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ORIGINAL RESEARCH

Effects of propofol-based total intravenous anesthesia on gastric cancer: a retrospective study

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Background: Several kinds of cancer surgeries with propofol-based total intravenous anesthesia (TIVA) have been shown to have better outcomes than those with sevoflurane-based inhalational anesthesia (INHA). However, the effects of this anesthetic technique have not been investigated in patients with gastric cancer. In this study, the authors retrospectively examined the link between the choice of anesthetic technique and overall survival in patients undergoing gastric cancer resection.

Methods: We conducted a retrospective analysis of the database of all patients undergoing gastric cancer resection for gastric cancer between 2007 and 2012. Patients who received TIVA or INHA were administered patient-controlled intravenous analgesia for 72–120 hours postoperatively. Survival was estimated using the Kaplan–Meier log-rank test, and associations between anesthetic technique and outcomes were analyzed using Cox proportional hazards regressions after propensity matching.

Results: A total of 2,856 anesthetics using INHA or TIVA were delivered in the study period. After propensity matching, 897 patients remained in each group. According to Kaplan–Meier analysis, the use of TIVA was associated with improved survival ($P<0.001$). TIVA was associated with a hazard ratio (HR) of 0.67 (95% confidence interval [CI]: 0.58–0.77) for death in univariate analysis and 0.65 (95% CI: 0.56–0.75) after a multivariate analysis of known confounders in the matched group. Cancer stage (HR =0.74, 95% CI: 0.64–0.86, $P<0.001$) and degree of differentiation (HR =1.28, 95% CI: 1.11–1.47, $P<0.001$) were also associated with survival in the univariate analysis in the matched group. In the multivariable Cox model, cancer stage (HR =0.72, 95% CI: 0.62–0.84, $P<0.001$) and degree of differentiation (HR =1.23, 95% CI: 1.07–1.42, $P<0.001$) were associated with survival in the matched group.

Conclusion: These results indicate that TIVA may be associated with improved survival in gastric cancer patients who undergo resection.

Keywords: anesthesia, propofol, sevoflurane, patient-controlled analgesia, gastric cancer, overall survival

Introduction

Gastric cancer is the second most common cause of global cancer mortality, and surgical removal of tumors remains a mainstay in the course of treatment.[1] Although surgical excision of primary or even metastatic tumors can save or extend life, it has long been acknowledged that the surgery itself may precipitate or accelerate tumor recurrence.[2] Surgery induces increased shedding of cancer cells into blood circulation,[3] suppresses antitumor immunity allowing circulating cells to survive,[4,5] upregulates adhesion molecules in target organs, recruits immune cells capable of entrapping tumor

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cells, and induces changes in the target tissue.[6,7] Moreover, it has been well established that surgery can cause selective suppression of T-helper-1 (Th1) function and a shift toward a T-helper-2 (Th2) cytokine pattern with cell-mediated immune suppression.[8–11] In addition to these changes directly related to surgical treatment, there are countless perioperative variables that can alter the oncological outcomes, including anesthetic management, blood transfusion, the development of hypothermia, and the evolution of postoperative complications.

It has recently been demonstrated that propofol could exert antitumor properties through several kinds of mechanisms, including the suppression of survival capability, tumor progression, and the invasion of cancer cells.[12–15] Moreover, propofol also stimulates the activation and differentiation of T-helper lymphocytes, a key step in anti-infective and antitumor immune responses.[16–18] In contrast, sevoflurane exhibited immunosuppression and tumorigenesis through a number of mechanisms, including suppression of natural killer (NK) cell activity and lymphocyte function, which induce proliferation, apoptosis, and invasion of cancer cells.[16,19–21] These results lead to the hypothesis that propofol-based total intravenous anesthesia (TIVA) may provide survival advantages compared with sevoflurane-based inhalational anesthesia (INHA). However, the effect of propofol-based TIVA on the outcome of gastric cancer resection has not been previously evaluated in the clinical setting. Therefore, we conducted a retrospective analysis of electronic records to make a comparison of overall survival in patients after gastric cancer resection, between propofol-based TIVA and sevoflurane-based INHA.

Methods

Ethics statement

This retrospective observational study complied with the guidelines of the Declaration of Helsinki, and was approved by the Ethics Committee of Harbin Medical University Cancer Hospital. As this study involved a retrospective review of existing data as well as medical records, and all individual information was securely protected by delinking identifying information from the main data set and was available only to investigators, the Institutional Review Board of Harbin Medical University Cancer Hospital approved this study and specifically waived the need for written informed consents. Consent was waived because this study was part of an audit, conformed to standards for minimal risk research, and did not affect patient safety or clinical care. Moreover, all of the data were analyzed anonymously.

Patient selection

After approval was received from the Ethics Committee of the Harbin Medical University Cancer Hospital, 2,856 gastric cancer cases were identified from the medical records of patients admitted to the hospital for gastric cancer resection between 2007 and 2012. We excluded patients who had metastasis, emergency operations, and/or laparoscopic procedures. Patients who experienced anesthesia and analgesia consistent with the following standard and postoperative pathologies of gastric cancer were included. Medical records for all of the included patients were obtained.

Anesthesia technique and grouping method

In both groups, anesthesia was induced with midazolam 0.05–0.15 mg/kg, 0.5 μg/kg fentanyl, and 1–2.5 mg/kg propofol. Patients were allocated into TIVA and INHA groups by the different anesthetic techniques used. In the TIVA group, anesthesia was maintained with propofol infusion and remifentanil. In the INHA group, anesthesia was maintained with sevoflurane and remifentanil infusion. Patients received patient-controlled intravenous analgesia with 3 μg/mL fentanyl or 0.5 μg/mL sufentanil for 72–120 hours postoperatively in both groups.

Data collection

The status of patients up to March 31, 2015 was determined from medical records, and the causes of death were recorded. The following information was obtained: demographic data, cancer stage, American Society of Anesthesiologists (ASA) grade, duration of surgery, degree of differentiation, transfusion, preoperative or postoperative adjuvant chemotherapy, and/or radiation therapy. Cancer stage was assessed based on the 7th edition of the American Joint Committee on Cancer Cancer Staging Manual. The degrees of differentiation included well differentiated, moderately differentiated, poorly differentiated, and other/unknown differentiated. Survival time was measured from the date of gastrectomy to death or to the last follow-up time before March 31, 2015.

Statistical approach

All statistical analyses were performed using SPSS17.0 (IBM; Armonk, NY, USA). To account for differences in baseline characteristics, propensity scores were obtained by using binary logistic regression using all the patients' demographics presented in Table 1. Matching was performed

Table 1 Correlation between two types of anesthesia and clinicopathological features in gastric cancer patients

Variables	Overall patients			Matched patients		
	TIVA (n=1,506)	INHA (n=1,350)	*P*-value	TIVA (n=897)	INHA (n=897)	*P*-value
Age (years)			0.174			1.000
<60	868 (57.6%)	744 (55.1%)		516 (57.5%)	516 (57.5%)	
≥60	638 (42.4%)	606 (44.9%)		381 (42.5%)	381 (42.5%)	
BMI (kg/m^2)			0.099			0.708
<20	359 (23.8%)	358 (26.5%)		235 (26.2%)	242 (27.0%)	
≥20	1,147 (76.2%)	992 (73.5%)		662 (73.8%)	655 (73.0%)	
Duration of surgery (hours)			0.593			0.962
<3.5	825 (54.8%)	753 (55.8%)		505 (56.3%)	504 (56.2%)	
≥3.5	681 (45.2%)	597 (44.2%)		392 (43.7%)	393 (43.8%)	
Gender			0.083			0.951
Female	1,193 (79.2%)	1,033 (76.5%)		738 (82.3%)	737 (82.2%)	
Male	313 (20.8%)	317 (23.5%)		159 (17.7%)	160 (17.8%)	
Smoking			0.131			0.925
No	726 (48.2%)	689 (51.0%)		442 (49.3%)	440 (49.1%)	
Yes	780 (51.8%)	661 (49.0%)		455 (50.7%)	457 (50.9%)	
Alcoholism			0.474			0.925
No	810 (53.8%)	708 (52.4%)		463 (51.6%)	465 (51.8%)	
Yes	696 (46.2%)	642 (47.6%)		434 (48.4%)	432 (48.2%)	
Hypertension			0.063			0.785
No	1,360 (90.3%)	1,190 (88.1%)		830 (92.5%)	833 (92.9%)	
Yes	146 (9.7%)	160 (11.9%)		67 (7.5%)	64 (7.1%)	
Ischemic cardiomyopathy			0.969			0.515
No	1,414 (93.9%)	1,268 (93.9%)		864 (96.3%)	869 (96.9%)	
Yes	92 (6.1%)	82 (6.1%)		33 (3.7%)	28 (3.1%)	
Diabetes			0.174			0.790
No	1,438 (95.5%)	1,274 (94.4%)		869 (96.9%)	867 (96.7%)	
Yes	68 (4.5%)	76 (5.6%)		28 (3.1%)	30 (3.3%)	
ASA			0.566			0.963
I	204 (13.5%)	199 (14.7%)		91 (10.1%)	89 (9.9%)	
II	1,197 (79.5%)	1,065 (78.9%)		770 (85.8%)	770 (85.8%)	
III	105 (7.0%)	86 (6.4%)		36 (4.0%)	38 (4.2%)	
Cancer stage			0.860			0.849
Lower (I–II)	844 (56.0%)	761 (56.4%)		499 (55.6%)	503 (56.1%)	
Higher (III)	662 (44.0%)	589 (43.6%)		398 (44.4%)	394 (43.9%)	
Tumor differentiation			0.632			0.919
Lower (1)	563 (37.4%)	493 (36.5%)		283 (31.5%)	281 (31.3%)	
Higher (2–4)	943 (62.6%)	857 (63.5%)		614 (68.5%)	616 (68.7%)	

Notes: Detected by Pearson's χ^2 tests. Degrees of differentiation: degree 1, poorly differentiated; degree 2, moderately differentiated; degree 3, well differentiated; degree 4, other/unknown differentiated. Cancer stages: stage I: T1, N0, M0/T2, N0, M0/T1, N1, M0; stage II: T3, N0, M0/T4a, N1, M0/T3, N1, M0/T2, N2, M0/T1, N3, M0; stage III: T2, N3, M0/T3, N2, M0/T3, N3, M0/T4a, N2, M0/T4a, N3, M0/any T4b, any N, M0; stage IV: any T, any N, M1.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; INHA, inhalational anesthesia; TIVA, total intravenous anesthesia.

using Greedy 5→1 Digit Match algorithm.[22] The correlation between the two groups of anesthesia (TIVA and INHA) and the pathologic features of patients were analyzed with the χ^2 test. Survival curves were obtained using the Kaplan–Meier method, and statistical analysis was performed using the log-rank test. A Cox proportional hazards regression model was performed for univariate and multivariate survival analyses. A value of $P<0.05$ was considered statistically significant.

Results

Patient characteristics

Using the inclusion and exclusion criteria described earlier, we identified a cohort of 2,856 patients (Figure 1), 52.7% of whom (n=1,506) were in the TIVA group, and 47.3% of whom (n=1,350) were in the INHA group. The median follow-up times for the TIVA and the INHA groups were 43.6 months and 39.7 months, respectively. The groups exhibited no differences in age, height, weight, duration of

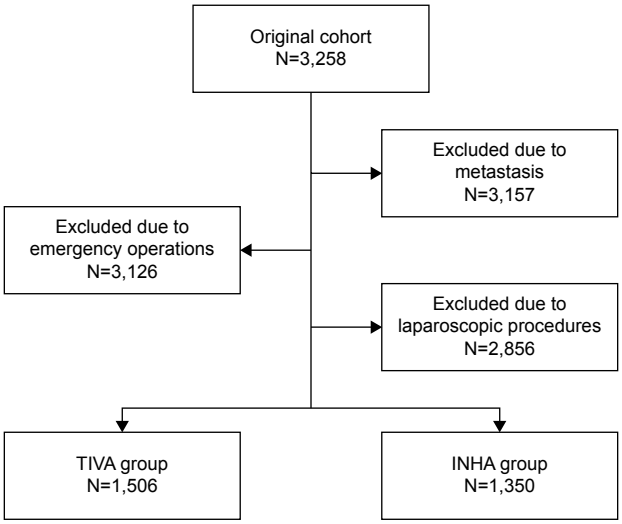

Figure 1 Patient identification and exclusion.
Abbreviations: INHA, inhalational anesthesia; TIVA, total intravenous anesthesia.

surgery, gender, smoking history, alcoholism, hypertension history, ischemic cardiomyopathy, diabetes, and ASA grade after surgery. Moreover, no differences in cancer stage or degree of differentiation were observed between the two groups (Table 1).

Association between TIVA use and overall survival

The mean survival time in the TIVA and INHA groups were 49.1 months and 40.6 months, respectively. In a log-rank test, perioperative TIVA use was associated with overall survival ($P<0.001$), with an estimated hazard ratio (HR) of 0.63 (95% confidence interval [CI]: 0.56–0.70) in the univariate analysis (Table 2). Cancer stage (HR =0.64, 95% CI: 0.57–0.72, $P<0.001$), degree of differentiation (HR =1.20, 95% CI: 1.07–1.35, $P<0.001$), and blood transfusion (HR =1.18, 95% CI: 1.02–1.37, $P=0.027$) were also associated with overall survival. However, chemotherapy (HR =0.90, 95% CI: 0.80–1.01, $P=0.062$) and age (HR =0.99, 95% CI: 0.88–1.11, $P=0.883$) were not found to be associated with survival. In the multivariate Cox model that considered only the statistical effect of TIVA use (Model 1, Table 3), cancer stage and degree of differentiation were associated with TIVA use, which exhibited an adjusted estimated HR of 0.61 (95% CI: 0.55–0.69, $P<0.001$). In the multivariate Cox model, cancer stage (HR =0.62, 95% CI: 0.55–0.70, $P<0.001$), degree of differentiation (HR =1.17, 95% CI: 1.04–1.31, $P<0.001$), and blood transfusion (HR =1.26, 95% CI: 1.09–1.47, $P=0.002$) were associated with survival. Kaplan–Meier estimates of survival as a function of postoperative time for the two groups are provided in Figure 2. The resulting curves differed significantly ($P<0.001$, log-rank test).

Propensity-matched analysis

Propensity-matched analysis resulted in 897 patients in each group, with similar baseline characteristics. TIVA was still associated with a reduced HR in both univariate (HR =0.67, 95% CI: 0.58–0.77) and multivariable (HR =0.65, 95% CI: 0.56–0.75) analyses. The association of other variables with outcome was similarly unaffected.

Discussion

This retrospective analysis of 2,856 patients who underwent gastric cancer resection evaluated overall survival in patients receiving sevoflurane-based INHA compared with TIVA using propofol and remifentanil. After propensity matching and adjustment for known confounding factors, our results seem to suggest an early and sustained beneficial effect of TIVA on tumor-related mortality after gastric cancer compared with sevoflurane-based inhalational anesthesia. There was a significant association between TIVA and improved survival. We found that TIVA can improve

Table 2 Univariate associations with survival

Factor	Overall patients			Matched patients		
	P-value	HR	95% CI	*P*-value	HR	95% CI
Blood transfusion (yes vs no)	0.027	1.18	1.02–1.37	<0.001	1.40	1.17–1.67
Cancer stage (lower vs higher)	<0.001	0.64	0.57–0.72	<0.001	0.74	0.64–0.86
Degree of differentiation (lower vs higher)	<0.001	1.20	1.07–1.35	<0.001	1.28	1.11–1.47
Chemotherapy (yes vs no)	0.062	0.90	0.80–1.01	0.191	0.91	0.79–1.05
Group (TIVA vs INHA)	<0.001	0.63	0.56–0.70	<0.001	0.67	0.58–0.77
Age (<60 years vs ≥60 years)	0.883	0.99	0.88–1.11	0.858	1.01	0.88–1.17

Abbreviations: CI, confidence interval; HR, hazard ratio; INHA, inhalational anesthesia; TIVA, total intravenous anesthesia.

Table 3 Multivariate associations with survival

Factor	Overall patients			Matched patients		
	P-value	HR	95% CI	*P*-value	HR	95% CI
Blood transfusion (yes vs no)	0.002	1.26	1.09–1.47	<0.001	1.42	1.18–1.70
Clinical stage (lower vs higher)	<0.001	0.62	0.55–0.70	<0.001	0.72	0.62–0.84
Degree of differentiation (lower vs higher)	<0.001	1.17	1.04–1.31	<0.001	1.23	1.07–1.42
Group (TIVA vs INHA)	<0.001	0.61	0.55–0.69	<0.001	0.65	0.56–0.75

Abbreviations: CI, confidence interval; HR, hazard ratio; INHA, inhalational anesthesia; TIVA, total intravenous anesthesia.

the outcome of patients with gastric cancer, which was consistent with a recent study, and it demonstrated that the patients receiving TIVA anesthesia had better survival compared with those receiving inhalational anesthesia.[23] Other variables associated with survival in multivariate analysis included age, cancer stage, degree of differentiation, and blood transfusion. Chemotherapy and radiation therapy were not associated with a better outcome. We identified associations between cancer stage, degree of differentiation, blood transfusion, and overall survival after gastric cancer resection. These findings were consistent with those of prior observational studies that evaluated other types of cancers, such as breast[15,24] and colorectal cancer,[25] and showed that these variables reduced the survival of patients after gastric cancer resection. In our study, we focused on the overall survival in patients receiving TIVA or INHA after gastric cancer resection.

The factors promoting metastasis and recurrence of primary tumors after surgery are diverse. Dissemination of tumor cells, drugs in anesthetic and analgesic processes,[26,27] destruction of the extracellular matrix,[28,29] release of vascular endothelial growth factor,[30] and postoperative immunosuppression[31,32] have been proposed as involved in metastasis and cancer recurrence. Surgical resection of tumors has been demonstrated to induce both the formation of new metastatic foci and lead to locoregional acceleration of tumor growth.[7] The immune system, and in particular, the cellular immune response that may protect against the proliferation of cancer cells and play a central part in postoperative clearance of cancer cells, is suppressed at the time of surgery. T lymphocytes and NK cells are two predominant cytotoxic effector cells that are the major components of cell-mediated immune responses. One study showed that major visceral surgery suppressed the capacity of circulating NK cells that play a key role in the defense against tumor cells through the release of interferon (IFN)-γ.[33] Another study demonstrated that T-cell suppression in patients undergoing major abdominal surgery was associated with increased T-regulatory cells and a marked induction of myeloid-derived suppressor cells.[34] Moreover, surgery induces impaired Th1 functions in humans. Impairment of Th1 responses, normally an essential step in specific

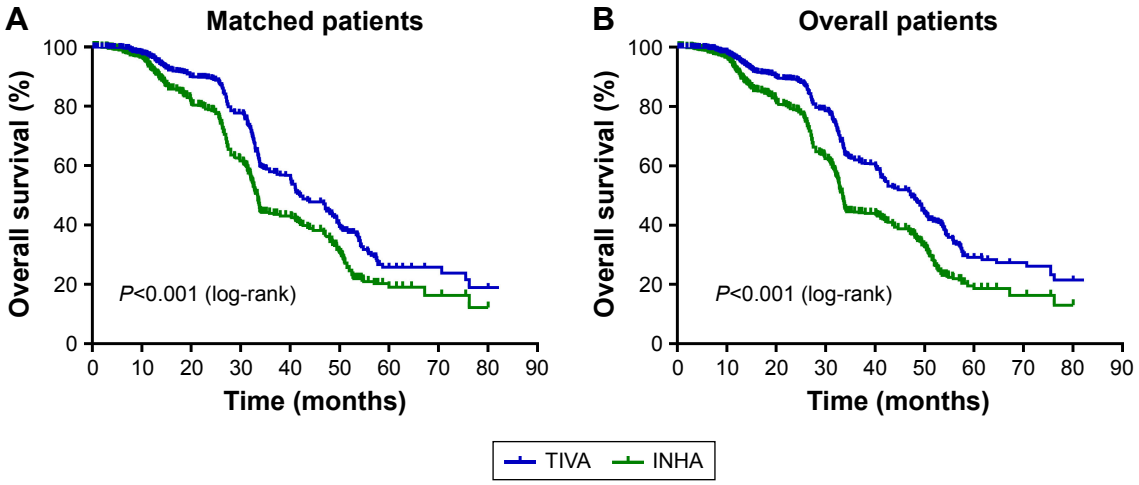

Figure 2 Kaplan–Meier survival curves for patients with TIVA use or INHA use, in matched patients (**A**) and overall patients (**B**) (univariate *P*<0.001*).
Abbreviations: INHA, inhalational anesthesia; TIVA, total intravenous anesthesia.

cellular immunity and proliferation of cytotoxic T cells, might also hamper antitumor cytotoxicity.[35] Additionally, surgery-associated physical injury increased the expression of Th2 cells and brought about impaired cell-mediated immunity.[36]

Propofol has been demonstrated to have protective effects on immune functions and exhibits a good inhibitory effect on tumor recurrence and metastasis.[37] Some studies have shown that propofol inhibits vascular proliferation and regeneration of esophageal squamous cell carcinoma and metastatic lesions through reduced ERK-VEGF/MMP-9 signaling.[38] Propofol suppresses tumor growth in a mouse model with preservation of in vitro cytotoxic T lymphocyte activity.[39] Propofol also reduces PGE2 production, which is a known mediator of pain and inflammation that inhibits NK cell cytotoxicity through EP2 and EP4 receptors, in vitro.[40,41] Moreover, another study has shown that propofol could elevate Th1 cytokine secretion and decrease Th2 cytokines, thus protecting against immunosuppression after surgery.[42] This attribute of propofol compared with volatile agents is consistent with the increased overall survival in the TIVA group in our present study. However, sevoflurane inhibited primary leukocyte integrin lymphocyte function and induced lymphocyte apoptosis through allosteric inhibition of LFA-1, thus promoting tumor recurrence and metastasis.[43] Patients with low levels of NK cell activity are predisposed to tumor progression.[44] A recent study has shown that sevoflurane reduced NK cell cytotoxicity through the reduction in CD16 and a failure to increase CD107α NK receptor expression.[45] Thus, sevoflurane could influence perioperative immunosuppression through diverse mechanisms that ultimately promote tumor recurrence and metastasis. Our results also showed that sevoflurane-based INHA reduced the survival of the patients after gastric cancer resection.

Ours is the first clinical study to show an association between INHA and a reduction in overall survival for gastric cancer patients who underwent resection, after multivariate analysis. A number of perioperative interventions have been posited to affect cancer cell proliferation at the time of surgery. In particular, data derived from animal and in vitro models have suggested a role for opioids in the promotion of tumor cell survival and of angiogenesis. Although this has led to the theory that regional anesthesia and the consequent minimization of opioid administration may lead to better cancer outcomes, clinical evidence is not conclusive.[46] Other interventions that have been suggested to have a beneficial impact impeding cancer cell growth in the perioperative period include the avoidance of blood transfusion and the use of cyclooxygenase-2 inhibitors, although again definitive clinical data are lacking.[47,48]

Transfusions might have an effect on patient survival after cancer surgery due to an immunosuppressive effect from such allogeneic material. Several possible mediators may contribute, such as allogeneic mononuclear cells, white-blood-cell-derived soluble mediators, and/or soluble human leukocyte antigen peptides circulating in allogeneic plasma.[49,50] Our study also found an association between perioperative blood transfusion and an increased hazard ratio for mortality, which is consistent with previous research. This may be due to the fact that blood transfusion can induce suppressed immune functions.

Our study has some unavoidable limitations. One potential limitation was that we did not collect certain clinical data, such as specific drugs administered, detailed surgical techniques, and perioperative opioid use, which induced biases. Another limitation was that we did not measure NK cell activity and markers of immunological function, such as cytokines and cortisol, to detect the mechanisms whereby immune systemic functions were reflected. A future prospective study would be useful to validate our conclusions. Definitive evidence of a causal link would have to come from an ongoing prospective trial.

Conclusion

In summary, we found that in a cohort of 2,856 patients, the mean survival times in the propofol and sevoflurane groups were 47.4 months and 43.5 months, respectively, revealing a significant association between TIVA use and improved survival in gastric cancer patients who underwent resection. In addition, cancer stage, degree of differentiation, and blood transfusion were also associated with survival in the univariate analysis and multivariable Cox model.

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Disclosure

The authors report no conflicts of interest in this work.

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