l'intervention, comparativement à 30 (2,2 %) des 1348 patients ayant reçu une chimiothérapie. La probabilité de mortalité n'a pas été statistiquement différente entre les deux groupes d'après notre modèle de régression logistique (rapport de cotes [RC] = 1,47; intervalle de confiance à 95 % [IC] : 0,82 à 2,64; P = 0,19). La complication observée la plus fréquente a été une infection de la cicatrice chez 13,1 % des patients n'ayant pas reçu de chimiothérapie et 14,2 % des patients ayant reçu une chimiothérapie. De même, il n'y a pas eu de différence entre les groupes pour l'ensemble des morbidités majeures (RC = 1,17; 95 % IC : 0,97 à 1,42; P = 0,09).*

Conclusion *L'administration préopératoire d'une chimiothérapie néoadjuvante chez des patients atteints de cancer et devant subir une excision chirurgicale n'a pas été associée à des taux de complications postopératoires précoces ou de mortalité plus élevés.*

Cancer is the second leading cause of death in the United States killing more than 500,000 Americans in 2009.[1] Surgery, radiation, and chemotherapy are the mainstays of cancer treatment. Chemotherapy can be used as a primary treatment or as an adjunct to surgery with or without concomitant radiation. Chemotherapy is sometimes used before surgery — as a neoadjuvant treatment — or after surgery, often for more advanced cancer.

Neoadjuvant chemotherapy is generally used when it is expected to shrink tumours and thus facilitate surgery or when it might reduce the risk of local or metastatic cancer recurrence.[2] On the other hand, chemotherapy also causes cardiac toxicity, pulmonary damage, and myelosuppression, with consequent anemia, coagulopathy, and infection risk. The anti-cancer benefits of neoadjuvant chemotherapy are thus balanced by the potential acute perioperative risk induced by these relatively toxic drugs.

Meta-analyses of randomized trials along with subsequent randomized trials suggest that neoadjuvant chemotherapy and/or radiation therapy slightly increases the risk of morbidity and mortality.[3-6] Nordlinger *et al.*[7] evaluated the effect of perioperative chemotherapy on hepatic metastasis and showed a 36% increase in complications with chemotherapy. Other studies, though, failed to show any association between preoperative chemotherapy and increased postoperative mortality or morbidity.[8-12]

The results of available studies are thus inconsistent; furthermore, they suffer from limited sample size and the fact that most were restricted to specific types of cancer. More inclusive studies with larger sample sizes are therefore warranted. We consequently tested the hypotheses that cancer chemotherapy within 30 days before surgery is associated with increased risk of 1) 30-day postoperative mortality; and, 2) a composite of major morbidities within 30 postoperative days.

Methods

With the approval of the Institutional Review Board, we analyzed patients enrolled in the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) registry from January 1, 2005 to December 31, 2009. A dedicated clinical nurse reviewer collected data from patients' medical records, physicians' office records, and telephone interviews with patients. The data were collected prospectively using standardized definitions of each variable and outcome. The accuracy and reproducibility of these data have been established.[13,14]

Data sources

Patients were identified by interrogating the ACS-NSQIP database for Current Procedural Terminology (CPT) codes relating to cancer surgery (Table 1). Patients were subsequently excluded if the extracted ACS-NSQIP record indicated: functionally dependent (patient's ability to perform activities of daily living in 30 days prior to surgery, dependent defined as the patient requiring total assistance for all activities of daily living), American Society of Anesthesiologists' physical status classification of "moribund" (patient who is not expected to survive without an operation), preoperative pneumonia (evidence of preoperative pneumonia determined by clinical, radiological and microbiological evidence), ventilator-assisted respiration during the 48 hr before surgery, preoperative coma, open-wound infection before surgery, or preoperative sepsis. In the ACS-NSQIP database, patients were defined as having

Table 1 Types of cancer and their associated CPT codes

Type of cancer	Associated CPT codes
Breast Cancer	19160, 19162, 19180, 19240
Colon Cancer	44320, 44140, 44141, 44143, 44145, 44146
Rectal Cancer	45110
Liver Cancer	47120, 47122, 47125,47130
Pancreatic Cancer	48140, 48150, 48153

CPT = Current Procedural Terminology

chemotherapy when they had any chemotherapy for malignancy within 30 days before surgery (hormonal therapy was not included).

Our primary outcomes were 30-day postoperative mortality and a collapsed composite (any *vs* none) of the major morbid outcomes listed in Table 2, each of which is potentially related to chemotherapy-induced toxicity. Crude odds ratios (OR) comparing chemotherapy patients with those who were not given chemotherapy were estimated to describe population trends; however, these results were subject to potential confounding because the baseline characteristics differed.

To limit confounding, we matched chemotherapy patients to non-chemotherapy patients on both propensity scores and CPT code. The propensity scores were estimated using logistic regression with chemotherapy as the response and the baseline variables as the predictors (see Table 3). A 1:1 greedy matching algorithm was used with 0.01 propensity score units as the maximum allowable distance for matching. Exact matching on CPT code was enforced. To evaluate the success of matching, absolute standardized difference (ASD, or the absolute difference in means or proportions divided by the pooled standard deviation) scores were calculated for all unmatched patients and the subset of matched patients. Absolute standardized difference scores were used to summarize balance between the two samples. Although there is no consensus on what value of standardized difference denotes important residual imbalance, values of < 0.1 are generally considered to represent reasonably balanced groups.[15] Potential confounders displaying such imbalance were used for statistical adjustment in all subsequent analyses.

Matched chemotherapy patients and non-chemotherapy patients were compared on 30-day mortality and the collapsed composite outcome using respective multivariable conditional logistic regression models. Conditional logistic regression accounts for any correlation in outcomes that may be exhibited among patients within a given matched pair. Variables with a standardized difference of > 0.1 were included in the model in an attempt to address any residual confounding. We used Wald's Chi square test for regression model parameters to evaluate the null hypothesis of no difference in outcomes between those who did and those who did not receive chemotherapy preoperatively. The type I error rate was set at 5%. Odds ratios and 95% confidence intervals (CI) were also estimated using the conditional logistic regression models.

Our collapsed composite outcome was defined as any or none of the major morbidities. However, because the major morbidity outcomes are likely not of equal weight, we performed a sensitivity analysis in which we weighted the major morbidity outcomes by clinical severity. First, three otherwise uninvolved anesthesiologists independently scored the relative severity of each individual outcome on a scale of 0-100, with 100 being the most severe. The average of those scores for a given outcome was defined as a severity weight for that outcome. The weights are given in Table 4. A multivariate generalized estimating equations (GEE) model was then used to estimate a severity-weighted common effects OR across the components.[16]

Table 2 Definitions of the major complications analyzed in this study

Complication	Definition	Overall Incidence	Matched Incidence
30-day mortality	postoperative 30-day mortality	1.7%	1.9%
Systemic infections	systemic inflammatory response syndrome (SIRS), sepsis, or septic shock	7.2%	7.0%
Respiratory morbidity	pneumonia, failure to wean from ventilation at 48 hr postoperative, or unplanned tracheal intubation	5.2%	4.3%
Wound infection	superficial and deep wound infections, organ/space infections, or wound disruptions	14.2%	13.6%
Urinary tract morbidity	urinary tract infections, progressive renal insufficiency, and acute renal failure	4.8%	5.2%
Central nervous system morbidity	stroke, coma greater than 24 hr postoperatively, and peripheral nerve injury	0.5%	0.2%
Thrombotic morbidity	pulmonary embolism, deep venous thrombosis, and thrombophlebitis	2.0%	2.2%
Cardiovascular morbidity	acute myocardial infarction and cardiac arrest requiring resuscitation	1.0%	0.9%
Other	failure of a graft, prosthesis, or flap	0.1%	0.1%
Collapsed composite	Any of the above outcomes (*vs* none)	23.4%	22.5%

Table 3 Summary of baseline factors among patients before and after propensity matching. Data are presented as a percentage, mean (standard deviation), or median [1st quartile, 3rd quartile]

Factor	All Cancer Patients ($n = 49{,}103$)			Matched Patients ($n = 2{,}696$)		
	Chemotherapy			Chemotherapy		
	No ($n = 47{,}499$)	Yes ($n = 1{,}604$)	ASD	No ($n = 1{,}348$)	Yes ($n = 1{,}348$)	ASD
Female	59	59	<0.01	59	60	0.02
Race			0.08			0.09
Hispanic	4	5		5	5	
Black	9	8		9	8	
White	76	76		75	76	
Asian or Pacific Islander	3	3		4	3	
Unknown/other	9	8		7	8	
Body mass index ($kg \bullet m^{-2}$)	27 [23, 31]	27 [23, 31]	0.09	27 [23, 31]	27 [23, 31]	0.02
Age	62 (14)	57 (13)	0.33	58 (14)	58 (12)	0.03
History of COPD	5	3	0.11	2	3	0.05
Type of cancer			0.59			0.00
Breast cancer	16	24		25	25	
Colon cancer	51	35		33	33	
Rectal cancer	4	9		9	9	
Liver cancer	11	24		25	25	
Pancreatic cancer	18	8		8	8	
Disseminated cancer	8	37	0.74	33	32	0.02
General anesthesia (*vs* other)	98	99	0.08	100	99	0.07
Dyspnea	10	10	<0.01	10	10	0.01
Hypertension	49	38	0.23	39	40	0.02
Renal failure	0	0	0.02	0	0	0.02
Diabetes mellitus			0.09			0.04
Insulin-dependent	5	4		86	87	
Orally-controlled	10	8		9	9	
None	85	88		5	4	
Current smoker (within one year)	19	18	0.02	18	18	0.00
Alcohol consumption (> 2 drinks/day within 2 weeks)	3	2	0.06	3	2	0.04
ASA classification			0.18			0.04
Healthy	4	2		2	2	
Mild disease	45	40		42	42	
Severe disease	47	53		53	52	
Life-threatening disease	4	5		4	4	
Emergency case	6	5	0.01	5	4	0.04
Congestive heart failure	1	0	0.06	0	0	0.00
Hemiplegia	0	1	0.02	0	1	0.02
Stroke	1	1	0.01	2	1	0.02
Bleeding disorders	4	4	0.04	4	4	0.01
Transfusion > 4 units before surgery	0	0	<0.01	0	0	0.00
Radiotherapy	3	22	0.59	15	17	0.06
Hematocrit (%)*	38 (5)	37 (5)	0.34	38 (5)	37 (5)	0.29
Platelet count (10^3 platelets$\bullet mL^{-1}$)*	260 [211, 320]	239 [184, 308]	0.23	251 [204, 308]	241 [186, 309]	0.11
PTT (sec)*	29 [26, 32]	28 [26, 31]	0.08	29 [26, 32]	29 [26, 31]	0.06

Table 3 continued

Factor	All Cancer Patients ($n = 49{,}103$)			Matched Patients ($n = 2{,}696$)		
	Chemotherapy			Chemotherapy		
	No ($n = 47{,}499$)	Yes ($n = 1{,}604$)	ASD	No ($n = 1{,}348$)	Yes ($n = 1{,}348$)	ASD
International normalized ratio of PT*	1 [1, 1]	1 [1, 1]	0.04	1 [1, 1]	1 [1, 1]	0.04

*These preoperative labs were not included in matching due to large amounts of missing data (data were missing for 4.9%, 5.9%, 44.3%, and 37.5% of patients, respectively)

ASA = American Society of Anesthesiologists; ASD = absolute standardized difference (absolute difference in means or proportions divided by the pooled standard deviation); COPD = chronic obstructive pulmonary disease; PTT = partial thromboplastin time; PT = prothrombin time

We used R statistical software version 2.13.0 (The R Foundation for Statistical Computing, Vienna, Austria) and SAS® statistical software version 9.2 (SAS Institute, Inc., Cary, NC, USA) for all statistical analyses.

Results

Among the 971,455 surgical cases available in the ACS-NSQIP database, 49,103 were ultimately available for use in our study after a series of inclusions and exclusions, which are summarized in the Figure. Only a tiny proportion of patients were classified as functionally dependent and thus excluded from analysis; we therefore assumed that the 259 patients in whom functional status was unavailable were functionally independent.

In our crude unadjusted analysis, we found that chemotherapy was associated with 30-day mortality (OR = 1.71; 95% CI 1.21 to 2.42; $P < 0.001$). Our collapsed composite outcome, on the other hand, did not differ significantly (OR = 1.07; 95% CI 0.93 to 1.22; $P = 0.825$). However, these unadjusted results were likely confounded by imbalances in important baseline variables (Table 3). For example, it was more likely that chemotherapy recipients would have disseminated cancer, would be younger, would not have hypertension, would have had radiotherapy, and would have breast, rectal, or liver cancer.

We successfully matched 1,348 pairs of chemotherapy recipients and non-recipients. A summary of baseline demographic and perioperative factors for all patients and matched patients can be found in Table 3. As the small ASD values show (no ASD values > 0.1), the propensity matched patients displayed a much better balance in baseline variables, indicating that propensity matching was successful in limiting the effects of these possible confounders on our analysis.

Postoperative 30-day outcomes for matched patients are summarized in Table 5. Twenty-one of the 1,348 (1.6%) non-chemotherapy patients died within 30 days after surgery, compared with 30 of the 1,348 (2.2%) chemotherapy patients. Based on our logistic regression model, the corresponding OR (95% CI) for mortality (chemotherapy *vs* non-chemotherapy) was estimated at 1.47 (0.82 to 2.64), which was not statistically significant ($P = 0.19$). Therefore we were unable to conclude that these two groups differed in their risk for mortality.

There was similarly no apparent difference between groups for the collapsed composite outcome (OR = 1.17; 95% CI 0.97 to 1.42; $P = 0.09$). In our common effect GEE analysis, the severity-weighted vector of outcomes yielded results that were similar to those of the collapsed

Table 4 Thirty-day major morbidities and their weights (used for the vector of weighted outcomes) as determined by averaging the scores of three independent anesthesiologists

Major morbidity	Severity Weight (%)
Superficial SSI	20
Urinary tract infection	23
Peripheral nerve injury	27
Wound disruption	27
DVT/Thrombosis	30
Deep SSI	33
Unplanned tracheal intubation	37
Failure of a graft, prosthesis, or flap	37
Organ/Space SSI	43
Failure to wean	47
Progressive renal insufficiency	47
Pneumonia	47
Pulmonary embolism	50
Acute renal failure	50
Stroke	63
Sepsis	63
Acute MI	67
Coma	70
Septic shock	80
Cardiac arrest	80
Mortality	100

SSI = surgical site infection; DVT = deep venous thrombosis; MI = myocardial infarction

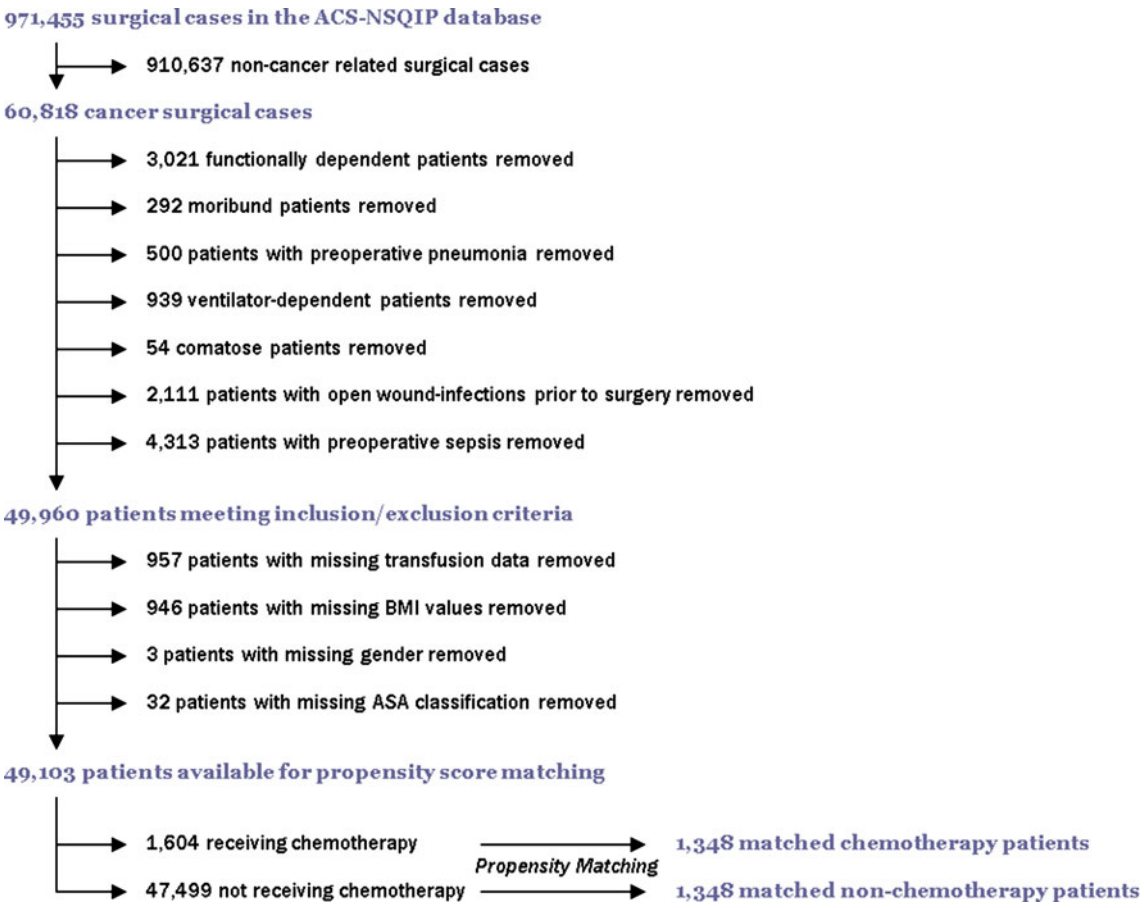

Figure Summary of study inclusion/exclusion criteria and results of matching procedure

composite outcome ($P = 0.22$). The OR (95% CI) estimating the global association between chemotherapy and major morbidity weighted by clinical severity of components was 1.15 (0.92 to 1.43).

Discussion

Our analysis indicates that the odds of mortality or composite morbidity 30 days after surgery appears not to differ in patients who were or were not given chemotherapy within 30 days before surgery. This result is surprising since all chemotherapeutic agents, regardless of type, produce a wide range of detrimental effects. For example, common chemotherapeutic drugs cause immune suppression, pulmonary and cardiac toxicity, and myelosuppression. Our results are consistent with some previous studies but diverge from others.

For example, some studies suggest that chemotherapy is a perioperative risk factor while other studies failed to show any association between neoadjuvant chemotherapy and perioperative morbidity or mortality.[9,17] Two other studies identified an increase in infectious complications and delayed wound healing with chemotherapy.[18,19] We note though that the infection studies were restricted to patients having surgery for rectal cancer, which has an extremely high baseline infection risk. In contrast, we included a broad range of surgical indications.

Meric *et al.*[9] found no association between chemotherapy and mortality and morbidity, which is consistent with our findings. In two other studies, there was also no association with chemotherapy and mortality or morbidity in patients having surgery for esophageal cancer. Our results are also consistent with Shapiro *et al.*[20] who did not find any intraoperative or postoperative complications in breast cancer patients given doxorubicin before surgery. A potential limitation of studies that did not identify an adverse effect of preoperative chemotherapy is that most were small and therefore possibly underpowered to detect important clinical outcomes. Our analysis of 2,696 matched patients is a much larger study to evaluate the potential adverse effects of preoperative chemotherapy. While our matched sample contained a sufficient number of events for detecting clinically meaningful differences in the composite outcome, the low incidence of mortality resulted in rather imprecise estimates of the effect of

Table 5 Association between chemotherapy status and major morbidity outcomes, including the composite outcome, before and after propensity matching

Outcome	Matched Patients (n = 2,696)			
	Chemotherapy			
	No (n = 1,348) n (%)	Yes (n = 1,348) n (%)	OR (95% CI)	P value
30-day mortality	21 (1.6)	30 (2.2)	1.47 (0.82 to 2.64)	0.19
Collapsed composite of major morbidities*	286 (21.2)	321 (23.8)	1.17 (0.97 to 1.42)	0.09
Weighted vector of major morbidities †	–	–	1.15 (0.92 to 1.43)	0.22
Individual morbidities				
Systemic infections	88 (6.5)	101 (7.5)	–	–
Respiratory	57 (4.2)	59 (4.4)	–	–
Wound infection	176 (13.1)	191 (14.2)	–	–
Urinary tract	63 (4.7)	77 (5.7)	–	–
Central Nervous System	3 (0.2)	2 (0.1)	–	–
Thrombotic	26 (1.9)	33 (2.4)	–	–
Cardiovascular	11 (0.8)	12 (0.9)	–	–
Other	0 (0.0)	2 (0.1)	–	–

*The collapsed composite is defined as any (*vs* none) of the major morbidities listed in Table 1

†The weighted vector of major morbidities used severity weights (as determined by three independent anesthesiologists) of each major morbidity in a multivariable generalized estimating equations (GEE) model to estimate the odds ratio, which is the estimated global association between chemotherapy and major morbidity weighted by the severity of its components

CI = confidence interval

chemotherapy on postoperative mortality (we had 51 deaths in our matched sample).

We exactly matched for type of surgery, which is a major determinant of early postoperative outcome. We similarly adjusted for all available imbalanced and preoperative baseline factors that may affect short-term perioperative outcomes. Nonetheless, our retrospective analysis was limited by availability of data in the ACS-NSQIP registry, which lacked important potential confounding variables, such as the type and staging of the cancer and the type of chemotherapy. The extent to which these and other potential confounding factors may have influenced our conclusions is unclear, but presumably, chemotherapy was more likely to have been used for advanced disease and thus in patients at greatest perioperative risk. Even considering this potential bias, our data did not suggest an increase in mortality or major morbidities in patients given preoperative chemotherapy. There are some other limitations of the ACS-NSQIP registry. The ACS-NSQIP is limited to the hospitals participating, which may not be a valid national representative sample of hospitals, although ACS-NSQIP is by far the largest available surgical registry. Furthermore, not all the cases are entered from participating hospitals; however, any bias relating to the chemotherapy status of patients entered in the registry is unlikely.

Our analysis was restricted to 30-day morbidities and mortality. We thus cannot estimate the longer-term (i.e., one-year) consequences of preoperative chemotherapy; however, since 30-day morbidity and mortality were comparable with and without chemotherapy, it appears that the acute effects are not harmful — leaving open the possibility of long-term benefit in terms of reducing the risk of cancer recurrence.

In summary, we found no association between the preoperative use of neoadjuvant chemotherapy and early postoperative complications or mortality in cancer patients undergoing resection surgeries. In cases where preoperative chemotherapy potentially reduces the risk of local or metastatic recurrence, our results suggest that it should generally not be avoided for fear of acute perioperative toxicity.

Conflicts of interest None declared.

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