

# Peritoneal Mesothelioma Treated by Induction Chemotherapy, Cytoreductive Surgery, and Intraperitoneal Hyperthermic Perfusion

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**Background and Objectives:** Peritoneal mesothelioma (PM) is a rare disease, with a poor prognosis. We decided to prospectively evaluate the prognostic impact of aggressive surgery followed by intraperitoneal chemotherapy with local hyperthermia.

**Patients and Methods:** In this prospective study, 19 patients with PM were treated by cytoreductive surgery (CRS) and intraperitoneal hyperthermic perfusion (IPHP). Mean follow-up was 27 months (range: 1–65). Fifteen (68%) patients had malignant disease, two had well-differentiated papillary mesothelioma, and two had multicystic PM. Thirteen (65%) patients received preoperative chemotherapy. Fifteen cases (75%) underwent optimal cytoreduction (residual disease <2.5 mm). One patient underwent the procedure twice due to locoregional progression. IPHP was performed with closed abdomen technique, using a preheated polysaline perfusate (42.5°C) containing cisplatin + mitomycin C or cisplatin + doxorubicin administered through a heart–lung pump for 60 or 90 min.

**Results:** Three-year overall and progression-free survival was 69 and 66%, respectively. The operative morbidity (grade II/III), mortality, and overall toxicity (grade I–IV) rates were 25, 0, and 30%, respectively. Seventeen (94%) out of 18 patients had resolution of ascites.

**Conclusions:** This therapeutic strategy proved feasible and was well tolerated. Early results seem promising and consistent with a potentially major impact on survival in selected patients with PM.

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**KEY WORDS:** peritoneal mesothelioma; peritonectomy; peritoneal chemotherapy

## INTRODUCTION

Peritoneal mesothelioma (PM) is a rare tumor, accounting for 10–20% of the 2,200 cases of malignant mesothelioma registered each year in the United States [1,2], and its occurrence can be related to asbestos exposure. Patients usually present with signs and symptoms of advanced disease, including pain, weight loss, abdominal masses, and ascites. The prognosis for patients with PM is poor, with a median overall survival of 12.5 months in the best series [3]. A variety of treatment options have been proposed, alone or in combination, but most have failed to demonstrate a significant impact in terms of palliation or disease-free and overall survival. The

mechanism of death is related to intraperitoneal progression and the disease remains in the abdominal cavity for most of its natural history [4]. This pattern of spread would seem to indicate the potential usefulness of selectively increasing drug concentration in the tumor-bearing area by direct intraperitoneal chemotherapy instillation

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[5]. However, establishing a pharmacokinetic advantage for cavity exposure does not necessarily lead to an increased delivery of the active drug to the tumor. Adhesions induced by previous surgery or by the tumor itself can block drug access to the tumor. Moreover, the limited ability of chemotherapeutic agents to further penetrate into tumor nodules may constitute another obstacle. In order to overcome these limitations, cytoreductive surgery (CRS) and intraperitoneal hyperthermic perfusion (IPHP) chemotherapy were combined in a unique treatment strategy. Recent Phase I/II investigations suggest that this approach may represent a potentially effective salvage therapy for patients with PM [6,7,8], as long-term survivors have been reported. The aim of this Phase II clinical study was therefore to evaluate this novel therapeutic approach in patients with malignant PM in terms of toxicity, morbidity, and survival.

## PATIENTS AND METHODS

### Patient Characteristics

From August 1995 to October 2002, 19 patients with PM were consecutively submitted to 20 CRS + IPHP at the National Cancer Institute of Milan.

Eligibility criteria were: histologically confirmed PM; age  $\leq 75$  years; Karnofsky performance status  $\geq 70$ ; no severe clinical dysfunction; no concomitant evidence of pleural extension; no other concomitant neoplasms; normal hematological, biochemical liver function, and creatinine clearance tests; written informed consent following the guidelines of the Ethical and Scientific Committee of the National Cancer Institute of Milan.

Patient characteristics are summarized in Table II. There were 9 (47%) males and 10 (53%) females, and mean age was 49 years (range: 24–66). The mean follow-up was 27 months (range: 1–65).

One patient (number 9) underwent a second procedure because of locoregional progression 1-year after the first intervention. Eighteen out of 19 patients presented ascites before the procedure.

Pathological evaluation comprised examination of hematoxylin and eosin-stained sections and immunohistochemical tests to differentiate from other peritoneal surface malignancies. Immunohistochemistry included cytokeratin (CK), epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), tumor-associated glycoprotein B72.3, monoclonal antibody Ber-EP4, vimentin, calretinin, and monoclonal antibody CD15. Fifteen (79%) patients had malignant mesothelioma, two had well-differentiated papillary mesothelioma (WDP), and two had multicystic PM (MCM). Of those with malignant mesothelioma, 13 had the epithelioid form (MEM), 1 had mixed type (MMIX), and 1 had fibrosarcomatous mesothelioma (MFS).

### Induction Chemotherapy

Before CRS, 13 (65%) patients with bulky disease, assessed preoperatively on the basis of clinical examination and abdominopelvic CT scan were submitted to presurgical chemotherapy. Six out of 13 (46%) were treatment-naïve patients when referred to our institution and received an induction therapy with epirubicin + ifosfamide before the procedure, while 7/13 (54%) had already received different chemotherapy schedules elsewhere and presented clinically operable disease. Treatment schedules and the number of cycles administered are outlined in Table II.

### Cytoreductive Surgery

Patients were put in the supine position with gluteal folds advanced to the break in the operating table to allow full access to the perineum. A three-way bladder catheter was placed to permit a cold lavage during hyperthermia in order to avoid mucosal damage. A large-bore silastic nasogastric tube was inserted into the stomach.

The surgical procedure started with a xyphopubic, midline incision, and the successive layers of abdominal wall were dissected until the parietal peritoneum was visualized. Then, the dissection of parietal peritoneum from the abdominal wall was started without opening the peritoneal cavity. The parietal peritoneum was then incised and full access to the abdominal cavity was achieved through the use of a Thompson self-retaining retractor.

Peritoneal carcinomatosis was classified as follows: P1 = dissemination into pelvic peritoneum; P2 = slight dissemination into remote peritoneum; P3 = marked dissemination into remote peritoneum [9]. Two (10%), 1 (5%), and 17 (85%) cases presented P1, P2, and P3 intraperitoneal dissemination, respectively. A ball-tip electro-surgical handpiece was used on pure cut at high voltage as the standard tool to dissect tumor on peritoneal surfaces.

CRS was carried out with one or more of the following procedures, depending on disease extension: (1) greater omentectomy, right parietal peritonectomy  $\pm$  right colon resection; (2) pelvic peritonectomy  $\pm$  sigmoid colon resection  $\pm$  hysterectomy; (3) lesser omentectomy and dissection of the duodenal–hepatic ligament  $\pm$  antrectomy  $\pm$  colectomy; (4) right upper quadrant peritonectomy with Glissonian's capsule; (5) left upper quadrant peritonectomy  $\pm$  splenectomy; (6) other intestinal resection and/or abdominal mass resection. Cytoreduction was classified into three levels according to the number of procedures performed: level I—1 to 2 procedures; level II—3 or 4 procedures; level III—5 or 6 procedures. The distribution of patients according to the level of CRS and mean duration of operation are reported in Table I.

**TABLE I. Distribution of Interventions According to the Level of Cyto-reduction and Corresponding Mean Duration of Operations**

Level of cyto-reduction	Number	%	Mean duration of operations in minutes (range)
I	4	20	329 (250–390)
II	6	30	456 (395–480)
III	10	50	521 (395–660)

Residual disease after surgery was classified according to Sugarbaker criteria [10]: cc-0, no residual disease; cc-1, minimal residual disease, 0–2.5 mm; cc-2, residual disease 2.5 mm–2.5 cm; cc-3, residual disease >2.5 cm. The surgical procedure was considered CRS when the tumor was completely removed or when there was minimal residual disease (cc-1). Conversely, it was regarded as debulking (DBK) surgery when the patient was suboptimally cyto-reduced despite the surgical effort (Table II).

### IPHP Technique

After cyto-reduction, four silicone catheters were placed in the abdominal cavity; one in the right sub-phrenic cavity, one in the deep pelvis, one in the left sub-phrenic cavity, and one in the superficial pelvic site cavity. In order to continuously monitor peritoneal temperature during IPHP, thermocouples were placed in the abdominal cavity. Following the closed abdomen

technique, the skin was closed with a running suture. The catheters were then connected to the extra-corporeal circuit. A heart–lung pump forced the instillation of a polysaline perfusate (4–6 L) containing cisplatin (CDDP, 25 mg/m<sup>2</sup>/L) plus mitomycin C (MMC, 3.3 mg/m<sup>2</sup>/L) or cisplatin (CDDP, 25 mg/m<sup>2</sup>/L) plus doxorubicin (Dx, 7 mg/m<sup>2</sup>/L) into the abdominal cavity through the circuit, at mean flow of 600 ml/min. The mean doses of drugs administered were 216 mg (range: 135–290) for CDDP; 31 mg (range: 20–40) for MMC; and 65 mg (range: 40–90) for Dx. A heat exchanger kept the perfusate at 44°C as it was being administered, so that the intracavitary perfusate was maintained at 42–43°C. The IPHP lasted 60–90 min, on the basis of the drug schedule. Following perfusion, the perfusate was quickly drained and the abdomen closed after careful intracavitary inspection.

### Follow-Up and Statistical Analysis

In the postoperative period, patients were assisted in an Intensive Care Unit for at least 7 days, where they were evaluated daily with laboratory and instrumental exams. Long-term follow-up was carried out by physical examination, tumor markers (Ca125, CEA, CA19.9), thoracic and abdominal CT scan every 3 months in the first year and every 6 months, thereafter. No second-look laparotomy was performed to assess tumor response or disease relapse. Analysis of treatment-related toxicity

**TABLE II. Patient Characteristics**

Patient	Sex/ Age	Histological subtype	Surgical procedure	Previous systemic chemotherapy (number of cycles)	IPHP	Residual disease	Months of follow-up	Final status
1	F 48	WDP	DBK	—	CDDP+MMC	cc-3	13	DOD (PRO)
2	F 44	MEM	Bx	EPI+IFO (6)	CDDP+MMC	cc-0	20	Lost to follow-up
3	F 51	MEM	DBK	CDDP+IFN (2)	CDDP+MMC	cc-3	8	DOD (PRO)
4	M 24	MEM	CRS	—	CDDP+MMC	cc-0	65	NED
5	F 60	MEM	CRS	—	CDDP+MMC	cc-1	61	NED
6	M 62	MEM	CRS	—	CDDP+MMC	cc-1	2	DOD (PRO)
7	M 51	MFS	DBK	CBDCA+VP16 (2)	CDDP+MMC	cc-2	16	DOD (PRO)
8	F 34	MEM	CRS	EPI+IFO (7)	CDDP+MMC	cc-0	52	NED
9 <sup>a</sup>	M 47	MEM	CRS Bx	EPI+IFO (6) CBDCA+VELBE (2)	CDDP+DX/CDDP+MMC	cc-1 cc-1	60	AWD
10	F 46	MCM	CRS	—	CDDP+DX	cc-1	44	NED
11	F 40	MMIX	CRS	PAC (6) EPI+IFO (2)	CDDP+DX	cc-0	40	NED
12	M 66	MEM	DBK	CDDP+IFO (3)	CDDP+DX	cc-2	39	AWD
13	M 45	MEM	CRS	EPI+IFO (3)	CDDP+DX	cc-1	24	AWD
14	F 66	MCM	CRS	CBDCA+GEM (6)	CDDP+DX	cc-0	23	NED
15	M 45	MEM	CRS	EPI+CTX+CDDP (IP) (3)	CDDP+DX	cc-0	19	DOD (PRO)
16	F 47	WDP	CRS	—	CDDP+DX	cc-0	15	AWD
17	F 59	MEM	CRS	EPI+IFO (3)	CDDP+DX	cc-1	11	AWD
18	M 60	MEM	DBK	CPT11 (5)/Ox (3) 5FU+CPT11 (3)/CBDCA (1)	CDDP+DX	cc-3	6	AWD
19	M 29	MEM	CRS	—	CDDP+DX	cc-0	1	NED

DBK, debulking; CRS, cytoreductive surgery; Bx, biopsy; IPHP, intraperitoneal hyperthermic perfusion; IP, intraperitoneal; MEM, malignant epithelial mesothelioma; MFS, malignant fibrosarcomatous mesothelioma; MMIX, malignant mixed type mesothelioma; WDP, well-differentiated peritoneal mesothelioma; MCM, multicystic peritoneal mesothelioma; EPI, epirubicin; CDDP, cisplatin; IFN, interferon; IFO, ifosfamide; CBDCA, carboplatin; VELBE, vinblastine; DX, doxorubicin; MMC, mitomycin C; Gem, gemcitabine; Ox, oxaliplatin; CPT11, irinotecan; NED, no evidence of disease; AWD, alive with disease; DOD, died of disease; PRO, progression.

<sup>a</sup>Submitted twice to the procedure.

was performed according to World Health Organisation criteria [11]. Overall survival was calculated from the date of surgery to the date of death or time of last follow-up and progression-free survival was calculated from the date of surgery to the date of disease progression or death, whichever occurred first. Estimated survival curve distribution was calculated by the Kaplan–Meier method.

## RESULTS

CRS was performed in 13 cases; five had DBK surgery due to extensive disease and two patients underwent biopsy only. On the basis of Sugarbaker criteria, eight (40%) cases presented cc-0, seven (35%) cc-1, two (10%) cc-2, and three (15%) cc-3 residual disease.

IPHP with CDDP + MMC was used in 9 (45%) procedures, while the combination CDDP + DX was used in 11 (55%).

Gastrointestinal toxicity was reported in three (15%) out of 20 procedures (one grade I and two grade II) and grade III nephrotoxicity was observed in one (5%) procedure. One patient developed chronic renal failure. There were no cases of hematological, cardiological, or neurological toxicity.

With regard to surgical morbidity, three (15%) cases of bowel fistula and one (5%) of postoperative infection were observed. One patient presented an acute hypotensive episode clinically diagnosed as cardiac arrest on the 8th day after the procedure. The patient was urgently resuscitated, without any short or long-term sequelae. There was a 25% grade II/III operative morbidity grade. No operative mortality was observed. The mean length of hospitalization was 32 days (range: 9–67).

Three-year overall and progression-free survival was 69 and 66% (Fig. 1), respectively. Four patients (nos. 3, 6, 7, 15) with diffuse malignant PM and one with borderline PM (no. 1) died from disease progression during follow-

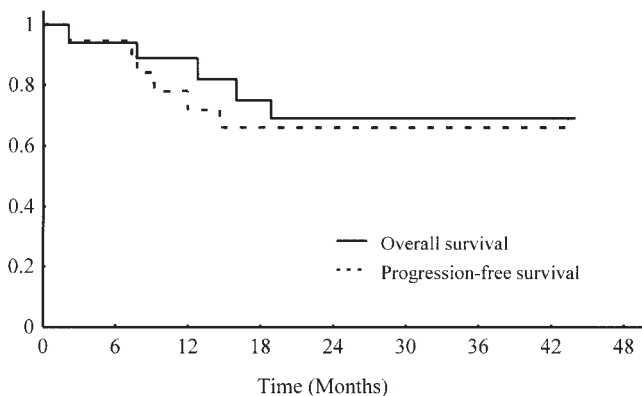


Fig. 1. Overall and progression-free survival in patients with peritoneal mesothelioma.

up. Complete resolution of ascites occurred in 17 out of 18 cases (94%).

## DISCUSSION

Current understanding of PM in terms of physiopathology, prognostic factors, and best therapeutic approach is limited due to the rarity of the tumor.

Although the median survival of patients with PM reported in most series is short, long-term survival has been described following intraperitoneal 32P combined with whole abdominal radiation [12]. Lederman et al. [13] reported the results of multimodality therapy in a series of 10 patients. Six of the 10 patients treated with sequential DBK, chemotherapy (five intraperitoneal and one intravenous), and whole abdominal irradiation achieved complete remission at 19+ to 78+ months of follow-up. Conversely, those who did not receive this combined approach were dead at 2–15. Similar results were obtained by Langer et al. [14], suggesting the relative role of surgical DBK on outcome. However, it is impossible to conclude that any treatment improves outcome over surgical cytoreduction alone as these studies were conducted on small series of patients, with a short follow-up, ill-defined eligibility criteria with the inclusion of patients with pleural disease, and absence of control groups.

The rationale for the tumor volume reduction is based on the enhancement of neoplastic chemosensitivity due to the recruitment of tumor cells to the growth phase and the possibility of clones of phenotypically resistant cells being removed by surgical resection. In Langer's study [14], 10 patients with histologically documented PM were treated with surgical DBK and intraperitoneal cisplatin, sodium thiosulfate rescue, and etoposide every 4 weeks for a maximum of six cycles. Median survival for patients whose tumors were surgically debulked to <2 cm prior to treatment was 22 months, whereas it was 5 months for those with measurable, surgically inaccessible disease; this difference was statistically significant. In Eltabbakh's study [15], 15 women with malignant PM were treated with surgery followed by systemic chemotherapy. The patients who underwent CRS survived longer than those who underwent biopsy only.

The limited sample size in our study precluded calculations from being made about the prognostic value of residual tumor. Nevertheless, five out of seven cases with completely cytoreduced disease (cc-0) are still alive with no evidence of disease (one patient died due to disease progression and the other was lost to follow-up) after a mean follow-up of 31 months. Conversely, four of the five patients with residual disease  $\geq 2.5$  mm (cc-1/2/3) died due to disease progression or were alive with disease (AWD) after a mean follow-up of 27 months. Whether

this apparent survival benefit is an expression of a lower tumor aggressivity or a result of the surgical effort is difficult to ascertain. An answer to such a question should be provided by another study with a different well formulated design.

We feel it is important to emphasize the difference between the cytoreduction performed in the aforementioned studies and that utilized in our investigation. In order to achieve minimum postoperative residual disease, we believe that more aggressive intervention is required, including peritonectomies and/or multiple organ resection [16]. Malignant mesotheliomas are diffuse tumors originating from mesothelial cells [17] that form the surface lining of three serosal cavities, pleura, peritoneum, and pericardium, which constitute the major sites of origin. Thus, such a radical surgical approach is an attempt to resect not only all the intracavitary tumor tissue but also the anatomical structure (i.e., the peritoneum) in which the neoplastic process originates and which represents a potential site of future disease progression. In our experience, major surgical aggressivity did not determine an increase in mortality or morbidity. Extensive surgical procedures including peritonectomies, splenectomy, bowel resection and sigmoidectomy were performed in 16 (80%) out of 20 interventions. Moreover, postoperative morbidity was low (25%), without any procedure-related death.

The combination of CRS and IPHP is an innovative treatment strategy that has evolved over the last two decades. Based on a strong scientific rationale, it permits the attainment of a synergistic effect that potentially overcomes the limitations of intraperitoneal chemotherapy (chemoresistance and limited drug availability in the tumor area). The employment of heat, as a fundamental component of this new therapeutic methodology, is justified by its own cancericidal property and chemosensitivity-modulating capacity. The biophysical effects of hyperthermia are not completely understood, but probably include membrane protein denaturation, increased vascular permeability [18,19], alterations in multimolecular complexes such as the insulin receptor [20] and in the cytoskeleton [18], and changes in enzyme complexes for DNA synthesis and repair [21]. Moreover, the architecture of the vasculature in solid tumors is chaotic, resulting in regions with low pH, hypoxia, and low glucose level [22]. This susceptible microenvironment renders solid tumors more sensitive to hyperthermia. In addition, at 40–42°C, neoplastic cells become more chemosensitive due to an increase in the intracellular concentration of drugs and in their activation process, especially for alkylating agents, and to alterations in the DNA repair process [23,24]. It has been demonstrated that the formation of platinum–DNA adducts after cisplatin exposure in hyperthermic conditions is enhanced and/or adduct re-

moval is decreased in heated cells, resulting in relatively higher DNA damage [25,26].

Since the purpose of locoregional treatment is to expose the tumor to a high drug concentration, simultaneously reducing the systemic side-effects, the most suitable drugs in the intraperitoneal approach are those of high molecular weight (with slow peritoneal absorption rate) and rapid systemic clearance. Pharmacokinetic studies have demonstrated an optimal ratio between the areas under the curve of mitomycin C, doxorubicin, and cisplatin administered intraperitoneally and those obtained by systemic administration (Table III) [27]. Chemotherapeutic regimens that have been reported to obtain a response in malignant mesothelioma are cisplatin [5,28], carboplatin [29], doxorubicin [30,31], paclitaxel associated with cisplatin [15], and mitomycin C [32,33]. We started the present study using the combination CDDP + MMC for the IPHP, but substituted mitomycin C for doxorubicin because of the better pharmacological profile of the latter (Table III). It is not possible to draw any conclusions about the advantage of one combination over the other in terms of tumor response, on the basis of current literature. We did not observe any influence of the IPHP drug regimen on survival or complications in our series.

A number of reports in the literature on the treatment of PM with CRS and IPHP have demonstrated encouraging results. Park et al. [6] treated 18 patients with primary PM with surgical DBK and IPHP as part of three consecutive Phase I trials conducted at the National Cancer Institute. The primary endpoints were the definition of dose-limiting toxicity and maximum tolerated dose (MTD) of CDDP administered via a 90-min continuous hyperthermic peritoneal perfusion (CHPP), initially alone and then with escalating doses of TNF. The mean follow-up was 19 months. The authors reported a 2-year overall survival of 80% and a median progression-free survival of 26 months. There was no treatment-related mortality and overall operative morbidity was 24%.

More recently, Sebbag et al. treated 33 PM patients with CRS, including peritonectomy procedures, and perioperative intraperitoneal chemotherapy (cisplatin + doxorubicin) [7]. Median survival was 31 months and overall survival at 3 years was 56%. The most significant

**TABLE III. Pharmacological Profile of Cisplatin, Doxorubicin, and Mitomycin C When Administered Intraperitoneally**

Drug	*AUC <sub>pe</sub> / <b>**AUC<sub>pl</sub></b>	Molecular weight (Kd)
Mitomycin C	23.5	334
Doxorubicin	500	544
Cisplatin	14	300

\*AUC<sub>pe</sub>: peritoneal area under curve; \*\*AUC<sub>pl</sub>: plasmatic area under curve.

positive prognostic factors were female sex, low prior surgical score, and completeness of cytoreduction and second-look surgery. The morbidity rate was 33% and perioperative mortality was 3%.

Loggie et al. conducted a prospective clinical trial in which 12 patients with PM underwent CRS followed by a 2-hr closed low-volume intraoperative intraperitoneal heated chemotherapy (IPHC) using mitomycin C [8]. One patient died from small bowel perforation 50 days after the procedure. Hematological toxicity of the procedure was minimal. Ascites was controlled in all patients and permanently resolved in 86% of patients presenting with ascites. Median survival was 34.2 months, with a median follow-up of 45.2 months. One patient was re-explored for ventral hernia 2 years post-IPHC, had negative peritoneal biopsies, and remains disease-free at 5 years.

One auto-criticism of our study is that the inclusion of patients with WDP and multicystic form could have favorably biased our results in terms of survival. We decided to submit these cases to CRS + IPHP on the basis of the uncertain nature of the lesions, which are classified as having a borderline malignant behavior, with a tendency to relapse. Moreover, there is one case report in the literature of the malignant transformation of a benign multicystic mesothelioma [34]. A separate analysis of our casuistic comprising only the diffuse malignant cases resulted in a overall survival rate of 68%, which is not statistically different from the OS of the whole series. Another limitation of our study concerns its uncontrolled design, which could have favored the selection bias, and consequently could have improved the results in terms of outcome.

### CONCLUSION

The resolution of ascites in the majority of our patients (94%) and the low treatment-related mortality/morbidity indicate that CRS + IPHP is a feasible and safe option for the palliation of patients with PM. Furthermore, in comparison with historical controls [2,3,30], the achievement of a 69% 3-year overall survival suggests that this new approach is a potentially effective treatment for selected patients with PM.

Further studies are needed to investigate issues such as predictive and prognostic factors, the impact of the extent of cytoreduction on survival, the role of previous anti-blastic treatment, and the most effective IPHP drug combination in order to identify the subset of patients that could benefit most from this promising therapeutic procedure. Although the low incidence of PM constitutes the major factor conditioning the feasibility of a randomized Phase III clinical trial, the confirmation of our findings will only be possible through further prospective controlled studies.

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