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RESEARCH ARTICLE

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Impact of neoadjuvant immunotherapy on postoperative complications after surgery for rectal cancer

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Abstract

Introduction: Despite the increasing use of immunotherapy in treating various cancer types, there is still limited understanding of its impact on surgical complications. We used a national database to examine the difference in surgical outcomes for rectal cancer patients who received standard neoadjuvant chemoradiation plus neoadjuvant immunotherapy and patients who received neoadjuvant chemoradiation only.

Methods: This retrospective cohort study used the National Cancer Database (NCDB). We selected patients aged 18–90 with T1-3, N1-2, and M0 rectal cancer who underwent curative-intent surgery between 2010 and 2020. We performed a 1:1 propensity match to control for patient age, sex, Charlson–Deyo comorbidity index, surgical approach, and tumor site. Our primary outcome was difference in surgical outcomes (hospital length of stay, unplanned 30-day readmission, 30-day mortality) between the two groups. Secondary outcomes included days from diagnosis to surgery and pathologic outcomes.

Results: Our study included 26 229 patients, of which 126 received immunotherapy in addition to chemoradiation and 26 103 received only chemoradiation. In our matched population of 125 pairs of patients, patients who received immunotherapy and chemoradiation underwent surgery later compared to patients who only received chemoradiation (median 245 vs. 144 days, $p < 0.001$). There were no significant differences in median length of stay (5 vs. 5 days, $p = 0.202$), unplanned 30-day readmission (7 vs. 9, $p = 0.617$), and 30-day mortality (0 vs. 1, $p = 1.000$) between the two groups.

Conclusion: Neoadjuvant immunotherapy for rectal cancer is not associated with adverse surgical outcomes. This work can help clinicians optimize treatment protocols and move closer toward strategies tailored to specific patient profiles.

KEYWORDS

chemotherapy, immunotherapy, postoperative complications, rectal cancer, surgery, surgical margin

Matthew Shou and Daniel Roy Sadek Habib contributed equally as the first authors.

1 | INTRODUCTION

The emergence of immune checkpoint inhibitors over the past decade has revolutionized care for many cancers.[1,2] Immunotherapy has shown promise in enhancing tumor regression rates, particularly in microsatellite instability-high (MSI-H)/deficient mismatch repair (dMMR) colorectal cancer subtypes.[3–5] Patients can now benefit from therapies with milder side effects compared to traditional chemotherapy, although unique immune-related adverse events have emerged.[6–8] This raises concerns about perioperative complications among patients receiving neoadjuvant immunotherapy.

While using radiation or chemotherapy in a neoadjuvant setting has been the standard practice for two decades, we have developed a good understanding of the impact of these treatments on surgical outcomes.[9–11] Current guidelines primarily address time for withholding systemic chemotherapy before surgery due to side effects such as poor wound healing and immunosuppression[12–14] as well as specific targeted therapies for a longer period due to higher rates of wound dehiscence and anastomotic leaks.[15–17] Although there are some single-institution studies assessing the impact of surgical outcomes in melanoma surgery and esophagectomy, there remains a gap in our understanding of surgical complication risk associated with immunotherapy for colon and rectal surgery.[18–21]

While guidelines exist for timing cessation of systemic chemotherapy and some targeted therapies before surgery, no such guidelines address immunotherapy. Understanding how neoadjuvant immunotherapy may enhance oncologic outcomes without compromising surgical safety is crucial for refining patient selection criteria for rectal cancer resection. This study aims to establish the impact of neoadjuvant immunotherapy on surgical outcomes for rectal cancer patients. Additionally, we seek to assess the impact of immunotherapy on the timing of surgery and pathologic outcomes (i.e., lymph nodes resected and residual tumor).

2 | MATERIALS AND METHODS

2.1 | Data source

Deidentified data on patients who underwent surgery for rectal cancer from 2010 to 2020 were extracted from the National Cancer Database (NCDB). NCDB has patients from over 1400 centers in the United States and provides HIPAA-compliant information regarding pre-, intra-, and postoperative variables.[22]

2.2 | Patient selection

We included patients aged 18–90 years undergoing non-palliative surgery for rectal cancer after neoadjuvant chemoradiation and immunotherapy from 2010 to 2020. We used patients with a tumor staging of T1-3, any N 1-3, and M0. We excluded patients who did not receive standard-of-care neoadjuvant chemoradiation according to guidelines from the National Comprehensive Cancer Network (NCCN).[23] We also excluded patients undergoing any combined surgery (such as liver resection) or patients with missing information for control variables.

2.3 | Clinical variables

We included the following patient characteristics provided in NCDB: patient age, sex, race, insurance, average income and percentage with high school degree above the median for the patient's zip code, medical facility type, Charlson–Deyo Comorbidity Index, clinical TNM stage, procedure at primary site, and surgical approach.

2.4 | Outcomes

The primary outcomes were hospital length of stay (LOS), unplanned 30-day readmission, and 30-day mortality. Secondary outcomes included days from diagnosis to surgery, residual tumor, and lymph nodes resected.

2.5 | Statistical analysis

We performed descriptive analyses reporting continuous variables as median (interquartile range) and categorical variables as frequencies (percentage) for patient characteristics. To control for confounders, we performed a 1:1 propensity match between neoadjuvant chemoradiation rectal cancer surgery patients with and without neoadjuvant immunotherapy. In the model, we adjusted for patient age, sex, Charlson–Deyo Comorbidity Index, surgical approach, and tumor site. We calculated the standardized mean difference before and after matching and considered a post-matching value <0.15 to be balanced. We performed the Wilcoxon rank-sum test with continuity correction for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables. We performed all statistical analyses using R statistical software version 4.3.2.

3 | RESULTS

3.1 | Patient characteristics

We included 26 229 patients in our study, of which 126 (0.48%) patients underwent neoadjuvant immunotherapy and chemoradiation, and 26 103 (99.52%) patients had standard neoadjuvant chemoradiation only. In the overall population, patients who received immunotherapy were more likely to be treated at a research/academic program (44.4% vs. 37.5%, $p < 0.05$), while patients who did not receive neoadjuvant immunotherapy were more likely to be treated at a comprehensive community health center (32.9% vs. 19.8%, $p < 0.05$; Table 1). Through propensity matching, 125 pairs of

TABLE 1 Characteristics of included patients receiving neoadjuvant chemoradiation and immunotherapy versus neoadjuvant chemoradiation only before stage IIIa–c rectal cancer surgery.

	Immunotherapy + chemoradiation (n = 126)	Chemoradiation only (n = 26 103)	p Value
Age, median [IQR]	56 [49.25–65]	58 [50–67]	0.071
Sex			0.342
Male	84 (66.7%)	16 329 (62.6%)	
Female	42 (33.3%)	9774 (37.4%)	
Race			0.554
White	103 (81.7%)	22 013 (84.3%)	
Black	10 (7.9%)	2221 (8.5%)	
Other	11 (8.7%)	1648 (6.4%)	
Insurance (primary payor at diagnosis)			0.157
Uninsured	5 (4.0%)	1087 (4.2%)	
Private/Managed Care	78 (61.9%)	14 042 (53.8%)	
Medicaid, Medicare, or Other Government	41 (32.5%)	10 677 (40.9%)	
Charlson–Deyo comorbidity index			0.399
0	99 (78.6%)	20 417 (78.2%)	
1	23 (18.3%)	4185 (16.0%)	
2+	4 (3.2%)	1501 (5.8%)	
Income above median			0.711
0–47 999	39 (31.0%)	8790 (33.7%)	
48k–63k	65 (51.6%)	13 589 (52.1%)	
Education above high school degree			0.153
≥10.9%	41 (32.5%)	10 401 (39.8%)	
<10.8%	63 (50.0%)	12 000 (46.0%)	
Clinical T stage			0.999
T1	2 (1.6%)	408 (1.6%)	
T2	13 (10.3%)	2714 (10.4%)	
T3	111 (88.1%)	22 981 (88.0%)	
Clinical N stage			**0.005**
N1	83 (65.9%)	19 606 (75.1%)	
N2	43 (34.1%)	6008 (23.0%)	
Facility type			**0.039**
Community program	4 (3.2%)	926 (3.5%)	
Comprehensive community	25 (19.8%)	8579 (32.9%)	
Integrated network program	27 (21.4%)	5245 (20.1%)	
Research/academic program	56 (44.4%)	9789 (37.5%)	
Surgical procedure at primary site			0.515
LAR + coloanal pull-through	84 (66.7%)	18 688 (71.6%)	
APR	38 (30.2%)	6432 (24.6%)	
Pelvic exenteration	4 (3.2%)	485 (1.9%)	

(Continues)

TABLE 1 (Continued)

	Immunotherapy + chemoradiation (*n* = 126)	Chemoradiation only (*n* = 26 103)	*p* Value
Surgical approach at primary site			0.312
Robotic-assisted	45 (35.7%)	7723 (29.6%)	
Laparoscopic	29 (23.0%)	6853 (26.2%)	
Open	52 (41.3%)	11 527 (44.2%)	

Abbreviations: APR, adominoperineal resection; IQR, interquartile range [Q1–Q3]; LAR, low anterior rcesection.

TABLE 2 Characteristics of a matched population of patients receiving neoadjuvant chemoradiation and immunotherapy versus neoadjuvant chemoradiation only before stage IIIa–c rectal cancer surgery.

	Immunotherapy + chemoradiation (*n* = 125)	Chemoradiation only (*n* = 125)	*p* Value
Age, median [IQR]	56 [50–65]	56 [50–65]	0.906
Sex			0.893
Male	83 (66.4%)	84 (67.2%)	
Female	42 (33.6%)	41 (32.8%)	
Race			0.263
White	103 (82.4%)	112 (89.6%)	
Black	9 (7.2%)	8 (6.4%)	
Other	11 (8.8%)	5 (4.0%)	
Insurance (primary payor at diagnosis)			0.665
Uninsured	5 (4.0%)	4 (3.2%)	
Private/Managed Care	77 (61.6%)	85 (68.0%)	
Medicaid, Medicare, or Other Government	41 (32.8%)	35 (28.0%)	
Charlson–Deyo comorbidity index			0.927
0	98 (78.4%)	101 (80.8%)	
1	23 (18.4%)	20 (16.0%)	
2+	4 (3.2%)	4 (3.2%)	
Income above median			0.357
0–47 999	39 (31.2%)	35 (28.0%)	
48k–63k	65 (52.0%)	76 (60.8%)	
Education above high school degree			0.708
≥10.9%	41 (32.8%)	41 (32.8%)	
<10.8%	63 (50.4%)	70 (56.0%)	
Clinical T stage			0.740
T1	2 (1.6%)	4 (3.2%)	
T2	13 (10.4%)	14 (11.2%)	
T3	110 (88.0%)	107 (85.6%)	
Clinical N stage			**0.032**
N1	82 (65.6%)	95 (76.0%)	
N2	43 (34.4%)	27 (21.6%)	

TABLE 2 (Continued)

	Immunotherapy + chemoradiation (n = 125)	Chemoradiation only (n = 125)	p Value
Facility type			0.355
Community program	4 (3.2%)	4 (3.2%)	
Comprehensive community	25 (20.0%)	36 (28.8%)	
Integrated network program	27 (21.6%)	27 (21.6%)	
Research/academic program	56 (44.8%)	45 (36.0%)	
Surgical procedure at primary site			0.981
LAR + coloanal pull-through	84 (67.2%)	87 (69.6%)	
APR	38 (30.4%)	36 (28.8%)	
Pelvic exenteration	3 (2.4%)	2 (1.6%)	
Surgical approach at primary site			0.873
Robotic-assisted	44 (35.2%)	46 (36.8%)	
Laparoscopic	29 (23.2%)	31 (24.8%)	
Open	52 (41.6%)	48 (38.4%)	

Note: One immunotherapy patient was removed in the matching process.

Abbreviations: APR, abdominoperineal resection; IQR, interquartile range [Q1–Q3]; LAR, low anterior resection.

patients were formed, and their characteristics are shown in Table 2. A post-matching standardized mean difference <0.15 for all variables confirmed appropriate matching (Supporting Information S1: Table 1).

3.2 | Surgical and pathological outcomes

When comparing the 125 patients who received neoadjuvant immunotherapy to the 125 matched patients who did not receive neoadjuvant immunotherapy (Table 3), there was no significant difference in 30-day mortality (0% vs. 0.80%, p = 1.000), unplanned 30-day readmission (5.6% vs. 7.2%, p = 0.617), or median [IQR] hospital LOS (5 [4–7] vs. 5 [4–6], p = 0.202) between the two groups.

Additionally, there was no significant difference in pathological outcomes such as positive surgical margins (4.0% vs. 4.8%, p = 0.800) and median number of lymph nodes harvested during the surgery (16 [12–21] vs. 16 [12–22], p = 0.983). Patients who received immunotherapy exhibited a longer median [IQR] time between diagnosis and definitive surgery compared to patients receiving neoadjuvant chemoradiation only (245 [151–303] days vs. 144 [123–188] days, p < 0.001).

4 | DISCUSSION

The findings of this study show that neoadjuvant immunotherapy does not adversely affect surgical or pathological outcomes compared to the current standard of care for clinical stage III rectal cancer. Hospital LOS unplanned 30-day readmission, 30-day mortality, surgical pathology, and lymph nodes resected were not significantly different across matched groups. Patients who receive immunotherapy and neoadjuvant chemoradiation undergo surgery later than patients who receive only neoadjuvant chemoradiation.

According to NCCN guidelines, immunotherapy for rectal cancer for dMMR/MSI-H rectal cancer is given for up to 6 months, during which the disease is reevaluated every 2–3 months.[23] Patients with persistent disease then undergo chemoradiation and restaging before surgical resection of the tumor. We speculate that this additional step in management is why patients who receive immunotherapy undergo surgery months later than patients who only receive chemoradiation. Despite this difference, immunotherapy use is not associated with worse perioperative outcomes and does not increase surgical complexity. Future work should explore the timing of neoadjuvant immunotherapy relative to chemotherapy and implications for holding neoadjuvant therapy before surgery.

Previous studies have identified adverse events related to immunotherapy use. Calini et al.[21] highlighted the potential risk of postoperative morbidity after emergent colorectal surgery in the setting of immunotherapy use. However, these four cases described immune-related colonic perforation necessitating emergency surgery and later developing septic shock rather than postoperative morbidity due to immunotherapy itself. Calini et al.[21] concluded that elective surgery in the setting of immunotherapy use is safe, but any patients on immunotherapy with acute abdominal symptoms should elicit a surgical consult to rule out colonic perforation. While our results show that postoperative mortality rates of patients who receive immunotherapy for rectal cancer are not different than patients receiving standard chemoradiation, we did not differentiate emergency versus elective surgery. Future work should further explore differences in the setting around surgery to determine in what instances special precautions should be implemented.

TABLE 3 Surgical and pathologic outcomes in a matched population of patients comparing neoadjuvant chemoradiation and immunotherapy versus neoadjuvant chemoradiation only before stage IIIa–c rectal cancer surgery.

	Immunotherapy + chemoradiation (n = 125)	Chemoradiation only (n = 125)	p Value
Days to definitive surgery, median [IQR]	245 [151–303]	144 [123–188]	**<0.001**
30-day mortality	0 (0%)	1 (0.80%)	1.000
Hospital LOS (days) median [IQR]	5 [4–7]	5 [4–6]	0.202
Unplanned readmission within 30 days of discharge	7 (5.6%)	9 (7.2%)	0.617
Scope of regional lymph node surgery, median [IQR]	16 [12–21]	16 [12–22]	0.983
Residual tumor, microscopic or macroscopic	5 (4.0%)	6 (4.8%)	0.800

Abbreviations: IQR, interquartile range [Q1–Q3]; LOS, length of stay.

One limitation of the present study is that only a subset of rectal cancers respond to immunotherapy. Patients who received immunotherapy in this study likely had the MSI-H and dMMR subtypes but were compared to patients who could have any subtype. To best account for this, we implemented strict inclusion criteria and a 1:1 propensity matching algorithm. Another limitation is that NCDB provides limited data on variables related to surgical outcomes. We are unable to determine the effect of immunotherapy use on colorectal-specific adverse events, such as rates of colitis or perforation. However, NCDB's strengths include its large patient population and cancer treatment data. Additionally, the validity of our approach is substantiated by Wong et al.[20] using NCDB's outcome variables as surgical complication risk proxies.

5 | CONCLUSIONS

There were no significant differences in surgical and pathological outcomes between patients who received neoadjuvant immunotherapy along with chemoradiation and patients who received neoadjuvant chemoradiation only. Patients who received neoadjuvant immunotherapy exhibited a longer time to surgery compared to patients who only received chemoradiation, likely due to immunotherapy administration preceding chemotherapy up to 6 months and hence extending the course of neoadjuvant therapy before surgery. This research addresses a critical knowledge gap surrounding the impact of neoadjuvant immunotherapy on surgical outcomes for rectal cancer patients, an area with limited existing data. This study discerns potential mediators influencing the relationship between immunotherapy and surgical complication risk, including cancer subtype, patient characteristics, and the timing of treatment administration. These findings can also help clinicians optimize treatment protocols and move closer toward strategies tailored to specific patient profiles.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from NCDB. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the author (s) with the permission of NCDB.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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