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Treatment for appendicitis in cancer patients on chemotherapy: a retrospective cohort study

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Purpose: Whether to perform surgery or conservatively manage appendicitis in immunosuppressed patients is a concern for clinicians. This study aimed to compare the outcomes of these 2 treatment options for appendicitis in patients with cancer undergoing chemotherapy.
Methods: This retrospective study included 206 patients with cancer who were diagnosed with acute appendicitis between August 2001 and December 2021. Among them, patients who received chemotherapy within 1 month were divided into surgical and conservative groups. We evaluated the outcomes, including treatment success within 1 year, 1-year recurrence, and the number of days from the diagnosis of appendicitis to chemotherapy restart, between the 2 groups.
Results: Among the 206 patients with cancer who were diagnosed with acute appendicitis, 78 received chemotherapy within 1 month. The patients were divided into surgery (n = 63) and conservative (n = 15) groups. In the surgery group, the duration of antibiotic therapy (7.0 days *vs*. 16.0 days, P < 0.001) and length of hospital stay (8.0 days *vs*. 27.5 days, P = 0.002) were significantly shorter than conservative groups. The duration from the diagnosis of appendicitis to the restart of chemotherapy was shorter in the surgery group (20.8 ± 15.1 days *vs*. 35.2 ± 28.2 days, P = 0.028). The treatment success rate within 1 year was higher in the surgery group (100% *vs*. 33.3%, P < 0.001).
Conclusion: Surgical treatment showed a significantly higher success rate than conservative treatment for appendicitis in patients less than 1 month after chemotherapy. Further prospective studies will be needed to clinically determine treatment options.
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Key Words: Appendicitis, Surgery, Conservative treatment, Neoplasms, Drug therapy

INTRODUCTION

Appendicitis accounts for more than 50% of emergency procedures in the field of surgery [1,2]. In particular, surgery for appendicitis is considered the gold standard in cases with features such as a large diameter of the appendix, appendicolith, periappendiceal infiltration, and rupture [3-5]. However, recent studies have reported that successful treatment can be achieved with conservative management in the case of early-stage appendicitis without these advanced features [6-8].

In contrast to the evidence for optimal treatment that is gradually accumulating in general patients with appendicitis, there are still no clear guidelines in special cases such as immunosuppressed states. In such patients, clinicians may have difficulty choosing between surgery or conservative management with antibiotics.

An immunosuppressed state can alter a patient's response to infection or surgical stress. This can make patients more susceptible to infection and reduce their wound-healing ability [9]. Many clinicians decide on the risk of surgery based on ANC,

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but there is still no clear evidence for this. There is also the opinion that surgery should be reconsidered because, although the neutrophil count is normal, the fragility of the immune system increases [10].

However, there have been contradictory reports. Immunosuppressed patients are more likely to develop more severe appendicitis than healthy individuals because infectious foci cannot be eliminated properly [11,12], and the patient's condition may not improve with conservative management.

In this study, we attempted to determine whether cancer patients who received chemotherapy progressed to a more advanced form than patients who did not receive chemotherapy, under the assumption that they were immunosuppressed. In addition, we aimed to determine the optimal treatment for appendicitis in patients receiving chemotherapy.

METHODS

The study was conducted according to the principles of the 1975 Declaration of Helsinki (as revised in 2008) and was approved by the Institutional Review Board of the National Cancer Center, Korea (No. NCC2023-0118). The need for informed consent was waived due to the retrospective study design.

Patients

This retrospective study involved 358 patients with appendicitis who were treated between August 2001 and December 2021 at the National Cancer Center in Korea. Among them, we selected patients with a cancer diagnosis prior to appendicitis. The exclusion criteria were as follows: absence of cancer history, surgery for appendiceal neoplasm or incidental appendectomy during curative surgery for cancer, insufficient medical records, and no record of actual appendicitis in the pathologic results. The study included 206 patients (Fig. 1).

Based on the clinical manifestations, laboratory findings, and CT findings, the physician made a decision regarding the diagnosis of acute appendicitis. The CT criteria for an acute appendicitis diagnosis were an enlargement of the appendix (outer diameter of >6 mm) with at least one of the following features: appendiceal wall thickening (≥3 mm), hyperenhancement of the appendiceal wall, and periappendiceal inflammation (e.g., an appendicolith, thickening of the cecal wall, or fluid collection around the appendix).

Based on the 1-month recovery period from neutropenia after chemotherapy, the patients were divided into a group that received chemotherapy within 1 month of appendicitis diagnosis and a group that did not receive chemotherapy. By comparing the 2 groups, we attempted to identify whether the group that received chemotherapy within 1 month showed worse clinical or laboratory characteristics. Patients with appendicitis who received chemotherapy within 1 month were divided into surgery and conservative groups. The surgery group consisted of patients who underwent surgery within 48 hours of appendicitis diagnosis. The conservative group included patients who

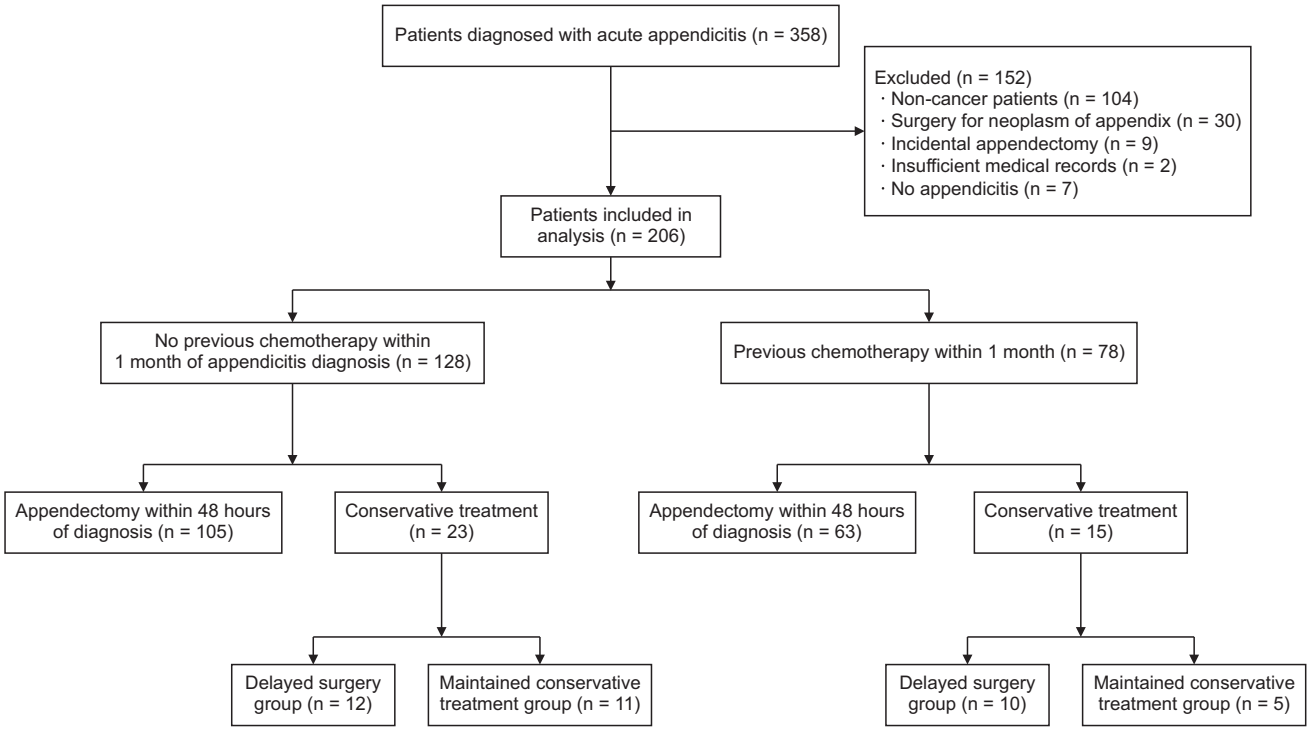

Fig. 1. Study flowchart.

received treatment such as antibiotics or percutaneous drainage at the discretion of the attending surgeon. If the surgeon decided that appendicitis had progressed 48 hours after the start of conservative treatment, delayed surgery was performed. In summary, we compared the surgery and conservative groups among patients with appendicitis who received chemotherapy within 1 month. Furthermore, we selected the patients with severe neutropenia among those with appendicitis who received chemotherapy within 1 month and compared the surgery and conservative groups.

Variables related to chemotherapy included the type and status of the primary cancer and the period from the diagnosis of appendicitis to the restart of chemotherapy. WBC and CRP levels were recorded on admission. We defined severe neutropenia as an ANC of <500/μL, and data were collected by dividing it into ANC <500/μL or ≥500/μL. In addition, the types and durations of antibiotics, admission to the intensive care unit, rehospitalization within 30 days after discharge, and complications were analyzed. The histopathological results after appendectomy were also reviewed.

Outcomes and definitions

The primary outcome was the treatment success rate in the surgery and conservative groups among patients with appendicitis who received chemotherapy within 1 month. Treatment success in the surgery group was defined as the absence of clinical symptoms after surgery and no appendicitis during the 1-year follow-up period. In the conservative group, treatment success was defined as the achievement of definitive improvement without requiring surgery within a follow-up period of 1 year. Recurrence was defined as appendicitis-associated symptoms and recurrence as confirmed by CT.

Secondary outcomes were the duration of antibiotic use, length of hospital stay, and days from the diagnosis of appendicitis to chemotherapy in both groups.

Statistical analysis

Categorical variables are expressed as numbers and percentages, whereas continuous variables are presented as means and standard deviations. Significant differences in categorical data were examined using the Pearson chi-square test. The Student t-test or the Mann-Whitney U-test was used to compare continuous variables between groups. A P-value of <0.05 was considered statistically significant in the analysis. All statistical analyses were conducted using R software ver. 4.1.2 (The R Foundation).

RESULTS

A total of 206 patients were included in this study (Supplementary Table 1). Patients were treated for various cancers as follows: gastric (n = 71, 34.5%), lung (n = 25, 12.1%), colorectal (n = 23, 11.2%), and hematological (n = 20, 9.7%) cancers.

Table 1. Clinical and laboratory characteristics between the 2 groups that received chemotherapy within 1 month

Characteristic	Surgery group	Conservative group	P-value
No. of patients	63	15	
Age (yr)	58 (43.0–67.0)	58 (20.0–66.0)	0.869
Sex, male:female	33 (52.4):30 (47.6)	7 (46.7):8 (53.3)	0.691
Duration of symptoms (hr)	20.0 (7.0–70.0)	16.0 (9.5–52.5)	0.659
Body temperature (°C)	36.8 (36.4–37.6)	37.1 (36.5–38.2)	0.483
Laboratory results			
WBC (/μL)	8,600 ± 7,378 (50–40,909)	5,516 ± 5,442(120–14,740)	0.101
ANC (/μL)			0.003
<500	4 (6.3)	6 (40.0)	
≥500	59 (93.7)	9 (60.0)	
CRP (mg/L)	6.61 ± 9.25 (0.06–48.19)	12.79 ± 12.14 (0.06–35.00)	0.101
Cancer status			0.369
No evidence of disease	37 (58.7)	11 (73.3)	
Stable disease	9 (14.3)	0 (0)	
Progressive disease	17 (27.0)	4 (26.7)	
Peritoneal seeding			0.577
Yes	5 (7.9)	0 (0)	
No	58 (92.1)	15 (100)	
Chemotherapy			0.296
Adjuvant	37 (58.7)	11 (73.3)	
Palliative	26 (41.3)	4 (26.7)	

Values are presented as number only, median (interquartile range), or mean ± standard deviation (range).

Table 2. Comparison of clinical results between the 2 groups that received chemotherapy within 1 month

Variable	Surgery group (n = 63)	Conservative group (n = 15)	P-value
Duration of antibiotics (day)	7.0 (4.0–10.0)	16.0 (11.0–22.0)	<0.001
Use of antibiotics			<0.001
Cephalosporin	43 (68.3)	3 (20.0)	
Non-cephalosporin[a]	20 (31.7)	12 (80.0)	
Name of surgery[b]			0.135
Appendectomy or cecectomy	60 (95.2)	8 (80.0)	
Extended surgery[c]	3 (4.8)	2 (20.0)	
Histology of appendix			0.023
Suppurative	33 (52.4)	3 (33.3)	
Abscess or perforation	22 (34.9)	2 (22.2)	
Chronic appendicitis	1 (1.6)	3 (33.3)	
Diverticulitis	1 (1.6)	0 (0)	
Appendiceal tumor	0 (0)	0 (0)	
Metastasis	6 (9.5)	1 (11.1)	
Length of hospital stay (day)	8.0 (5.0–16.0)	27.5 (8.75–39.75)	0.002
ICU admission	2 (3.2)	2 (13.3)	0.165

Values are presented as median (interquartile range) or number (%).
ICU, intensive care unit.
[a]Tazobactam, meropenem, vancomycin, quinolone, teicoplanin, aminoglycosides, linezolid, and antifungal agents. [b]Analyzed in surgically treated cases (n = 73). [c]Ileocecectomy and right hemicolectomy.

Table 3. Comparison of outcomes during the 1-year follow-up of patients

Variable	Surgery group (n = 63)	Conservative group (n = 15)	P-value
Complications			>0.999
No complications	51 (81.0)	12 (80.0)	
Surgical site infection			
Superficial infection	1 (1.6)	0 (0)	
Deep organ infection	3 (4.8)	1 (6.7)	
Wound dehiscence	3 (4.8)	1 (6.7)	
Ileus	5 (7.9)	1 (6.7)	
Period from diagnosis of appendicitis to chemotherapy restart (day)	20.8 ± 15.1 (1–86)	35.2 ± 28.2 (15–104)	0.028
Readmission within 30 days	2 (3.2)	1 (6.7)	0.478
Treatment success within 1 year	63 (100)	5 (33.3)	<0.001
1-year recurrence	0 (0)	0 (0)	-

Values are presented as number (%) or mean ± standard deviation (range).

Appendicitis on chemotherapy *vs.* non-chemotherapy

Among them, 78 patients received chemotherapy within 1 month of the date of appendicitis diagnosis, and 128 patients did not receive chemotherapy. The clinical characteristics of patients according to previous history of chemotherapy are presented in Supplementary Table 2. There were no significant differences in symptom duration or body temperature between the 2 groups. However, the group that received chemotherapy within 1 month included more patients with decreased WBC (6,820.0 ± 7,119.5 cells/μL *vs.* 10,090.0 ± 4,674.4 cells/μL, P < 0.001) and severe neutropenia with ANC <500/μL (10 [12.8%] *vs.* 1 [0.8%], P < 0.001). The CRP levels did not show a difference between the 2 groups (7.80 ± 10.07 *vs.* 6.84 ± 7.28, P = 0.449). A comparison of the clinical results of patients according to previous history of chemotherapy is shown in Supplementary Table 3. In the group that received chemotherapy within 1 month, the median (interquartile range [IQR]) duration of antibiotic use (8.0 [4.8–13.0] days *vs.* 6.0 [3.26–10.0] days, P = 0.252) and the length of hospital day (9.0 [6.0–18.0] days *vs.* 7.0 [5.0–10.0] days, P = 0.048) were longer than in the no chemotherapy group. The chemotherapy group showed a higher proportion of non-cephalosporin antibiotic use (41.0% *vs.* 24.2%, P = 0.011).

Table 4. Comparison between surgery and conservative groups in patients who received chemotherapy within 1 month of appendicitis (ANC <500/μL)

Variable	Surgery group (n = 4)	Conservative group (n = 6)	P-value
Age (yr)	16 (16–68)	20 (5–66)	0.610
Sex, male:female	3 (75.0):1 (25.0)	2 (33.3):4 (66.7)	0.524
Duration of symptoms (hr)	24 (14–60)	11 (3–90)	0.381
Body temperature (°C)	37.6 (37.6–39)	38.0 (37.0–39.0)	0.714
CRP (mg/L)	21.4 (9.0–31.4)	16.5 (1.3–35.0)	0.714
Duration of antibiotics (day)	14 (12–15)	14 (11–44)	0.352
Use of antibiotics			-
Cephalosporin	0 (0)	0 (0)	
Non-cephalosporin	4 (100)	6 (100)	
Length of hospital stay (day)	18 (17–53)	23 (8–146)	>0.999
ICU admission	0 (0)	1 (16.7)	>0.999
Period from diagnosis of appendicitis to chemotherapy restart (day)	21 (11–86)	16 (15–60)	0.730
Readmission within 30 days	0 (0)	0 (0)	-
Treatment success within 1 year	4 (100)	1 (16.6)	0.048
1-year recurrence	0 (0)	0 (0)	-

Values are presented as median (range) or number (%).

Surgery *vs.* conservative groups on chemotherapy

Table 1 shows the comparison of the surgery and conservative groups in patients with previous chemotherapy within 1 month. The proportion of patients with ANC <500/μL was higher in the conservative group (6 of 15, 40.0%) than in the surgery group (4 of 63, 6.3%; P = 0.003). In a comparison of clinical results, patients in the conservative group had a longer duration of antibiotics (median [IQR]: 16.0 [11.0–22.0] days *vs.* 7.0 (4.0–10.0) days, P < 0.001) and a higher proportion of non-cephalosporin antibiotic use (80.0% *vs.* 31.7%, P < 0.001) (Table 2). In the pathological results of 73 patients who underwent surgery, metastasis was found in 7 patients. The median length of hospital stay was longer in the conservative group than in the surgery group (27.5 [IQR, 8.75–39.75] days *vs.* 8.0 [IQR, 5.0–16.0] days, P = 0.002).

There were no significant differences in postoperative complications between the 2 groups. However, the number of days from the diagnosis of appendicitis to the date of restarting chemotherapy was relatively longer in the conservative group (35.2 ± 28.2 [IQR, 15–104] days *vs.* 20.8 ± 15.1 [IQR, 1–86] days, P = 0.028). Two patients in the surgery group (primary cancer progression and periappendiceal abscess) and 1 patient in the conservative treatment group (periappendiceal abscess) were rehospitalized within 30 days of discharge (Table 3). The treatment success rate within 1 year was 100% in the surgery group and 33.3% in the conservative group (P < 0.001). Ten of the 15 patients in the conservative group underwent delayed surgery. There was no case of 1-year recurrence in either group.

Surgery *vs.* conservative groups with severe neutropenia (ANC <500/μL) receiving chemotherapy

Among patients with appendicitis who received chemotherapy within 1 month, there were 10 patients with ANC <500/μL (4 patients in the surgery group and 6 patients in the conservative group) (Table 4).

There were no significant differences in the median duration of antibiotics (14 [range, 12–15] days *vs.* 14 [range, 11–44] days, P = 0.352) or the number of days from the diagnosis of appendicitis to the date of restarting chemotherapy (21 [range, 11–86] days *vs.* 16 [range, 15–60] days, P = 0.730) between the 2 groups. The treatment success rate within 1 year was 100% in the surgery group and 16.7% in the conservative group (P = 0.048). There were no cases of recurrence within 1 year in either group.

DISCUSSION

In our study, we compared the treatment options for appendicitis in cancer patients undergoing chemotherapy. Among patients with cancer who were diagnosed with acute appendicitis and received chemotherapy within 1 month, the treatment success rate was higher, and the time until the next chemotherapy was shorter in the surgery group than in the conservative group.

Neutropenia possibly had a significant impact on the decision for conservative management in this study. Among patients who received chemotherapy within 1 month, 4 of 63 (6.3%) in the surgery group and 6 of 15 (40.0%) in the conservative group had ANC <500/μL. In addition, treatment methods were

determined based on various clinical situations. Comorbidities or progressive disease status of cancer may have influenced the decision for conservative management (Supplementary Table 4). In our study, out of the 15 patients, 10 ultimately did not achieve treatment success with conservative management and underwent delayed surgery. However, only 2 patients had abscesses requiring percutaneous drainage, and among them, 1 did not undergo delayed surgery. Thus, it is assumed that receiving delayed surgery as a planned intervention was rare.

Opinions regarding the management of infections in neutropenic patients with acute appendicitis still differ regarding whether surgery or conservative treatment, including antibiotics, is optimal. Invasive procedures such as surgery can worsen the inflammatory state in immunosuppressed patients. Jolissaint et al. reported that mortality and morbidity were 11.8% and 54.5%, respectively, when surgery was performed for acute abdomen in neutropenic patients, increasing to 24.6% and 61.4%, respectively, in patients with ANC <500/μL [13]. Therefore, they suggested that conservative management should be prioritized in patients with severe neutropenia if they are hemodynamically stable.

However, it is challenging to determine whether ANC <500/μL in immunosuppressed patients is due to cytopenia after chemotherapy or a severe septic condition. Additionally, it is difficult to predict whether neutropenia will recover or worsen with conservative management, including antibiotics. Instead, while waiting for recovery from neutropenia, it is possible to miss the optimal time for surgery. In our study, 4 of 10 patients with appendicitis with ANC <500/μL underwent surgery, and all showed treatment success. Of the 6 patients who received conservative treatment, 5 (83.3%) eventually underwent surgery and showed no recurrence for 1 year. Therefore, surgery may also be considered for patients with severe neutropenia.

Regular and continuous agent administration has a significant impact on the oncological outcomes of patients receiving chemotherapy [14]. If the discontinuation period of chemotherapy is prolonged, its effectiveness may decrease, and resistance mechanisms may develop; therefore, the discontinuation period should be minimized as much as possible. Hanna et al. [15] reported that a delay of 4 weeks or more in neoadjuvant chemotherapy for bladder cancer, adjuvant and neoadjuvant chemotherapy for breast cancer, and adjuvant chemotherapy for colon and rectal cancer is associated with worse overall survival. In our study, the period from the diagnosis of appendicitis to chemotherapy restart was significantly shorter in the surgery group. Surgery may be considered to reduce the delay in restarting chemotherapy compared to conservative treatment.

In this study, when patients were receiving chemotherapy, the group that received conservative treatment for appendicitis had a longer overall period of antibiotic use and a higher rate of broad-spectrum antibiotic use than the group that underwent surgery. The longer antibiotics are used, the more likely antibiotic-resistant bacteria will develop, making it easier to develop opportunistic infections caused by harmful bacteria such as pseudomembranous colitis [16]. It can also lead to the impairment of organs that excrete drugs, such as the liver and kidneys [17,18]. In particular, these negative effects may be more severe in patients with cancer whose organ function is impaired due to chemotherapy. Performing surgery may reduce the duration of antibiotic use and decrease the need for broad-spectrum antibiotics, which can be beneficial for patients; however, further studies are needed to confirm this finding.

With the increasing number of patients with cancer, the number of immunosuppressed patients receiving chemotherapy for cancer has increased, and the number of patients requiring emergency surgery has also increased. In such cases, the decision between surgery and conservative management has always concerned clinicians. This study had several important implications; we reported that surgery for appendicitis in immunosuppressed patients increases the treatment success rate and reduces the treatment period.

Our study had some limitations. First, because this was a retrospective study, selection bias is possible. There may have been reasons for conservative management. Conservative treatment may be selected in patients with high comorbidity or a poor general condition. Second, the number of patients who received conservative management was smaller than those who underwent surgery. Therefore, the statistical power for comparing the 2 groups was not strong. However, considering that delayed surgery was performed in 10 of the 15 patients who underwent conservative management, there was a significant difference in the treatment success rate. Third, the number of patients with severe neutropenia was relatively small. Therefore, it may be difficult to determine whether all patients who received chemotherapy were immunosuppressed. Lastly, we do not have information on patients in our study who may be in an immunosuppressed state even without receiving chemotherapy, such as those taking immunosuppressants due to organ transplantation or hematopoietic stem cell transplantation for hematologic malignancy. A large-scale study is needed to study more cases of severe neutropenia.

In conclusion, surgical treatment showed a significantly higher success rate than conservative treatment for appendicitis in patients less than 1 month after chemotherapy. Surgery for appendicitis may be the optimal treatment option, even for patients undergoing chemotherapy.

SUPPLEMENTARY MATERIALS

Supplementary Tables 1–4 can be found via https://doi.org/10.4174/astr.2024.107.1.1.

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Conflict of Interest

Sung Sil Park, serving as the member of Editorial Board of *Annals of Surgical Treatment and Research*, did not participate in the review process of this article. No other potential conflicts of interest pertinent to this article were reported.

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