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ASO RESEARCH LETTER

Association of Neoadjuvant Immunotherapy With Postoperative Major Morbidity After Oncologic Surgery

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ABSTRACT

Background. Despite increasing use of immunotherapy in the treatment of various cancer types, understanding of its impact on postoperative complications still is limited. This study aimed to characterize the association between neoadjuvant immunotherapy and surgical outcomes for rectal, colon, anal, esophageal, lung (non-small cell), and oral cavity cancers.

Methods. Using the National Cancer Database (NCDB), the study selected patients ages 18–90 years who underwent non-palliative oncologic surgery between 2010 and 2020. The primary outcome was major morbidity, defined as hospital length of stay within the top decile of each surgery subtype, unplanned 30-day readmission, or 30-day mortality. Multivariable logistic regressions for major morbidity were performed to assess neoadjuvant immunotherapy effects by cancer type while controlling for patient demographics, Charlson-Deyo comorbidity index, cancer staging, procedure type, surgical approach, and other treatment (e.g., chemotherapy or radiotherapy).

Results. Of 1,348,334 cases with any of the six cancer types, the study sample included 953,612 cases. Of these cases, 4771 (0.5 %) involved neoadjuvant immunotherapy, and 948,841 (99.5 %) did not. The pooled odds ratio was 0.98 (95% confidence interval [CI] 0.81–1.19). Neoadjuvant immunotherapy was not significantly associated with major morbidity after surgery for rectal (adjusted odds ratio [aOR], 0.83; 95% CI 0.60–1.16), colon (aOR, 1.27; 95% CI 0.87–1.85), anal (aOR, 1.90; 95 % CI 0.16–23.15), esophageal (aOR, 0.35; 95% CI 0.08–1.49), lung (non-small cell) (aOR, 1.06; 95% CI 0.65–1.73), or oral (aOR, 1.10; 95% CI 0.61–2.00) cancer.

Conclusions. Neoadjuvant immunotherapy is not significantly associated with postoperative complications across several cancer types. As the largest study on neoadjuvant immunotherapy postoperative complications, this study suggests that surgery in the setting of neoadjuvant immunotherapy is safe.

Keywords Anal cancer · Colon cancer · Esophageal cancer · Non-small cell lung cancer · Oral cancer · Immunotherapy · Neoadjuvant · Postoperative complications

Immunotherapy has revolutionized cancer treatment, with increasing adoption across various cancer types.[1] Whereas the impact of neoadjuvant chemotherapy on surgical outcomes has been extensively studied,[2] few studies have assessed surgical complication risks associated with neoadjuvant immunotherapy.[3,4] Determining whether neoadjuvant immunotherapy compromises surgical safety is crucial for refining patient selection for cancer resection. This study aimed to characterize the association between neoadjuvant immunotherapy use and surgical outcomes for rectal, colon,

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TABLE 1 Characteristics of patients who received neoadjuvant immunotherapy versus no neoadjuvant immunotherapy before<AQ4> receiving non-palliative rectal, colon, anal, esophageal, lung (non-small cell), or oral cavity cancer surgery

	Rectum		Colon		Anus		Esophagus		Lung (non-small cell)		Oral cavity	
	Immuno-therapy	No immuno-therapy	Immuno-therapy	No immuno-therapy	Immuno-therapy	No immuno-therapy	Immuno-therapy	No immuno-therapy	Immuno-therapy	No immuno-therapy	Immuno-therapy	No immuno-therapy
	(n = 1352)	(n = 109,607)	(n = 2025)	(n = 468,074)	(n = 59)	(n = 19,664)	(n = 79)	(n = 6966)	(n = 982)	(n = 275,735)	(n = 274)	(n = 68,795)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Median age (IQR)	55 (47–63)	61 (52–70)	58 (49–67)	68 (58–78)	59 (50 – 67.5)	59 (51–69)	63 (55–70)	64 (58–70)	65 (59–71)	68 (61–74)	60 (51 – 67)	64 (55–72)
Sex												
Male	890 (65.8)	66,360 (60.5)	1069 (52.8)	23,1597 (49.5)	32 (54.2)	9097 (46.3)	69 (87.3)	5644 (49.5)	510 (51.9)	126,024 (45.7)	182 (66.4)	40,442 (58.8)
Female	462 (34.2)	43,247 (39.5)	956 (47.2)	236,477 (50.5)	27 (45.8)	10,567 (53.7)	10 (12.7)	1322 (50.5)	472 (48.1)	149,711 (54.3)	92 (33.6)	28,353 (41.2)
Race												
White	1158 (85.7)	92,939 (84.8)	1653 (81.6)	384,898(82.2)	44 (74.6)	16,112 (82.0)	77 (97.5)	6356 (91.2)	844 (85.9)	239,540 (86.9)	239 (87.2)	61,036 (88.7)
Black	93 (6.9)	9229 (8.4)	248 (12.2)	57,912 (12.4)	8 (13.6)	2862 (14.6)	1 (1.3)	357 (5.1)	82 (8.4)	23,595 (8.6)	18 (6.6)	3332 (4.8)
Other	89 (6.6)	6598 (6.0)	109 (5.4)	21,849 (4.7)	6 (10.2)	476 (2.4)	0 (5.4)	203 (2.9)	50 (5.1)	10,880 (3.9)	17 (6.2)	3679 (5.3)
Insurance (primary payor at diagnosis)												
Uninsured	46 (3.4)	3874 (3.5)	62 (3.1)	12,857 (2.8)	2 (3.4)	708 (3.6)	3 (3.8)	109 (1.6)	7 (0.71)	4038 (1.5)	9 (3.3)	2057 (3.0)
Private/managed care	835 (61.8)	51,791 (47.3)	1093 (54.0)	155,923 (33.3)	29 (49.2)	8331 (42.4)	36 (45.6)	2903 (41.7)	391 (39.8)	81,696 (29.6)	137 (50.0)	28,344 (41.2)
Medicaid, Medicare, or other government	448 (33.1)	52,685 (48.1)	853 (42.1)	294,033 (62.8)	28 (47.5)	10,359 (52.7)	38 (48.1)	3880 (55.7)	564 (57.4)	187,321 (67.9)	121 (44.2)	37,197 (54.1)
Charlson Comorbidity Index												
0	1088 (80.5)	82,427 (75.2)	1567 (77.4)	313,828 (67.0)	43 (72.9)	14,495 (73.7)	61 (77.2)	4812 (69.1)	634 (64.6)	149,231 (54.1)	196 (71.5)	50,949 (74.1)
1	198 (14.6)	19,251 (17.6)	320 (15.8)	97,589 (20.8)	9 (15.3)	2741 (13.9)	13 (16.5)	1558 (22.4)	228 (23.2)	81,090 (29.4)	56 (20.4)	12,082 (17.6)
2+	66 (4.9)	7929 (7.2)	138 (6.8)	56,657 (12.1)	7 (11.9)	2428 (12.3)	5 (6.3)	596 (8.6)	120 (12.2)	45,414 (16.5)	22 (8.0)	5764 (8.4)
Income above median ($)												
0–47,9999	421 (31.1)	38,565 (35.2)	635 (31.4)	165,662 (35.4)	16 (27.1)	7434 (37.8)	19 (24.1)	2281 (32.7)	310 (31.6)	94,842 (34.4)	87 (31.8)	21,595 (31.4)
>48,000k	686 (50.7)	55,666 (50.8)	1040 (51.4)	240,409 (51.4)	36 (61.0)	9688 (49.3)	43 (54.4)	3617 (51.9)	544 (55.4)	141,211 (51.2)	143 (52.2)	36,219 (52.6)

Table 1 (continued)

	Rectum		Colon		Anus		Esophagus		Lung (non-small cell)		Oral cavity	
	Immuno-therapy	No immuno-therapy	Immuno-therapy	No immuno-therapy	Immuno-therapy	No immuno-therapy	Immuno-therapy	No immuno-therapy	Immuno-therapy	No immuno-therapy	Immuno-therapy	No immuno-therapy
	(*n* = 1352)	(*n* = 109,607)	(*n* = 2025)	(*n* = 468,074)	(*n* = 59)	(*n* = 19,664)	(*n* = 79)	(*n* = 6966)	(*n* = 982)	(*n* = 275,735)	(*n* = 274)	(*n* = 68,795)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Education above high school degree												
≥ 10.9 %	486 (35.9)	45,785 (41.8)	733 (36.2)	194,964 (41.7)	27 (45.8)	8481 (43.1)	19 (24.1)	2642 (37.9)	411 (41.9)	109,907 (39.9)	118 (43.1)	25,085 (36.5)
< 10.8 %	621 (45.9)	48,603 (44.3)	946 (46.7)	211,830 (45.3)	25 (42.4)	8660 (44.0)	43 (54.4)	3263 (46.8)	444 (45.2)	126,609 (45.9)	112 (40.9)	32,853 (47.8)
Clinical T stage												
T1	24 (1.8)	8993 (8.2)	82 (4.0)	46,540 (9.9)	2 (3.4)	3836 (19.5)	2 (2.5)	1176 (16.9)	220 (22.4)	150,032 (54.4)	23 (8.4)	25,177 (36.6)
T2	64 (4.7)	13,134 (12.0)	40 (2.0)	20,188 (4.3)	5 (8.5)	3588 (18.2)	15 (19.0)	1222 (17.5)	310 (31.6)	67,924 (24.6)	78 (28.5)	15,623 (22.7)
T3	690 (51.0)	51,817 (47.3)	254 (12.5)	48,979 (10.5)	6 (10.2)	1457 (7.4)	49 (62.0)	3251 (46.7	252 (25.7)	18,838 (6.8)	75 (27.4)	4782 (7.0)
Clinical N stage												
N0	343 (25.4)	58,321 (53.2)	817 (40.3)	303,424 (64.8)	28 (47.5)	14,130 (71.9)	17 (21.5)	3449 (49.5)	410 (41.8)	220,464 (80.0)	102 (37.2)	49,435 (71.9)
N1	522 (38.6)	29,528 (26.9)	482 (23.8)	32,027 (6.8)	4 (6.8)	1189 (6.0)	35 (44.3)	2261 (32.5)	201 (20.5)	17,350 (6.3)	45 (16.4)	4994 (7.3)
N2	336 (24.9)	10,104 (9.2)	128 (6.3)	10,321 (2.2)	1 (1.7)	579 (2.9)	18 (22.8)	634 (9.1)	313 (31.9)	13,154 (4.8)	110 (40.1)	5999 (8.7)
Facility type												
Community program	22 (1.6)	5201 (4.7)	56 (2.8)	41,727 (8.9)	0 (0.0)	1116 (5.7)	0 (0.0)	99 (1.4)	13 (1.3)	9813 (3.6)	1 (0.36)	1493 (2.2)
Comprehensive community	303 (22.4)	39,888 (36.4)	464 (22.9)	196,648 (42.0)	11 (18.6)	6839 (34.8)	6 (7.6)	1673 (22.6)	185 (18.8)	104,848 (38.0)	7 (2.6)	13,209 (19.2)
Integrated network program	229 (16.9)	21,666 (19.8)	348 (17.2)	97,558 (20.8)	6 (10.2)	3656 (18.6)	15 (19.0)	1302 (18.7)	123 (12.5)	55,744 (20.2)	17 (6.2)	8925 (13.0)
Research/ academic program	659 (48.7)	38,246 (34.9)	1010 (49.9)	117,721 (25.2)	36 (61.0)	6673 (33.9)	56 (70.9)	3905 (56.1)	648 (66.0)	102,784 (37.3)	225 (82.1)	41,606 (60.5)
Neoadjuvant chemo-therapy	1330 (98.4)	61,973 (56.5)	1953 (96.4)	5249 (1.1)	13 (22.0)	1500 (7.6)	76 (96.2)	4625 (66.4)	635 (64.7)	11,914 (4.3)	89 (32.5)	591 (0.86)
Neoadjuvant radiation	852 (63.0)	60,939 (55.6)	0 (0)	0 (0)	7 (11.9)	1435 (7.3)	53 (67.1)	4332 (62.2)	167 (17.0)	7053 (2.6)	21 (7.7)	295 (0.43)

Table 1 (continued)

	Rectum		Colon		Anus		Esophagus		Lung (non-small cell)		Oral cavity	
	Immuno-therapy	No immuno-therapy	Immuno-therapy	No immuno-therapy	Immuno-therapy	No immuno-therapy	Immuno-therapy	No immuno-therapy	Immuno-therapy	No immuno-therapy	Immuno-therapy	No immuno-therapy
	(n = 1352)	(n = 109,607)	(n = 2025)	(n = 468,074)	(n = 59)	(n = 19,664)	(n = 79)	(n = 6966)	(n = 982)	(n = 275,735)	(n = 274)	(n = 68,795)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Procedure[a]/primary tumor subsite[b]												
1	982 (72.6)	81,899 (74.7)	826 (40.8)	164,792 (35.2)	41 (69.5)	17,282 (87.9)	46 (58.2)	4146 (59.5)	68 (6.9)	32,234 (11.7)	49 (17.9)	14,237 (20.7)
2	291 (21.5)	24,686 (22.5)	1118 (55.2)	289,169 (61.8)	18 (30.5)	2382 (12.1)	33 (41.8)	2820 (40.5)	823 (83.8)	232,273 (84.2)	6 (2.2)	5569 (8.1)
3	79 (5.8)	3022 (2.8)	66 (3.3)	11,749 (2.5)	N/A	N/A	N/A	N/A	8 (0.81)	2075 (0.75)	20 (7.3)	6472 (9.4)
4	N/A	N/A	15 (0.74)	2364 (0.51)	N/A	N/A	N/A	N/A	83 (8.5)	9153 (3.3)	199 (72.6)	42,517 (61.8)
Surgical approach at primary site												
Robot-assisted	396 (29.3)	24,908 (22.7)	201 (9.9)	43,706 (9.3)	4 (6.8)	514 (2.6)	10 (12.7)	873 (12.5)	249 (25.4)	53,322 (19.3)	0 (0)	0 (0)
Laparoscopic	298 (22.0)	30,465 (27.8)	611 (30.2)	203,163 (43.4)	15 (25.4)	6288 (32.0)	30 (38.0)	2161 (31.0)	252 (25.7)	75,130 (27.2)	0 (0)	0 (0)
Open	658 (48.7)	54,234 (49.5)	1213 (59.9)	221,205 (47.3)	40 (67.8)	12,862 (65.4)	39 (49.4)	3932 (56.4)	481 (49.0)	147,283 (53.4)	274 (100)	68,795 (100)

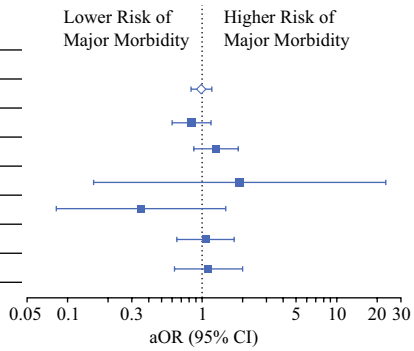
IQR, interquartile range; N/A,

[a]Rectal procedures: (1) low anterior resection (LAR); (2) abdominoperineal resection (APR); (3) pelvic exenteration. Colon procedures: (1) partial colectomy, segmental resection; (2) subtotal colectomy/hemicolectomy; (3) total colectomy; (4) total proctocolectomy. Anal procedures: (1) local tumor destruction; (2) APR. Esophageal procedures: (1) partial esophagectomy; (2) total esophagectomy. Lung procedures: (1) lobe resection or bilobectomy; (2) lobectomy with mediastinal lymph node dissection; (3) pneumonectomy; (4) pneumonectomy with mediastinal lymph node dissection

[b]Oral cavity subsite: (1) gum; (2) lip; (3) mouth floor; (4) tongue

FIG. 1 Adjusted odds ratios for major morbidity associated with neoadjuvant immunotherapy by cancer type.

Cancer Type	Adjusted OR (95%CI)	P-value
Pooled	0.98 (0.81-1.19)	0.852
Rectal	0.83 (0.60-1.16)	0.282
Colon	1.27 (0.87-1.85)	0.220
Anal	1.90 (0.16-23.15)	0.615
Esophageal	0.35 (0.08-1.49)	0.156
Lung (non-small cell)	1.06 (0.65-1.73)	0.821
Oral Cavity	1.10 (0.61-2.00)	0.743



anal, esophageal, lung (non-small cell), and oral cavity cancers. We hypothesized that neoadjuvant immunotherapy is not associated with increased risk of surgical complications.

MEHODS

Using the National Cancer Database (NCDB), which contains de-identified patient data from more than 1400 centers in the United States,[5] we selected patients 18 to 90 years of age who underwent non-palliative oncologic surgery for rectal, colon, anal, esophageal, lung (non-small cell), or oral cavity cancer between 2010 and 2020. Together with cases that had missing data, the study excluded minimally invasive oral cavity cases and colon cases involving radiation because these options are not standard of care and likely reflect database discrepancies.

Neoadjuvant immunotherapy was defined as immunotherapy administered as first-course therapy before the date of surgery. Our primary outcome was major morbidity, defined as hospital length of stay within the top decile of each surgery subtype, unplanned 30-day readmission, or 30-day mortality. This is similar to the approach described by Wong et al.[3]

Multivariable logistic regressions for major morbidity were performed on R statistical software (version 4.3.2) to calculate the individual and pooled odds ratios of major morbidity from neoadjuvant immunotherapy by cancer type while controlling for patient demographics, Charlson-Deyo comorbidity index, clinical cancer staging, procedure type, surgical approach, and other treatment (e.g., chemotherapy or radiotherapy). This study was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[6]

RESULTS

Of 1,348,334 cases with any of the six cancer types, our sample included 953,612 cases (eFig. 1 in Supplement 1). Of these cases, 4771 (0.5 %) involved neoadjuvant immunotherapy and 948,841 (99.5 %) did not (Table 1). The pooled odds ratio of major morbidity associated with neoadjuvant immunotherapy was 0.98 (95 % CI, 0.81–1.19). Figure 1 shows that neoadjuvant immunotherapy was not significantly associated with major morbidity after surgery for rectal (adjusted odds ratio [aOR], 0.83; 95 % CI, 0.60–1.16), colon (aOR, 1.27; 95 % CI, 0.87–1.85), anal (aOR, 1.90; 95 % CI, 0.16–23.15), esophageal (aOR, 0.35; 95 % CI, 0.08–1.49), lung (non-small cell) (aOR, 1.06; 95 % CI, 0.65–1.73), or oral (aOR, 1.10; 95 % CI, 0.61–2.00) cancer. Lack of insurance (compared with private insurance) was associated with increased odds of major morbidity for all cancer types (eTable 1 in Supplement 1).

DISCUSSION

This study did not observe an association between neoadjuvant immunotherapy and an increased risk of surgical complications, including extended hospital length of stay, unplanned 30-day readmission, or 30-day mortality. This finding held true across all major cancer types studied, including rectal, colon, anal, esophageal, non-small cell lung, and oral cavity cancers. These results corroborate prior studies limited to single-organ sites from institutional case series.[4] This is an important and increasingly relevant finding because more surgeons are considering operating on patients who have recently completed or are currently undergoing immunotherapy.

The limitations of this study included the small sample for anal cancer, the lack of detailed surgical complication information for each cancer type, and the use of NCDB to study surgical outcomes. Although neoadjuvant immunotherapy is not standard care, we focused on short-term surgical risks and controlled for patient and surgical factors using multivariable logistic regression, leveraging NCDB's national scope to offer broader insights than single-center studies. Our method of applying NCDB outcome variables to create a major morbidity variable as a surgical complication proxy has been previously validated.[3]

This study observed no association between neoadjuvant immunotherapy and risk of surgical complications. As immunotherapy becomes more prevalent in cancer treatment, understanding its impact on surgical outcomes is crucial for optimizing patient care. Further studies with more detailed data on surgical complications are needed to confirm and expand upon our findings.

SUPPLEMENTARY INFORMATION The online version contains supplementary material available at https://doi.org/10.1245/s10434-024-16284-8.

DISCLOSURES

There are no conflicts of interest.

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