Proteinemia as a Prognostic Factor in Colorectal Cancers beyond Surgery and Chemotherapy

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Abstract

Background Globally, 1,096,601, 704,376, and 48,541 new colon, rectum, and anus cancer cases were recorded in 2018, respectively. Besides, 551,269, 310,394 and 19,129 cases of colon, rectum, and anus cancer deaths occurred in the same year. As a result, these cancers ranked in the third level of cancer incidence, and in the second level of cancer mortality. As it is known, all cancer patients are subjected to cancer-induced and therapy-induced nutritional deficiencies (mainly of proteins and calories). The present study aimed to assess proteins level in colorectal cancer (CRC) patients who underwent surgery and chemotherapy.

Methods A combined retrospective and prospective study was performed. The present study enrolled 100 CRC patients with their data on surgical procedures and chemotherapy management. Assessments of the studied samples were conducted as a baseline before receiving chemotherapy and preoperatively as **P0**, while the period after that was termed as **P1**. The serum samples were collected to measure protein concentration. Total Protein Kit, Micro was used.

Results The mean age of the patients was 50.7 ± 12.88 years old. Only 8% had a positive CRC family history. Rectosigmoid cancer represented the most frequent site, figured in 41% of the cases, followed by rectum cancer. Multiple sites of CRC metastasis were recorded in 15% of the patients. All patients received chemoradiation. Folinic acid (leucovorin), 5-FU, and oxaliplatin (FOLFOX) was the most used regimen, administered in 40% of the patients. Oxaliplatin and capecitabine (also called Xeloda) (XELOX) were administered in 14% of the patients. Folinic acid (leucovorin), 5-FU, oxaliplatin, and irinotecan (FOLFOXIRI) were administered in 16% of the patients. Single-agent oxaliplatin or carboplatin were administered in 6% of the patients, each. 5-FU plus leucovorin was administered to12% of the patients. Three patients received irinotecan, and oxaliplatin (IROX). One patient received folinic acid (leucovorin), 5-FU and irinotecan (FOLFIRI). Also, Gemzar was administered to two patients only. A total of 80% of the patients underwent several surgical procedures. Anterior perineal resection (APR) and total mesorectal excision (TME) were the most common two surgeries,

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performed in 20 and in 30% of the patients, respectively. In P0 status, 44% of the patients suffered from low protein levels, and 13% of the patients were within the normal level. These findings were statistically different ($p = 0.03$). After CRC management (i.e., P1 status), 70% of the patients had protein deficiency. These results have strong significant differences ($p = 0.000$). The mean of protein concentration declined gradually after management, from 8.82 ± 0.9 µg/L to 6.21 ± 0.78 µg/L, with a strong association between a reduction in proteins levels towards deficiency and surgical procedures and chemotherapy protocols ($p = 0.000$).

Conclusion The incidence of CRC is increasing annually, and the chance of being diagnosed with this type of cancer has risen in recent years. In the present study, the male to female ratio was 1:1.5, and the 5th decade of life was the most common age for the diagnosis of CRC. A negative family history and bowel inflammatory diseases (IBD) history did not exclude people from exposure to the incidence of CRC. Colorectal cancer with localized and moderately differentiated adenocarcinoma were the most common types in the present work. Tumor distance from the anal verge seems to be very important and plays a significant role in the choosing of surgical intervention types and chemoradiation protocols. Colorectal cancer acts as a complex condition and, in addition to its management, nutritional state influences it in different mechanisms. Most patients suffered from hypoproteinemia after surgery and chemoradiation. As a result, alteration in the treatment outcomes, delaying in wound healing, and an increase in postoperative complications may occur.

Introduction

Globally, 1,096,601, 704,376 and 48,541 new colon, rectum, and anus cancer cases were recorded in 2018, respectively.[1] Besides, 551,269, 310,394 and 19,129 cases of colon, rectum, and anus cancer deaths occurred in the same year.[1–4] As a result, these cancers ranked in the third level of cancer incidence, and in the second level of cancer mortality.[1] The incidence rates are higher, which is about 3-fold in developed countries in comparison with developing countries.[1]

In 2018, Bray et al.[1] mentioned in a Global Observatory Cancer (GLOBOCAN) reports that European countries have the highest colon cancer incidence rates, besides Australia, Northern America, and Eastern Asia. Although they reported similar incidence rates of rectal cancers,[1] whereas colorectal cancer (CRC) incidence rates are low in Africa and Southern Asia.[1] In Iraq, the Iraqi Cancer Registry (ICR) recorded 1,086 cases of CRC in 2011, and this number raised to 1,454 patients in 2015.[5,6] In 2020, Siegel et al.[7] reported $\sim$ 147,950 individuals newly diagnosed with CRC in the USA and 53,200 deaths.

Those cancers are considered as a marker of socioeconomic development of countries,[1] and planning the assessment of the clinical alterations that occur in these diseases is necessary for choosing the adequate proteins intervention with the best impact on nutritional status, body composition, treatment efficacy and, ultimately, to reduce complications and improve survival and quality of life.[8] The increment in the incidence rates of CRC may be altered by dietary patterns, obesity, and lifestyle factors.[1,8]

In addition, when assessing CRC risk factors, World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recorded data with convincing evidence that red meat, alcoholic drinks, and body fatness raises risk, whereas physical activities are protective.[1,9]

As it is known, all cancer patients are subject to cancer-induced and therapy-induced nutritional deficiencies (mainly protein and caloric).[8,10,11] These conditions are not solved by the consumption of high-protein nutrients, and the pathophysiology behind that is induced by metabolic alterations caused by the presence of CRC.[11] The primary potentially curative therapy for CRC is surgery, in addition to chemotherapy and radiotherapy in neoadjuvant and adjuvant forms.[2–4,11,12]

The present study tries to assess protein concentration as a nutrient and prognostic factor in CRC patients who underwent surgery and chemotherapy.

Methods

Study Setting and Design

The present study was a combined retrospective and prospective study performed at the National Cancer Center during the period from January 2019 to May 2019. The present study enrolled 100 CRC patients with their data on surgical procedures and chemotherapy management. Assessments of the studied samples were be conducted as a baseline before receiving chemotherapy and preoperatively as **P0**, while the period afterwards was termed as **P1**.

Inclusion Criteria

1. All CRC patients.
2. All patients aged $\geq$ 18 years old.

Exclusion Criteria

1. Patients in the postoperative state and/or in the second cycle of chemotherapy.
2. Unstable patients.

Data Collection

Data collected included gender, age, family history, smoking, alcoholism, comorbidity, bowel inflammatory diseases (BID), tumor site, histopathology, stage, grade, tumor distance from the anal verge, metastasis, surgery type, chemoradiotherapy (CRT).

Sample Collection

The serum samples were left to clot for $\sim$ 2 hours, then were centrifuged for 20 minutes at 1000 $\times$ g. Then, the supernatant was collected,[13] using the Total Protein Kit, Micro; 2020, Sigma-Aldrich Co. LLC.; St. Louis; USA (Catalog no. TP0100).[13]

Principle

The process was a sandwich enzyme-linked immunosorbent assay (ELISA) technology,[13] and the biotin conjugated anti-Total HSP-90 antibody was used as detection antibody.[13]

Preparation

We diluted 30 mL of concentrated wash buffer into 750 mL of wash buffer with distal water (DW). The 100 ng/ml of standard solution (SS) was prepared by adding 1 ml of sample/standard dilution buffer into one standard tube and mixing. An aliquot of 0.3 ml of the sample/standard dilution buffer was deposited into each tube. Then, 0.3 ml of the 100 ng/ml SS was added of into the first tube and mixed.[13]

Procedure

Starting by aliquot 0.1 ml of 100 ng/ml, 50 ng/ml, 25 ng/ml, 12.5 ng/ml, 6.25 ng/ml, 3.125 ng/ml, 1.563 ng/ml, standard solutions into the standard wells. Then, 0.1 ml of sample/standard dilution buffer was added into the control well. Then, 0.1 ml of diluted sample was added into test wells. Then, the plate was sealed with a cover and was incubated at 37°C for 90 minutes. Afterwards, the content was discarded and the plate was clapped on absorbent filter papers. Then, 0.1 ml of Biotin-detection antibody was added into the standard, the test sample, and the zero wells. Then, the plate was sealed and incubated at 37°C for 60 minutes. Then, the plate was washed 3 times with Wash Buffer (Sigma-Aldrich Co. LLC.; St. Louis; USA). Then, 0.1 ml of Strept Avidin-Biotin Complex (SABC) working solution was added into each well, the plate was covered, and the working solution was incubated at 37°C for 30 minutes, then it was washed 5 times with Wash Buffer. Afterwards, 90 µl of TMB substrate was added into each well, the plate was covered, and the substrate was incubated at 37°C in the dark for between 15 and 30 minutes. Finally, 50 µl of stop solution was added into each well and mixed.[13]

Statistical Analysis

Patient data were entered and analyzed using the IBM SPSS Statistics for Windows, Version 25 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean, standard deviation (SD), frequencies, and proportions. Statistical tests were applied according to the type of variables; a Paired *t*-test for grouped samples was used to compare the means of a continuous variable. The Pearson correlation (2-sided) test was used to compared grouped samples. A level of significance of $p \leq 0.05$ was considered a significant difference or correlation.

Results

The present study was composed of 40% male and 60% female subjects, with a mean of age of 50.7 $\pm$ 12.88 years old.

Most of the patients with CRC were between 51 and 60 years old, corresponding to 26% of the sample. Only 8% of the patients had a positive family history of CRC. Smoking patients corresponded to 60% of the sample, and the non-smokers to 40%. A total of 29% of the patients were alcoholics. A total of 49 out of 100 patients were obese. Body surface area (BSA) was above the normal index in 49% of the sample. Comorbidities were present in 38% of the sample. A total of 10% of the patients had IBD , while 90% did not present IBD. A total of 72% of CRC patients lived in the capital Baghdad. A total of 45% of females were housewives. A total of 25% of the patients did not work. (►**Table 1**).

Rectosigmoid cancer represented the most frequent site, corresponding to 41% of the cases, followed by rectum cancer. Adenocarcinoma was the most common histopathology, diagnosed in 66% of the patients. The tumors were localized in 46% of the cases, whereas spreading was found in 34% of the patients. Moderate differentiation was observed in 60% of the patients, while poorly-patterned tumors were present in 15% of the patients. A total of 15 (15%) tumors were located at a distance $<$ 5 cm from the anal verge, while those located at a distance between 5 and 10 cm corresponded to 40 (40%) of the cases. Tumors at a distant location from the anal verge corresponded to 45%. Multiple sites of CRC metastasis were recorded in 15% of the cases. Hepatic lesions were seen in 6 patients. Pulmonary metastases were found in two patients. Lytic bony lesions were present in 5% of the patients. Recurrence was present in 6% of the cases, while 66% of the patients did not have metastasis. (►**Table 1**).

All patients received chemoradiation. Folinic acid (leucovorin), 5-FU, and oxaliplatin (FOLFOX) were administered in 40% of the patients, and was the most used regimen. Oxaliplatin and capecitabine (also called Xeloda) (XELOX) were administered to 14% of the patients. Folinic acid (leucovorin), 5-FU, oxaliplatin, and irinotecan (FOLFOXIRI) were administered in 16% of the patients. Single-agent oxaliplatin or carboplatin were administered to 6% of the patients, each. 5-FU plus leucovorin were administered to 12% of the patients. Three patients received irinotecan, and oxaliplatin (IROX). One patient received folinic acid (leucovorin), 5-FU, and irinotecan (FOLFIRI). In addition, Gemzar was administered to only two patients (►**Table 1**).

Table 1 Patients, colorectal cancer, and management baseline characteristics ($n = 100$)

Variables		*n* (%)
Gender	Male	40 (40)
	Female	60 (60)
Age (years old) 50.7 ± 12.88	20–30	4 (4)
	31–40	10 (10)
	41–50	16 (16)
	51–60	26 (26)
	61–70	24 (24)
	>70	20 (20)
Family history	Positive	8 (8)
	Negative	92 (92)
Smoking	Smoker	60 (60)
	Nonsmoker	40 (40)
Alcoholism	Yes	29 (29)
	No	71 (71)
BSA (m^2) 1.7 ± 0.39	< 1.7	31 (31)
	1.7	20 20)
	> 1.7	49 (49)
Comorbidity	Present	38 (38)
	Absent	62 (62)
IBD	Present	10 (10)
	Absent	90 (90)
Address	Babil	4 (4)
	Baghdad	72 (72)
	Basra	1 (1)
	Diyala	6 (6)
	Misan	1 (1)
	Musol	2 (2)
	Ramadi	4 (4)
	Tikreit	5 (5)
	Wasit	5 (5)
Occupation	Government employed	24 (24)
	Nonemployed	25 (25)
	Housewife	45 (45)
	Student	6 (6)
Colorectal cancer sites	Rectum	25 (25)
	Anorectal	8 (8)
	Rectosigmoid	41 (41)
	Cecum	3 (3)
	Right colon	10 (10)
	Transverse	5 (5)
	Left colon	8 (8)
Histopathology	Adenocarcinoma	66 (66)
	Mucinous	12 (12)
	Signet-ring cell	4 (4)
	Undifferentiated	10 (10)
	Adenosquamous	4 (4)
	Squamous	4 (4)
Stages	Localized	46 (46)
	Regional	20 (20)
	Distant metastasis	34 (34)
Grades	Well differentiated	25 (25)
	Moderately differentiated	60 (60)
	Poorly differentiated	15(15)
Distance from the anal verge	< 5 cm	15 (15)
	5–10 cm	40 (40)
	> 10 cm	45 (45)
Metastatic patterns	Liver	6 (6)
	Lung	2 (2)
	Local recurrence	6 (6)
	Bone	5 (5)
	Multiple metastases	15 (15)
	No metastases	66 (66)
Chemotherapy	Received	100 (100)
	No	0
Chemotherapy protocols	5-FU plus leucovorin	12 (12)
	FOLFOX	40 (40)
	XELOX	14 (14)
	FOLFIRI	1 (1)
	Oxaliplatin	6 (6)
	IROX	3 (3)
	FOLFOXIRI	16 (16)
	Carboplatin	6 (6)
	Gemzar	2 (2)
Radiotherapy	Received	100 (100)
	No	0
Surgery	APR	20 (20)
	LAR + loop ileostomy	5 (5)
	LAR without ileostomy	8 (8)
	TME	30 (30)
	Local excision	7 (7)
	Laparotomy	10 (10)
	No surgery	20 (20)

Abbreviations: FOLFIRI; folinic acid (leucovorin), 5-FU, oxaliplatin, and irinotecan; FOLFOX, folinic acid (leucovorin), 5-FU, and oxaliplatin; FOLFOXIRI, folinic acid (leucovorin), 5-FU, oxaliplatin, and irinotecan; IROX, irinotecan and oxaliplatin; XELOX, oxaliplatin and capecitabine (also called Xeloda).

Table 2 Protein concentration before and after ($n = 100$)

Protein	P0	P1	Paired *t*-test	95%CI	*p-value*
	n (%)				
Hypoproteinemia (< 67 g/L)	44 (44)	70 (70)	5.281	38.285–84.374	0.000
Normal (67–86 gl/L)	13 (13)	20 (20)			
Hyperproteinemia (> 86 g/L)	43 (43)	10 (10)			
Mean ± SD	8.82 ± 0.9	6.21 ± 0.78			
***p-value* (one-sample test)**	0.03	0.000			

Abbreviations: CI, confidence interval; SD, standard deviation.

A total of 80% of the patients underwent several surgical procedures. APR and TME were the most common surgeries, performed in 20 and 30% of the patients, respectively. Local excision was performed in 7% of the patients. A total of 10% of the patients underwent laparotomy. Loop ileostomy was performed in 5% of the patients, whereas it was not done in 8% (►**Table 1**).

In the P0 status, 44% of the patients suffered from low protein levels, 13% of the patients were within the normal level, and 43% of the patients had hypoproteinemia. These findings were statistically different ($p = 0.03$).

After CRC management (i.e., P1 status), 70% of the patients had protein deficiency. Normal protein levels were observed in 20% of the patients, while 10% of the patients still had a high concentration of proteins. These results have strong significant differences ($p = 0.000$) (►**Table 2**).

The mean protein concentration declined gradually after management, from 8.82 ± 0.9 µg/L to 6.21 ± 0.78 µg/L, with a strong association between a reduction in proteins level towards deficiency and surgical procedures and chemotherapy protocols ($p = 0.000$) (►**Table 2**) (►**Fig. 1**).

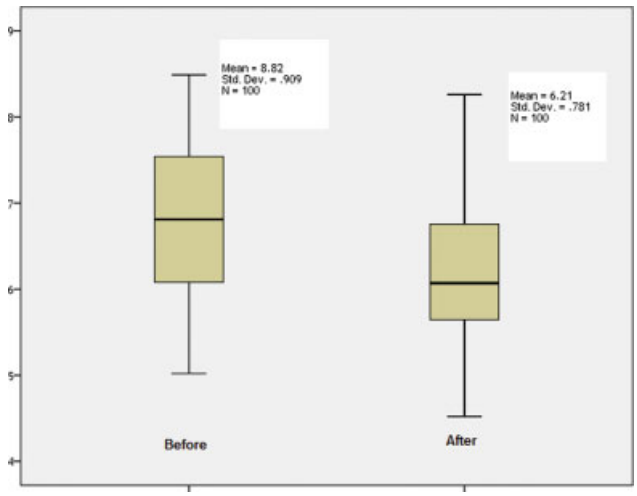

Fig. 1 Box plot of protein concentrations before and after surgery and chemotherapy of colorectal cancer (CRC).

Discussion

Several studies conducted in Iraq postulated different findings for CRC. Some of the studies agree with most of the results of the present study, such as those by Radhi et al., in Al-Diwaniyah,[14] Alsafi et al., in Karbala,[15] Alshewered et al., in Baghdad,[2] Alrubaia et al., in Baghdad,[3] while others were not in line with the present study, such as those by Alhilfi et al., in Misan,[4] and by Khalil et al., in Duhok.[16]

In Iraq, the incidence of CRC is increasing annually, and the chance of being diagnosed has risen in recent years, which may be attributed to increased awareness of symptoms like bleeding per rectum (BPR) and constipation, and to the early detection of small lesions secondary to the more widespread use of colonoscopy, and fine-needle aspiration of any suspicious lesion in treatment centers.

In the present study, the male to female ratio was 1:1.5, and the 5th decade of life was the common age for the diagnosis of CRC. Other researchers said that age is an essential factor for the occurrence and management of CRC,[12,17] and reports registered in the ICR for a period of 10 years and in the National Cancer Hospitals for 3 years found that the male to female ratio varied from 1.17:1 to 1.28:1.[18]

A negative family history and IBD history does not exclude people from exposure to CRC incidence. Tobacco smoking and alcohol consumption may be a risk, but the findings of the present study did not support that.

Different factors were shown to raise the risk of incidence of colon cancer, including older age, male gender, positive family history, IBD, being taller or obese, eating processed meat, refined grains, starches, and sugars, alcoholism and smoking, and low folate ingestion.[1,7,11,14,17] Only increasing age, female gender, and excessive alcohol consumption have been associated with rectal cancer.[7,12,14,17]

With a low socioeconomic status, insufficient screening methods, doubtful early detection, low educational level, mistakes in diagnosis, and unavailability of diagnostic tools, the mean age of CRC diagnosis was > 50 years old. In Western countries, 8% of CRC cases were recorded at ages < 40 years old, whereas Egypt, Saudi Arabia, the Philippines, and Iran recorded rates of 38, 21, 17, and between 15 and 35% for the same age group, respectively.[6,19–21]

There was no correlation between nutritional status and income, education, and type of IBD, and no correlation was

observed between the most consumed anti-inflammatory and inflammatory foods and BMI.[22]

Most of the patients were addressed in Baghdad, which is the capital of Iraq. However, we received many colonoscopy reports from other sites.

Those may be reflected in the non-real figures due to several patients like to do a colonoscopy in different places and even outside Iraq, besides that many cases of CRC diagnosed by imaging studies and undergo surgery without doing colonoscopy or sigmoidoscopy, resulted in many missing cases.

Most of the studied patients had a rectosigmoid tumor, which is similar to that reported by Giovannucci et al., who reported that the most common site is the sigmoid, followed by the rectum, the cecum, the rectosigmoid junction, the transverse colon, and the ascending colon.[23] However, these findings differ from those of other studies.[4,14–16]

Localized and moderately differentiated CRC adenocarcinoma were the most common subtypes observed in the present study, which supports that CRC tumors originate in the mucosal layer and that all of them are adenocarcinomas.[17] All researchers in Iraq support these findings.[2–4,14–16,18,24]

However, these findings are different from the Surveillance, Epidemiology, and End Results Program (SEER) data that reported the localized site of CRC was (47%), regional (36.5%), metastatic (16.5%) of CRC cases. This can be due to different sample sizes, early diagnosis and treatment provided by screening programs, good health education, and awareness in the US and other developed countries.[25,26]

The distance of the tumors from the anal verge seems to be very important and plays a significant role in the decision-making regarding surgical intervention types and chemoradiation protocols. Here, most cases had tumors that were distant from the and verge (i.e., >5 cm). A study by Khan et al. reported that the distance of CRC from the anal verge influenced the use of neoadjuvant treatment and, ultimately, the R0 resection rate. The tumor location and the distal tumor margin are essential factors upon which the surgical plan for patients with CRC is based. Accurate measurement is necessary for planning the surgical procedure, even sphincter-saving resection.[27]

All patients received chemotherapy of different regimens, whether they were in early or advanced stages of CRC. Also, all patients were treated by radiotherapy (RT). Besides, 80% of the patients underwent surgery. All these management combinations followed international guidelines of several trials worldwide, such as the National Cancer Institute (NCI) and Mayo/NCCTG 79–47–51 trials; NSABP R-01, R-02 trials; EORTC trial 22921; NSABP R0–354 and the German CAO/ARO/AIO 94 trials; STAR-01, ACCORD, and NSABP R-04 trials; UK MRC CR07 trial; Dutch Colorectal Cancer Group CKVO and Swedish Rectal Cancer trials; German Rectal Cancer Trial CAO/ARO/ AIO-94; and the Polish Colorectal Study Group trial.[11,28–34]

As it is known CRC is a complex cancer and it influences the nutritional state in different manners.[35] It is reported that between 15 and 40% of the patients have weight loss and that between 40 and 80% of the patients suffer from malnourishment during management.[36]

Regarding the results of proteinemia, most of the patients (70%) suffered from hypoproteinemia after surgery and chemoradiation. In this state, malnutrition may develop and cause alterations in the treatment outcomes, delaying wound healing and increasing postoperative complications. Besides, malnutrition can cause impairment tolerance and response to chemotherapy.[37] In addition to the disease, antineoplastic treatments and/or surgery have a significant impact on the nutritional status of the patients.[14,34,38]

During chemotherapy and radiotherapy, nausea and vomiting are very common and lead to poor nutritional status, which further increases surgical morbidity and postoperative complications.[38–41]

The nutritional supplement not presented for all cancerous patients, and this postulated a guide to the multidisciplinary team in the management of CRC for including nutritional intervention for those patients.

Cancer patients do not meet the recommended intake (1.2–1.5 g/kg/day) of proteins, not even that recommended for healthy individuals (0.8 g/kg/day).[42] Limited protein intake documented mainly from nutrition impact symptoms that affect dietary intake.[43] Recent guidelines suggest a higher range of protein intake (1.2–1.5 g/kg/day) due to the positive results of higher protein intake in protein balancing and in maintaining muscle mass. Of additional interest is a recent study showing an inverse association between red meat consumption and 7-year mortality among 992 individuals with stage III colon cancer,[44] suggesting that higher protein intake may be beneficial in cancer. In a review by Gangadharan et al., the authors explained in detail the effect of surgery, chemotherapy, and radiotherapy on protein concentrations in CRC.[10]

Conclusions

The incidence of CRC is increasing annually, and the chance of being diagnosed has risen in recent years. In the present study, the male to female ratio was 1:1.5, and the 5th decade of life was the most common age for the diagnosis of CRC. A negative family history and IBD history did not exclude individuals from exposure to CRC incidence. Localized and moderately differentiated CRC adenocarcinoma was the most common subtype in the present study. The distance of the tumors from the anal verge seems to be very important and plays a significant role in the decision-making regarding surgical intervention types and chemoradiation protocols. Colorectal cancer act as a complex condition, in addition to their management, are influences the nutritional state in different mechanisms. Most patients suffered from hypoproteinemia after surgery and chemoradiation. As a result, alteration in the treatment outcomes, delays in wound healing, and increase in postoperative complications may develop.

Ethical Approval

The present study followed the Declaration of Helsinki and was approved by the local ethics committee of the

center. Informed written consent was obtained from all patients.

Conflict of Interests

The authors have no conflict of interests to declare.

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