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ORIGINAL ARTICLE

Is advanced age a hesitation for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in colorectal cancer?

Naciye Cigdem Arslan[1], Tayfun Bisgin[2], Canan Altay[3], Tugba Yavuzsen[4], Aziz Karaoglu[4], Aras Emre Canda[2], Sulen Sarioglu[5], Selman Sokmen[2]

[1]Department of General Surgery, Medipol University, 34320, Istanbul, Turkey; [2]Department of General Surgery, Dokuz Eylul University, 35340, Izmir, Turkey; [3]Department of Radiology, Dokuz Eylul University, 35340, Izmir, Turkey; [4]Department of Medical Oncology, Dokuz Eylul University, 35340, Izmir, Turkey; [5]Department of Pathology, Dokuz Eylul University, 35340, Izmir, Turkey

Summary

Purpose: *The purpose of this study was to assess the feasibility and safety of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in elderly patients with peritoneal carcinomatosis of colorectal cancer.*

Methods: *Patients who underwent curative complete CRS and HIPEC for peritoneal carcinomatosis of colorectal cancer with minimum follow-up of 24 months were included in the analysis. Charlson comorbidity index and ECOG performance status were used to evaluate preoperative condition. Patients were tiered into two groups according to age (<65 and ≥65 years). Postoperative morbidity, mortality, recurrence, and overall survival were compared between groups.*

Results: *One-hundred patients were meeting the inclusion criteria. Median age was 56 years (ranging, 20-86). The origin of peritoneal carcinomatosis (PC) was colon in 77 and rectum in 23 patients. There were 31 patients in the elderly group. Mean hospital stay was 17±11.8 and 16.8±14.3 days in young and elderly groups (p=0.937). In young patients, postoperative morbidity was seen in 26 (37.6%) patients versus 9 (29%) patients in elderly group (p=0.272). Mortality was higher in elderly group (n=4, 12.9%) than in the younger group (n=5, 7.2%), but the difference was not statistically significant (p=0.287). Median follow-up was 25 months (ranging, 2-112). Local and/or distant recurrence occurred in 30 (43.4%) patients in the young group and 9 (29%) patients in elderly group (p=0.169). Two-years disease-free survival was similar: 67.1% in the young and 74% in the elderly groups (p=0.713).*

Conclusions: *CRS and HIPEC offer comparable oncologic outcome in meticulously selected medically-fit elderly patients without increased postoperative morbidity and mortality.*

Key words: *cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, older age, peritoneal carcinomatosis*

Introduction

Peritoneal carcinomatosis (PC) of advanced colorectal cancer (CRC) is a stage IV peritoneal metastatic disease with poor natural history of approximately 6 months median survival [1]. New chemotherapeutics and targeted biologic agents have provided a survival benefit reported between 13-34 months [2-4], however, cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is the only potentially curative treatment approach offering a long-term survival [5]. This complex cancer surgery combines multivisceral resections, peritonectomies, and intra-

Correspondence to: Naciye Cigdem Arslan, MD. Department of General Surgery, Medipol University Hospital, Birlik mah Bahceler cd 5, 34230, Istanbul, Turkey.
Tel: +90 2124401000, Fax: +90 2124401010, E-mail address: cigdemarslan@hotmail.it
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peritoneal chemotherapy to completely resect the overall disease, which in turn results in prolonged operative time, increased blood loss, physiologic dearrangements, and often the need of intensive care unit stay. In parallel with the difficulty of achieving complete cytoreduction, the well-documented diagnostic and staging limitations of conventional radiologic studies to detect and score the disease, particularly in recurrent cases, and the relatively high postoperative morbidity and mortality rates after CRS and HIPEC are major concerns when selecting ideal candidates for the procedure. Particularly in elderly population, such complex abdominopelvic surgery and HIPEC may be challenging and demanding for the surgical team and the oncologic center.

Currently, CRS and HIPEC can be performed with acceptable postoperative morbidity and mortality in experienced certified centers [6], however, age still remains an independent risk factor for poor outcomes after major oncologic surgery [7]. The majority of the studies focusing on CRS and HIPEC in elderly population have suggested comparable morbidity and mortality rates but there are very limited data regarding final oncologic outcomes [8-11]. In this study we assessed the surgical and oncologic outcomes after CRS and HIPEC in patients older than 65 years with PC of CRC.

Methods

Prospectively collected data of 290 patients with PC who underwent CRS and HIPEC by the same surgical team at our institution between October 2007 and June 2016 was analyzed. Patients with PC from CRC origin with a minimum follow-up of 24 months were included in the study. Exclusion criteria were the non-colorectal primary tumor origin, proactive HIPEC treatment in locally advanced tumors, palliative interventions, and the emergent surgery. The study was approved by the local ethics committee. Informed consents for surgical procedure and also for collecting and using data in clinical studies were received from all patients.

Patients were tiered into two groups: young group (≤65 years old) and elderly group(>65 years old). Postoperative morbidity, mortality, recurrence, and survival were compared.

Preoperative assessment

The eligibility of the patients for CRS and HIPEC was decided by the multidisciplinary tumor board. All the patients had biopsy-proven CRC. Thoraco-abdominal computed tomography and/or positron emission tomography were performed for preoperative staging. The performance status was evaluated by ECOG performance scale. Co-morbidities were assessed by Charlson co-morbidity index (CCI) [12]. To be able to perform potentially radical complete cytoreduction with curative intent was the major selection criterion. Diffuse small bowel and/or portal pedicle involvement, retroperitoneal plaque-like involvement, bilateral ureteric and/or extensive iliac vascular invasion, circumscribed pelvic tumor infiltration, extra-abdominal non-oligometastatic distant metastasis, and impossibility to perform complete cytoreduction were our absolute contraindications for CRS and HIPEC. Patient's performance and co-morbidities were considered individually. Surgery was planned at least 4 weeks after last chemotherapy cycle in patients who received neoadjuvant treatment.

Cytoreductive surgery

All the patients had mechanical bowel preparation and venous thromboembolism prophylaxis. Intravenous 1.5 g cefuroxime axetil and 500 mg metronidazole were administered 30 min before surgery and repeated in every 3 hrs. The aim of CRS was to radically remove all the macroscopic disease as described by Sugarbaker [13]. Peritoneal carcinomatosis index (PCI) was calculated intraoperatively to score the extent and the burden of the disease [14]. At the end of surgery, completeness of cytoreduction was recorded according to residual tumor score [15]: No residual tumor, CC-0; residual tumor ≤2.5 mm, CC-1; and residual tumor >2.5 mm, CC-2. (Figures 1 and 2). Anastomoses were performed before HIPEC.

Hyperthermic intraperitoneal chemotherapy

HIPEC was administered by a perfusion system (The Belmont® Rapid Infuser RI-2, Boston, MA, USA) with the closed abdominal technique. Oxaliplatin 430 mg/m^2 was delivered into the abdomen in 3-5 liters of ringer lactate solution through two inflow drains and received back from two outflow drains for 30 min. A constant intraabdominal temperature at 42.5 °C was maintained by two thermal probes.

Postoperative care and follow-up

Postoperative morbidity and HIPEC toxicity were recorded according to "Common Terminology Criteria for Adverse Events" criteria [16]. Hospital mortality and death within 30 days after surgery were recorded as mortality.

For the first year, physical examination and CEA measurements were performed every three months, thoraco-abdominal computed tomography every 6 months. For the second year, physical examination and CEA measurements were performed twice a year and computed tomography once a year. Patients underwent colonoscopy at the end of the first year.

Statistics

SPSS 22.0 was used for analyses. Continuous variables were expressed as means and ranges, and categorical variables as frequencies and percentages. Association between categorical variables and age was determined with the chi-square test. Association between continuous variables and age was tested by independent samples *t*-test. Survival rates were calculated using Kaplan-Meier method and were compared with the log-rank test. P values <0.05 were defined as statistically significant.

Results

One hundred patients met the inclusion criteria. Mean age was 55.4±13.2 years (range 20-86). Fifty-six (56%) patients were female and 44 (44%) male. Primary tumors were colon in 77 (77%) patients and rectum in 23 (23%) patients. There were 69 (65%) patients in the young and 31 (31%) in the elderly group. The CCI was ≥8 in 17 (17%) patients: 6 in 69 (69%) patients, 7 in 14 (14%) patients, 8 in 10 (10%) patients, 9 in 6 (6%) patients and 10 in 1 (1%) patients. Mean BMI was 26.2±4.1 kg/m^2. Mean preoperative serum albumin was 3.6±0.7 g/dl. ECOG performance score was 1 in 14 (14%) patients, 2 in 64 (64%), and 3 in 22 (22%). Forty-seven (47%) patients received neoadjuvant chemotherapy. There were no differences between groups in terms of demographic and clinical characteristics (Table 1).

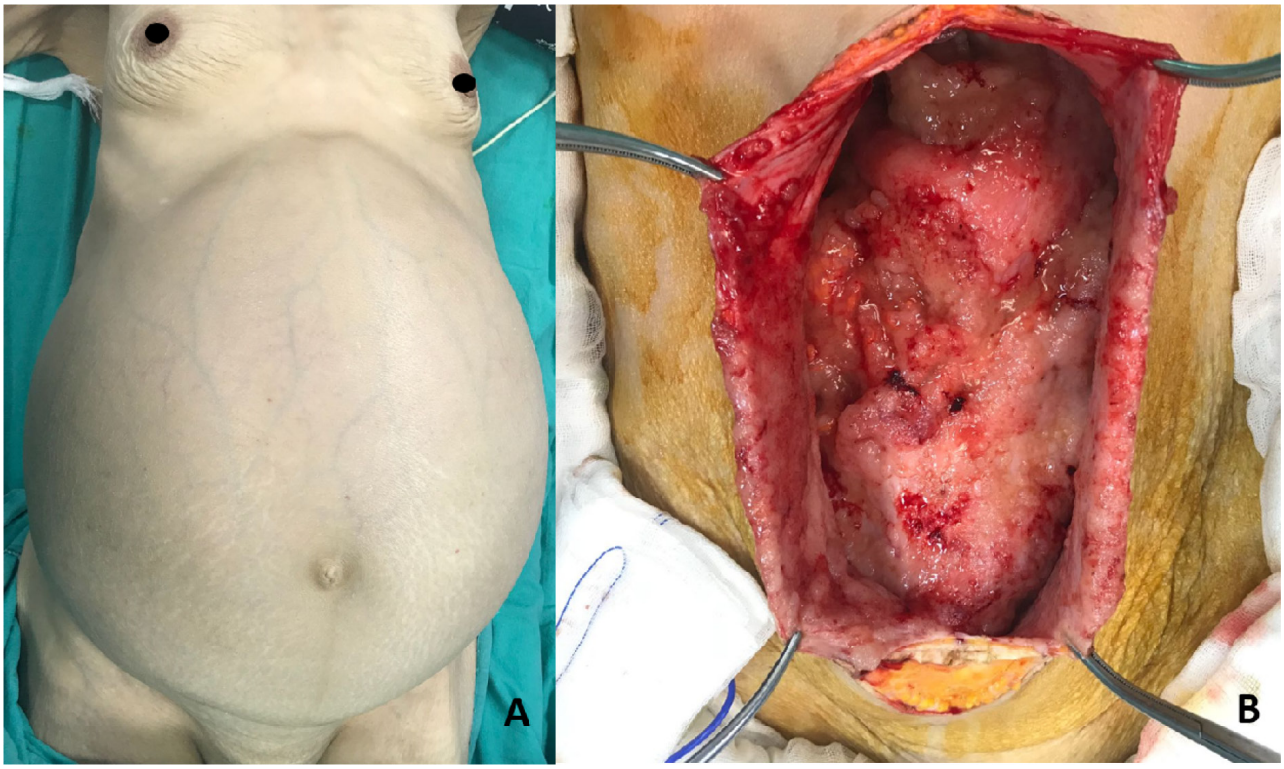

Figure 1. Intraoperative photos of a 67-year old woman with peritoneal carcinomatosis of rectal adenocarcinoma. **A:** Ascites and cachexia, **B:** High tumor burden with omental cake and diffuse invasion of the peritoneal surfaces.

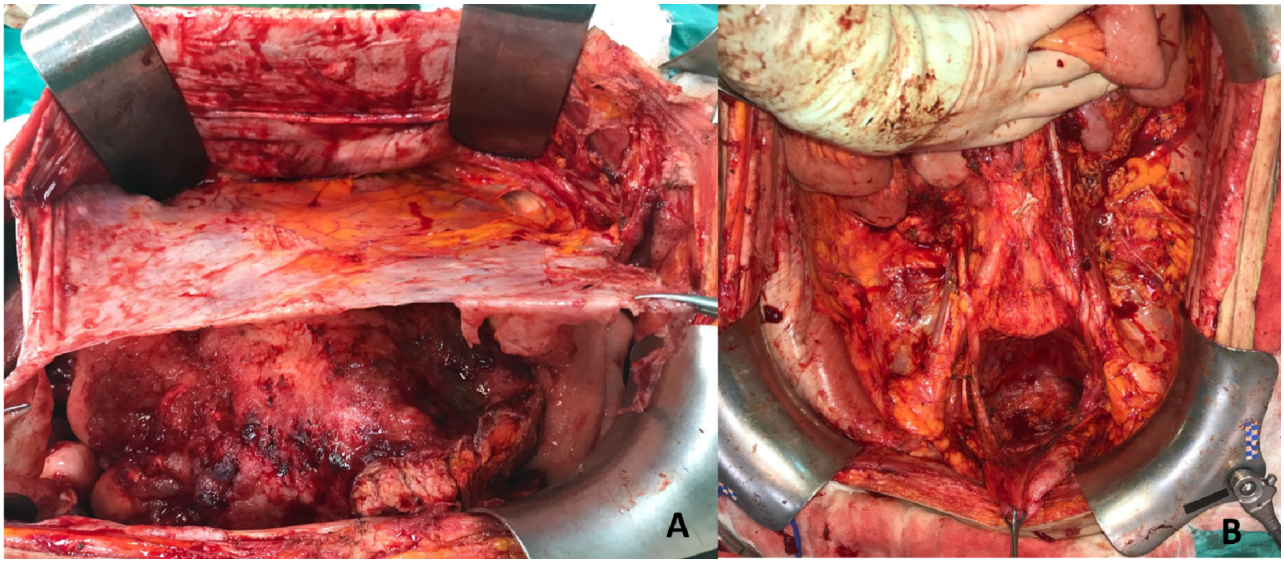

Figure 2. Cytoreductive surgery in the same patient in Figure 1. **A:** Right side peritonectomy. **B:** View of pelvis after complete cytoreduction.

Mean operative time was 312.7±140.7 min. Mean PCI was 12.2±6.1 (Figure 1). Mean number of resected organs was 3.2±1.9. Sixty (60%) patients had one or more gastrointestinal anastomosis. Mean number of anastomosis was 0.9±0.7. Diverting or end-stoma was performed in 36 (36%) patients. CC-0 cytoreduction was achieved in 87 (87%) of the patients (Figure 2). Mean hospital stay was 17±11.8 days in the young group and 16.8±14.3 days in the elderly group (p=0.937). Sixteen (16%) patients needed postoperative intensive care: 10 (14.5%) in the young and 3 (9.6%) in the elderly groups (p=0.367). Surgical characteristics and outcomes were not different between groups (Table 2).

Overall, 32 (32%) patients had postoperative morbidity: 23 (37.6%) in the young group and 9 (29%) in the elderly group (p=0.272). Thirteen (13%) patients had HIPEC toxicity. The incidence of HIPEC toxicity was similar between groups (14.5% in the young and 9.6% in the elderly groups, p=0.378). Postoperative death occurred in 5 (7.2%) patients in the young and 4 (12.9%) patients in the elderly group (p=0.287). Postoperative morbidity was similar between groups (Table 2).

Median follow-up was 25 months (2-112). Distant and/or local recurrence were seen in 39 (42.8%) patients; 30 (49.1%) were seen in the young group and 9 (33.3%) in the elderly group (p = 0.169). Two-year disease-free survival rates were

Table 1. Demographic and clinical characteristics of the patients

Characteristics	*Age <65 (n=69)*	*Age ≥65 (n=31)*	*p*
Sex			
Female	38	18	
Male	31	13	
Primary tumor			0.418
Colon	54	23	
Rectum	15	8	
Charlson comorbidity index ≥8	10	7	0.390
ECOG score			0.077
1	13	1	
2	40	24	
3	16	6	
Preoperative albumin, g/dl (mean±SD)	3.7±0.8	3.4±0.3	0.426
Neoadjuvant chemotherapy (+)	34	13	0.322

Table 2. Surgical characteristics and outcomes

Characteristics	*Age <65 (n=69)*	*Age ≥65 (n=31)*	*p*
Operative time (min, mean±SD)	321.8±147.6	319.8±130.7	0.955
PCI (mean±SD)	12±6.2	13.6±6.3	0.457
Complete cytoreduction	58 (84%)	29 (93.5%)	0.334
Stoma (+)	28	8	0.115
Number of resected organs (mean±SD)	3.2±1.9	3.8±2.2	0.255
Gastrointestinal anastomosis (+)	45	25	0.158
Hospital stay (day, mean±SD)	17±11.8	16.8±14.3	0.937
Intensive care unit stay (+)	10 (14.5%)	6 (19.3%)	0.367
Overall morbidity	23 (37.6%)	9 (29%)	0.272
HIPEC toxicity	10 (14.5%)	3 (9.6%)	0.378
Mortality	5 (7.2%)	4 (12.9%)	0.287
Two-year overall survival	76.5%	77%	0.618
Two-year disease-free survival	67.1%	74%	0.713
Recurrence	30 (49.1%)	9 (33.3%)	0.169

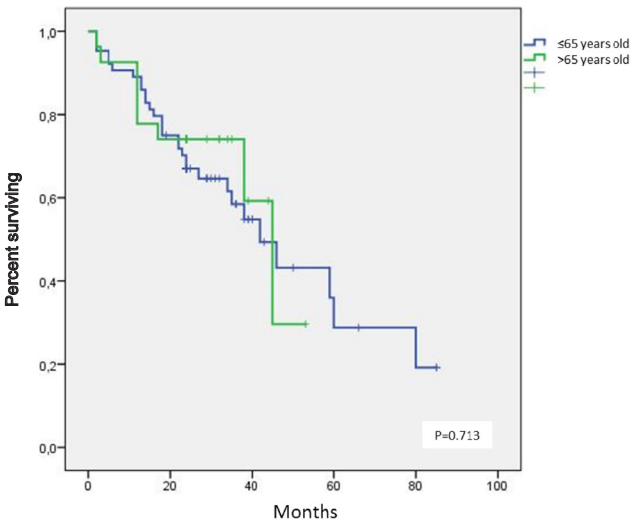

Figure 3. Two-year disease-free survival in the young and elderly group.

67.1% and 74% in the young and elderly patients, respectively (p=0.713). The difference was not statistically significant (Figure 3).

Discussion

PC of advanced CRC has a poor prognosis which has been increased to 12-24 months with novel chemotherapy agents [2]. Several randomized controlled trials showed improved survival with CRS and HIPEC when compared with systemic chemotherapy or CRS alone [5]. This clinical benefit on oncologic outcome is deeply affected by the extent of disease and completeness of cytoreduction. A randomized controlled trial of PC from CRC reported 45% disease-free survival with HIPEC after complete cytoreduction and less than 10% in incomplete CRS group after 8-year follow-up [17]. These results indicated that the complete surgical elimination of disease which comes with marathon-complex surgery performed in highly experienced centers, prolonged operative time, and increased blood loss which are a prerequisite for optimum oncologic outcome. In addition to the extent of surgery, these immunocompromised patients with PC usually carry several risk factors such as nutritional deficiency, poor performance, multiple co-morbidities, and previous non-standard surgery and/or prolonged neoadjuvant therapies. The toxicity of HIPEC also predispose to postoperative complications [18,19].

In recent years, the increase in cancer prevalence and life-expectancy, and the developments in modern health services have led to an increase in the number of patients treated with cancer in elderly population. As age is a well-known risk factor for postoperative complications and mortality [7,20], advanced age has been a hesitation for aggressive surgery. The morbidity and mortality after CRS and HIPEC have been reported 12-56% and 0-12%, respectively [6]. Today in experienced centers with high-volume cases, CRS and HIPEC can be performed with acceptable surgical results [21], however there are limited data in the literature assessing the safety and feasibility in elderly patients.

In 2015, Huang et al. [11] compared the results of 124 elderly patients (≥65 years old) with 487 young patients (<65 years old) treated for PC from different origins. This study included both HIPEC and early postoperative (non-hyperthermic) intraperitoneal chemotherapy procedures. The grade III-IV morbidity rate was 42% in the young and 40% in the elderly groups (p=0.644). Hospital mortality was 2% in the young and 3% in the elderly groups (p=0.607). In subgroup analysis, hospital mortality was higher (5%) in 20 patients >70 years old. Median overall survival was 58 months in young patients and 34 months in elderly patients. The 5-year overall survival rates were 47.7% in young and 42.9% in elderly patients (p=0.698). Age was not an independent prognostic factor of survival in this study. In our study, patients were homogeneous regarding the origin of PC and type of intraperitoneal chemotherapy. Our overall morbidity rate for >65 year-old patients was 29% and comparable with the young patient group in this study and previously published series of our group [18, 22]. We preferred to perform a 2-year disease-free survival analysis as the median follow-up of our patients was 25 months. Our results showed that age had no effect on recurrence and 2-year disease-free survival.

Some other reports including smaller patient groups suggested that CRS and intraperitoneal chemotherapy can provide comparable survival rates in the elderly without increased risk of morbidity and mortality [8,9,23,24]. In contrast, higher risk of morbidity and mortality has been suggested in larger studies. Alyami et al. [25] reported significantly more cardiovascular complications in 188 patients older than 70 years old when compared with 704 younger matches (13.8% vs. 9.2%, p=0.044). The overall morbidity rates were comparable. The 90-day mortality was 5.4% and higher in the elderly group than younger cohorts (2.7%), but the difference was not significant (p=0.078). The authors concluded that medical conditions due to age may have an adverse effect on postoperative complications. Conformably with these results, 30-day mortality was increased with age in our series (7.2% vs. 12.9%). The small number of the patients may hinder the difference to reach a statistical significance (p=0.287).

In another study, results of 81 patients older than 70 years old indicated increased major complications (38% vs. 23%, p=0.002) and mortality (13.6% vs. 3.9%, p<0.001) at 1 and 3 months when compared with younger patients [26]. In the same study presence of complications was an independent factor for reduced survival. However, the authors preformed a subgroup analysis of more recent cases and found a significant annual reduction in morbidity and mortality rates. They concluded that surgical outcome of CRS and HIPEC in elderly was associated with the learning curve and the age alone is not a contraindication. Previously published data support the effect of experience on postoperative complications and mortality [18, 27, 28]. In the present study we did not perform a learning-curve analysis. The small number of patients and lack of multivariate analysis to identify risk factors for morbidity and mortality were other limitations of our study.

In parallel with the increase of elderly population and life expectancy, cancer treatment at older ages has become more of an issue during recent years. Moreover, the experience on CRS and HIPEC has been accumulating rapidly. In the future, more patients at advanced age may be potential candidates for surgical treatment of PC. The limited literature data indicates that age alone is not a contraindication for CRS and HIPEC. Increased surgical morbidity and mortality were reported in only one study [26] and associated with learning curve. There is no consensus for the maximum age that CRS and HIPEC can be performed at, however, most of the institutes have strict criteria for patient selection regarding the extent of disease and patient performance. Similarly, with the elderly patient group, we did not have any patients with ECOG performance score >3 in the young patient group. We consider that experience of the center and individual assessment of every patient are the main crucial issues influencing postoperative outcome. The life expectancy and performance of the patients independently of age, benefits and risks of the procedure must be well-judged and discussed with the patient.

Conclusion

Older patients are a heterogeneous group, and although tolerability of multi-modality therapy may be a real challenge for many of them, a very carefully selected medically-fit older patients may be undertreated based on their age alone. Management of older patients with peritoneal metastases is particularly challenging owing to limited prospective data in this population. Specified treatments of CRS and HIPEC can provide comparable oncologic outcome in elderly population with no discriminating increase in morbidity and mortality. Age alone is not a hesitation for major oncologic surgery in strictly selected patients.

Conflict of interests

The authors declare no conflict of interests.

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