Original Article

Multiple primary tumors in patients with surgically treated pancreatic cancer: a SEER population-based study

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Background: With improving survival after pancreatic cancer (PC) resection, questions emerge concerning risk and patterns of metachronous tumors. We aimed to determine the incidence of multiple primary cancers among postoperative PC survivors.

Methods: Patients undergoing PC surgery from 1975 to 2020 were identified in the Surveillance, Epidemiology, and End Results (SEER) registry. Standardized incidence ratios (SIRs) compared observed-to-expected cancers based on U.S. population rates. Cumulative incidence of secondary tumors was analyzed with Cox regression and cancer-specific survival with Kaplan-Meier curves.

Results: Of 6,100 resected PC patients, 267 (4.38%) developed multiple cancers over 6.2 years median follow-up period. Subsequent malignancies showed a rising cumulative incidence extending beyond 5 years. Lung cancer was the predominant second primary in both males (n=36, SIR 1.87) and females (n=32, SIR 2.17). Prostate (n=33) and breast (n=25) cancers were also common. Risk varied by latency period and gender.

Conclusions: Postoperative PC patients face a measurable risk for secondary cancers. Enhanced long-term surveillance has the potential to improve early detection and outcomes in this survivor population. Our data provides real-world evidence which could help inform surveillance guidelines in the future.

Keywords: Pancreatic cancer (PC); multiple primary malignancies; incidence; onset time; postoperative survivorship

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Introduction

Multiple primary cancers, defined as more than one synchronous or metachronous malignancy in the same individual, but does not include instances of the metastasis of initial primary cancers, are an increasingly important issue in cancer survivorship (1). The North American Association of Central Cancer Registries (NAACCR) stratifies "multiple primary cancers" into distinct categories based on the timing of occurrence. These are delineated as "synchronous", wherein the cancers manifest concurrently or within six months, and "metachronous" referring to cancers that emerge sequentially, with an interval

exceeding six months between each diagnosis. Conversely, the Surveillance, Epidemiology, and End Results (SEER) Program, which was used in our study, adopts a narrower criterion for synchronous multiple primary cancers, categorizing those diagnosed within two months of the initial primary tumor under this classification (2). This distinction underscores the variability in defining temporal thresholds for cancer classification, which has implications for epidemiological surveillance, clinical management, and outcomes research. Depending on the definition used, studies report various ranges of the overall frequency of multiple primaries (3). The risk of developing multiple tumors is rising due to a number of factors including an increasing population of cancer survivors, long-term side effects of chemotherapy and radiation therapy, increased diagnostic sensitivity, and the lingering effects of genetic and behavioral cancer risk factors (1,4,5).

However, the possibility of multiple tumors is sometimes neglected during follow-up of cancer patients, especially those who have undergone potentially curative surgery. Distinguishing whether a new lesion represents recurrent disease, or a secondary primary malignancy poses a significant challenge in this population (6).

Pancreatic ductal adenocarcinoma (PDAC) is one of the most fatal cancer types, with 5-year survival around only 10% for all stages combined (7). Due to the poor prognosis of unresected pancreatic cancer (PC), there is little data available regarding the development of multiple primaries in this patient population. It is estimated that about 15–20% of pancreatic tumors are resectable at diagnosis (8). Patients undergoing surgical resection for early-stage disease exhibit improved survival compared to those with advanced disease (9).

In this study utilizing the SEER registry, we sought to analyze the incidence of metachronous secondary malignant neoplasms in PC patients that who had undergone surgical resection. We hypothesized that a subset of postoperative survivors would face measurable risk for additional primary cancers over long-term follow-up. Characterizing these risks has the potential to guide screening practices and improve early detection of second malignancies in this unique patient population. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-13/rc).

Highlight box

Key findings

- Our research uncovered that roughly 4% of postoperative pancreatic cancer (PC) patients developed multiple primary cancers, predominantly lung, prostate, and breast cancers. We observed a continual rise in the incidence of secondary malignancies beyond 5 years post-surgery, indicating a need for extended surveillance. Notably, gender-specific differences in secondary tumor rates and types were evident.

What is known and what is new?

- Existing knowledge confirms better survival outcomes for early-stage PC patients undergoing surgery.
- Our study extends this by analyzing the incidence and patterns of subsequent cancers in this group, highlighting gender-specific risks and the prevalence of secondary tumors, an area previously underexplored.

What is the implication, and what should change now?

- The study's findings suggest a pivotal shift in clinical practice towards personalized, long-term monitoring for secondary cancers in PC survivors. Given the higher incidence of metachronous tumors found in our cohort compared to other cancer populations, there is a clear need for revised clinical guidelines focusing on targeted, gender-specific surveillance. This includes integrating enhanced screening for secondary malignancies, particularly lung cancer, into survivorship care. Our research underscores the importance of further investigation into effective screening and management strategies for multiple primary tumors to improve early detection and patient outcomes.

Methods

Study population

Data were obtained from the SEER Research Data 8 Registries database, April 2023 release. We identified patients aged 18 years or older who were diagnosed with pancreatic adenocarcinoma [International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) site code C25.0-C25.9 and histology code 8140/3] between 1975 and 2020, and underwent surgical resection. Patients were excluded if data were not available regarding cause of death or duration of follow-up. To isolate the prognostic impact of multiple primary cancers from the mortality risks of PC surgery, we excluded patients who received a second cancer diagnosis within six months of their initial PC diagnosis. This approach ensures a clearer understanding of multiple primary cancers' effects on patient outcomes, by eliminating the confounding factor of surgical mortality. A flow diagram of cohort selection is provided in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as

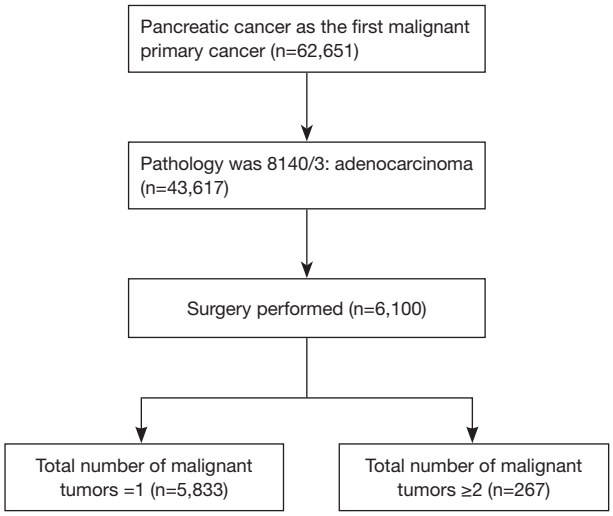

Figure 1 Flow diagram of cohort selection.

revised in 2013).

Variable definition

The SEER variable "First Malignant Primary Indicator" was used to identify patients with pancreatic adenocarcinoma as their first primary malignancy. Development of secondary primary cancers was determined by the variable "Total Number of In Situ/Malignant Tumors for the Patient", with patients having two or more reported malignant primaries classified as having multiple tumors. To specifically evaluate death due to PC versus other or non-cancer causes, cancer-specific survival (CSS) was used as the survival endpoint for prognosis analyses. CSS was defined as the interval between the date of diagnosis of the initial PC primary and the date of death attributable specifically to PC. For patients with multiple primaries, the onset time of secondary malignancies was calculated as the duration between the date of PC diagnosis and the date of diagnosis of the subsequent new primary tumor.

Statistical analysis

Univariate analysis using the Chi-squared (χ^2) test was conducted with R software (version 4.3.0) to evaluate differences in demographic and clinicopathological characteristics between groups. Standardized incidence ratios (SIRs) for secondary primaries were calculated using SEER*Stat (version 8.4.2) to quantify the risk of subsequent cancers following an initial pancreatic adenocarcinoma diagnosis. SIRs were determined by dividing the observed number of second malignancies by the expected number based on age- and gender-specific incidence rates from the US standard population. The SIR provides an estimate of the relative risk (RR) for development of secondary cancers compared to baseline US population rates. The cumulative incidence of subsequent primaries over time was analyzed using Cox regression models. Differences in CSS between groups were depicted with Kaplan-Meier curves, with the log-rank test used to assess statistical significance between survival curves. Median survival times were estimated from the Kaplan-Meier data. All reported P values were two-sided, with P<0.05 considered statistically significant.

Results

Characteristics of patients

The study included 6,100 patients who underwent surgical resection for PDAC, of which 267 (4.38%) developed multiple primary cancers. As shown in *Table 1*, the majority of patients were aged 45–79 years old (89.2%), white race (77.75%), and had tumors located in the pancreatic head (79.85%).

Comparing patients with single versus multiple primaries, those with multiple tumors were more likely to be male (57.68% *vs.* 51.48%, P=0.04). In addition, receipt of radiation therapy (41.95% *vs.* 33.57%, P=0.005) and chemotherapy (65.92% *vs.* 56.93%, P=0.004) were both significantly more common among those diagnosed with secondary malignancies. This is likely reflective of extended survival due to these additional treatments (*Figure 2*). Improved survival with adjuvant treatments may allow increased time for emergence of metachronous second cancers.

There were no statistically significant differences in age distribution, race, or pancreatic tumor site between patients with single and multiple tumors. Further analysis is warranted to elucidate risk factors leading to the development of secondary cancers among postoperative PDAC survivors.

Patterns of subsequent malignancies

The incidence of second primary malignancies was analyzed separately for males and females (*Tables 2,3*). In males, the most frequent sites of subsequent cancers were lung and bronchus (n=36, SIR 1.87, P<0.05), prostate (n=33, SIR 0.76), and

Table 1 Demographic and clinical features of postoperative pancreatic cancer patients

Variable	Total (n=6,100)	Results		χ^2	P
		One primary (n=5,833)	Multiple primary (n=267)		
Sex, n (%)				3.924	0.04
Male	3,157 (51.75)	3,003 (51.48)	154 (57.68)		
Female	2,943 (48.25)	2,830 (48.52)	113 (42.32)		
Age, years, n (%)				3.091	0.37
≤44	218 (3.57)	212 (3.63)	6 (2.25)		
45–64	2,576 (42.23)	2,469 (42.33)	107 (40.07)		
65–79	2,865 (46.97)	2,728 (46.77)	137 (51.31)		
≥80	441 (7.23)	424 (7.27)	17 (6.37)		
Race, n (%)				1.020	0.79
White	4,743 (77.75)	4,531 (77.68)	212 (79.40)		
Black	484 (7.93)	467 (8.01)	17 (6.37)		
Hispanic	420 (6.89)	401 (6.87)	19 (7.12)		
Asian or Pacific Islander	453 (7.43)	434 (7.44)	19 (7.12)		
Site, n (%)				0.250	0.61
Head	4,871 (79.85)	4,661 (79.91)	210 (78.65)		
Body & tail	1,229 (20.15)	1,172 (20.09)	57 (21.35)		
Radiation, n (%)				7.997	0.005
Yes	2,070 (33.93)	1,958 (33.57)	112 (41.95)		
No	4,030 (66.07)	3,875 (66.43)	155 (58.05)		
Chemotherapy, n (%)				8.422	0.004
Yes	3,497 (57.33)	3,321 (56.93)	176 (65.92)		
No	2,603 (42.67)	2,512 (43.07)	91 (34.08)		

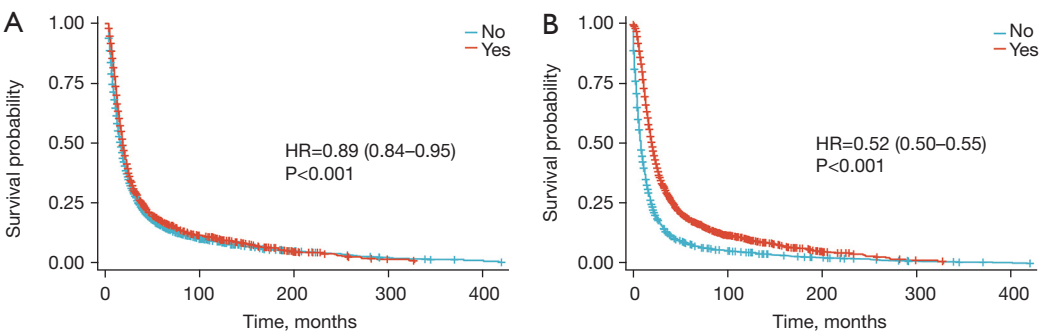

Figure 2 Impact of adjuvant therapy on cancer-specific survival for resected pancreatic cancer. Kaplan-Meier curves show (A) cancer-specific survival based on use of radiation therapy (red, no radiation; blue, radiation) and (B) cancer-specific survival based on chemotherapy administration (red, no chemotherapy; blue, chemotherapy). P values from log-rank tests and hazard ratios with 95% confidence intervals are inset, demonstrating significantly longer survival with use of radiation (P<0.001, HR: 0.89, 95% CI: 0.84–0.95) and chemotherapy (P<0.001, HR: 0.52, 95% CI: 0.50–0.55) after adjusting for clinical factors. HR, hazard ratio; CI, confidence interval.

Table 2 Standardized incidence ratios of top ten subsequent malignancies in male pancreatic cancer survivors

Events	2–11 months		12–59 months		60–119 months		≥120 months		Total	
	O	O/E	O	O/E	O	O/E	O	O/E	O	O/E
Lung and bronchus	6	1.11	19	2.16*	9	2.71*	2	1.17	36	1.87*
Prostate	7	0.54	14	0.69	6	0.87	6	1.86	33	0.76
Colon and rectum	2	0.53	9	1.5	4	1.83	2	1.81	17	1.3
Urinary bladder	2	0.72	5	1.05	3	1.52	0	0	10	0.93
Miscellaneous	0	0	3	1.3	3	3.01	2	3.25	8	1.53
Stomach	1	1.23	4	2.96	2	3.92	0	0	7	2.39
Non-Hodgkin lymphoma	0	0	5	1.76	2	1.8	0	0	7	1.12
Melanoma of the skin	0	0	0	0	2	1.45	4	4.58*	6	0.79
Small intestine	1	5.43	1	3.15	0	0	2	29.87*	4	5.78*
Esophagus	0	0	3	3.05	0	0	0	0	3	1.4

Excess risk is per 10,000; *, P<0.05. O, observed; E, expected.

Table 3 Standardized incidence ratios of top ten subsequent malignancies in female pancreatic cancer survivors

Events	2–11 months		12–59 months		60–119 months		≥120 months		Total	
	O	O/E	O	O/E	O	O/E	O	O/E	O	O/E
Lung and bronchus	5	1.25	12	1.79	13	5.17*	2	1.28	32	2.17*
Breast	6	0.71	8	0.57	8	1.64	3	1.06	25	0.83
Colon and rectum	0	0	2	0.42	4	2.2	1	0.89	7	0.66
Stomach	0	0	3	4.38	0	0	2	11.35*	5	3.24*
Melanoma of the skin	2	2.22	1	0.63	2	3.26	0	0	5	1.43
Corpus uteri	0	0	1	0.33	1	0.95	1	1.7	3	0.46
Ovary	0	0	3	2.24	0	0	0	0	3	1.03
Kidney	1	1.6	1	0.92	0	0	0	0	2	0.85
Thyroid	1	1.81	2	2.13	0	0	0	0	3	1.52
Miscellaneous	1	1	1	0.56	1	1.27	0	0	3	0.73

Excess risk is per 10,000; *, P<0.05. O, observed; E, expected.

colorectal (n=17, SIR 1.30). Other common sites included urinary bladder (n=10, SIR 0.93) and stomach (n=7, SIR 2.39).

In female postoperative PC survivors, the most common secondary primaries were lung and bronchus (n=32, SIR 2.17, P<0.05), breast (n=25, SIR 0.83), and colorectal (n=7, SIR 0.66). Cancers of the stomach (n=5, SIR 3.24, P<0.05) and ovary (n=3, SIR 1.03) were also in the top sites for subsequent tumors.

SIRs compare the observed incidence to expected rates based on the general US population. Elevated SIRs, like those for lung and stomach cancers, indicate an excess occurrence compared to baseline. These results suggest that certain survivors of resected pancreatic tumors are at increased risk for second cancers of the lung, stomach, and other sites over time.

Onset time of subsequent malignancies

The time interval between resection of the primary pancreatic tumor and diagnosis of the most frequent secondary cancers was analyzed. For lung cancer (*Figure 3A*), the median onset time was 40.5 months (95% CI: 30–62 months). Prostate

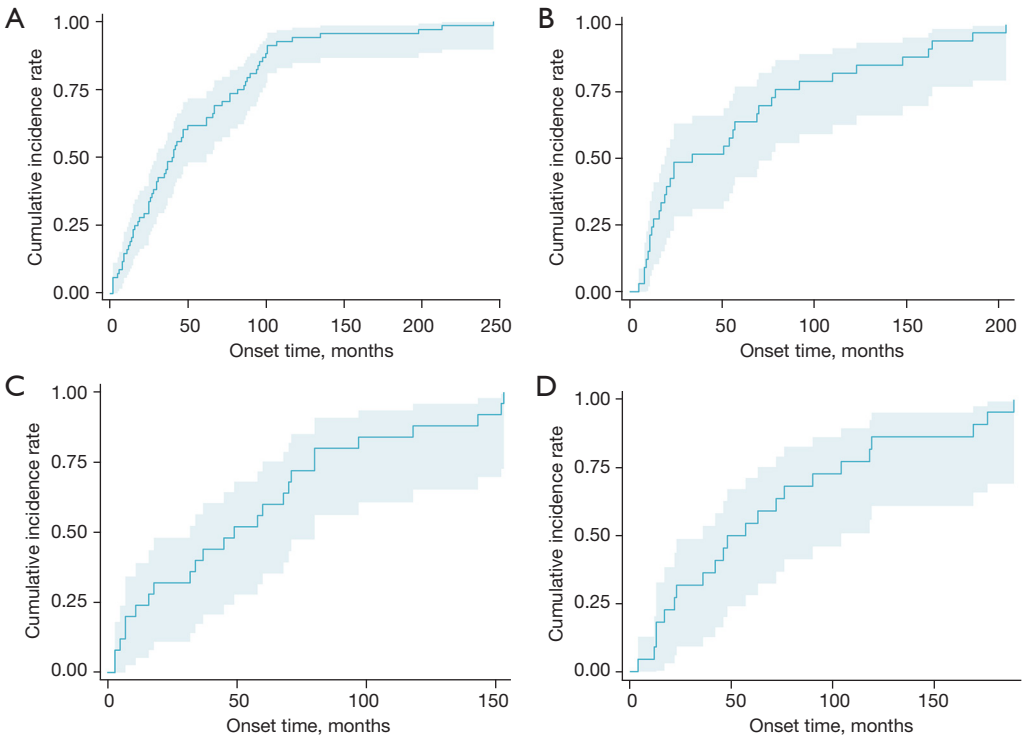

Figure 3 Cumulative incidence of the four most common secondary malignancies over time. Cumulative incidence is shown for (A) lung and bronchus cancer, (B) prostate cancer, (C) breast cancer, and (D) colorectal cancer after surgical resection of pancreatic ductal adenocarcinoma. Dashed lines indicate the 95% confidence intervals around the median onset time in months, derived from Cox regression modeling.

cancer occurred sooner, with a median of 34 months to diagnosis after pancreatic surgery (95% CI: 19–77 months) (*Figure 3B*). Breast cancer had a median onset time of 49 months (95% CI: 32–80 months) (*Figure 3C*). Finally, the median time to diagnosis of a metachronous colorectal cancer was 52.5 months post-pancreatectomy (95% CI: 36–104 months) (*Figure 3D*).

These results demonstrate the continued risk of second tumors even beyond 5 years of follow-up after resection of PDAC. Lung and prostate cancers tend to emerge earlier, while breast and colorectal malignancies arise slightly later during surveillance. This information may help guide screening and improve early detection of the most likely secondary cancer sites.

Discussion

As improved surgical techniques and systemic therapies allow more PC patients to achieve long-term survival (10), our analysis addresses the understudied yet increasingly critical issue of metachronous tumors affecting this population. While second primaries pose a known concern in breast, prostate and select other malignancies, few reports have investigated multiple primary cancers specifically among postoperative PDAC survivors. Population-based estimates for this cohort are lacking, histologic associations are unclear, and implications on prognosis and survivorship remain uncharacterized. By evaluating SEER data spanning four decades, our study begins to fill this knowledge gap—analyzing one of the largest resected PC cohorts to date to delineate metachronous malignancy patterns. Our data establish a baseline understanding of timing, frequency and common sites of second tumors, while highlighting the need for further exploration into prevention, surveillance and impact on outcomes.

In this population-based analysis of over 6,000 surgically resected PDAC cases, we found 4.4% of patients developed multiple primary cancers over a median follow-up of 5 years. The percentage of metachronous tumors appears higher than the 2–17% range reported for some other

cancer survivor populations (3,11). This likely reflects extended survival in our cohort due to early-stage disease amenable to surgery. Improved survival allows time for emergence of second cancers related to genetic factors, late effects of cancer therapy, or screening sensitivity (12).

We identified lung and bronchus as the most common site of secondary primaries in both males and females. Others have reported elevated risks of lung cancer following resected PC as well (13). Shared environmental exposures like tobacco smoke or genetic predispositions may contribute to the association (14,15). Breast and prostate cancers were also among the top subsequent sites, consistent with data across cancer survivors (16-18). Unique strengths of our analysis include evaluating the postoperative population specifically using a robust dataset like SEER, assessing gender-specific differences in second cancer patterns, and providing data on onset times of common metachronous malignancies.

The phenomenon of multiple primary tumors has been the extensively investigated in numerous studies. Notably, Shin *et al.* analyzed over 1,300 surgically resected PC cases, similarly showing an 8.4% incidence of metachronous secondary malignancies associated with modestly improved survival outcomes compared to solitary PC (19). Our results reinforce the conclusions that subsets of postoperative PC survivors, especially those diagnosed at earlier stages, face increased risks for additional secondary tumors which can impact clinical care and outcomes if detected early. In our postoperative PDAC cohort, we observed a 4.4% incidence of multiple primaries, most commonly lung, prostate and breast cancers. This is fairly aligned with the 4–9% range reported in esophageal cancer studies (20,21), suggesting potentially comparable risks of metachronous tumors, at least among surgically resected cases.

Several limitations should be considered when interpreting the data. Details on adjuvant chemotherapy, radiation dosing, family cancer history, and screening tests were not available, which can influence rates of second cancers. The multiple primaries reported here would require pathological confirmation to differentiate new versus recurrent primaries in clinical practice. Lastly, our findings require external validation in additional cohorts like institutional data or cancer registries outside the US.

In conclusion, our results underscore the need for surveillance of postoperative PC patients not just for disease recurrence but also emergence of unrelated second tumors over time. This has significant implications for survivorship care, as early detection of metachronous cancers found at earlier stages can profoundly impact mortality outcomes.

Conclusions

In this large population-based analysis, we found that a notable proportion of postoperative PC survivors develop secondary primary malignancies. The cumulative incidence continued to rise beyond 5 years of follow-up, emphasizing the need for lifelong surveillance in this cohort. Lung cancer was the most prevalent metachronous tumor, followed by prostate and breast cancer. Knowledge of site-specific risks and typical onset times can facilitate earlier detection and improved outcomes from second cancers.

Our study underscores the significant benefits of enhanced surveillance for secondary malignancies in patients who have undergone PDAC resection, an area lacking evidence-based recommendations currently. Taken together, our findings highlight multiple primary tumors as a key issue impacting the survivorship experience in this population. Further research into the efficacy of targeted screening approaches is warranted. Enhanced awareness among patients and providers will help drive advances in prevention and personalized management for survivors of PC surgery.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-13/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-13/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-13/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the

Declaration of Helsinki (as revised in 2013).

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