

Safety of appendectomy in pediatric patients with synchronous oncologic diagnosis: An analysis using the National Surgical Quality Improvement Project, Pediatric

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Abstract

Background Optimal treatment of children who develop appendicitis while undergoing treatment for an oncologic diagnosis has not been defined, in part due to theoretical concerns for an increased risk of post-operative wound complications. We hypothesized that synchronous oncologic diagnosis conferred no increased odds of developing a wound complication in pediatric patients undergoing appendectomy. **Methods** Retrospective cohort study using the National Surgical Quality Improvement Program, Pediatric (2012-2017) of patients <18 years of age undergoing appendectomy. The main exposure variable was active treatment for an oncologic diagnosis. The primary outcomes of interest were 30-day wound complications (superficial or deep infections or dehiscence, and abscess). For univariate analysis comparison of baseline differences between patients with/without a cancer diagnosis we employed Pearson's χ^2 and two sample t-tests. Multivariate logistic regression was used to evaluate which covariates were independently associated with our outcome. **Results** We identified 28219 patients who had undergone appendectomy; 95 (0.3%) were undergoing oncologic treatment at time of surgery. Patients in the cancer group were more likely to be receiving steroids, have lower white blood cell counts and have higher American Society of Anesthesiology classes compared to the non-cancer patients. Age, gender, rates of perforation and laparoscopy were similar between the two groups. Patients with an active cancer diagnosis suffered wound complications (measured individually and as an aggregate) at no higher odds than those without a cancer diagnosis. **Conclusion** Pediatric patients undergoing treatment for cancer do not have increased odds of suffering post-operative wound complications following appendectomy compared to the general population.

Safety of appendectomy in pediatric patients with synchronous oncologic diagnosis: An analysis using the National Surgical Quality Improvement Project, Pediatric 11This paper was presented in poster format at the 2020 American Pediatric Surgical Association (virtual), May, 2020.

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Key Words: Appendicitis, Appendectomy, Oncology, Pediatric

Abbreviation Key :

NSQIP-P National Surgical Quality Improvement Project, Pediatric

WBC White blood cell

SSI Surgical site infection

ANC Absolute neutrophil count

OR Odds ratio

CI Confidence interval

Abstract

Background

Optimal treatment of children who develop appendicitis while undergoing treatment for an oncologic diagnosis has not been defined, in part due to theoretical concerns for an increased risk of post-operative wound complications. We hypothesized that synchronous oncologic diagnosis conferred no increased odds of developing a wound complication in pediatric patients undergoing appendectomy.

Methods

Retrospective cohort study using the National Surgical Quality Improvement Program, Pediatric (2012-2017) of patients <18 years of age undergoing appendectomy. The main exposure variable was active treatment for an oncologic diagnosis. The primary outcomes of interest were 30-day wound complications (superficial or deep infections or dehiscence, and abscess). For univariate analysis comparison of baseline differences between patients with/without a cancer diagnosis we employed Pearson's χ^2 and two sample t-tests. Multivariate logistic regression was used to evaluate which covariates were independently associated with our outcome.

Results

We identified 28219 patients who had undergone appendectomy; 95 (0.3%) were undergoing oncologic treatment at time of surgery. Patients in the cancer group were more likely to be receiving steroids, have lower white blood cell counts and have higher American Society of Anesthesiology classes compared to the non-cancer patients. Age, gender, rates of perforation and laparoscopy were similar between the two groups. Patients with an active cancer diagnosis suffered wound complications (measured individually and as an aggregate) at no higher odds than those without a cancer diagnosis.

Conclusion

Pediatric patients undergoing treatment for cancer do not have increased odds of suffering post-operative wound complications following appendectomy compared to the general population.

Introduction

Appendicitis is the most common surgical emergency in the pediatric age group. Appendectomy is curative and associated with low rates of wound complications. More controversial is the optimal management of appendicitis in children undergoing treatment for malignancy. In these patients, appendectomy is often deferred or delayed due to theoretical concerns for increased risks of wound complications, intra-abdominal abscess and enteric suture-line dehiscence secondary to treatment related leukopenia and immune compromise. Whether these risks are increased, and medical management is superior to appendectomy in children with appendicitis and concomitant cancer diagnosis/treatment is unknown.

In light of these concerns we sought to determine if children undergoing treatment of malignancy had higher odds of developing a mechanical or infectious wound complication following appendectomy compared to children without cancer.

Methods

This was a retrospective cohort study using the American College of Surgeons National Surgical Quality Improvement Program-Pediatric (NSQIP-P) database (2012-2017). The NSQIP-P is a multi-institutional, multispecialty, clinical surgical outcomes database that includes a sampling of cases by most pediatric surgical specialties up to 30 days after a surgical procedure (excluding trauma and transplant cases) in patients younger than 18 years of age. Data for the NSQIP-P are collected in 8-day cycles for a select group of surgical procedures. These data include patient demographics, preoperative laboratory values, preoperative risk factors, *Current Procedural Terminology* codes for the procedure performed, operative details and 30-day complications.

We included patients ≥ 18 years undergoing appendectomy. Patient variables included age, gender, preoperative WBC, whether or not the patient had current chemotherapy treatment or active cancer diagnosis, laparoscopic vs open appendectomy, and perforated vs non-perforated appendicitis. WBC counts were grouped by following the National Cancer Institute's common terminology criteria for adverse events: grade 1 leukopenia as $\geq 3000/\text{mm}^3$, grade 2 as $2000 < 3000/\text{mm}^3$, grade 3 as $1000 < 2000/\text{mm}^3$, and grade 4 as $< 1000/\text{mm}^3$. The primary outcomes of interest were 30-day wound complications (superficial or deep infections or dehiscence, and abscess). Pearson's χ^2 and two sample t tests were used to compare outcomes in a univariate analysis; multivariable logistic regression was used to calculate odds of complications. Additionally, a sensitivity analysis was performed by repeating the multivariable logistic regression on only patient records that had a preoperative WBC count.

Readmission rates were calculated using NSQIP flags for hospital readmission within 30 days of operation, while reasons for readmission were assessed using the NSQIP flag for "readmission related to surgery."

Results

Patient demographics

We identified 28219 patients who underwent appendectomy; 95 (0.3%) had a synchronous cancer diagnosis and/or were undergoing chemotherapy. The group was 59.7% male with a median age of 11 years (interquartile range, 8-14). WBC counts were missing in 3155 (11.2%) of patients. American Society of Anesthesia (ASA) Class was missing in 18 (0.06%) of patients. No statistically significant differences were observed between the patients on the basis of age, gender, race, cardiac risk factors, proportion of cases performed laparoscopically or proportion of cases found to have perforated appendicitis. Patients with cancer had lower WBC counts and higher ASA Classes than those without (Table 1).

Wound complications—univariate analysis

Overall wound complications – superficial or deep surgical site infections (SSI), superficial or deep wound dehiscence, or deep organ space infections (abscess) – occurred in 2/95 (2.1%) in patients with cancer compared to 1169/28124 (4.2%) of patients without cancer ($p=0.32$). Examining incidences of specific wound infections showed no statistically significant differences between the groups (Table 2). There were indeed no suture line wound dehiscences in the cancer group.

Wound complications – multivariable logistic regression

On multivariable logistic regression, cancer diagnosis had no association with odds of suffering an aggregate wound complication (aOR 0.27, 95% C.I. 0.05-1.39) or any individual wound complication (for SSI, aOR 0.40, 95% C.I. 0.03-5.47; for abscess, aOR 0.30, 95% C.I. 0.04-2.34); for other categories too few counts to calculate aOR) (Table 3). Those factors that did have an association with odds of suffering an aggregate wound complication were: WBC 1001-2000 vs WBC ≥ 3000 (aOR 6.16, 95% C.I. 1.60-23.75); laparoscopic vs open operation (aOR 0.73, 95% C.I. 0.59-0.86); perforated vs non-perforated appendicitis (aOR 4.75, 95%

C.I. 4.19-5.38); non-white vs white race (aOR 1.22, 95% C.I. 1.07-1.39); and increasing ASA Class (Table 4).

Sensitivity analysis

Because WBC counts were missing in nearly 12% of patient records, we repeated the univariate and multivariate analysis to include only those patients with WBC counts and ASA Class available. While the demographic analysis demonstrated small differences in gender distribution, perforation rate and cardiac risk factors between the cancer and non-cancer patients that were not seen in the larger cohort, odds of wound complications – either in aggregate or individually – did not change in the sensitivity analysis (Supplemental Tables 1 and 2).

Readmission after appendectomy

Among the 95 patients with cancer, 21 (22.1%) were readmitted to the hospital within 30 days of discharge. This compares to 983/28124 (3.5%) in the non-cancer group. However, only one of those 21 patients (4.8%) in the cancer group was admitted for a reason related to surgery, as opposed to 828/983 (84.2%) in the non-cancer group.

Discussion

In this retrospective study we found that pediatric patients with an active oncologic diagnosis who underwent appendectomy did not have higher odds of suffering post-operative complications including superficial or deep SSI's, superficial or deep wound dehiscence, deep organ space infections or suture line dehiscence as compared to patients without cancer. The literature on post-operative morbidity in cancer patients, particularly in pediatrics, is sparse. Indeed, most have focused specifically on patients with neutropenia, rather than cancer, although there is an obvious and nearly 1:1 overlap in these groups among available studies on appendicitis.

Some studies have suggested an elevated risk of surgical complications in pediatric neutropenic patients and by extrapolation led to inference that appendicitis should be treated non-operatively if possible^{1,2}. Pudela et al. reported a case series of 3 neutropenic patients, all with underlying oncologic diagnoses and each treated differently – one with antibiotics alone, one with interval appendectomy after up-front antibiotic therapy, and one with urgent operation – concluding that therapy should be tailored, but implying that medical management may be the prudent course¹. Wiegering et al.'s study of 5 neutropenic oncology patients from one institution reported symptom resolution after antibiotic therapy for appendicitis in all patients, with 6-month to 3-year-followup². One patient underwent prophylactic appendectomy prior to bone marrow transplantation. The acceptance of these studies is buoyed, in part, by the ample literature demonstrating that non-operative management of appendicitis with antibiotic therapy alone can – in the short term – have successful outcomes that approach those of surgical appendectomy^{3,4}.

Other studies evaluating neutropenic pediatric patients with appendicitis have come to opposite conclusions, demonstrating relative safety of surgery in the face of neutropenia, and thus have implied that surgical treatment is preferable to medical treatment of appendicitis^{5,6,7}. Mortellaro et al. included 11 neutropenic patients from 2 institutions, all with an oncologic diagnosis⁵. All underwent appendectomy and had hospital lengths of stay comparable to the groups' previously published outcomes data on appendectomy in non-neutropenic patients. Although the paper did not report on any complications in the group of 11, the authors concluded that appendectomy in neutropenic patients was "*tolerated well with a low risk of surgical complications*." Scarpa et al.'s show heterogeneous treatment strategies among 30 neutropenic children with appendicitis (90% of whom had a hematological malignancy) from 8 French institutions⁶. Among the 30, 6 underwent immediate operation, 17 underwent delayed operation after initial antibiotic therapy, while the remaining 7 were treated with antibiotics alone. Wound complications were reported in 2 patients but it was unclear to which surgical group they belonged.

All of the available studies were conducted as single institution or small multi-center data collections, and individually included no more than 30 patients. They also were very inconsistent and vague in reporting surgical complications.

The literature on overall surgical intervention in neutropenic patients, pediatric or adult, is quite sparse. Jolissaint et al. reported on nearly 250 neutropenic adult patients from a single institution undergoing abdominal surgery, finding that ANC < 500 and emergency surgery carried a relatively higher risk of morbidity and mortality compared to less severe neutrophilia and/or elective surgery⁸. Badgwell et al. concluded in a single-institution study of 60 neutropenic adult patients undergoing urgent abdominal surgery that delay until severe neutropenia can be improved – usually by administration of colony-stimulating factors – may have beneficial effects⁹. Grant et al., examining 4389 adult patients undergoing chemotherapy for cancer in the NSQIP database, showed that leukopenia itself was not an independent risk factor for perioperative morbidity or mortality¹⁰. The authors did not, however, compare these results to the non-cancer population.

Further muddying the waters is a 2015 report by Gulack et al. using the NSQIP adult database to examine the association of leukopenia and perioperative complications in patients undergoing exclusively emergency surgery¹¹. Among the 20443 included patients undergoing emergency laparotomy, leukopenia was independently associated with increased odds of both post-operative morbidity and mortality.

Our study was strengthened by higher overall numbers than other pediatric reports (95 patients in total with a cancer diagnosis), a comparison cohort group of patients without cancer that allowed for risk stratification and multivariable logistic regression to identify covariates independently significant for increase odds of developing a wound complication, as well as the unique feature of the NSQIP database’s reporting structure that actively seeks out evidence of 30-day complications by a trained analyst. In addition to looking for 30-day complications, NSQIP reports 30-day hospital readmissions, which can also be an important metric to examine. Although quite a high proportion of the 95 patients with a cancer diagnosis were readmitted within 30 days of operation, only a scant 5% of readmissions were related to the surgery itself (compared to the 85% surgery-related rate among readmissions in the non-cancer cohort); this again suggests that operating on appendicitis in children with a synchronous oncologic diagnosis may be safe and prudent.

Our study has several limitations that are worth noting. There are those relevant to any database study, including its retrospective nature, risk of coding and reporting error, and missing data points. The last was addressed by a sensitivity analysis that did not change the overall outcomes based on missing WBC and ASA Class data points. In addition, NSQIP-P reports only total WBC counts but does not include neutrophil counts, so we were unable to include neutropenia specifically as a risk factor. The flag for cancer diagnosis includes both “active cancer diagnosis” and “undergoing chemotherapy” so we were unable to categorize specifically treatment vs overall diagnosis as possible risk factors. Specific type of cancer diagnosis was also not uniformly available, further limiting our ability to stratify our findings.

In conclusion, pediatric patients undergoing treatment for cancer do not have increased odds of suffering post-operative wound complications following appendectomy compared to the general population. These findings refute beliefs that surgical risks are prohibitively high in patients with appendicitis who have a synchronous cancer diagnosis and support surgical appendectomy as the appropriate first-line treatment. Further studies may help define any subgroups that are particularly at risk for surgical complications – such as patients with markedly low ANCs, those with specific types of cancer – although the feasibility of these studies is questionable given the small patients numbers involved.

Conflict of Interest

None of the authors have any financial conflict of interest to disclose.

References

1. Pudela C, Lancaster S, McGahren E, Petersen WC. Appendicitis in Neutropenic Pediatric Oncology Patients: A Case Series and Review of the Literature [published online ahead of print, 2020 Feb 19]. *J Pediatr Hematol Oncol* . 2020. doi:10.1097/MPH.0000000000001762.
2. Wiegering VA, Kellenberger CJ, Bodmer N, Bergtraesser E, Niggli F, Grotzer M, Nadal D, Bou-ruin JP. Conservative management of acute appendicitis in children with hematologic malignancies during chemotherapy-induced neutropenia. *J Pediatr Hematol Oncol* . 2008;30(6):464-467.

- doi:10.1097/MPH.0b013e318168e7cb.
3. Huang L, Yin Y, Yang L, Wang C, Li Y, Zhou Z. Comparison of Antibiotic Therapy and Appendectomy for Acute Uncomplicated Appendicitis in Children A Meta-analysis. *JAMA Pediatr.* 2017 May;171(5):426–429. doi:0.1001/jamapediatrics.2017.0057.
 4. Georgiou R, Eaton S, Stanton MP, et al. Efficiency and Safety of Nonoperative Treatment for Acute Appendicitis: A Meta-analysis. *Pediatrics.* 2017;139(3):e20163003.
 5. Mortellaro VE, Juang D, Fike FB, Saites CG, Potter DD Jr, Iqbal CW, Synder CL, St. Peter SD. Treatment of appendicitis in neutropenic children. *J Surg Res.* 2011;170(1):14–16. doi:10.1016/j.jss.2011.03.061.
 6. Scarpa AA, Hery G, Petit A, Brethon B, Jimenez I, Gandemer V, Abbou S, Haouy S, Breaud J, Poiree M. Appendicitis in a neutropenic patient: a multicentric retrospective study. *J Pediatr Hematol Oncol.* 2017;39(5):365–369. doi:10.1097/MPH.0000000000000834
 7. Tierney JS, Novotny NM. Appendectomy in neutropenic children: a safe and expedient solution to a challenging problem. *J Surg Res.* 2012;178(1):110–112. doi:10.1016/j.jss.2011.05.065
 8. Jolissaint JS, Harary M, Saadat LV, Madenci AL, Dieffenbach BV, Al Natour RH, Tavakkoli A. Timing and Outcomes of Abdominal Surgery in Neutropenic Patients. *Gastroenterol.* 2018;154(6):S1295.
 9. Badgwell BD, Cormier JN, Wray CJ, Borthakur G, Qiao W, Rolston KV, Pollock RE. Challenges in surgical management of abdominal pain in the neutropenic cancer patient. *Ann Surg.* 2008;248(1):104–109. doi:10.1097/SLA.0b013e3181724fe5.
 10. Grant HM, Davis LL, Garb J, Arenas RB, Stefan MS. Preoperative Leukopenia Does Not Affect Outcomes in Cancer Patients Undergoing Elective and Emergent Abdominal Surgery: A Brief Report. [published online ahead of print, 2019 Oct]. *Am J Surg.* 2020. doi:10.1016/j.amjsurg.2019.10.031.
 11. Gulack BC, Englum BR, Lo DD, Nussbaum DP, Keenan JE, Scarborough JE, Shapiro ML. leukopenia Is Associated With Worse but Not Prohibitive Outcomes Following Emergent Abdominal Surgery. *J Trauma Acute Care Surg.* 2015 Sep;79(3):437–443. doi:10.1097/TA.0000000000000757.

Legends

TABLE 1 Demographics

TABLE 2 30-day outcomes by presence of synchronous oncologic diagnosis

TABLE 3 Adjusted odds ratios of wound complications associated with synchronous oncologic diagnosis

TABLE 4 Adjusted odd ratios for risk factors for aggregate wound complications

TABLE S1 Demographics after sensitivity analysis for missing CBC and ASA Class values

TABLE S2 30-day outcomes by presence of synchronous oncologic diagnosis after sensitivity analysis for missing white blood cell and American Society of Anesthesiology Class values

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