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Peritoneal Spread of Low-grade Appendiceal Tumours – 2 Days of Early Postoperative Intra-peritoneal Chemotherapy Are Enough

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Abstract. *Background/Aim: While controversial, cytoreductive surgery (CRS) with heated intra-peritoneal chemotherapy (HIPEC) and early postoperative intra-peritoneal chemotherapy (EPIC) remains the mainstay of treatment for low grade appendiceal neoplasm with pseudomyxoma peritonei (PMP). Our study aimed to investigate the difference in survival when administering HIPEC alone vs. HIPEC + EPIC. Additionally, we examined whether the duration of EPIC affects survival. Patients and Methods: We compared the difference in survival in 238 patients who underwent CRS + HIPEC alone vs. CRS + HIPEC/EPIC combination for low grade appendiceal cancer. We also compared short course (1-2 days) vs. long course (3-5 days) of EPIC. Results: HIPEC/EPIC combination group (n=179) showed a significantly better 5-year survival of 95% compared to 71% in HIPEC alone (n=59). There was no statistically significant difference in 5-year survival between short course (n=22) and long course of EPIC (n=157). Conclusion: Combined use of HIPEC and EPIC improves 5-year survival in low-grade appendiceal neoplasm. Two days of EPIC are sufficient.*

Appendiceal tumours are rare neoplasms accounting for 1% of all cancers and are subdivided into high-grade and low-grade depending on histological evidence of cell atypia. Historically, peritoneal spread of appendiceal neoplasm was lethal, with a median survival of 3 years (1). More recently however, a combination of cytoreductive surgery (CRS) and heated intra-peritoneal chemotherapy (HIPEC) has demonstrated 20-year survival rates of 70% (1). Due to the poor penetration of systemic chemotherapy to the peritoneum secondary to poor blood supply, intra-peritoneal chemotherapy offers a superior method of delivery that enables direct loco-regional contact of cytotoxic agents with tumour cells (2, 3). Furthermore, systemic toxicity is lower compared to intravenous infusions due to first pass metabolism through the liver (3, 4). The addition of early postoperative intra-peritoneal chemotherapy (EPIC) has become a topic of debate, with some evidence showing that a combination of CRS, HIPEC, and EPIC has better survival outcomes than just CRS and HIPEC alone in low grade appendiceal cancer.

EPIC was pioneered by Sugarbaker back in the 1990s (1, 2). 5-Fluorouracil (5-FU) is often used because it is cell cycle specific and can target all residual cells with a dwell time of 23 hours (3, 4). As adhesions take approximately 5 days to develop and can lead to non-uniform 5-FU distribution, EPIC is given for a total of 5 days (3). Furthermore, studies have shown that after subsequent instillations of intra-peritoneal chemotherapy, there is increased clearance of 5-FU from the abdominal cavity with increasing levels absorbed into the bloodstream by day 5 of chemotherapy. It is proposed that this is due to the cumulative inflammatory effects of 5-FU on the peritoneum, which is independent of drug dose (5). Therefore, the 5-day regimen is considered to give maximal penetration of 5-FU into tumour cells before diminished loco-regional efficacy.

For those with peritoneal metastases, a combination of CRS and HIPEC has shown 5-year and 10-year survival of 86% and 74%, respectively, in patients with low grade

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appendiceal mucinous neoplasm (5). The increased rate of complications in patients who receive EPIC has sparked debate over the overall efficacy of EPIC with HIPEC compared to HIPEC alone (5-7). Studies have shown that the use of EPIC is associated with grade III/IV post-operative complications of up to 58% compared to 20-25% in HIPEC alone (6). As a result, some institutes such as the National Centre Singapore ceased to offer EPIC due to high rates of complications (7).

There are currently no clear data investigating whether the duration of EPIC makes a difference in the survival of patients with low-grade appendiceal neoplasm. The objective of this study was to determine if the combination of CRS, HIPEC with EPIC was superior to CRS and HIPEC alone in low grade appendiceal tumours in our centre. Furthermore, we investigated the difference in survival in patients who received EPIC for less than three days (short course) compared to those who received EPIC for three days or greater (long course).

Patients and Methods

General methods. The Department of Liver Surgery and the Peritonectomy Unit maintain a prospective database collecting key clinical information since 1996. The data included are currently up until July 2019. Clinical information including the diagnostic information and procedures performed are collected as cases and registered and used for daily reporting. The status of patients was updated using clinic notes and from ongoing episodes of care using the hospital based patient information administration systems (PAS).

The entire cohort was queried and filtered for cases undergoing CRS due to peritoneal involvement from a neoplasm and appendiceal dissemination. Data on patient information including age, sex, date of death, last follow up, American Society of Anesthesiologists (ASA) index, peritoneal cancer index (PCI), completeness of cytoreduction (CC) score, morbidity grade, drugs administered at HIPEC, and days of EPIC administered were extracted.

Patients. A retrospective study of prospectively collected data of patients with low grade appendiceal tumours who underwent CRS and HIPEC with or without the addition of EPIC by one surgical team at St George Hospital in Sydney, Australia between 1996 to July 2018, was undertaken.

Low-grade appendiceal tumours were defined by histological analysis post-operatively. Patients were divided into groups based on the treatment received. Group 1 included patients who received HIPEC only (n=59). Group 2 included patients who received HIPEC and EPIC irrespective of the days of treatment (n=197). Group 3 included patients who received HIPEC and EPIC (<3 days). Group 4 included patients who received HIPEC and EPIC (3-5 days). Some patients in this study received more than one CRS.

Pre-operative management. The pre-operative management included a physical examination, blood tests, and computed tomography (CT) of the chest, abdomen, and pelvis. Some patients had additional positron emission tomography (PET) scans.

CRS. The technique used for CRS is based on the Sugarbaker approach (8, 9) and included primary tumour removal, gastrointestinal tract resections, resection of tumour nodules and peritonectomy. The aim of CRS was for complete macroscopic disease removal. Upon entering the abdomen, the PCI score was calculated using established guidelines (10) to accurately score macroscopic disease from 0-39. Completeness of the macroscopic resection was graded at the completion of surgery using the CC score.

HIPEC. After CRS, HIPEC was performed using mitomycin or oxaliplatin given at 41.5 degrees Celsius. A special coliseum was built to allow for safe deliverance of chemotherapy agents intraperitoneally. The choice of chemotherapy agent was decided by the medical oncology team. Mitomycin C was administered for 90 min whereas oxaliplatin was administered for 60 min.

EPIC. On day 1, a leak test was performed to ensure safe deliverance of chemotherapy. The test involves administration of 1 l of 0.9% sodium chloride via the intra-peritoneal Tenkoff catheter, while intraabdominal drains are clamped. EPIC was then commenced on days 2-6 postoperatively in an intensive care unit (ICU) setting. An infusion of 5-FU 650 mg/m^2 mixed with 50 mEq of sodium bicarbonate was administered through the intra-peritoneal catheter. The intra-peritoneal drains were then clamped for 23 h. The fluid is then drained over 1 h before the process is repeated for a total of 5 days. Adverse events such as haemodynamic instability, cardiac arrhythmias, poor tolerance or renal dysfunction were the main reasons for early cessation of EPIC.

Post-operative management. All complications post-surgery were recorded based on the Clavien-Dindo Classification (CDC) of surgical complications with major morbidity defined as grade III or IV. All patients were followed up on a three-monthly basis for 5 years. Some patients were followed up for longer than 5 years by the surgical team or medical oncology team. Follow up reviews often included examination, tumour markers, and CT scans. For the study, the follow up periods were defined at 12, 36, and 60 months.

Survival analysis method. Data were analysed using IBM® SPSS® software Version 24, IBM Corp, 2016. Multivariate analysis was carried out using SPSS® and univariate analysis for determining the significance of differences was calculated using Graph Prism®. Both the mean with corresponding standard deviation and the median with corresponding range of values were determined and presented in the patient characteristics table for all variables. The mean value is used to report continuous variables, while the median value is used for categorical variables. Incidence and rate of incidence were reported for binary variables as percentages, standardised to the log of 102.

Persons not marked as dead before the last follow up date were allocated a status of alive at the time of their follow-up date. The last follow up date for cases was included in the survival calculations and marked as "lost to follow up" at that time point and censored from the overall population at risk group at that time point.

Cox regression method for proportional hazard ratio was used to measure survival probability at a given time (t), calculated as part of the hazard function at time (t). The Kaplan–Meier technique was then utilised to plot the survival curve. Microsoft EXCEL® was used to determine the final status and the lost to follow up cases including the survival proportion and probability of survival over time.

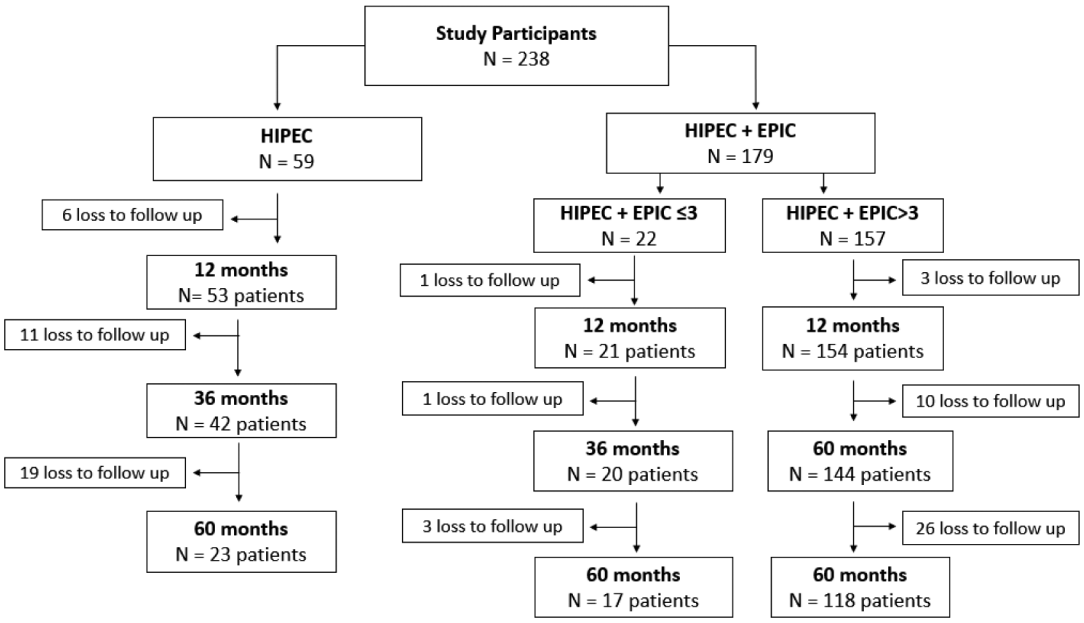


Figure 1. *Descriptive results.*

Results

A total of 238 patients were derived from the database for this study (Figure 1). These included patients who underwent CRS + HIPEC (n=59) and CRS + HIPEC + EPIC (n=179). The CRS + HIPEC + EPIC group was further sub-divided into those who received EPIC for less than three days and those who received it for three days or more. A total of 80 patients were lost to follow up, 36 in the HIPEC group and 44 in the HIPEC + EPIC Group.

The patient characteristics are demonstrated in Table I for all four groups. Univariate analysis shows statistically significant differences in mean PCI scores (p=0.022), age (p=0.001), and CC score ($p\leq$0.001) between the groups. The overall morbidity rate (Clavien-Dindo score) was not statistically significantly different between the groups (p=0.708). The chemotherapy of choice was predominantly Mitomycin C in all groups.

Risk of mortality outcomes. Overall, patients who had HIPEC + EPIC (n=179) had significant better survival rates at all three time points compared to patients who had HIPEC alone (n=59). At 5 years, the HIPEC alone group had a 40% increased risk of mortality when compared to HIPEC and EPIC (HR=1.40; 95%CI=1.39-1.41, p=0.014).

Survival outcomes were then compared using subgroup analysis (Table II). The subgroup of HIPEC + EPIC was divided into a short course (<3 days) and long course (3-5 days) of EPIC. There were 22 patients who received the short course and 157 patients who received the long course. At 5 years, HIPEC alone compared with HIPEC + EPIC short course demonstrated a 41% increased risk of mortality (HR=1.41, 95%CI=1.40-1.42; p<0.001). Similarly, HIPEC alone compared with HIPEC + EPIC long course demonstrated a 39% increased risk of mortality (HR=1.39; 95%CI=1.38-1.40, p=0.014).

Overall survival outcome. As seen on the Kaplan–Meier curve in Figure 2, the addition of EPIC shows markedly improved survival when compared with HIPEC alone. At all time points, the groups receiving EPIC in addition to HIPEC had better survival. At 5 years, the HIPEC + EPIC group showed a statistically improved survival when compared to HIPEC alone (p=0.014). HIPEC alone had a 71% overall survival compared to 95% in the HIPEC + EPIC group overall. HIPEC + EPIC <3 days also showed a statistically significant improved survival of 95% ($p\leq$0.001). Similarly, the group which received HIPEC + EPIC (3-5 days) had an overall survival of 94% (p=0.0014).

Discussion

Low-grade appendiceal peritoneal disease has extremely good survival outcomes with complete CRS and intra-peritoneal chemotherapy (11, 12). Given the excellent prognosis associated with the histology, it is pertinent that treatment is aggressive. Compared to the 15% of colorectal cancers which present with peritoneal disease, almost all of

Table I. *Patient characteristics in low grade appendiceal neoplasm.*

Variables	Categories	HIPEC group (n=59)	HIPEC_EPIC group (n=179)	HIPEC_EPIC <3 group (n=22)	HIPEC_EPIC ≥3 group (n=157)	*p*-Value	Univariate
Gender	Male [N (Percent)]	31 (52.54%)	75 (41.90%)	10 (45.45%)	65 (41.40%)	0.484	
	Female [N (Percent)]	28 (47.46%)	104 (58.10%)	12 (54.55%)	92 (58.60%)		
Age	Years [Mean (SD)]	58.33 (13.85)	52.63 (13.09)	60.06 (13.60)	51.59 (12.72)	0.001	0.001
	Median (Range)	60.33 (28.76-81.28)	53.87 (15.03-77.87)	63.31 (15.03-77.87)	52.82 (21.62-75.47)		
PCI	Mean (SD)	25.07 (12.45)	22.87 (10.49)	28.77 (07.12)	22.04 (10.63)	0.022	0.022
	Median (Range)	28 (0-39)	23 (3-39)	30.5 (15-39)	22 (3-39)		
	0-10	11 (18.64%)	28 (15.64%)	0 (0%)	28 (17.83%)		
	11-20	4 (6.78%)	49 (27.37%)	3 (13.64%)	46 (29.30%)		
	21-30	19 (32.2%)	49 (27.37%)	8 (36.36%)	41 (26.11%)		
	>30	25 (42.37%)	53 (29.61%)	11 (50.00%)	42 (26.75%)		
Morbidity rate (Clavien Dindo Classification)	Median (Range)	2 (0-5)	0 (0-2)	3 (0-4)	2 (0-4)	0.708	
	0-2	33 (55.93%)	101 (56.42%)	9 (40.91%)	92 (58.60%)		
	3-4	22 (37.29%)	78 (43.58%)	13 (59.09%)	65 (41.40%)		
CC Score	Median (Range)	1 (0-2)	0 (0-2)	1 (0-2)	0 (0-1)	<0.001	<0.001
	CC0-1	55 (93.22%)	178 (99.44%)	21 (95.45%)	157 (100%)		
	CC2-3	4 (05.08%)	1 (00.56%)	1 (04.55%)	0 (0%)		
Chemotherapy type administered at HIPEC	Mitomycin C	49 (83.05%)	177 (98.88%)	22 (100%)	155 (98.73%)	<0.001	<0.001
	Oxaliplatin	9 (15.25%)	2 (01.12%)	0 (0%)	2 (01.27%)		
	Cisplatin	1 (01.69%)	0 (0%)	0 (0%)	0 (0%)		

Table II. *Survival outcomes at 12, 36, and 60 months.*

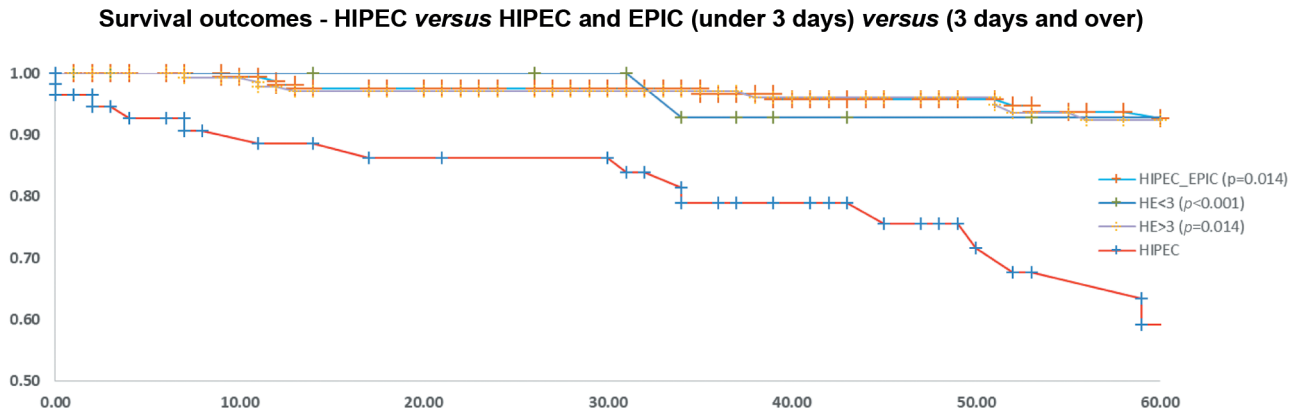
Time in months	HIPEC + EPIC vs. HIPEC	95% Confidence interval		*p*-Value	HIPEC + EPIC <3 vs. HIPEC	95% Confidence interval		*p*-Value	HIPEC + EPIC ≥3 vs. HIPEC	95% Confidence interval		*p*-Value
12.00	1.13	1.12	1.14	0.056	1.13	1.13	1.14	-	1.11	1.10	1.12	0.232
36.00	1.21	1.20	1.22	0.003	1.18	1.17	1.19	-	1.20	1.19	1.21	0.002
60.00	1.40	1.39	1.41	0.014	1.41	1.40	1.42	<0.001	1.39	1.38	1.40	0.014

Hazard ratio: Survival.

appendiceal neoplasms present in the disseminated state. In mucinous disease, most people die due to loss of intestinal function associated with the mucin load in the abdomen and pelvis (11, 12).

Sugarbaker (1995) showed that survival outcomes of appendiceal tumours with CRS and EPIC showed good survival outcomes (1). Not surprisingly, complete cytoreduction is required for optimal results (11, 12). In the large multi-institutional registry, it was shown that the combination of CRS, HIPEC, and EPIC yielded significantly better survival outcomes in low grade appendiceal neoplasms with PMP compared to CRS and HIPEC alone (5). The 5-year and 10-year survival was quoted to be 91% and 79%, respectively, with CRS, HIPEC, and EPIC. These data are similar to the results of our study that showed a survival of 95% in the group that received CRS, HIPEC, and EPIC. There appears to be a significant benefit in survival of low-grade appendiceal tumours when HIPEC is used in combination with EPIC rather than giving just HIPEC alone. These results have been reflected in other studies in literature (5, 12-15). Chua *et al*. show a similar 5-year survival of 86% in the group that received HIPEC and EPIC compared to 64% in those that received HIPEC or EPIC alone (15). Huang *et al*. also reflected an improved survival with HIPEC and EPIC but quoted a lower 5-year survival of 62%.

One of the reasons why EPIC has fallen out of favour is due to the adverse events secondary to toxicity. Several studies have shown increased rates of complication, increased length of hospital stay, and morbidity associated to EPIC toxicity (1, 5-7). Common reported adverse events include pleural effusions, fistulas, intra-abdominal collections, pneumothorax, bleeding, and re-operation, all of which prolong hospital stay (5-7). EPIC was associated with statistically significant increased length of hospital stay in conjunction with HIPEC



Survival in months	12 mths	36 mths	60 mths
HIPEC_EPIC	0.99	0.97	0.95
HE<3	1.00	1.00	0.95
HE>=3	0.98	0.97	0.94
HIPEC	0.9	0.83	0.71

Population at risk	12 mths	36 mths	60 mths
HIPEC_EPIC	176	168	141
HE<3	21	20	17
HE>=3	154	144	118
HIPEC	53	42	23

Figure 2. *Survival outcomes – intra-peritoneal chemotherapy (HIPEC) versus HIPEC and early postoperative intra-peritoneal chemotherapy (EPIC) (under 3 days) versus (3 days and over).*

(16). McConnell *et al*. also found that the rate of grade III/IV complications was significantly higher in the group with HIPEC and EPIC *versus* HIPEC alone (44.7% *vs*. 31.0%; p=0.05) (16).

Similarly, Tan found that the complication rates were significantly increased with the use of EPIC, quoting an up to 58% rate (7). Contradicting this, Huang showed no significant differences in terms of in-hospital mortality, major morbidity rate, length of ICU stay or total hospital stay between those who received HIPEC only *versus* HIPEC and EPIC (14). Acknowledging a risk of morbidity associated with EPIC, this study was able to show that shorter duration of EPIC may still be effective in low-grade appendiceal neoplasm with PMP. Interestingly, our study showed no significant differences in survival if HIPEC + EPIC was used for less than three days or greater than or equal to three days compared to HIPEC alone. Both groups had statistically significant improved survival when compared to HIPEC only.

This result is profound as it suggests that the survival advantage can be retained with a shorter duration of EPIC. It is possible that the effect of EPIC may not be related to the duration of therapy and increased survival outcomes can still be gained on reduced regimens. This has the benefit of potentially reducing patient exposure to potential EPIC-related side effects as well as reducing the length of hospital stay and burden on the healthcare system. Although further reproducible research and prospective studies are required, this study will hopefully guide future management and potentially assist in tailoring treatment regimens based on patient pre-morbid status, as those with poor functional baseline may not tolerate a prolonged course of EPIC but may still benefit from a less than three-day course.

An exciting avenue of future research and treatment is sequential postoperative intraperitoneal chemotherapy (SPIC) (17). Given the efficacy of intraperitoneal deliverance of chemotherapy, longer adjuvant intraperitoneal chemotherapy may be of further benefit in peritoneal carcinomatosis. Further research on outcomes from the combination of CRS, HIPEC, EPIC and/or SPIC may be of value.

Limitations. There are several limitations to this study. The sample size in the HIPEC and EPIC group (<3 days) was relatively small and thus, there is risk of an inflated effect size estimation and low statistical power when compared to the group that received 3-5 days of treatment. The patient demographics between HIPEC only and HIPEC + EPIC showed a heterogeneous population with statistically significant differences in PCI score, gender, and chemotherapy agent received. Similarly, patients that received less than 5 days of treatment were self-selected due to adverse outcomes, haemodynamic instability or contraindications to EPIC. The reason for early cessation of EPIC was not recorded in our current database. It is possible

that these patients have baseline characteristics that may have attributed an inherent bias in our results.

This study only looked at the 5-year survival of patients who received EPIC. Given the relatively good survival associated with low-grade neoplasm, a longer follow up may be warranted. Other indicators of survival outcomes such as disease-free interval and recurrence rates may have provided valuable information regarding the overall benefits of EPIC. Finally, as a single centre retrospective study, there was no randomisation or blinding in this study.

Conclusion

Low-grade appendiceal tumours are rare cancers with no consensus or guidelines on management. We have found that a regimen of CRS, HIPEC, and EPIC improves overall survival at 12, 36, and 60 months compared to CRS and HIPEC alone. There was also no difference in survival if less than three days of EPIC was given compared to three days or more, calling into question the need of the traditional five-day regimen. Our study supports potentially decreasing the days required for EPIC therapy to decrease rates of toxicity, length of hospital stay, and cost to the healthcare system with no impact on survival.

We can report that 2 days of treatment with EPIC appears to provide a survival advantage and that even less may be adequate. This is significant because reduction in the duration of treatment may mean significant reduction in the associated morbidity, and reduced ICU and hospital stay and overall cost to the healthcare system.

Conflicts of Interest

The Authors report no conflicts of interest in regard to this study.

Authors' Contributions

All Authors contributed to the writing of this article. Prof. Morris and Dr. Alzahrani were the principal surgeons and supervisors in this study and contributed to the study design. Drs Rao and Mui contributed to manuscript preparation, while Dr. Matar was responsible for reviewing, editing, and submitting the manuscript. Shoma Barat assembled data and conducted the statistical analysis.

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