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The effect of neoadjuvant radiation therapy on perioperative outcomes among patients undergoing resection of retroperitoneal sarcomas*

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Abstract

Background—Neoadjuvant radiation therapy (RT) has several theoretical benefits in the treatment of retroperitoneal sarcoma (RPS), but concerns remain about treatment toxicity and perioperative morbidity. There are limited data regarding its effect on perioperative outcomes,

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most of which come from small, single-institution series. The purpose of this study was to evaluate the short-term (30-day) postoperative morbidity and mortality associated with neoadjuvant RT following resection of RPS.

Methods—The 2005–2011 National Surgical Quality Improvement Program Participant User File was queried for patients undergoing RPS resection. Subjects were stratified by use of neoadjuvant RT. Perioperative variables and short-term 30-day outcomes were compared. Groups were then propensity matched using a 2:1 nearest-neighbor algorithm and multivariable logistic regression was performed to assess neoadjuvant RT as a predictor of short-term 30-day outcomes.

Results—A total of 785 patients were identified. Neoadjuvant RT was administered to 71 (9.0%). Patients who received neoadjuvant RT were slightly younger (56 vs. 62 years, $p < 0.001$), but otherwise the groups were similar. After propensity matching, all baseline characteristics were highly similar. Median operative time was longer in the neoadjuvant RT group (279 vs. 219 min, $p < 0.01$), but there were no differences in mortality (1.4 vs. 2.1%, $p = 0.71$), major complications (28.2 vs. 25.2%, $p = 0.69$), overall complications (35.2 vs. 33.2%, $p = 0.83$), early reoperation (5.6 vs. 7.4%, $p = 0.81$), or length of stay (7 vs. 7 days, $p = 0.56$). Following further adjustment with logistic regression, we confirmed that there were no differences in 30-day mortality or morbidity between patients who did and did not receive neoadjuvant RT.

Conclusions—Neoadjuvant RT does not appear to increase short-term (30-day) morbidity or mortality following resection of RPS. Continued investigation is needed to better define the role for radiation therapy among patients with this disease.

Keywords

Retroperitoneal sarcoma; Sarcoma; Radiation therapy; Radiotherapy; Neoadjuvant; Preoperative; Outcomes; Short-term outcomes; 30-day outcomes

Introduction

Retroperitoneal sarcomas represent a rare malignancy of multiple histological subtypes, the most common being liposarcoma (~40%) and leiomyosarcoma (~25%) [1]. Five-year survival for all subtypes is approximately 60% [2]. The most important factor affecting survivability is tumor grade, reflecting both the aggressive metastatic behavior and increased incidence of local recurrence among higher-grade sarcomas [2]. Outside of tumor biology, extent of resection (R0 vs. R1/R2) is the most important predictor of survival, with incomplete resection conferring a 70% greater risk of death [2]. Yet, R0 resection is often difficult to achieve, especially for large tumors that encroach on vital organs and other structures, and incomplete resection occurs in up to 20% of cases [2,3].

Neoadjuvant radiation therapy (RT) has several theoretical benefits for the treatment of retroperitoneal sarcomas. First, it may improve tumor resectability, particularly for larger tumors in close proximity to important structures [4]. By performing RT in the preoperative period, the tumor volume itself can be used to plan more precisely the radiation field, and also protect adjacent tissues by expanding nearby organs away from the field [3]. Moreover, by delivering RT prior to surgery, the presence of intact vasculature may reduce tumor hypoxia, thereby improving radiation response [3]. Finally, there are several reports

indicating that preoperative RT may decrease rates of locoregional recurrence, although this remains unclear [4–7]. Despite these theoretical benefits, however, to date there is no Level 1 evidence supporting the use of RT. The first phase 3 randomized trial addressing this question was prematurely terminated due to lack of adequate patient accrual, and efforts are just now underway to recruit patients for a second trial [8,9].

Given the uncertainty regarding long-term oncologic benefits, greater attention has been focused on treatment toxicity and perioperative morbidity. Although it is now generally well-accepted that preoperative RT can be safely and feasibly administered to the retroperitoneum [3,10], there are limited outcomes data regarding short-term postoperative outcomes, most of which come from small, single-institution series. Moreover, among the few studies that describe perioperative outcomes, surgery-specific data (e.g. type of morbidity, length of stay, readmission rates) are largely missing or incomplete. The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) represents the largest risk-adjusted clinical database of surgical outcomes in the United States [11]. Because NSQIP captures validated 30-day outcomes for nearly 100% of major operations at participant sites [11,12], it is a particularly valuable tool for evaluating outcomes in rare patient populations. Thus, the purpose of this study was to utilize a large national database to better understand the effect of preoperative radiation therapy on short-term perioperative outcomes following resection of retroperitoneal sarcomas.

Methods

The Duke University Institutional Review Board approved this retrospective review of the National Surgical Quality Improvement Program (NSQIP). The NSQIP Participant User Files for 2005 through 2011 were utilized for this retrospective analysis. Patients were identified as having undergone resection of a retroperitoneal sarcoma first by querying all patients with International Classification of Diseases Ninth Revision (ICD-9) code 158.0 (primary malignancy of the retroperitoneum), and then filtering by Current Procedural Terminology (CPT) code: 49200/49201 (excision or destruction, open, intra-abdominal or retroperitoneal tumors or cysts or endometriomas), 49203/49204/49205 (excision or destruction, open, intra-abdominal tumors, cysts, or endometriomas, 1 or more peritoneal, mesenteric, or retroperitoneal primary or secondary tumors), 49000 (exploratory laparotomy, exploratory celiotomy with or without biopsy), 49010 (exploration, retroperitoneal area with or without biopsy).

Subjects with associated CPT codes that were not consistent with the diagnosis of sarcoma were excluded. These included 58240/58950/58957, as these codes specifically state the procedure was performed for a primary gynecologic malignancy. Subjects were then stratified by the use of neoadjuvant RT (radiotherapy for malignancy in last 90 days). If there was no data available on use of preoperative RT, subjects were excluded. Baseline characteristics and outcomes between groups were compared using Pearson's chi-square test for categorical variables and Student's *t*-test for continuous variables.

Because there were likely fundamentally non-random differences between these two groups, we then conducted a propensity analysis using a 2:1 nearest neighbor algorithm to control

for bias at the level of treatment decision. Patients were matched on the following variables, defined *a priori* as potentially confounding the decision to treat with neoadjuvant RT: age, sex, body mass index, diabetes mellitus, COPD, coronary artery disease, bleeding disorders, dyspnea, functional status, ASA classification, existing DNR order, tobacco use, alcohol use >2 drinks/day, recent steroid use, and year of operation. Our primary outcome measures were 30-day morbidity and mortality. Secondary endpoints included major complications, surgical site infection, and early reoperation. First, we compared the 23 outcomes captured by NSQIP between the propensity-matched groups. Next, in order to estimate the effect of neoadjuvant RT on our primary and secondary endpoints, and to control for residual bias, a non-parsimonious multivariable logistic regression model was created that excluded variables with less than five occurrences to avoid overfitting. We included the following variables: use of preoperative radiation, concomitant major organ resection, use of intraoperative radiation therapy, age, sex, body mass index, ASA classification, diabetes, coronary artery disease, dyspnea, bleeding disorders, tobacco use, recent weight loss, recent steroid use, case contamination, and trainee participation.

In light of the substantial completeness of the NSQIP data, missing data was handled using complete case analysis. We made an affirmative decision to control for type I error at the level of the comparison, and *p*-values <0.05 were used to indicate statistical significance for all comparisons. All statistical analyses were performed using R (The R Foundation for Statistical Computing, version 3.0.2, Vienna, Austria).

Results

Initially, 1071 patients were identified with a primary diagnosis of a retroperitoneal mass. Of these, 174 had associated CPT codes that were not consistent with a diagnosis of sarcoma, and were thus excluded. Another 112 patients did not have available data regarding the use of neoadjuvant RT, and were also excluded. This resulted in a total study population of 785 patients. Subjects were then stratified neoadjuvant RT (72 patients, 9.2%) and no neoadjuvant RT (714 patients, 91%). During our study period, there was an increase in the use of neoadjuvant RT, from less than 3% of patients in 2005, to nearly 10% in later years (Fig. 1).

Patients who underwent neoadjuvant RT prior to resection were slightly younger (56 vs. 62 years, *p* = 0.001), but otherwise there were no baseline differences between groups (Table 1). This included sex distribution, preoperative comorbidities, tobacco/alcohol use, preoperative chemotherapy, use of intraoperative RT, and need for concomitant major organ resection.

After propensity matching, all variables between groups were highly similar, including age (56 vs. 55, *p* = 0.913). Aside from their malignancies, patients in both groups tended to be relatively healthy, including low rates of diabetes (9.9 vs. 7%, *p* = 0.655), coronary artery disease (4.2 vs. 2.8%, *p* = 0.688), chronic obstructive pulmonary disease (1.4 vs. 1.4%, *p* = 0.999), and end-stage renal disease (0 vs. 0.7%, *p* = 0.999). Few patients in either group were treated with chemotherapy within 30 days prior to surgery (4.2 vs. 6.3%, *p* = 0.755). Also, the use of intraoperative RT was uncommon in both groups (5.6 vs. 4.2%, *p* = 0.734).

Most patients required concomitant resection of an adjacent organ (60.6 vs. 63.4%, $p = 0.802$). The most commonly resected organs (Table 2) were the colon (23.4%), kidney (21.9%), and small bowel (7.8%).

Among propensity-matched groups, there was no difference in 30-day mortality (1.4 vs. 2.1%, $p = 0.999$) or overall complication rate (35.2 vs. 29.6%, $p = 0.498$). Similarly, there were no differences in major complications, surgical site infection, or early return to the operating room. Although there was no difference in the use of intraoperative RT or concomitant major organ resection, operative time was longer in the group treated with neoadjuvant RT (median 279 vs. 228 min, $p = 0.020$). Overall length of hospital stay was seven days in both groups. A full list of complications and outcomes by group is shown in Table 3. Following further adjustment with logistic regression, we confirmed that there were no differences in 30-day mortality or postoperative morbidity between patients who did and did not receive neoadjuvant RT (Fig. 2).

Discussion

The use of neoadjuvant RT for patients with retroperitoneal sarcomas has increased substantially over the past decade, as is reflected in our analysis, where the incidence escalated from 3% in 2005 to nearly 10% in 2011. While there are several theoretical advantages of preoperative RT (e.g. improved resectability, decreased locoregional recurrence), the expansion of this treatment modality has occurred in the absence of Level 1 evidence demonstrating a survival benefit. As the European Organisation for Research and Treatment of Cancer has just begun to recruit patients for a prospective trial evaluating preoperative RT for this malignancy (EORTC 62092-22092) [9]—with results therefore years away—focus has shifted to the safety profile of radiation therapy administered to the retroperitoneum. Caudle and colleagues have suggested that while treatment-related toxicities may be relatively common, only a small fraction—in their series, one of 14 patients—result in dose-limiting toxicity that prevents patients from completing treatment [3]. These data are supported by other larger studies, including a series of 41 patients out of the University of Toronto Sarcoma Group, in which no patient experienced severe acute toxicity (Radiation Therapy Oncology Group 3), required treatment-related hospitalization, or underwent early termination of radiotherapy [13].

A second concern—and one that is equally if not more understudied—is the effect of preoperative RT on short-term perioperative outcomes. In extremity sarcomas, increased morbidity has been well documented among patients treated with preoperative RT, particularly with regard to wound healing and infection in patients with tumors located in the lower extremity [14]. In 2000, Meric and colleagues first described the postoperative complications associated with neoadjuvant chemotherapy among 309 patients treated for soft tissue sarcomas, evaluating the effect of preoperative RT as a secondary endpoint [10]. They found a 50% increase in wound complications among patients treated with preoperative RT. However, only 108 patients in their study had retroperitoneal/visceral sarcomas, among whom just 39 were treated with neoadjuvant RT. Subsequently, the Caudle study surveyed postoperative morbidity among their 14 subjects; however, because all patients in their series received preoperative RT, there was no treatment naïve group

available for comparison [3]. Several other small, single-institution series have attempted to define the perioperative morbidity associated with neoadjuvant RT; however, all of these studies have been limited by either sample size, evaluation of additional treatment modalities, or a lack of granular surgery-specific outcomes data [15–17].

Here, we utilize the American College of Surgeons National Surgical Quality Improvement Program to address the question of whether neoadjuvant RT affects perioperative outcomes among patients undergoing resection of retroperitoneal sarcomas. The NSQIP database provides a broad source of validated data from a spectrum of American academic and community medical centers [11,12]. As such, we are able here to provide the largest series to date evaluating this patient population. While we found that patients who received neoadjuvant RT were slightly younger, there were otherwise no identifiable baseline differences between groups. The rate of concomitant major organ resection was similar in both groups (60.6 vs. 63.4%), as was the administration of intraoperative RT (5.6 vs. 4.2%). A small but similar number of patients in each group (4.2 vs. 6.3%) also received neoadjuvant chemotherapy. Given that preoperative chemotherapy is not routinely recommended for patients with retroperitoneal sarcomas at most cancer centers, this may represent patients involved in ongoing clinical trials. Nonetheless, given the possibility that preoperative chemotherapy may affect outcomes, we included this variable in our propensity adjustment model, and were therefore able to adequately compare patients who received or did not receive neoadjuvant chemotherapy. Despite these similarities between groups, there was a statistically significant increase in median operative time (279 vs. 228 min) for patients who had received preoperative RT. The reason for this is unclear, but may be related to fibrosis or reactive changes from radiation, differences in tumor size (which is not available in the NSQIP user file), or more aggressive tumor biology with involvement of adjacent structures (although, as mentioned above, concomitant organ resection was similar between groups).

While operative times may have been longer in the RT group, there were no differences in hospital length of stay, 30-day mortality, or postoperative 30-day morbidity. These findings are in keeping with previous research in this area, including a similar analysis by Bartlett and colleagues in 2013 using the NSQIP database [18]. Although we approached the question with different methodologies, we found similar results with an even larger sample size (785 vs. 696 patients). These two analyses demonstrate how large data sources can be handled differently between groups, and highlight the importance of attempting to answer important clinical questions with different techniques in order to obtain the most robust results.

Although NSQIP represents the largest source of validated and externally audited surgical outcomes data, there are still several limitations that must be acknowledged. First, due to the inherent limitations of a large retrospective analysis, we are unable to fully account for selection bias regarding which patients were chosen to receive neoadjuvant RT. Although our propensity match adjusts for bias at the level of treatment decision, the NSQIP database is conspicuously missing data on tumor characteristics such as size and grade. These factors are amongst the most important in considering which patients to treat with radiation therapy. However, if we are to assume that patients who received neoadjuvant RT may have had

larger and higher grade tumors, that would likely shift the complication bias towards patients who had preoperative RT, and again, we do not detect a higher rate of perioperative morbidity in this cohort. Moreover, it is worth noting that there was no difference in the rate of concomitant organ resection, even before propensity matching, which suggests that size and tumor aggressiveness may not have been different between groups. Our analysis is further limited by the variables and postoperative outcomes captured through NSQIP. Thus, although we can categorize patients by RT within 90 days prior to surgery, we do not know the radiation dose delivered nor the details of the how the radiation therapy was administered (i.e. 3D-conformal radiation therapy vs. intensity modulated radiation therapy). This is of particular importance given recent trends towards escalating doses of radiotherapy for higher-grade sarcomas [19–21]. Moreover, we are unable to assess short-term oncologic outcomes such as margin status nor longer-term variables and outcomes such as adjuvant RT, survival, and disease recurrence.

Nonetheless, in this study we demonstrate that neoadjuvant RT does not appear to affect 30-day morbidity and mortality following resection of retroperitoneal sarcomas. While continued investigation is needed to better define the role for radiation therapy among patients with this disease, concerns about increased postoperative morbidity may be exaggerated or unfounded, and should not be the primary factor precluding its use in appropriately selected cases.

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Abbreviations

RT	Radiation therapy
RPS	Retroperitoneal sarcoma
NSQIP	National Surgical Quality Improvement Program
ICD-9	International Classification of Diseases Ninth Revision
CPT	Current Procedural Terminology
EORTC	European Organisation for Research and Treatment of Cancer

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Figure 1.
Rate of preoperative RT for retroperitoneal sarcomas by year.

Figure 2.
Adjusted odds of morbidity and mortality for neoadjuvant RT, after propensity matching.

Table 1

Baseline characteristics of patients undergoing resection.

Variable	Overall <i>n</i> = 786	No RT <i>n</i> = 714	Preop RT <i>n</i> = 72	<i>P</i> -value
Age (years)	61 (51.25, 70)	61.5 (52, 71)	56.5 (47, 64.25)	0.001
Female sex	396 (50.4%)	359 (50.4%)	37 (51.4%)	0.965
ASA Class 3	485 (61.8%)	441 (61.9%)	44 (61.1%)	0.999
Preoperative sepsis				0.055
None	749 (96.4%)	679 (96.2%)	70 (98.6%)	
SIRS	22 (2.8%)	22 (3.1%)	0 (0%)	
Sepsis	5 (0.6%)	5 (0.7%)	0 (0%)	
Septic shock	1 (0.1%)	0 (0%)	1 (1.4%)	
Dyspnea	101 (12.8%)	97 (13.6%)	4 (5.6%)	0.063
Non-independent functional status	26 (3.3%)	24 (3.4%)	2 (2.8%)	0.999
DNR status	5 (0.6%)	4 (0.6%)	1 (1.4%)	0.382
Tobacco use	97 (12.3%)	91 (12.7%)	6 (8.3%)	0.370
Alcohol use	12 (1.5%)	11 (1.5%)	1 (1.4%)	0.999
Diabetes	98 (12.5%)	90 (12.6%)	8 (11.1%)	0.858
COPD	23 (2.9%)	22 (3.1%)	1 (1.4%)	0.714
CAD	59 (7.5%)	55 (7.7%)	4 (5.6%)	0.643
Dialysis dependence	3 (0.4%)	3 (0.4%)	0 (0%)	0.999
Bleeding disorder	29 (3.7%)	25 (3.5%)	4 (5.6%)	0.329
Recent steroid use	17 (2.2%)	14 (2%)	3 (4.2%)	0.198
Disseminated malignancy	71 (9%)	65 (9.1%)	6 (8.3%)	0.999
Recent weight loss	66 (8.4%)	59 (8.3%)	7 (9.7%)	0.840
Recent chemotherapy (30d)	32 (4.1%)	29 (4.1%)	3 (4.2%)	0.999
Concomitant resection of adjacent organ	460 (58.5%)	416 (58.3%)	44 (61.1%)	0.732
Contaminated/dirty case	33 (4.2%)	31 (4.3%)	2 (2.8%)	0.760

Table 2

Breakdown of concomitant organ resections.

Concomitant organ resection	Cases (n)	% of all cases
Any concomitant procedure	539	60.0%
Colon	210	23.4%
Kidney	197	21.9%
Small intestine	70	7.8%
Other	68	7.6%
Adrenal	64	7.1%
Lung/Diaphragm	60	6.7%
Pancreas	60	6.7%
Vascular resection	54	6.0%
Gallbladder	49	5.5%
Spleen	42	4.7%
Liver	33	3.7%
Gynecologic	31	3.5%
Ureter	19	2.1%
Stomach	18	2.0%
Bladder	4	0.4%
Testicle	3	0.3%
Esophagus	2	0.2%
Vertebrae	2	0.2%

Table 3

Adjusted univariate outcomes after propensity matching.

Variable	No XRT <i>n</i> = 144	Preop XRT <i>n</i> = 72	<i>P</i> -value
Mortality (30d)	4 (2.8%)	2 (2.8%)	0.999
Overall complication rate	52 (36.1%)	26 (36.1%)	0.999
Major complication rate	38 (26.4%)	21 (29.2%)	0.787
Early return to the OR	11 (7.6%)	4 (5.6%)	0.778
Length of stay (days)	7 (5, 10)	7 (6, 11)	0.244
Operative time (min)	240 (171.5, 336.5)	278 (209.8, 388.2)	0.014
Superficial SSI	9 (6.2%)	4 (5.6%)	0.999
Deep SSI	3 (2.1%)	0 (0%)	0.552
Organ space SSI	8 (5.6%)	3 (4.2%)	0.755
Wound dehiscence	0 (0%)	0 (0%)	0.999
Sepsis	8 (5.6%)	7 (9.7%)	0.394
Septic shock	5 (3.5%)	0 (0%)	0.172
Pneumonia	4 (2.8%)	0 (0%)	0.304
Reintubation	3 (2.1%)	1 (1.4%)	0.999
Prolonged (>48 h) vent dependence	4 (2.8%)	5 (6.9%)	0.164
Pulmonary embolism	3 (2.1%)	0 (0%)	0.552
Acute kidney injury	2 (1.4%)	1 (1.4%)	0.999
Renal failure	5 (3.5%)	0 (0%)	0.172
Urinary tract infection	7 (4.9%)	3 (4.2%)	0.999
Stroke	0 (0%)	0 (0%)	0.999
Coma	0 (0%)	0 (0%)	0.999
Cardiac arrest	0 (0%)	1 (1.4%)	0.333
Myocardial infarction	0 (0%)	0 (0%)	0.999
Postoperative bleeding	22 (15.3%)	10 (13.9%)	0.946
Deep venous thrombosis	6 (4.2%)	2 (2.8%)	0.722