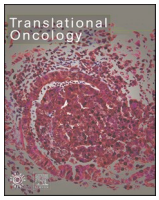
Translational Oncology 52 (2025) 102239

Contents lists available at ScienceDirect

Translational Oncology

journal homepage: www.elsevier.com/locate/tranon



Early onset pancreatic cancer: A review

Dong Luo [a,b,c], Yixiong Li [a,b], Xiao Yu [d], Liandong Ji [a,b,*], Xuejun Gong [a,b,*]

[a] Department of Pancreatic Surgery, Xiangya Hospital, Central South University, Changsha, Hunan Province, 410008, China
[b] National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, Hunan Province, 410008, China
[c] Department of General, Visceral and Transplant Surgery, European Pancreas Centre, Heidelberg. University Hospital, Heidelberg, Germany
[d] Department of Hepatopancreatobiliary Surgery II, Third Xiangya Hospital, Central South University, Changsha, 410013, China

ARTICLE INFO

Key words:
Early-onset pancreatic cancer
Clinical characteristics
Molecular characteristics
Survival outcomes

ABSTRACT

Early-onset pancreatic cancer (EOPC) is usually defined as patients with pancreatic cancer before the age of 50 years, which is relatively rare. However, the research on EOPC is somewhat obscure, and the specific clinical and molecular characteristics of this condition are debated. In this review, we discussed the differences between EOPC and late-onset pancreatic cancer (LOPC) or average-onset pancreatic cancer (AOPC) with a focus on clinical and molecular characteristics, survival outcomes and treatment to promote the diagnosis and treatment of EOPC.

Introduction

The incidence of cancer has been continually increasing in young adults in recent years. Early-onset cancer (EOC) is usually defined as patients with cancer before the age of 50 years [1]. The practical importance of EOC goes far beyond the simple age differences. Compared to their respective counterparts, EOCs have unique clinical manifestation and molecular characteristics. On one hand, EOCs generally show more malignant and aggressive biological behaviors in general, leading to a worse prognosis [2,3]. Furthermore, young patients with EOCs are more likely to develop specific germline mutations and adverse genetic abnormalities [4]. On the other hand, due to their better physical condition, young patients are more likely to have access to full-course or more aggressive therapies and tolerate side effects and complications at the same time [5].

A recent study reported that the incidence rates of early-onset cancer increased from 2010 to 2019, with gastrointestinal cancers showing the fastest growth, reflected in an annual percentage change (APC) of 2.16 % [6]. For instance, the burden of upper gastrointestinal (UGI) cancers among young individuals has risen significantly in the Eastern Mediterranean region. This finding highlights the necessity for further investigation into specific risk factors and their roles in the carcinogenesis of early-onset UGI cancers. Moreover, it emphasizes the importance of understanding differences between early-onset and late-onset UGI cancers [7]. Pancreatic cancer, one of the most aggressive malignancies, had an estimated 66,440 new cases and 51,750 deaths in 2024, making it the tumor with the lowest five-year survival rate [8]. Between 2000 and 2021, the age-standardized incidence rate (ASIR) of pancreatic cancer increased (APC: 0.27 %, 95 % CI 0.14 %–0.41 %), as did the age-standardized death rate (ASDR) (APC: 0.18 %, 95 % CI 0.02 %–0.34 %)[9].

Studies suggested that early onset pancreatic cancer (EOPC) may represent a unique subgroup due to its special clinical features and distinctive molecular characteristics [10,11]. However, current data on the comparison of the clinical and molecular characteristics of EOPC and late onset pancreatic cancer (LOPC) or average onset pancreatic cancer (AOPC) appear to be contradictory. Beeghly-Fadielet's study showed that EOPC patients have a significant advantage in survival time and are considered a distinct subgroup in pancreatic cancer [12]. On the contrary, studies have shown that the mutational landscape of the main driver genes and the level of changes in the overall methylation profiles between the EOPC and LOPC/AOPC groups are comparable, suggesting that EOPC and LOPC/AOPC have similar molecular signature profiles [13,14]. The above analysis showed that the clinical and molecular characteristics of EOPC have not been very well studied and determined. This raised two very important scientific questions: (1) What are the really significant clinical and molecular features of EOPC compared to control patients (LOPC/AOPC)? (2) Is there really an age-related

* Corresponding authors at: Department of Pancreatic Surgery/ National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, Hunan Province, 410008, China.
E-mail addresses: ja19841013@csu.edu.cn (L. Ji), peigong158@csu.edu.cn (X. Gong).

https://doi.org/10.1016/j.tranon.2024.102239
Received 18 July 2024; Received in revised form 17 November 2024; Accepted 7 December 2024
1936-5233/© 2024 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

prognostic difference between EOPC and LOPC/AOPC patients? Therefore, it is of great significance to elucidate the clinical and molecular characteristics of EOPC, then to gain a deeper understanding and explore a better therapeutic approach for EOPC.

In this review, we performed an analysis to assess the clinical and molecular characteristics of EOPC, which was based on databases from PubMed,Web of Science,Embase and Cochrane between January 2007 and January 2023. Articles (all cohort studies) focused on EOPC were included according to inclusion (①research focused on EOPC (including studies that reported EOPC or EOPC vs. AOPC); ②original data were available; ③ studies in the English literature) and exclusion criteria (①Research on EOPC combined with other types of tumor. ②Reviews, conference abstracts, meta-analyses, case reports, commentaries and editorials were excluded. ③Full-text articles are unavailable). By revealing the clinical,molecular and survival similarities and differences between EOPC and the control group, we aim to expect that the information contained in this article would lead to better understanding, prevention and treatment of EOPC, and ultimately reduce the overall burden of pancreatic cancer.

Overview

Pancreatic cancer is one of the most lethal types of cancers [15], and its incidence and mortality are increasing. The incidence of pancreatic cancer has increased by 1.0 % per year [8,16], and the rate of death has increased by 0.2 % per year since 2000 [16]. Pancreatic cancer is the third leading cause of death in 2024 [8], and is projected to be the second most common cause of cancer-related death by 2040 [17] in the US. Furthermore, approximately 50 % of pancreatic cancer are in an advanced stage at diagnosis [18] and have a 5-year relative survival rate of 13 % [8,16], the lowest rate among cancers.

Cancer typically develops in older people older than 55 years [19]. Pancreatic cancer affects mainly the elderly and is predominantly diagnosed after the age of 70 years [20], and the median age at diagnosis is 71 years [18]. 11.4 % of patients diagnosed with pancreatic cancer are under 55 years of age [21]. Raimondi et al. first introduced the concept of early-onset pancreatic cancer (EOPC, pancreatic cancer patients diagnosed before 50 years) in 2007[22]. The understanding and knowledge of EOPC have been deepened with the increasing attention to EOPC research since then. According to the Surveillance, Epidemiology, and End Results (SEER) data [23–25] and the North American Association of Central Cancer Registries (NAACCR) data [26], several studies have reported that the incidence of EOPC has increased in recent decades.

Age cut-off point

Although EOPC research has increased in recent years, there is no consistent age cut-off point to define EOPC. Different studies used different age cut-off points. The suggested age cuto-ffs were 40 years [24], 45years [27], 50 years [28], 55years [29], and 60 years [30]. Most studies defined EOPC populations as people younger than 50 years of age at the time of diagnosis of pancreatic cancer. In addition, some studies defined patients younger than 45 years as very early-onset pancreatic cancer (VEOPC)[31,32]. However, Tsang et al. explain the age cut-off point for patients with EOPC from a molecular perspective [29]. They explored the frequency of CDKN2A SNVs/indels among the age of pancreatic cancer onset. Their work did not find CDKN2A SNV/indels in patients with advanced pancreatic cancer younger than 53 years or patients with resectable pancreatic cancer younger than 42 years. Interestingly, CDKN2A SNV/indel rates began to move toward the plateau at the 55-year threshold in both groups, supporting 55-year as the age cutoff of EOPC. This is the first study to elaborate on the relationship between the EOPC threshold and the molecular landscape, providing convincing molecular evidence for the age cut-off point of the EOPC. In conclusion, there is no standard definition of EOPC, which may explain the differences between EOPC and control patients.

Similarly, there is no uniform definition for the agreement on which age constitutes control patients. Patients in the control group were divided into two different types. Most studies defined control patients as later-onset pancreatic cancer (LOPC). These patients are diagnosed with ages older than the corresponding age cut-off point, such as 40y [24], 45y [33], 50y [12], and 60y [30]. While the rest of the studies defined the control group as average onset pancreatic cancer (AOPC, pancreatic cancer patients older than average onset age 70 years)[14,29,34,35]. Therefore, control patients can be defined as LOPC or AOPC. This may also be one of the reasons for the different characteristics of EOPC compared to the control patients.

Incidence

The relative frequency of EOPC varies in different studies, from 4.4 % to 17 % [26,36–39]. Although heterogeneous, EOPC only accounts for a small fraction of all pancreatic cancer cases. EOPC has been poorly studied, and one of the reasons may be the low frequency of EOPC in the population of pancreatic cancer.

Characteristics specific to EOPC

Data on the clinical and molecular characteristics of EOPC compared to patients in the older group are conflicting. Beeghly-Fadiel's work indicated that EOPC is distinct from typical age-onset pancreatic cancer (LOPC) and is hypothesized to be a distinct subset of PC [12]. On the contrary, Raffenne's study suggested that EOPC has a molecular profile similar to that of AOPC [14]. LOPC/AOPC exhibited age-related characteristics, including an increase in DNA repair gene signatures, an up-regulation of oxidative stress defenses, and an increase in proteome carbonylation. However, these alterations were more predominant in non-tumor tissues. Both the mutational landscape of the essential driver genes and the global methylation profile were comparable between the two groups, showing that EOPC and LOPC/AOPC have a similar molecular profile. This raises two important questions: (1) What are the clinical and molecular characteristics specific to EOPC compared to control group patients? (2) Are there age-related differences in prognosis between patients with EOPC and LOPC / AOPC?

a) Clinical characteristics

Compared to AOPC/LOPC patients, EOPC patients appeared to receive more treatment (including surgery, radiation, and chemotherapy) [25,26,37–41], have a more advanced stage [37,38,40–43], and are more male [22,25,26,37,38,44], smokers [22,32,43–45] and alcohol users [31,32]. EOPC was located more frequently in the head of the pancreas [24,31], associated with a lower Charlson / Deyo comorbidity score [37] or Charlson age-comorbidity index(CACI)[35]. Additionally, EOPC had more private health insurance [26,37], PanIN [46], a family history of pancreatic neoplasia [31], and pain symptoms [31].

Patients with EOPC receive more therapies than patients with AOPC or LOPC [25,26,37–41]. Several potential causes may explain this phenomenon. First, younger patients are more likely to seek and receive therapy than older patients [26]. Second, different health insurance coverages can affect access to therapy in the United States. EOPC patients seem to have more private insurance than older patients [26], giving them more access to high-level cancer care. Third, younger patients have better health status, fewer comorbidities [37], and fewer complications after curative resections [35]. They may be better candidates for higher intensity chemotherapy, radiation therapy, and surgery, which may be contraindicated in older and frailer patients. Last but not least, clinicians may consider a more aggressive treatment for EOPC patients because the potential number of life years lost is greater in this population.

EOPC patients were more likely to be male than control patients

(LOPC/AOPC) [22,25,26,37,38,44]. One possible explanation for the higher incidence of EOPC in males could be smoking, a well-established risk factor for EOPC [22]. Males generally smoke more than females, and individuals who are more susceptible to pancreatic damage from tobacco-derived carcinogens may develop pancreatic cancer at an earlier age [22,26,38].

Studies confirmed that EOPC patients presented a more advanced stage than older patients [37,38,40–43]. The underlying reason is not yet clear. Some explanations were that there was a delay in seeking medical attention from younger patients or diagnosis by physicians due to insufficient suspicion of pancreatic malignancy in this younger patient population [37].

EOPC patients were more likely to be smokers or early smokers [22, 32,43–45] and alcohol users [31,32]. Studies found that smokers developed pancreatic cancer one decade [47] or two decades [48] earlier than non-smokers. Smoking is a strong risk factor for pancreatic cancer, particularly among males and those under 50 years of age [47]. According to one study, EOPC patients were more frequently current smokers (56 % vs. 28 %, $p = 0.001$) and started smoking at a significantly lower mean age (19.8 years, 95 %CI, 16.7–22.9) as compared to older patients (26.1, 95 %CI, 24.2–28, $p = 0.001$) [43]. Furthermore, alcohol use of more than 26 g daily was also associated with an increased risk for EOPC (OR 1.49, 95 % CI 1.21–1.84). Alcohol intake appeared to have an age-dependent effect and the strongest association was with very early onset pancreatic cancer (VEOPC) [32]. This trend may be explained by the significant increase in the prevalence, incidence, and mortality of alcohol-associated liver disease (ALD) among adolescents and young adults [49]. This rise could be attributed to the growing influence of the alcohol industry and the adoption of Western norms regarding alcohol consumption in these populations. In summary, alcohol consumption and tobacco use are correlated with a dose-dependent risk increase of EOPC [50] and have a combined effect on age at diagnosis [51].

EOPC seems to be located more frequently in the head of the pancreas [24,31]. Analysis of tumor anatomy showed a growing incidence of EOPC in the head of the pancreas (3.63 % annual change), while late-onset pancreatic cancer showed a growing incidence in the body and tail of the pancreas (8.62 % annual change) [24]. Regardless of age, the analysis indicated that compared to the head of the pancreas, the tail of the pancreas is associated with 20 % higher mortality [24], which may be explained by the fact that the masses of the pancreatic tail do not obstruct the common bile duct and lead to obstructive jaundice and pancreatic tail lesions often present with metastases. However, recent work noted unique gene expressions in the head compared to body and tail of the pancreas, suggesting that the head and body/tail pancreatic cancer are not the same tumor [52]. A meta-analysis indicated that the long-term prognosis of head cancer was better than body/tail cancers (HR =0.96, 95 % CI: 0.92–0.99; $p = 0.02$), and the location of the primary tumor in the pancreatic head at the time of diagnosis is a predictor of better survival [53]. In summary, anatomy or primary tumor location may be associated with survival outcomes in early pancreatic cancer.

Young patients had lower Charlson age comorbidity index (CACI) scores [37] or scores and fewer complications after curative resections [35]. CACI is a measure of comorbidity to standardize the evaluation of patients who underwent surgery and is a useful prognostic index after pancreatectomy for pancreatic cancer [54]. In summary, the younger group may have an overall better health state and a relatively lower rate of comorbidities.

EOPC patients tended to be more frequently privately insured [26, 37], which increased access to high-quality care in some countries with developed health insurance systems. Furthermore, EOPC had more pancreatic intraepithelial neoplasia (PanIN) [46], endocrine cancer [39], a family history of pancreatic neoplasia, and pain symptoms [31], which were correlated with an elevated risk of EOPC.

Deaths from cancers attributable to high body mass index (BMI) have increased by 35 %, and disability-adjusted life-years have risen by 34 % [55]. Overweight or obesity in early adulthood was associated with a higher risk of pancreatic cancer and a younger age of onset. Obesity (BMI $>$ 30) in younger adults (20–49 years) was linked to an earlier onset of pancreatic cancer by 2–6 years [56]. However, cohort studies did not identify significant differences in obesity-related risk factors between EOPC and older patients (LOPC/AOPC) of pancreatic cancer [38,41,43,44].

The above discussion showed that EOPC has distinctive clinical characteristics, such as more treatment, advanced stage, male sex, smoking, alcohol intake, location in the head of the pancreas, and better functional status, which are relatively consistent in different studies. More research is required to validate the characteristics of PanIN, family history of pancreatic neoplasia and pain symptoms, and private insurance. These characteristic analyses suggest that EOPC are a subset of pancreatic cancer with distinct clinical characteristics.

Treatment in EOPC

Higher utilization of treatment is associated with better oncologic outcomes for patients with pancreatic cancer [57]. The differences of utilization and patterns of treatment refusal between EOPC and AOPC patients are notable because they seem to affect oncological outcomes [26]. EOPC patients received more treatment, including surgery, radiation, and chemotherapy than their older counterparts [25,26,37–41].

Specifically, all treatment methods, including surgery alone, chemotherapy alone, chemoradiation alone, and surgery plus chemoradiation, were more prevalent among patients with EOPC [26]. EOPC was related with approximately 3- to 4-fold higher odds of obtaining therapy compared to AOPC. EOPC was independently linked with receiving multimodal chemotherapeutic and multimodal surgical treatment. The rates of surgery alone and chemotherapy alone have grown for both EOPC and AOPC patients, although the rates of radiation treatment have fallen dramatically, which is consistent with best-practice guidelines. In particular, the rates of non-surgical multimodal therapy have declined, while surgical multimodal therapy has grown; this predicts that patients with pancreatic cancer will be subjected to more aggressive surgical interventions over time [26]. Notably, however, a large number of patients did not receive no treatment in both cohorts (19 % and 39 % for EOPC and AOPC, respectively)[26], suggesting significant room for improvement in access to utilization of best practice care for across all age onset pancreatic cancer patients. In conclusion, patients with EOPC appear to receive more standard of care and multimodal treatment, while patients with AOPC are more likely to be undertreated for pancreatic cancer [26].

Molecular characteristics

Several studies showed that EOPC seems to have distinct molecular characteristics compared to LOPC/AOPC. The EOPC tumors presented a distinctive pattern of biallelic CDKN2A mutation and increased FOXC2 based on genomic and transcriptomic analysis [29], enriched wild-type RAS [28], higher mutation rates of SMAD4, increased activation of the transforming growth factor-β (TGF-β) pathway, higher expression of phospho-GSK3[34], higher prevalence of germline mutations (genes commonly mutated in pancreatic cancer, mainly BRCA1, BRCA2, CDKN2A, TP53, etc.)[30]. However, one work confirmed that the EOPC has a comparable molecular profile compared to LOPC by multi-omics comparison analysis [14].

EOPC showed a significantly lower frequency of somatic single nucleotide variant (SNV)/insertions/deletions (indel) in CDKN2A and were more likely to achieve a biallelic mutation of CDKN2A through homozygous copy loss [29] compared to intermediate/AOPC. Pathogenic variants (PVs) in the CDKN2A gene increase the risk of pancreatic cancer (~5–24 % lifetime risk), and individuals also tend to have an earlier onset of cancer [58]. The p16ink4a protein, encoded by CDKN2A, inhibits the phosphorylation of RB1(RB-pathway) and restrains exit from the G1-phase (control over G /S progression through) of the cell

cycle [59], acting as a CDK4/6 inhibitor. Ninety percent of pancreatic cancer cases harbor RAS alterations [60,61], and the absence of the p16ink4a protein seems to accelerate the progression of KRAS-mutant pancreatic cancer cells, suggesting a targetable site of action [62,63]. Tsang's work also found that FOXC2 significantly increased in EOPC [29]. FOXC2 is a key player in the epithelial-mesenchymal transition (EMT) and angiogenesis during tumor development and progression [64].

EOPCs were enriched in wild-type RAS (15.9 %) and pathogenic germline variant (PGV)[28]. Research from the Memorial Sloan Kettering Cancer Centre (MSK) showed that only 5.4 % of pancreatic cancer had wild-type KRAS, consistent with the findings of large-scale sequencing work, which found that more than 90 % of PC harbored RAS alterations [60,61]. Varghese's work showed that 15.9 % had RAS wild-type in their EOPC cohort [28], suggesting that EOPC may be enriched for wild-type RAS tumor. Furthermore, EOPC patients with wild-type RAS had more targetable alterations [28]. Recent findings described that patients with targetable alterations had an increased survival time after receiving targeted therapy [65]. Similarly, the presence of the PGV was associated with an improvement in OS [28]. In summary, these analyses provided opportunities for therapeutic actionability and improved outcomes for EOPC patients.

Higher mutation rates of SMAD4, increased activation of TGF-β pathway and higher expression levels of phospo-GSK3 were higher in EOPC [34]. SMAD4 plays a vital role in gene transcription and tumor suppression by regulating the TGF-β signaling pathway [66]. TGF-β also plays a crucial role in pancreatic cancer stem cells and tumor microenvironment [67]. TGF-β signaling is transduced through two pathways of SMAD (SMAD4, canonical pathway) and non-Smad (PI3K-Akt, non-canonical pathway)[67]. Once SMAD4 is inactivated, the TGF-β pathway is not suppressed, resulting in accelerated cell growth [68,69]. Activation of PI3K/Akt activates NF-κB and maintains the stabilization of c-Myc, which promotes cell proliferation [34]. In conclusion, critical components of two distinct signaling pathways, SMAD4 (TGF beta pathway) and PI3K-Akt related proteins (PI3 K pathway) display a trend of differential expression in EOPC compared to AOPC.

EOPC had a higher prevalence of germline mutations (13 mutations were tested: ATM, APC, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PMS2, PALB2, STK11, TP53, and EPCAM)[30]. Germline mutations for genes associated with an increased risk of pancreatic cancer were found more frequently (nearly 2–4 times) in patients younger than 42 years than in those younger than 60 years [30], suggesting that germline mutations are highly prevalent in EOPC patients, and young age is a powerful predictor of germline alterations in individuals with pancreatic cancer.

EOPC patients are often diagnosed at advanced stages and have poor prognoses, but they do not exhibit significantly higher rates of patients with genetic factors [70]. In contrast, it has been reported that patients with familial pancreatic cancer and hereditary pancreatic cancer syndromes often develop pancreatic cancer at a young age [71,72]. Approximately 10 % of pancreatic cancer patients reportedly have a family history [73], with genetic abnormalities identified in only 20 % of familial pancreatic cancer patients, these mutations include BRCA1/2, PALB2, ATM, and MLH1[74,75]. Hereditary tumors developing pancreatic cancer include hereditary pancreatitis(PRSS1, SPINK1, CFTR, CTRC), hereditary breast and ovarian cancer (HBOC, BRCA1/2), Peutz-Jeghers syndrome (PJS, STK11/LKB1), familial atypical multiple mole melanoma syndrome (FAMMM, CDKN2A/p16), familial adenomatous polyposis (FAP, APC), and Lynch syndrome (hereditary non--polyposis colorectal cancer [HNPCC], MLH1, MSH2, MSH6, PMS2), each of which are autosomal dominant hereditary diseases, and mutations involved in these genes significantly increase the risk of pancreatic cancer [70].

Another work by Raffenne et al.[14] demonstrated that the mutational landscape of the main driver genes and the global methylation profile were similar between EOPC and AOPC/LOPC. Interestingly, EOPC displayed age-related alterations, such as enriched DNA repair gene signatures, upregulated oxidative stress defenses, and enhanced proteome carbonylation, were more significant in non-tumor tissues, suggesting that pancreatic cancer in young and old patients exhibits comparable molecular characteristics.

Studies on the molecular landscape of EOPC are still relatively limited. Coupled with the low frequency of EOPC, the sample size remains an inherent limitation for EOPC studies. Research on EOPC is limited to tissues because of its specificity. Specifically, existing studies are mainly based on tissue samples, and no studies based on cell lines, organoids, or animal models have been reported in EOPC so far, which limits the research on EOPC. The molecular study of EOPC will be more in-depth with the development and application of EOPC research models.

Survival outcomes of EOPC

Pancreatic cancer is a deadly disease with a poor prognosis. What is the exact prognosis of EOPC compared to AOPC/LOPC? In fact, patients with EOPC had better survival [12,26,30,33,35–37,76], similar survival [24,27,29,34,38,39,41–43] and worse survival [40] compared to control patients (LOPC/AOPC) from published studies (Table 1).

EOPC presented better survival outcomes than control patients

Despite suggestive features of aggressive tumor biology at presentation, EOPC was independently associated with better OS than older patients (AOPC or LOPC) [12,26,30,33,35–37,76]. External treatment received and intrinsic biological characteristics may explain the favorable survival outcome in EOPC. For therapies, notably, EOPC appears to have higher rates of surgical resection [37,41,76]. Surgical resection remains the only curative option for pancreatic cancer treatment [77]. In terms of biologic behaviour, first. Patients with pancreatic cancer of tail lesions have a lower rate of resectability and poorer overall survival compared to head lesions [78]. Second, patients with prevalent germline mutations were associated with better outcomes [30]. Third, younger patients may be more suitable for higher intensity treatment. Therefore, the improved survival rate in the young group may reflect a general better state of health and a relatively lower rate of comorbidities.

EOPC presented similar outcomes with LOPC/AOPC

No differences in survival outcomes were observed between age-of-onset groups [24,27,29,34,38,39,41–43]. In fact, patients with EOPC seemed to show some more aggressive characteristics, young people seemed to be more suitable candidates for surgery and chemotherapy [36,38]. Additionally, the rates of R0 and surgical types were similar between the younger and older groups [27]. These analyses suggested that although EOPC seems to have different clinical and molecular profiles, there is no change in survival outcomes.

EOPC presented worse survival outcomes compared to control patients

However, survival analysis performed by some studies demonstrated reduced OS in EOPC patients [40]. Clinical data on other types of cancer reported that early-onset cancers could grow faster and are biologically more aggressive than later-onset cancers. Early-onset colorectal cancer patients tend to present with advanced-stage disease, which is associated with increased mortality [2]. Early onset breast cancer patients exhibit a higher rate of advanced stages at diagnosis, relapse, and death, exhibiting a worse prognosis than older patients due to the aggressive nature of cancer subtypes [3]. In addition, EOPC patients presented higher rates of several factors associated with a decreased OS, including the later stage of the disease, male sex, than late-onset patients [37]. Therefore, EOPC also has a worse survival outcome than later-onset cancer.

In conclusion, the potential reasons for the differences in OS are as follows: (1) The age cutoff point defined for EOPC varied. The age definition for EOPC was 40 years, 45 years, 50 years, 55 years, and 60

Table 1
Survival outcomes of EOPC compared to counterpart patients (LOPC/AOPC).

Outcomes (EOPC vs. LOPC/ LOPC)	Cut-off Age	Average age (year)	Stage (III/IV,%)	Female (%)	Country	Median survival(month) /Survival rate		P-value	References
No differences (n = 8)									
	55	NA	NA	NA	Spain	11	9	>0.05	[29][1]
	55	NA	0/6	29/55	Australian	15	17	>0.05	[34]
	45	NA	23.5/23.5	29/41.2	South Korea	17	32	0.54	[27]
	50	45/70.2	84/67	NA	Italy	11	12	0.99	[43]
	50	45.71/66.19	77.1/59	29/46	UK	12	9	0.168	[38]
	50	44/67.2	62/68	37/43	USA	24.2	14	0.06	
	40	NA	62.8/67.8	38.7/48.7	USA	7	6	0.310	[24]
	50	46.5/68	79/79	39/39	Sweden	5.7	5.3	0.84	[41]
Better survival (n = 8)									
	50	NA	60/57.2	39.8/45.8	USA	9.36 (HR:0.82[1]*)	8	0.045	[12]
	45	41/75	3/4	56/48	USA	19	16	0.007	[35]
	45	NA	70.1/NA	46/NA	USA	41.8	18–22	<0.05[2]*	[36]
	60	48.44/60.56	NA	55.6/39.8	USA	70.4	32.6	0.03	[30]
	45 (VEOPC)		18.5/16.2	42.6/49.3	China	NA	NA	<0.001[3]*	[33]
	50	44.5/70.2	62.1/55.2	42.9/50	USA	9.2	6	<0.001	[37]
	50	NA	62.72/ 58.13	40.7/ 50.16	USA	21.6	7.3	0.001	[79]
	50	NA	60/57	44/50	USA	72.4 %	53.3 %	<0.05[4]*	[26]
Worse survival (n = 2)									
	50	49/69	70.2/64.6	42/48.8	Sweden	6.1 %	8.6 %	0.003[5]*	[40]
	45	41/62	71.2/78.14	25/36.1	China	8 ± 0.5	NA	NA	[44]

1*. EOPC was associated with significantly better survival (adjusted HR: 0.82, 95 % CI: 0.67–1.00). 2*. Patients with stages I-II disease may have an improved prognosis. 3*. EOPC patients had a decreased risk of cancer death than older patients. 4*. One-year OS was higher for EOPC versus AOPC across each stage. 5*. EOPC was associated with poorer 5-year OS. NA: not available. Comparison grouping method for average age, stage, and female percentage: EOPC / LOPC or AOPC.

years from different studies. (2) The definition of control groups from the publications was also varied. Interestingly, it includes LOPC and AOPC. (3) EOPC patients have a better overall health status, relatively lower rates of comorbidities (4) Younger patients may be more willing to pursue and receive therapy. (5) The EOPC presented aggressive biology [42] and the proportion of advanced and resectable patients included was heterogeneous [40].

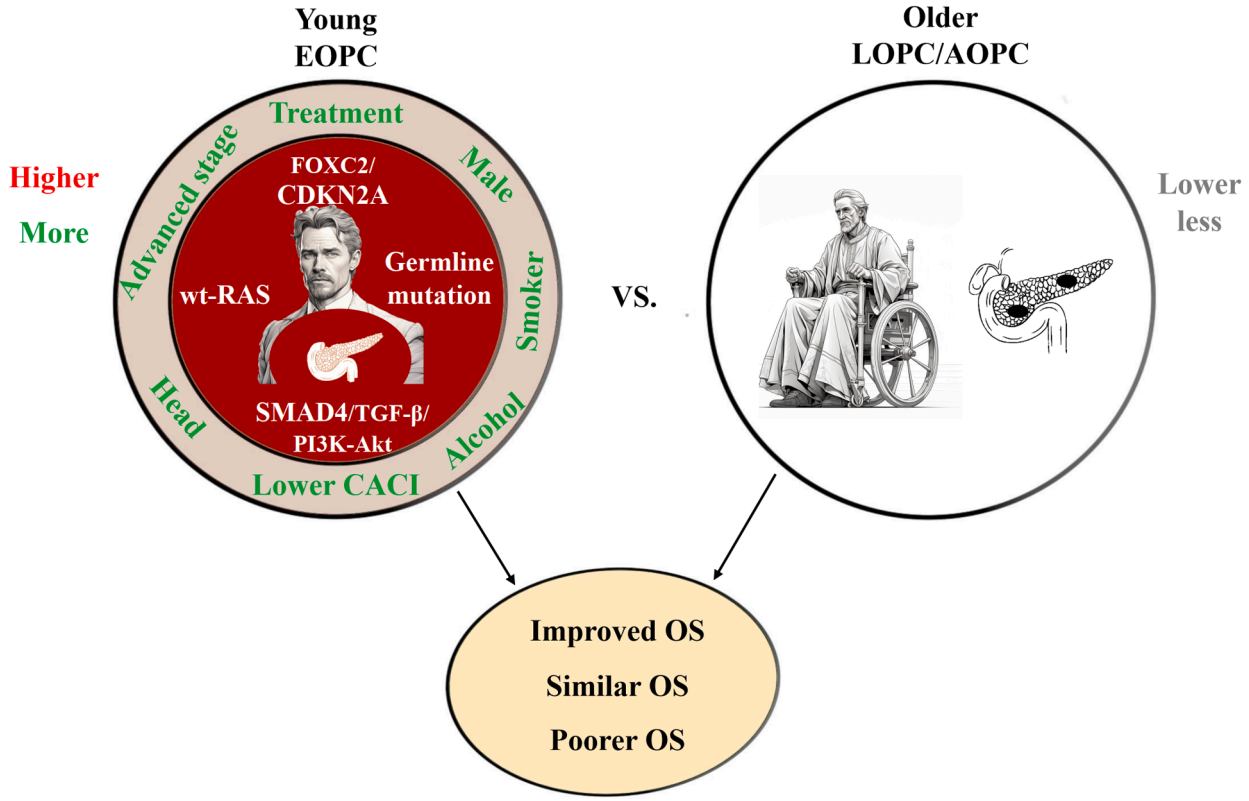


Fig. 1. Overview of features and oncologic outcomes between EOPC and LOPC/AOPC.

Conclusion

In conclusion, this review presented a relatively comprehensive analysis of EOPC, suggesting that EOPC is a rare subgroup with distinctive clinical and molecular characteristics (Fig. 1). There is no uniform definition of an age limit for EOPC, nor for the control group (LOPC or AOPC). Current studies are dominated by clinical data analyses, and studies at the molecular level are far from sufficient. Specific clinical characteristics of EOPC patients, such as EOPC patients are more likely to receive treatment (including surgery, radiation, and chemotherapy), have more advanced stage, male, smokers, and alcohol users, and present more location in the head of the pancreas, and a better functional status. EOPC patients mainly present no difference in survival outcomes and better survival outcomes compared to AOPC/LOPC. Our findings herald a promising future for EOPC research. In summary, this study improves our understanding of EOPC and captures the research trends and most influential topics in the field.

CRediT authorship contribution statement

Dong Luo: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yixiong Li:** Writing – review & editing, Project administration, Funding acquisition. **Xiao Yu:** Writing – review & editing, Methodology. **Liandong Ji:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Conceptualization. **Xuejun Gong:** Writing – review & editing, Validation, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This research was supported by Key research and development project in Hunan Province in 2024 (grant number: 2024JK2111). Dr. Dong Luo also appreciated the nice support from Prof. Oliver Strobel, Prof. Martin Schneider, and Dr. Carl Stephan Leonhardt during Dong Luo's stay and study at the Department of General, Visceral and Transplant Surgery, European Pancreas Centre (EPZ), Heidelberg University Hospital, Germany.

References

[1] T.C. He, J.A. Li, Z.H. Xu, et al., Biological and clinical implications of early-onset cancers: a unique subtype, Crit. Rev. Oncol. Hematol. 190 (2023) 104120.
[2] F.A Sinicrope, Increasing incidence of early-onset colorectal cancer, N. Engl. J. Med. 386 (16) (2022) 1547–1558.
[3] R. Kumar, C. Abreu, M. Toi, et al., Oncobiology and treatment of breast cancer in young women, Cancer Metastas. Rev. (2022).
[4] N. Hughes, D. Stark, The management of adolescents and young adults with cancer, Cancer Treat. Rev. 67 (2018) 45–53.
[5] L.S. Jarvela, H. Niinikoski, P.M. Lahteenmaki, et al., Physical activity and fitness in adolescent and young adult long-term survivors of childhood acute lymphoblastic leukaemia, J. Cancer. Surviv 4 (4) (2010) 339–345.
[6] B. Koh, D.J.H. Tan, C.H. Ng, et al., Patterns in cancer incidence among people younger than 50 years in the US, 2010 to 2019, JAMA Netw. Open 6 (8) (2023) e2328171.
[7] P. Danpanichkul, T. Auttapracha, S. Kongarin, et al., Global epidemiology of early-onset upper gastrointestinal cancer: trend from the Global Burden of Disease Study 2019, J. Gastroenterol. Hepatol. 39 (9) (2024) 1856–1868.
[8] R.L. Siegel, A.N. Giaquinto, A Jemal, Cancer statistics, 2024, CA Cancer J. Clin. 74 (1) (2024) 12–49.
[9] P. Danpanichkul, K. Suparan, P. Tothanarungroj, et al., Epidemiology of gastrointestinal cancers: a systematic analysis from the Global Burden of Disease Study 2021, Gut (2024).
[10] Y. Li, X. Zhang, Pancreatic cancer in young adults - an evolving entity? Am. J. Cancer. Res. 13 (7) (2023) 2763–2772.
[11] F. Castet, C. Fabregat-Franco, G. Castillo, et al., Clinical and genomic characterisation of early-onset pancreatic cancer, Eur. J. Cancer 194 (2023) 113338.
[12] A. Beeghly-Fadiel, H.N. Luu, L.P. Du, et al., Early onset pancreatic malignancies: clinical characteristics and survival associations, Int. J. Cancer 139 (10) (2016) 2169–2177.
[13] Y. Nodari, M. Gentiluomo, B. Mohelnikova-Duchonova, et al., Genetic and non-genetic risk factors for early-onset pancreatic cancer, Dig. Liver Dis. 55 (10) (2023) 1417–1425.
[14] J.M. Raffenne, F.A. Martin, R. Nicolle, et al., Pancreatic ductal adenocarcinoma arising in young and old patients displays similar molecular features, Cancers (Basel) 13 (6) (2021).
[15] A.A. Connor, S. Gallinger, Pancreatic cancer evolution and heterogeneity: integrating omics and clinical data, Nat. Rev. Cancer 22 (3) (2022) 131–142.
[16] Society. A C. Cancer Facts & Figures 2022: Atlanta: American Cancer Society, 2022.
[17] L. Rahib, M.R. Wehner, L.M. Matrisian, et al., Estimated projection of US cancer incidence and death to 2040, JAMA Netw. Open 4 (4) (2021) e214708.
[18] W. Park, A. Chawla, E.M O'reilly, Pancreatic cancer: a review, JAMA 326 (9) (2021) 851–862.
[19] C. Marosi, M. Köller, Challenge of cancer in the elderly, ESMO Open 1 (3) (2016) e000020.
[20] Surveillance E, And End Results (Seer) Program. Pancreas.SEER Incidence Rates by Age at Diagnosis, 2015-2019. Surveillance, Epidemiology, and End Results (SEER) Program, 2022.
[21] S. Gaddam, Y. Abboud, J. Oh, et al., Incidence of pancreatic cancer by age and sex in the US, 2000-2018, Jama-J. Am. Med. Associat. 326 (20) (2021) 2075–2077.
[22] S. Raimondi, P. Maisonneuve, J.M. Lohr, et al., Early onset pancreatic cancer: evidence of a major role for smoking and genetic factors, Cancer Epidemiol. Biomarkers Prev. 16 (9) (2007) 1894–1897.
[23] V.L. Gordon-Dseagu, S.S. Devesa, M. Goggins, et al., Pancreatic cancer incidence trends: evidence from the Surveillance, Epidemiology and End Results (SEER) population-based data, Int. J. Epidemiol. 47 (2) (2018) 427–439.
[24] D. Ramai, G. Lanke, J. Lai, et al., Early- and late-onset pancreatic adenocarcinoma: a population-based comparative study, Pancreatology 21 (1) (2021) 124–129.
[25] M. Lapelusa, C. Shen, N.D. Arhin, et al., Trends in the incidence and treatment of early-onset pancreatic cancer, Cancers (Basel) 14 (2) (2022).
[26] L.V. Saadat, J.F. Chou, M. Gonen, et al., Treatment patterns and survival in patients with early-onset pancreatic cancer, Cancer 127 (19) (2021) 3566–3578.
[27] J.S. Kang, J.Y. Jang, W. Kwon, et al., Clinicopathologic and survival differences in younger patients with pancreatic ductal adenocarcinoma-A propensity score-matched comparative analysis, Pancreatology 17 (5) (2017) 827–832.
[28] A.M. Varghese, I. Singh, R. Singh, et al., Early-onset pancreas cancer: clinical descriptors, genomics, and outcomes, Jnci-J. National Cancer Instit. 113 (9) (2021) 1194–1202.
[29] E.S. Tsang, J.T. Topham, J.M. Karasinska, et al., Delving into early-onset pancreatic ductal adenocarcinoma: how does age fit in? Clin. Cancer Res. 27 (1) (2021) 246–254.
[30] S.A. Bannon, M.F. Montiel, J.B. Goldstein, et al., High prevalence of hereditary cancer syndromes and outcomes in adults with early-onset pancreatic cancer, Cancer Prev. Res. 11 (11) (2018) 679–686.
[31] Ş. Bunduc, R. Iacob, R. Costache, et al., Very early onset pancreatic adenocarcinoma - clinical presentation, risk factors and therapeutic options, Chirurgia (Bucur.) 113 (3) (2018) 405–411.
[32] R.R. Mcwilliams, P. Maisonneuve, W.R. Bamlet, et al., Risk factors for early-onset and very-early-onset pancreatic adenocarcinoma a pancreatic cancer case-control consortium (PanC4) analysis, Pancreas 45 (2) (2016) 311–316.
[33] D.J. Dai, Y.M. Wang, X.Y. Hu, et al., Prognostic analysis of very early onset pancreatic cancer: a population-based analysis, Peerj 8 (2020).
[34] I. Ben-Aharon, M. Elkabets, R. Pelossof, et al., Genomic landscape of pancreatic adenocarcinoma in younger versus older patients: does age matter? Clin. Cancer Res. 25 (7) (2019) 2185–2193.
[35] J. He, B.H. Edil, J.L. Cameron, et al., Young patients undergoing resection of pancreatic cancer fare better than their older counterparts, J. Gastrointest. Surg. 17 (2) (2013) 339–344.
[36] A. Duffy, M. Capanu, P. Allen, et al., Pancreatic adenocarcinoma in a young patient population-12-year experience at memorial sloan kettering cancer center, J. Surg. Oncol. 100 (1) (2009) 8–12.
[37] J.E. Ordonez, C.A. Hester, H. Zhu, et al., Clinicopathologic features and outcomes of early-onset pancreatic adenocarcinoma in the United States, Ann. Surg. Oncol. 27 (6) (2020) 1997–2006.
[38] C. Ntala, S. Debernardi, R.M. Feakins, et al., Demographic, clinical, and pathological features of early onset pancreatic cancer patients, BMC Gastroenterol. (2018) 18.
[39] A.A. Wheeler, M.B Nicholl, Age influences likelihood of pancreatic cancer treatment, but not outcome, World J Oncol 5 (1) (2014).
[40] D. Ansari, C. Althini, H. Ohlsson, et al., Early-onset pancreatic cancer: a population-based study using the SEER registry, Langenbecks Arch. Surg. 404 (5) (2019) 565–571.
[41] B. Tingstedt, C. Weitkamper, R. Andersson, Early onset pancreatic cancer: a controlled trial, Ann Gastroenterol 24 (3) (2011) 206–212.
[42] T. Takeda, T. Sasaki, Y. Inoue, et al., Early-onset pancreatic cancer: clinical characteristics and survival outcomes, Pancreatology 22 (4) (2022) 507–515.

[43] M. Piciucchi, G. Capurso, R. Valente, et al., Early onset pancreatic cancer: risk factors, presentation and outcome, Pancreatology 15 (2) (2015) 151–155.
[44] Q.L. Jiang, S.S. Zhang, Y.T. Chen, et al., Risk factors for early-onset pancreatic cancer patients, and survival analysis, Int. J. Clin. Exp. Med. 10 (6) (2017) 9416–9423.
[45] A.M. Alkashash, M.A. Elsebaie, M.H. Bikhet, et al., Predictors of survival among early onset pancreatic adenocarcinoma patients a tertiary care center experience, Chirurgia (Bucur.) 116 (1) (2021) 24–33.
[46] L. Liszka, J. Pajak, S. Mrowiec, et al., Precursor lesions of early onset pancreatic cancer, Virchows. Arch. 458 (4) (2011) 439–451.
[47] S.J. Rulyak, A.B. Lowenfels, P. Maisonneuve, et al., Risk factors for the development of pancreatic cancer in familial pancreatic cancer kindreds, Gastroenterology 124 (5) (2003) 1292–1299.
[48] A.B. Lowenfels, P. Maisonneuve, D.C. Whitcomb, et al., Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis, Jama-J. Am. Med. Associat. 286 (2) (2001) 169–170.
[49] P. Danpanichkul, V.L. Chen, P. Tothanarungroj, et al., Global epidemiology of alcohol-associated liver disease in adolescents and young adults, Aliment. Pharmacol. Ther. 60 (3) (2024) 378–388.
[50] M.A. Anderson, E. Zolotarevsky, K.L. Cooper, et al., Alcohol and tobacco lower the age of presentation in sporadic pancreatic cancer in a dose-dependent manner: a multicenter study, Am. J. Gastroenterol. 107 (11) (2012) 1730–1739.
[51] R.E. Brand, J.B. Greer, E. Zolotarevsky, et al., Pancreatic cancer patients who smoke and drink are diagnosed at younger ages, Clin. Gastroenterol. Hepatol. 7 (9) (2009) 1007–1012.
[52] D.J. Birnbaum, F. Bertucci, P. Finetti, et al., Head and body/tail pancreatic carcinomas are not the same tumors, Cancers (Basel) 11 (4) (2019).
[53] G. Tomasello, M. Ghidini, A. Costanzo, et al., Outcome of head compared to body and tail pancreatic cancer: a systematic review and meta-analysis of 93 studies, J. Gastrointest. Oncol. 10 (2) (2019) 259–269.
[54] D. Dias-Santos, C.R. Ferrone, H. Zheng, et al., The Charlson age comorbidity index predicts early mortality after surgery for pancreatic cancer, Surgery 157 (5) (2015) 881–887.
[55] D.J.H. Tan, C.H. Ng, M. Muthiah, et al., Rising global burden of cancer attributable to high BMI from 2010 to 2019, Metabolism 152 (2024) 155744.
[56] D. Li, J.S. Morris, J. Liu, et al., Body mass index and risk, age of onset, and survival in patients with pancreatic cancer, JAMA 301 (24) (2009) 2553–2562.
[57] K.Y. Bilimoria, D.J. Bentrem, C.Y. Ko, et al., National failure to operate on early stage pancreatic cancer, Ann. Surg. 246 (2) (2007) 173–180.
[58] K. Pauley, A. Khan, W. Kohlmann, et al., Considerations for germline testing in melanoma: updates in behavioral change and pancreatic surveillance for carriers of CDKN2A pathogenic variants, Front. Oncol. (2022) 12.
[59] A.K. Witkiewicz, K.E. Knudsen, A.P. Dicker, et al., The meaning of p16(ink4a) expression in tumors Functional significance, clinical associations and future developments, Cell Cycle 10 (15) (2011) 2497–2503.
[60] M.A. Lowery, E.J. Jordan, O. Basturk, et al., Real-time genomic profiling of pancreatic ductal adenocarcinoma: potential actionability and correlation with clinical phenotype, Clin. Cancer Res. 23 (20) (2017) 6094–6100.
[61] N. Waddell, M. Pajic, A.M. Patch, et al., Whole genomes redefine the mutational landscape of pancreatic cancer, Nature 518 (7540) (2015) 495–501.
[62] S.W. Lowe, Hot papers - cancer - oncogenic ras provokes premature cell senescence associated with accumulation of p53 and p16INK4a by M. Serrano, A.W. Lin, M.E. McCurrach, D. Beach, S.W. Lowe - Comments, Scientist 13 (22) (1999) 15. -15.
[63] R.H. Hruban, C. Iacobuzio-Donahue, R.E. Wilentz, et al., Molecular pathology of pancreatic cancer, Cancer Journal 7 (4) (2001) 251–258.
[64] T. Wang, L. Zheng, Q. Wang, et al., Emerging roles and mechanisms of FOXC2 in cancer, Clin. Chim. Acta 479 (2018) 84–93.
[65] M.J. Pishvaian, E.M. Blais, J.R. Brody, Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: a retrospective analysis of the Know Your Tumor registry trial (vol 21, pg 508, 2020), Lancet Oncology 21 (4) (2020) E182. -E182.
[66] C. Taniguchi, A. Maitra, It's a SMAD/SMAD World, Cell 161 (6) (2015) 1245–1246.
[67] W. Shen, G.Q. Tao, Y. Zhang, et al., TGF-beta in pancreatic cancer initiation and progression: two sides of the same coin, Cell Biosci 7 (2017) 39.
[68] L. Levy, C.S. Hill, Smad4 dependency defines two classes of transforming growth factor beta (TGF-beta) target genes and distinguishes TGF-beta-induced epithelial-mesenchymal transition from its antiproliferative and migratory responses, Mol. Cell. Biol. 25 (18) (2005) 8108–8125.
[69] P. Singh, J.D. Wig, R. Srinivasan, The Smad family and its role in pancreatic cancer, Indian J. Cancer 48 (3) (2011) 351–360.
[70] H. Eguchi, S. Kobayashi, K. Gotoh, et al., Characteristics of early-onset pancreatic cancer and its association with familial pancreatic cancer and hereditary pancreatic cancer syndromes, Ann. Gastroenterol. Surg. 4 (3) (2020) 229–233.
[71] T.A. James, D.G. Sheldon, A. Rajput, et al., Risk factors associated with earlier age of onset in familial pancreatic carcinoma, Cancer 101 (12) (2004) 2722–2726.
[72] K.A. Brune, B. Lau, E. Palmisano, et al., Importance of age of onset in pancreatic cancer kindreds, J. Natl. Cancer Inst. 102 (2) (2010) 119–126.
[73] D.K. Bartsch, T.M. Gress, P. Langer, Familial pancreatic cancer–current knowledge, Nat. Rev. Gastroenterol. Hepatol. 9 (8) (2012) 445–453.
[74] H. Matsubayashi, K. Takaori, C. Morizane, et al., Familial pancreatic cancer: concept, management and issues, World J. Gastroenterol. 23 (6) (2017) 935–948.
[75] E.E. Salo-Mullen, E.M. O'reilly, D.P. Kelsen, et al., Identification of germline genetic mutations in patients with pancreatic cancer, Cancer 121 (24) (2015) 4382–4388.
[76] O.B. Alese, R.J. Jiang, W. Shaib, et al., Young adults with pancreatic cancer national trends in treatment and outcomes, Pancreas 49 (3) (2020) 341–354.
[77] W. Hartwig, J. Werner, D. Jager, et al., Improvement of surgical results for pancreatic cancer, Lancet Oncology 14 (11) (2013) E476–E485.
[78] A. Artinyan, P.A. Soriano, C. Prendergast, et al., The anatomic location of pancreatic cancer is a prognostic factor for survival, Hpb 10 (5) (2008) 371–376.
[79] O.B. Alese, R. Jiang, W. Shaib, et al., Young adults with pancreatic cancer: national trends in treatment and outcomes, Pancreas 49 (3) (2020) 341–354.