Patient characteristics associated with definitive diagnosis of metastatic pancreatic cancer in those initially diagnosed with cancer of unknown primary

LARISSA LEE WHITE[1], JULIE SMITH-GAGEN[2], LESLIE ELLIOTT[2] and MINGGEN LU[2]

[1]Kaiser Permanente Colorado, Institute for Health Research, Aurora, CO 80014;
[2]School of Public Health, University of Nevada, Reno, NV 89557, USA

Received July 6, 2023; Accepted October 24, 2023

DOI: 10.3892/mco.2023.2697

Abstract. Cancer of unknown primary (CUP) and pancreatic cancer (PC) are malignancies associated with poor prognosis. CUP is the fourth most common cause of cancer mortality in the US, and median survival time is 3-4 months. PC is the third most common cause of cancer mortality in the US, and median survival time for patients with stage 3 or 4 PC is 2-3 months. The present study aimed to understand the patient characteristics of those initially misdiagnosed with CUP who ultimately received a diagnosis of PC. The present study used 2010-2015 Surveillance, Epidemiology, and End Results-Medicare data, a US population-based cancer registry linked to Medicare health insurance claims. Odds ratios (ORs) and 95% confidence intervals were calculated using two binary logistic regression models to compare the characteristics of patients who received definitive diagnosis between the CUP-PC group (those with an initial diagnosis of CUP who eventually received a stage 3 or 4 PC diagnosis) and the PC group (those diagnosed with stage 3 or 4 PC only). Approximately 26% of patients who received a definitive diagnosis of metastatic PC started with an initial diagnosis of CUP (n=17,565). The odds of definitive PC diagnosis in patients with CUP were lower for those with a comorbidity score of 0 [OR, 0.85 (95% CI: 0.79, 0.91)] and epithelial/unspecified histology [OR, 0.76 (95% CI: 0.71, 0.82)]. The odds of definitive PC diagnosis in patients with CUP were higher for patients of other race [OR, 1.27 (95% CI: 1.13, 1.43)] compared with white patients. Definitive diagnosis of PC in patients with CUP was lower in patients who were older with fewer or no comorbidities and unspecified histology. The complexity of CUP diagnosis and patient performance status may influence delays in diagnosis to a known primary site.

Correspondence to: Dr Larissa Lee White, Kaiser Permanente Colorado, Institute for Health Research, 2550 S. Parker Road, Suite 200, Aurora, CO 80014, USA
E-mail: larissa.l.white@kp.org

Abbreviations: CUP, cancer of unknown primary; PC, pancreatic cancer; SEER, Surveillance, Epidemiology, and End Results; ICD-O-3, International Classification of Diseases for Oncology, Third Edition; OR, odds ratio; CI, confidence interval

Key words: cancer of unknown primary, pancreatic cancer, Medicare, health services, epidemiology

Introduction

Cancer of unknown primary (CUP), also known as occult cancer, accounts for approximately 3-5% of all cancers and is the fourth most common cause of mortality due to cancer in the US (1,2). CUP is defined as a case of metastatic cancer where the origination site cannot be determined (1). Median survival after CUP diagnosis is approximately 3-4 months, with less than 25% of patients alive after one year (1,2). Patients with CUP are categorized into two prognostic subgroups according to their clinicopathologic characteristics. The majority of patients with CUP (80-85%) belong to unfavorable subsets (3). The favorable risk cancer subgroup (15-20%) includes patients with neuroendocrine CUP, peritoneal adenocarcinomatosis of a serous papillary subtype, isolated axillary nodal metastases in females, squamous cell carcinoma involving non-supraclavicular cervical lymph nodes, single metastatic deposit from unknown primary and men with blastic bone metastases and PSA expression (3). Very recently, new favorable subsets of CUP seem to emerge including colorectal, lung and renal CUP which underlies specific treatments (3).

Patients with CUP receive significantly less treatment yet use more health services when compared to patients with metastatic cancer of a known site (4). In the era of targeted therapies, accurate histopathological and molecular classification of tumors is essential to administer the best tailored therapeutic strategy (5). Classifications based on epigenetic alterations have served this purpose. Indeed, cancer cells are characterized by a massive overall loss of DNA methylation (20-60% overall decrease in 5-methylcytosine), and by the simultaneous acquisition of specific patterns of hypermethylation at CpG islands of certain promoters, which can alter gene function, thereby contributing to cancer progression (5).

Relatedly, pancreatic cancer accounts for approximately 3% of all cancers and is the third most common cause of mortality due to cancer in the U.S. (6). The most critical prognostic

factor for pancreatic cancer is stage at diagnosis (7). Median survival time after stage 1 and stage 2 pancreatic cancer diagnosis is 4 months, with stage 3 and stage 4 pancreatic cancer decreasing survival time to 2-3 months (8). Approximately 53% of pancreatic cancer patients are diagnosed after metastasis has occurred (9). Since CUP and metastatic pancreatic cancer are comparable in incidence and survival outcome, there may be similarities in patient characteristics of those initially misdiagnosed with CUP who ultimately receive a diagnosis of pancreatic cancer. Definitive diagnosis is crucial to the prognosis of patients diagnosed with CUP, but studies examining characteristics of this outcome are limited (10,11). Therefore, we sought to build upon our previous research (12) to examine patient characteristics associated with definitive diagnosis of metastatic pancreatic cancer in older patients who initially present with CUP.

Materials and methods

Study population. This retrospective cohort study uses 2010-2015 Surveillance, Epidemiology, and End Results (SEER)-Medicare data, a national population-based cancer registry linked to Medicare claims. The cohort consisted of patients identified in the SEER dataset diagnosed with CUP, International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes C80.9 and those diagnosed with stage 3 and stage 4 pancreatic cancer (ICD-O-3 codes C250-C259), between January 1, 2010 and December 31, 2015. Initial CUP diagnosis was defined by the date of the first biopsy or date of ICD-O-3 diagnosis, whichever came first. Patients had to be continuously enrolled in Medicare fee-for-service (both Part A and B) beginning 1 year prior to diagnosis through the observation period. Only the first reported primary cancer for each patient was included, that is, this was the first time the patients had been diagnosed with any type of cancer. Exclusion criteria were used to maximize patients whose claims data were complete: patients were excluded if enrolled in Medicare due to chronic disability, as well as those diagnosed only on a death certificate, at autopsy, or in a nursing home as their care was likely dissimilar to other patients. Only claims paid by Medicare were included so as to avoid erroneous billing codes. The final cohort consisted of 68,146 patients, of which 17,565 were initially diagnosed with CUP prior to a pancreatic cancer diagnosis.

Patient characteristics. Patient characteristics included sex, age in four groups (65, 66-74, 75-84, 85 and older), race [White, Black, and Other (which included Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, and Multi-racial; per the race variable definition in the SEER data dictionary)], ethnicity (Latino or Non-Latino; per the ethnicity variable definition in the SEER data dictionary), area of residence (rural or urban), and histology of the primary tumor (adenocarcinoma, squamous cell carcinoma, epithelial/unspecified, and neuroendocrine). Comorbidity was assessed utilizing the Klabunde adaptation of the Charlson comorbidity score (13).

Definitive diagnosis. Odd ratios (OR) and 95% confidence intervals (CI) were calculated using two binary logistic regression models to analyze the patient characteristics of who received definitive diagnosis between the CUP-Pancreas group (those with an initial diagnosis of CUP who eventually received a stage 3 or 4 pancreatic cancer diagnosis) and the Pancreas group (those diagnosed with stage 3 or 4 pancreatic cancer only). All analyses were conducted using SAS, version 9.4 (Cary, NC).

Table I. Descriptive characteristics of definitive pancreatic cancer diagnosis in those initially diagnosed with CUP compared to those diagnosed with pancreatic cancer only, SEER-Medicare, 2010-2015.

Characteristic	CUP-pancreas (n=17,565) (%)	Pancreas (n=50,581) (%)
Sex		
Female	9,387 (53.4)	25,897 (51.2)
Male	8,178 (46.6)	24,684 (48.8)
Age at diagnosis, years		
65	2,025 (11.5)	12,038 (23.8)
66-74	6,031 (34.3)	16,237 (32.1)
75-84	6,553 (37.3)	15,123 (29.9)
85+	2,956 (16.9)	7,183 (14.2)
Race		
White	14,329 (81.6)	41,122 (81.3)
Black	2,123 (12.1)	5,564 (11.0)
Other	1,113 (6.3)	3,895 (7.7)
Ethnicity		
Non-Latino	16,212 (92.3)	46,180 (91.3)
Latino	1,353 (7.7)	4,401 (8.7)
Urban		
Yes	10,379 (59.1)	30,602 (60.5)
No	7,186 (40.9)	19,979 (39.5)
Charlson comorbidity score		
0	5,337 (30.4)	21,649 (42.8)
1	4,748 (27.0)	12,797 (25.3)
2+	7,480 (42.6)	16,135 (31.9)
Histology		
Adenocarcinoma	10,661 (60.7)	29,843 (59.0)
Epithelial unspecified	3,627 (20.6)	11,077 (21.9)
Neuroendocrine	3,070 (17.5)	9,105 (18.0)
Squamous cell carcinoma	207 (1.2)	556 (1.1)

CUP, cancer of unknown primary; SEER, Surveillance, Epidemiology, and End Results.

Results

Patient characteristics. There were 68,146 patients who received a definitive diagnosis of stage 3/4 pancreatic cancer between 2010-2015. Approximately 74% were diagnosed with pancreatic

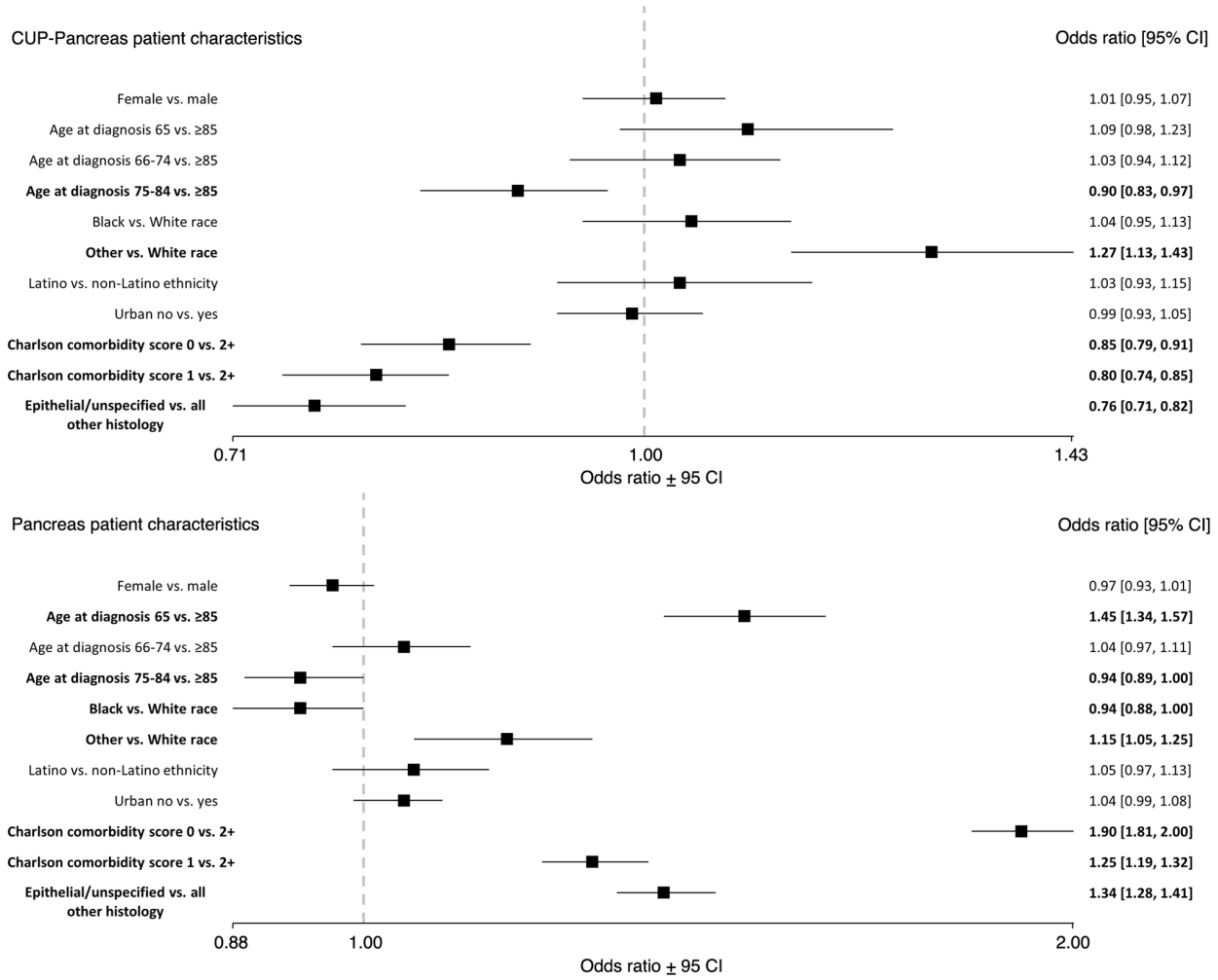

Figure 1. ORs of definitive pancreatic cancer diagnosis in those initially diagnosed with CUP (n=17,565) compared to those diagnosed with pancreatic cancer only (n=50,581) by patient characteristics, SEER-Medicare, 2010-2015. Bold indicates statistical significance (P<0.05). CUP, cancer of unknown primary; CI, confidence interval; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results.

cancer only (n=50,581) and 26% started with an initial diagnosis of CUP (n=17,565). The CUP-Pancreas group were 53.4% female, 37.3% were between the ages of 75-84, 81.6% were White, 92.3% were non-Latino, 59.1% lived in an urban area, 42.6% had a Charlson comorbidity score of 2 or higher, and 60.7% were histologically confirmed as adenocarcinoma (Table I). Of the cases diagnosed with pancreatic cancer only, characteristics were generally similar to those initially diagnosed with CUP, however, 29.9% were between the ages of 75-84 and 31.9% had a Charlson comorbidity score of 2 or higher.

Definitive diagnosis of CUP-Pancreas group. CUP patients between the ages of 75-84 had lower odds of definitive pancreatic cancer diagnosis [OR, 0.90 (0.83, 0.97)] compared to patients 85 years or older (Fig. 1). CUP patients had lower odds of definitive pancreatic cancer diagnosis for those with a Charlson comorbidity score of 0 [OR, 0.85 (0.79, 0.91)] or 1 [OR, 0.80 (0.74, 0.85)] compared to a score of 2 or higher; and lower odds of definitive pancreatic cancer diagnosis for epithelial/unspecified histology compared to all other histology types [OR, 0.76 (0.71, 0.82)]. CUP patients who identified as a race other than Black or White had higher odds of definitive pancreatic cancer diagnosis [OR, 1.27 (1.13, 1.43)] compared to White patients.

Definitive diagnosis of pancreas only group. Pancreatic only patients between the ages of 75-84 had lower odds of definitive diagnosis [OR, 0.94 (0.89, 1.00)] compared to patients 85 years or older (Fig. 1). Pancreatic only patients who identified as Black had lower odds of definitive diagnosis [OR, 0.94 (0.88, 1.00)] compared to White patients. Pancreatic only patients of 65 years had higher odds of definitive diagnosis [OR, 1.45 (1.34, 1.57)] compared to patients 85 years or older. Pancreatic only patients who identified as a race other than Black or White had higher odds of definitive diagnosis [OR, 1.15 (1.05, 1.25)] compared to White patients; higher odds of definitive diagnosis for those with a Charlson comorbidity score of 0 [OR, 1.90 (1.81, 2.00)] or 1 [OR, 1.25 (1.19, 1.32)] compared to a score of 2 or higher; and higher odds for definitive diagnosis for epithelial/unspecified histology compared to all other histology types [OR, 1.34 (1.28, 1.41)].

Discussion

To our knowledge, this is the first population-based study focusing on metastatic pancreatic cancer in patients initially diagnosed with CUP. CUP patients had higher odds of receiving a definitive pancreatic cancer diagnosis if they

identified as a race other than Black or White. CUP patients had lower odds of receiving a definitive pancreatic cancer diagnosis if they were older, had fewer or no comorbidities, and histology confirmed as epithelial/unspecified. Patients with comorbidities may receive health services more often than patients without comorbidities, thus are more likely to come in contact with the health care system (14). However, older patients with comorbidities may be unable to complete the diagnostic workup necessary to make a definitive diagnosis (15). Characteristics associated with delay of definitive diagnosis in CUP to a specified primary site including older age, epithelial/unspecified histology, and higher comorbid burden of disease correspond with current scientific literature on CUP patterns of care, namely population-based studies focusing on patient characteristics and healthcare utilization (4,16,17), adherence and diagnostic guidelines (10), and risk factors and clinical management (18,19).

In patients diagnosed with stage 3 or stage 4 pancreatic cancer only, definitive diagnosis was similar to CUP patients by race, however, this subpopulation was younger and had fewer comorbidities overall. Furthermore, the comorbidity score and whether histology was epithelial/unspecified were not barriers to definitive diagnosis for the pancreatic cancer only group, suggesting there are imbalances in delivery of care compared to patients initially diagnosed with CUP. This is likely due to (a) the complexity of identifying the primary tumor site in CUP, whereas in identification of pancreatic cancer, the clinician at least has a point from which to begin a well-informed diagnostic process; and (b) poor performance status of the patient with CUP, a potential confounder this study could not account for.

These findings further elucidate the health disparities evident in CUP and pancreatic cancer diagnoses. Scientific literature on cancer health disparities reports higher incidence of metastatic pancreatic cancer among Black and Latino patients, as well as lower occurrence of treatment (primarily surgical intervention), poor access to quality health care, and higher rates of overall morbidity and mortality (20-22). An area of future research should focus on the patterns of care associated with race, ethnicity, and social determinants of health (to include socioeconomic status) in patients diagnosed with CUP and pancreatic cancer, especially those in younger age groups given increased incidence of pancreatic cancer in this population.

While SEER-Medicare data provided a robust sample size, there are limitations in this study. Our study population was limited to patients 65 years and older and did not include patients with private insurance coverage. However, the age range of an average patient with CUP is 80 years or older and the vast majority of patients 65 years and older are insured through Medicare (23). This study only investigated patients with a final metastatic pancreatic cancer diagnosis. It is also important to note clinicians may need to report a definitive diagnosis to justify treatment for insurance claims. Claims data for administrative and billing purposes might be inaccurate from a biological or clinical disease perspective.

There are significant deficiencies in the research of other CUP-primary site cancers, for example ovarian and lung cancers, as well as available studies comparing site-specific therapy and empiric chemotherapy (24). These deficiencies include limitations in recruitment methodology, study design, heterogeneity among the CUP classifiers (e.g., epigenetic vs. transcriptomic profiling), and incomparable therapies (24). An assessment of recently published CUP literature recommends two comprehensive clinical trial designs to address these limitations (24). Both designs are amenable to implementing the latest diagnostics and therapeutic advances to improve the quality of CUP research and the prognosis of many patients (24).

This brief report discusses patient characteristics associated with the definitive diagnosis of metastatic pancreatic cancer in patients who initially presented with CUP based on a large and representative population-based cohort. This profile elucidates that about a quarter of patients who initially present with CUP receive a definitive pancreatic cancer diagnosis and are typically older with a higher burden of comorbidities. These characteristics may contribute to delays in definitive diagnosis, thereby negatively affecting survival and quality of life. Future studies should focus on patterns of care and survival outcomes in patients who initially present with CUP with other primary site cancers.

Acknowledgements

Not applicable.

Funding

This work was supported by the National Institutes of Health (grant no. P30 CA042014-30).

Availability of data and materials

The data that support the findings of this study are available from the National Cancer Institute but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the National Cancer Institute.

Authors' contributions

LLW was involved in study conceptualization, study design, data management, data programming, formal analysis, manuscript writing, manuscript review and editing, and funding acquisition. JSG was involved in study conceptualization, data management, data programming, manuscript review and editing, and funding acquisition. LE was involved in study design, and manuscript review and editing. ML was involved in formal analysis, and manuscript review and editing. LLW and JSG confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval was waived by the Institutional Review Board at University of Nevada, Reno in view of the retrospective nature of the study, citing SEER-Medicare data are exempt [CFR 46.104(4)].

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. National Cancer Institute (NCI). Cancer of unknown primary-health professional version. National Cancer Institute, 2017. https://www.cancer.gov/types/unknown-primary/hp.
2. Pavlidis N and Pentheroudakis G: Cancer of unknown primary site. Lancet 379: 1428-1435, 2012.
3. Rassy E, Parent P, Lefort F, Boussios S, Baciarello G and Pavlidis N: New rising entities in cancer of unknown primary: Is there a real therapeutic benefit? Crit Rev Oncol Hematol 147: 102882, 2020.
4. Schaffer AL, Pearson SA, Dobbins TA, Er CC, Ward RL and Vajdic CM: Patterns of care and survival after a cancer of unknown primary (CUP) diagnosis: A population-based nested cohort study in Australian government department of Veterans' Affairs clients. Cancer Epidemiol 39: 578-584, 2015.
5. Moran S, Martinez-Cardús A, Boussios S and Esteller M: Precision medicine based on epigenomics: The paradigm of carcinoma of unknown primary. Nat Rev Clin Oncol 14: 682-694, 2017.
6. American Cancer Society (ACS). Key statistics for pancreatic cancer. American Cancer Society, 2020. https://www.cancer.org/cancer/pancreatic-cancer/about/key-statistics.html#references.
7. Henrikson NB, Aiello Bowles EJ, Blasi PR, Morrison CC, Nguyen M, Pillarisetty VG and Lin JS: Screening for pancreatic cancer: Updated evidence report and systematic review for the US preventive services task force. JAMA 322: 445-454, 2019.
8. Khalaf N, El-Serag HB, Abrams HR and Thrift AP: Burden of pancreatic cancer: From epidemiology to practice. Clin Gastroenterol Hepatol 19: 876-884, 2021.
9. Zhang Q, Zeng L, Chen Y, Lian G, Qian C, Chen S, Li J and Huang K: Pancreatic cancer epidemiology, detection, and management. Gastroenterol Res Pract 2016: 8962321, 2016.
10. Sève P, Mackey J, Sawyer M, Lesimple T, de La Fouchardière C, Broussolle C, Dumontet C and Ray-Coquard I: Impact of clinical practice guidelines on the management for carcinomas of unknown primary site: A controlled 'before-after' study. Bull Cancer 96: E7-E17, 2009.
11. Pentheroudakis G, Stahel R, Hansen H and Pavlidis N: Heterogeneity in cancer guidelines: Should we eradicate or tolerate? Ann Oncol 19: 2067-2078, 2008.
12. Smith-Gagen J, Drake CM, White LL and Pinheiro PS: Extent of diagnostic inquiry among a population-based cohort of patients with cancer of unknown primary. Cancer Rep Rev 3, 2019.
13. Klabunde CN, Warren JL and Legler JM: Assessing comorbidity using claims data: An overview. Med Care 40 (8 Suppl): IV26-IV35, 2002.
14. Department of Health Pharmaceutical Oncology Initiative (DHPOI). The impact of patient age on clinical decision-making in oncology. London, UK: Department of Health, 2012.
15. Massarweh NN, Park JO, Bruix J, Yeung RS, Etzioni RB, Symons RG, Baldwin LM and Flum DR: Diagnostic imaging and biopsy use among elderly medicare beneficiaries with hepatocellular carcinoma. J Oncol Pract 7: 155-160, 2011.
16. Schaffer AL, Pearson SA, Perez-Concha O, Dobbins T, Ward RL, van Leeuwen MT, Rhee JJ, Laaksonen MA, Craigen G and Vajdic CM: Diagnostic and health service pathways to diagnosis of cancer-registry notified cancer of unknown primary site (CUP). PLoS One 15: e0230373, 2020.
17. Jones W, Allardice G, Scott I, Oien K, Brewster D and Morrison DS: Cancers of unknown primary diagnosed during hospitalization: A population-based study. BMC Cancer 17: 85, 2017.
18. Rassy E and Pavlidis N: The currently declining incidence of cancer of unknown primary. Cancer Epidemiol 61: 139-141, 2019.
19. Pavlidis N, Rassy E and Smith-Gagen J: Cancer of unknown primary: Incidence rates, risk factors and survival among adolescents and young adults. Int J Cancer 146: 1490-1498, 2020.
20. Noel M and Fiscella K: Disparities in pancreatic cancer treatment and outcomes. Health Equity 3: 532-540, 2019.
21. Tavakkoli A, Singal AG, Waljee AK, Elmunzer BJ, Pruitt SL, McKey T, Rubenstein JH, Scheiman JM and Murphy CC: Racial disparities and trends in pancreatic cancer incidence and mortality in the United States. Clin Gastroenterol Hepatol 18: 171-178.e10, 2020.
22. Zhou H, Zhang Y, Wei X, Yang K, Tan W, Qiu Z, Li S, Chen Q, Song Y and Gao S: Racial disparities in pancreatic neuroendocrine tumors survival: A SEER study. Cancer Med 6: 2745-2756, 2017.
23. Federal Interagency Forum (FIF) on Aging-Related Statistics. Older Americans: Key indicators of well-being. U.S. Government Printing Office, 2015.
24. Rassy E, Labaki C, Chebel R, Boussios S, Smith-Gagen J, Greco FA and Pavlidis N: Systematic review of the CUP trials characteristics and perspectives for next-generation studies. Cancer Treat Rev 107: 102407, 2022.