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A single-center experience

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AIM: *The traditional treatment for appendiceal cancer with peritoneal spread is cytoreductive surgery (CRS) but added HİPEC chemotherapy to cytoreductive surgery and has shown that it improves overall survival. The aim of this study was to report the results of CRS and HIPEC treated patients with appendiceal cancers which is based on the experience of at Surgical oncology department.*
MATERIAL-METHOD: *Ankara University School of Medicine, Deparment of Surgical Oncology. The data of patients who underwent CRS + HIPEC for appendiceal cancer between January 2008 - January 2019 was retrospectively analysed. 40 patients who underwent CRS + HIPEC were evaluated retrospectively. Patients with unresectable liver metastasis, large retroperitoneal tumor, tumoral infiltration in the intestinal mesentery and liver hilum were excluded from the study.*
RESULTS: The *mean (±sd) PCI was 17.98 (±8.21). Twenty six patients's completeness of cytoreduction score was 0(65.0%), 10(25.0%) CCS-1, 3(7.5%) CCS-2 and 1(2.5%) CCS-3. There was statistically significant difference with prognosis between ccr score, ASA, lymphovascular invasion, PCI score, albumin categories.*
CONCLUSIONS: *In selected patients survival can be increased. However, it is thought that cytoreductive surgery should be performed even if completeness of cytoreduction score is two. In our study we represent that >17PCI patients could be managed by CRS/HIPEC if the CC score ≤2 can be reached. Our results suggest that the CRS/HIPEC procedure can improve the benefits of larger patient group and provides longer survival.*

KEY WORDS: Appendiceal Neoplasms, Cytoreductive Surgery, Hyperthermic Intraperitoneal Chemotherapy

Introduction

Appendiceal cancers are very rare cancers with an incidence of 0.1 per 1000000, less than two percent of all appendectomies, and the diagnosis of cancer is usually made during the specimen examination [1,2]. The most common type of appendix tumors are the carcinoid types, and the second most common adenocarcinomas are mucinous; signet rings and goblet cell components can also be seen [3]. In rare cases, peritoneal pseudomyxoma develops with a mucin spread to the peritoneal region, in many cases, as a result of the perforation of the appendix mucinous cancer. The traditional treatment for appendiceal cancer with peritoneal spread is cytoreductive surgery. Sugarbaker added hyperthermic intraperitoneal chemotherapy to cytoreductive surgery and has shown that it improves overall survival [4]. In recent years, it has been stated that Peritoneal Cancer

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ABBREVIATION

ASA: American Society of Anesthesiologists
CC: Completeness of Cytoreduction
CRS: Cytoreductive Surgery
HIPEC: Hyperthermic Intraperitoneal Chemotherapy
HG-AMN: High-Grade Appendix Mucinous Neoplasia
HG-PD: High-Grade Peritoneal Disease
LG-AMN: Low-Grade Appendix Mucinous Neoplasia
LG-PD: Low-Grade Peritoneal Disease
LS: Lesion Size
LVI: Lymphovascular Invasion
MAC: Mucinous Adenocarcinoma
PCI: Peritoneal Cancer İndex
PMP: Pseudomyxoma peritonei
PSOGI: Peritoneal Surface Oncology Group International
SD: standard deviation
SRC: Signet Ring Cell Cancer
SRD: Signet Ring Disease
WHO: World Health Organization

İndex (PCI) over 20 in many malignancies may constitute a contraindication for cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC), while it is thought that cytoreductive surgery and HIPEC may be effective in patients with a PCI score above 17 and a completeness of cytoreduction (CC) score of 2 and below, especially in appendix cancers. Overall survival was also improved according to recent studies by CRS and HIPEC [5,6]. This study aimed to evaluate the results of patients with appendiceal cancer treated with CRS-HIPEC and was based on the experience of the Department of Surgical Oncology.

Material and Method

The data of patients who underwent CRS + HIPEC for appendiceal cancer between January 2008-January 2019 was retrospectively analyzed. Patients with comorbidities who could not tolerate general anesthesia or who had unresectable liver metastasis, a large retroperitoneal tumor, tumor infiltration of the liver hilum, and intestinal mesentery were excluded. Forty patients were included in this study.

Data Collection

Preoperative American Society of Anesthesiologists (ASA) scoring, surgery and pathology reports, hematological and biochemical parameters, and tumor markers were evaluated. Radiological screenings (computed tomography, ultrasonography, PET-CT, magnetic resonance imaging) were retrospectively analyzed. Values of CEA higher to 5 ng/ml were defined as high, levels of Ca19-9 higher 37 u/l were defined as high. Values of albumin lower to 3,5 g/dl were defined as hypoalbuminemia.

All patients were placed in the Surgical Procedures lithotomy position. A midline incision from the xiphoid to the pubis was performed to enter the abdomen. In all patients, exploration was achieved using a Rochard 60 x 135 mm abdominal retractor (60-7442, Condor-Med Tec, Salzkotten, Germany). Then, the peritoneal cancer index (PCI) defined by Sugarbaker was calculated for each patient [7]. We grouped the LS_0 (lesion size) as follows: no macroscopic tumoral lesion, LS_1 (the presence of tissue of less than 5 mm), LS_2 (the presence of tumor tissue between 5 mm-5 cm), and LS_3 (the presence of tumoral tissue greater than 5 cm). Then the lesion was rated with a score of 0 to 39 (Fig. 1). None of the patients were excluded from the surgical treatment because of a high PCI index.

The following resections were performed: right upper quadrant peritonectomy, left upper quadrant peritonectomy, anterior parietal peritonectomy, pelvic peritonectomy, right diaphragm peritonectomy, left diaphragm peritonectomy, large omentectomy, small omentectomy, and visceral resections, if required (Fig. 2).

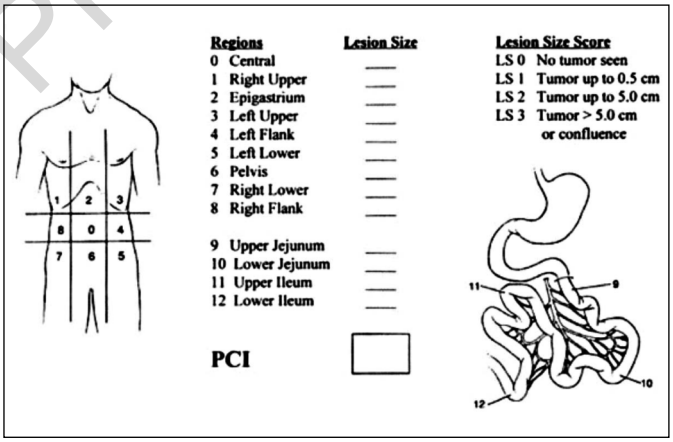

Fig. 1: Peritoneal cancer index classification according to Sugarbaker.

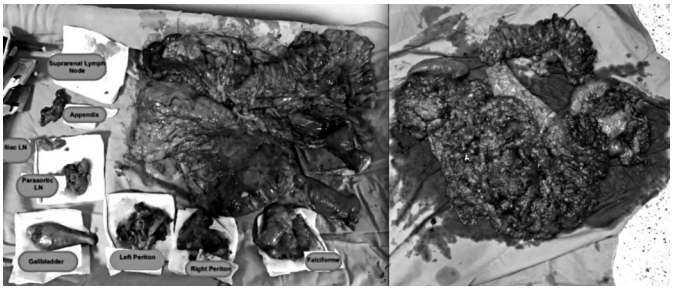

Fig. 2: Complete cytoreduction.

Non-excision sites were also coagulated with electrocautery. If anastomosis was required or a stoma was performed, these procedures completed after HIPEC. For the evaluation of the remaining tumor tissue after cytoreductive surgery, the CC (completeness of cytoreduction) classification method described by Sugarbaker was used [8]. After cytoreduction, four (28-fr) silicone drains and two heat probes were placed, and the abdomen was closed. Then, chemotherapy perfusion was started. Mitomycin 20 mg/m^2 and carboplatin 450 mg/m^2 were used as chemotherapeutic drugs. The chemotherapy solution was heated to 42°C with the HIPEC device (HT2000, Therma Solutions, Minnesota, USA). The temperature of the lumens filled in the patient should be a maximum of 42°C. The intraperitoneal volume was calculated. The intraabdominal region of the patient was filled with chemotherapy solution 500 ml -1000 ml more than the calculated volume. The temperature of the patient's chemotherapy solution was adjusted not to exceed 42°C, and the chemotherapy solution did not fall below 40°C in the peritoneal region. To achieve these optimum values, we tried to keep the perfusion rate at least 1500 ml/min-1600 ml/min during the process.
Postoperative follow-up started 2-3 weeks after discharge. The patients were called for controls every 6 months for the first 3 years and physical examination, thoracoabdominopelvic tomography and tumor markers were checked in the controls.

Statistical Analysis

The data were analyzed by SPSS 11.5 for Windows. (SPSS Inc., IA, USA) The mean ± standard deviation and the median (minimum-maximum) for quantitative variables and the number of patients (percentage) were used for qualitative variables. Chi-square and Fisher Exact tests were used to examine the relationship between two qualitative variables. Survival analyses on qualitative variables were performed using the Kaplan-Meier method, and significant differences between the groups were determined using the log-rank test. Multivariate analyses were performed using the Cox proportional hazard model to identify factors affecting survival. In the univariate Kaplan-Meier analysis, variables with a P-value below 0.25 were included in the Cox proportional hazard model. The statistical significance level was determined as 0.05.

Results

In the study, the mean ± standard deviation and median (minimum-maximum) values of the patients were found to be 57.20 ± 13.06 and 58.50 (31.00-85.00). Sixteen patients (40%) were female, and 24 patients (60%) were male. Seventeen (42.5%) of the patients were deceased while 23 (57.5%) were alive.

Ten patients (25%) had adenocarcinoma while 30 patients (75%) had mucinous carcinoma. Four (40%) of the adenocarcinoma patients survived while 6 (60%) were deceased. While 19 (63.3%) of the mucinous carcinomas were alive, 11 (36.7%) were deceased. There was no statistically significant difference between the two groups (p= 0.138). All descriptive values are shown in Table I.
All patients underwent standard right hemicolectomy, omentectomy, and peritonectomy. In addition to these procedures, organ resection was added in necessary cases. All patients underwent hyperthermic intraperitoneal chemotherapy with mitomycin-c 20 mg/m^2 and carboplatin 450 mg/m^2 for one hour after cytoreduction. Perioperative blood product was used in 18 (45%) patients.
Twelve patients had undergone previous surgical procedures. Nine of these 12 patients had undergone appendix-related procedures. According to the ASA of the scores of the patients, four (10%) were ASA3, 18 (45%) were ASA2, and 18 (45%) were ASA1. There was a statistically significant difference between ASA scores and prognosis (p=0.009).
LVI (Lymphovascular Invasion) was present in 29 (72.5%) patients whereas LVI was not seen in 11 (27.5%) patients. Thirteen (44.8%) of the patients with

Table I - *Descriptive values.*

	Variables	n	%
Diagnosis	Adenocancer	10	25.0
	Mucinous	30	75.0
Claven Dindo	1	13	32.5
	2	14	35.0
	3	6	15.0
	4	3	7.5
	5	4	10.0
CCS	0	26	65.0
	1	10	25.0
	2	3	7.5
	3	1	2.5
ASA	1	18	45.0
	2	18	45.0
	3	4	10.0
Gender	Male	24	60.0
	Female	16	40.0
PMP	Negative	15	37.5
	Positive	25	62.5
LVI	Negative	11	27.5
	Positive	29	72.5
Status	Exitus	17	42.5
	Alive	23	57.5
Ca19_9	Normal	11	27.5
	High	29	72.5
CEA	Normal	13	32.5
	High	27	67.5
PCI	Normal	20	50.0
	High	20	50.0
Albumin	Normal	24	60.0
	High	16	40.0

TABLE II - *Kaplan-Meier analysis results.*

Variables		Survival				Survival time		
		1 year (%)	2 year (%)	3 year (%)	5 year (%)	Average±SD	Median±SD	p value
Overall		67.7	50.9	50.9	50.9	71.24±10.45	-	-
Diagnosis	Adenocancer	44.4	33.3	33.3	-	20.44±5.88	11.00±2.98	0.138
	Mucinous	75.4	57.1	57.1	57.1	79.04±11.92	-	
CCS	0	82.4	66.4	66.4	66.4	90.78±12.29	-	0.011
	1	50.0	20.0	-	-	14.30±3.29	11.00±4.74	
	2	33.3	33.3	33.3	-	16.33±11.70	2.00±-	
	3	-	-	-	-	4.00±-	4.00±-	
ASA	1	81.9	75.6	75.6	75.6	56.89±6.59	-	0.009
	2	63.8	30.4	30.4	30.4	47.86±15.39	19.00±4.86	
	3	25.0	-	-	-	7.75±3.31	2.00±5.00	
PMP	Negative	55.3	47.4	47.4	47.4	38.07±8.93	13.00±-	0.548
	Positive	74.7	52.4	52.4	52.4	73.86±13.29	-	
LVI	Negative	90.9	90.9	90.9	90.9	65.64±6.07	-	0.027
	Positive	59.4	38.7	38.7	38.7	56.66±11.67	19.00±6.59	
Ca19_9	Normal	90.0	66.7	66.7	66.7	53.80±8.71	-	0.125
	High	59.0	44.8	44.8	44.8	62.95±12.37	19.00±6.44	
CEA	Normal	83.9	54.4	54.4	54.4	46.58±8.58	-	0.381
	High	59.4	49.9	49.9	49.9	68.46±12.82	15.00±-	
PCI	Normal	94.1	71.7	71.7	71.7	57.06±6.38	-	0.001
	High	41.7	29.8	29.8	29.8	43.48±13.43	11.00±3.25	
Albumin	Normal	79.2	60.6	60.6	60.6	49.05±6.88	-	0.043
	Low	50.0	35.7	35.7	35.7	50.97±15.17	11.00±14.00	

TABLE III - *Cox regression analysis results.*

Variables		Survival	Confidence Interval		
		Hazard Ratio	Lower Limit	Upper Limit	p value
ASA	1	1 (Reference)	-	-	-
	2	3.038	1.933	9.884	0.035
	3	6.934	2.434	33.522	0.016
PCI	Normal	1 (Reference)	-	-	-
	High	4.863	1.543	15.330	0.007

LVI survived while 16 (55.2%) died. Ten (90.9%) of the patients without LVI survived, and one (9.1%) died. In terms of prognosis, it was found that the prognosis was worse in patients with LVI (p= 0.027).

Sixteen patients received neoadjuvant therapy and 24 did not. There was no statistically significant difference between prognosis and neoadjuvant therapy (p= 0.087).

The mean peritoneal cancer index of the patients was 17.98; the lowest was five while the highest was 34. In our study, we divided PCI into two groups as above, 17 and above or below 17. Twenty patients had PCI values of 17 and below while 20 patients had values above 17. Seven (35%) of the patients with PCI values above 17 were alive and 13 (65%) were deceased. In patients with values of 17 and under, 16 (80%) were alive and four (20%) were deceased. According to the Kaplan-Meier and Cox Regression analyses, a statistically significant difference was found between PCI index and prognosis (p= 0.001).

After the surgery, the CC scores were as follows: CCS 0:26 (65%), CCS 1 10 (25%), CCS 2 (7.5%), and CCS 3 1 (2.5%). Nineteen (73.1%) of the patients with CCS-0 were alive and 7 (26.9%) were deceased. The patients with CCS-1, 3 (30%) survived, and 7 (70%) died. One (33.3%) of the patients with CCS-3 was alive and two (66.7%) were deceased. One patient with CCS-3 was deceased. According to the Kaplan-Meier analysis, a statistically significant difference was found between the CC score and the prognosis (p=0.011).

When the preoperative albumin values of the patients were examined, values below 3.5 g/dl were considered as low albumin. Sixteen patients (40%) had hypoalbuminemia and 24 patients (60%) did not. Six patients (37.5%) survived while 10 patients (62.5%) died of hypoalbuminemia. According to the Kaplan-Meier analysis, a statistically significant relationship was found between hypoalbuminemia and prognosis (p=0.043).

In the univariate analysis according to the Kaplan-Meier analysis, the CCS, ASA, LVI, and PCI scores, and albumin values were found to have statistically significant differences with prognosis (p values 0.011, 0.009, 0.027, 0.001, 0.043). (Table II) The effect of PCI, LVI, Albumin, ASA score and CC score on overall survival are shown in Fig. 3.

In the multivariate analysis according to the Cox regression analysis, the PCI and ASA scores were found to be statistically significant in terms of prognosis (p=0.001) (Table III).

When the five explanatory variables in the study are considered together, the results of the significant model obtained when the Cox regression analysis was performed

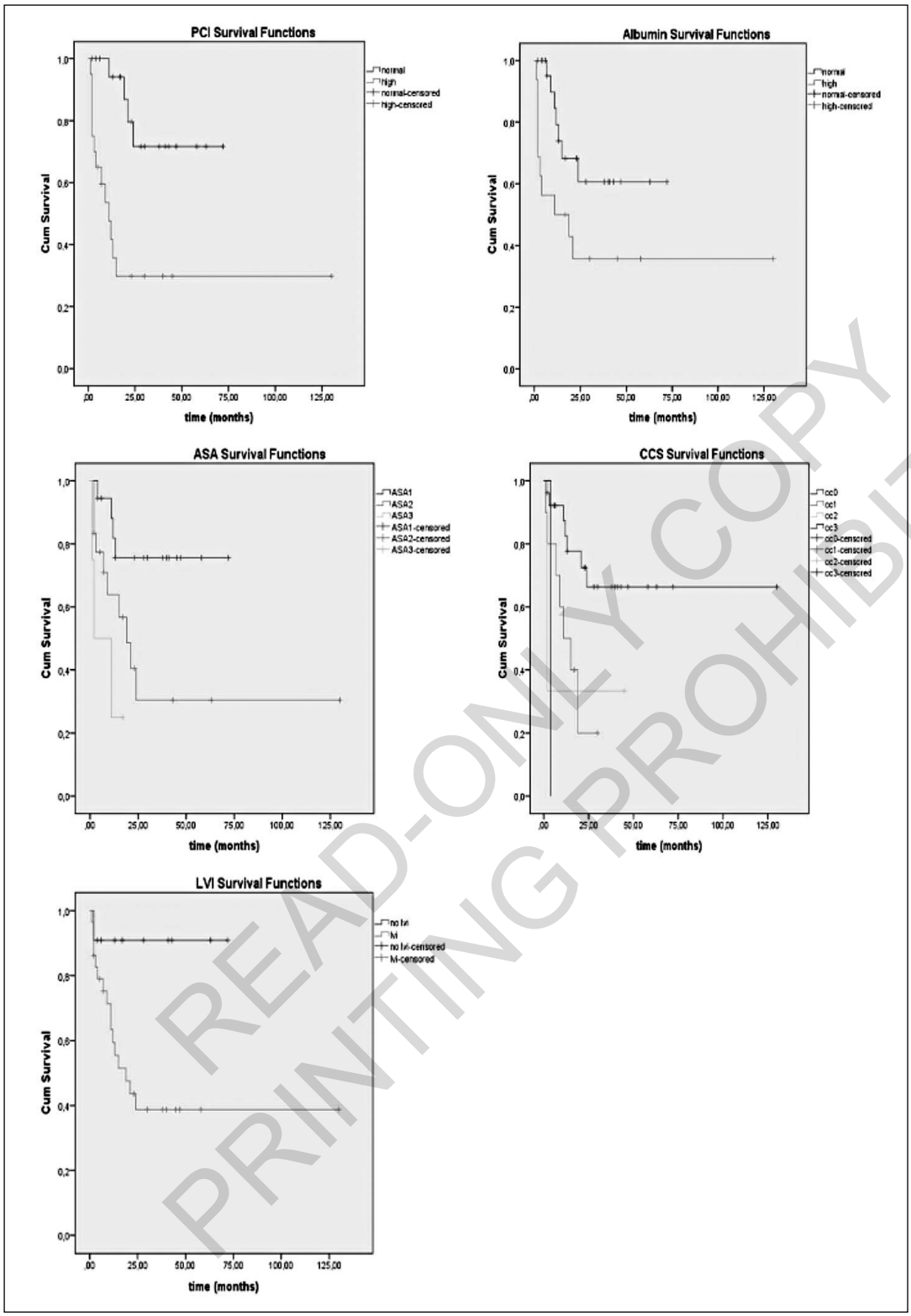

Fig. 3: The effect of PCI, LVI, Albumin, ASA score and CC score on overall survival.

by the reverse selection method to determine which factors affect survival are given in Table III. As shown in Table III, the ASA and PCI variables remained in the model ($p < 0.005$). We can say that patients with an ASA value of two are approximately 3.038 times more at risk than patients with an ASA value of one, and those with an ASA value of three are 6.934 times more at risk than those with of an ASA value of one. We can say that those with high PCI values are 4.863 times more at risk than those with normal scores.

In terms of postoperative morbidity and mortality, five patients were admitted to the clinic with ileus during the postoperative period. The patients' complaints improved after medical treatment. Two patients had pulmonary embolism and the patients were heparinized with the treatment dose. A postoperative hernia occurred in three patients, and intestinal perforation occurred in one patient. An intestinal fistula developed in one patient, and a rectovesical fistula developed in one patient. In terms of postoperative mortality, two (5%) patients died postoperatively.

Discussion

The rare occurrence of appendix tumors actually makes management of this disease difficult. The surgery is the only curative option in some cancer cases and surgical treatment is the only curative approach for cancer of the appendix. Until recently, the treatment approach in appendiceal cancer with peritoneal spread was palliative; however, curative approaches are increasing due to the change in treatment procedures.

In recent years, CRS + HIPEC has been used in appendiceal cancers [9,10] and is the first choice in our clinic. The first combined treatment approach was introduced by Spratt et al. (1980) in cases of peritoneal spread cancer [11]. There are no contraindications for the procedure except for patients who have a medical condition that cannot tolerate general anesthesia and can be safely applied even in to older patients. This study shows the experience of cytoreductive surgery and HIPEC in appendiceal cancer with peritoneal spread.

In our study, although they were short follow-up cases, we had a five year survival rate with our patients and 53.1% of them survived without progression or relapse. Our results show that the CRS/HIPEC procedure minimizes disease progression or recurrence and provides a long survival period to patients even if recurrence or progression occurs.

The PCI index shows the spread of the disease during the procedure, and higher values indicate that the spread and volume of the disease are high and with a poor prognostic factor This connection has already been shown in cancers with peritoneal spread in areas other than the appendix [12]. In the literature, a high PCI score is a poor prognostic factor [13-15]. In our study, a high PCI score was found to be statistically significant as a poor prognostic factor and is an important prognostic factor. However, in some studies, the PCI score is not associated with prognosis but can provide information about whether a full resection can be performed [16]. As a result, the PCI score is a criterion that will help us with the extension of the disease, surgery and prognosis.

The CCR classification method used to evaluate the remaining tumor tissue after surgery is also an important prognostic factor. CIP-1 and CCR-1 are actually seen as full cytoreduction because the effectiveness of HIPEC is up to a depth of three mm. In our study, the survival of patients with CCS-0 was 73.07% while the survival of patients with CCS-1 was 30%. Our study showed that the survival rate of CCS-0 cases was higher than that of CCS-1 cases. However, CCS-0 increases the importance of cytoreduction and different adjuvant treatment methods should be developed to improve survival in non-CCS-0 cytoreductions. At the same time, these results show that preoperative imaging methods should also be applied to select patients with suitable PCI and upon whom CCS-0, CCS-1 cytoreduction could be performed. Because of the rarity of appendix tumors, the efficacy of CRS and HIPEC could not be compared one to one. All patients underwent both procedures. It has been shown in the literature that the prognosis is better and disease-free survival is longer in patients undergoing complete resection [17].

There is currently no consensus on the efficacy of neoadjuvant therapy. Although some studies have shown the efficacy of neoadjuvant therapy [18], these studies are very few and more evidence is required. There is no effective result from neoadjuvant therapy in our study. We think that it would be difficult to determine the patient to be referred to as neoadjuvant treatment in such aggressive tumors.

There are different approaches to the treatment modality of appendiceal cancer and its peritoneal spread, and there are some advocates for chemotherapy. However, as in our study, many studies have shown that cytoreduction and HIPEC have higher survival rates than chemotherapy alone. In a study by Lieu et al., patients with peritoneal spread appendix cancer who underwent chemotherapy alone were compared to patents who were treated with SRC and/or HIPEC. The overall survival was 4.2 years in the CRS group and 1.2 years in the chemotherapy group [19]. In the same study, CCS-0 and CCS-1 were compared, and it was shown that the CCS-0 treated patients had a higher survival rate.

In our study, there was no statistical significance between higher levels of CEA and Ca 19-9 and survival. ($p>0.05$) However, many studies reflect on prognosis, and they suggest that tumor markers are not only used for disease follow-up but can also can help to predict SRC and HIPEC efficacy [20]. In some studies, serum CEA levels above three ng/ml are a poor prognostic factor [21]. In another study, it was shown that disease-free survival is better in patients with CEA values of less than three ng/ml [22]. The reason for statistically non-significance in our study may be the low sample size and the absence of long-term follow-up.

We used mitomycin-c 20 mg/m^2 and carboplatin 450 mg/m^2 as the intraperitoneal chemotherapeutic agent in our clinic. However, 5FU is available in centers using oxaliplatin. There are many studies in the literature about which agent is more effective [23]. In a previous study, there was no difference [24]. In another study, mitomycin

was shown to be superior to other agents [25].
In our study, it was found that low albumin values had an effect on prognosis in univariate analyzes ($p<0.05$). Postoperative morbidity is high, especially in patients undergoing CRS/HIPEC. Therefore, preoperative albumin values and nutritional status should be evaluated in all patients. In accordance with this information, we think that adequate nutritional support may improve survival in patients with low preoperative albumin values and poor nutritional status. In the related literature, many studies have shown that preoperative nutritional support reduces postoperative complications and mortality [26, 27]. The importance of nutritional support for postoperative recovery is mentioned in another study [28].
In our study, postoperative morbidity was 32.5%, and mortality was 2.5%. Intestinal fistula and postoperative hernia developed as surgical morbidity. The occurrence of the fistula is thought to be due to defects in the seromuscular layer while separating adhesions during surgery. In addition, anastomosis leak is another cause of fistula. We think that intraperitoneal hyperthermic chemotherapy is not a cause of fistula because anastomosis was performed after intraperitoneal chemotherapy in patients with fistula. In some studies in the literature, it has been shown that intraperitoneal hyperthermic chemotherapy does not increase the risk of intestinal perforation and fistula development [29,30].
There were limiting factors in our study. Forty patients undergoing CRS and HIPEC are not sufficient for long-term follow-up. The series needs to be increased. The short follow-up period of recently operated-on patients is also a limiting factor. A detailed comparison between CCS 0-1-2-3 could not be done because the sample size was too small. Other limiting factors were the fact that it was a retrospective study and the lack of a control group.

Conclusion

Cytoreduction + HIPEC is the gold standard in the treatment of peritoneal spread appendiceal tumors. Good long-term results are beginning to be obtained with this procedure. In previous years, patients with peritoneal spread appendix cancers were considered as end-stage cancer patients and there was no hope for a cure, but CRS + HIPEC procedure is an effective solution with successful long-term results and curative results. This suggests that cytoreductive surgery should be performed even in patients with a CC score of two. Our study recommends cytoreductive surgery and HIPEC in patients with PCI >17 if the CC score can regress to two or below. Survival may be improved in selected patients without distant metastases with low tumor volume. In our institution, the decision to perform cytoreductive surgery and HIPEC in appendix cancers is not made according to the cut-off value of PCI. If CC score 0-1-2 can be performed, we think that cytoreductive surgery and HIPEC can be performed. Therefore, we think that the decision of cytoreductive surgery and HIPEC should be considered together with the ccs score, not just the pci score. Our results show that the SRC/HIPEC procedure enables longer survival in the larger patient population.

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Riassunto

Il trattamento tradizionale per il cancro dell'appendice con diffusione peritoneale è la chirurgia citoriduttiva (CRS), ma l'aggiunta della chemioterapia HİPEC alla chirurgia citoriduttiva ha dimostrato di migliorare la sopravvivenza globale. Lo scopo di questo studio è stato quello di riportare i risultati dei pazienti trattati con CRS e HIPEC in tumori appendicolari che si basa sull'esperienza del Dipartimento di Oncologia Chirurgica della Facoltà di Medicina dell'Università di Ankara.
I dati di 40 pazienti sottoposti a CRS + HIPEC per cancro appendicolare tra gennaio 2008 e gennaio 2019 sono stati analizzati in modo retrospettivo. Sono stati esclusi dallo studio i pazienti con metastasi epatiche non resecabili, grande tumore retroperitoneale, infiltrazione tumorale nel mesentere intestinale e dell'ilo epatico.
Risultati: la media (± sd) del PCI era 17,98 (± 8,21). Il punteggio di completamento della citoriduzione di ventisei pazienti era 0 (65,0%), 10 (25,0%) CCS-1, 3 (7,5%) CCS-2 e 1 (2,5%) CCS-3. È risultata una differenza statisticamente significativa nella prognosi tra punteggio ccr, ASA, invasione linfovascolare, punteggio PCI, categorie di albumina.
Conclusioni: in pazienti selezionati la sopravvivenza può essere aumentata con questa associazione. Tuttavia, si ritiene che la chirurgia citoriduttiva debba essere eseguita anche se il punteggio di completezza della citoriduzione è due. Nel nostro studio risulta che pazienti con PCI > 17 potrebbero essere gestiti con CRS / HIPEC se può essere raggiunto il punteggio cc ≤2. I nostri risultati suggeriscono che la procedura CRS / HIPEC può migliorare i benefici di un gruppo di pazienti più ampio e fornisce una sopravvivenza più lunga.

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