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Contents

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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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MINIREVIEWS

Clinical implications and perspectives of portal venous circulating tumor cells in pancreatic cancer

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Abstract

Despite recent improvements in the diagnosis and treatment of pancreatic cancer (PC), clinical outcomes remain dismal. Moreover, there are no effective prognostic or predictive biomarkers or options beyond carbohydrate antigen 19-9 for personalized and precise treatment. Circulating tumor cells (CTCs), as a member of the liquid biopsy family, could be a promising biomarker; however, the rarity of CTCs in peripheral venous blood limits their clinical use. Because the first venous drainage of PC is portal circulation, the portal vein can be a more suitable location for the detection of CTCs. Endoscopic ultrasound-guided portal venous sampling of CTCs is both feasible and safe. Several studies have suggested that the detection rate and number of CTCs may be higher in the portal blood than in the peripheral blood. CTC counts in the portal blood are highly associated with hepatic metastasis, recurrence after surgery, and survival. The phenotypic and genotypic properties measured in the captured portal CTCs can help us to understand tumor heterogeneity and predict the prognosis of PC. Small sample sizes and heterogeneous CTC detection methods limit the studies to date. Therefore, a large number of prospective studies are needed to corroborate portal CTCs as a valid biomarker in PC.

Key Words: Circulating tumor cell; Pancreatic cancer; Portal vein; Outcomes; Prognosis; Survival

Core Tip: Circulating tumor cells (CTCs) are emerging minimally invasive biomarkers for evaluating tumor characteristics; however, limited CTCs are detected in the peripheral blood. Portal venous blood, which does not undergo hepatic filtration, can theoretically harbor a large number of CTCs and can be safely assessed using endoscopic ultrasound. The efficacy of CTCs in portal venous blood have shown encouraging results (*i.e.*, higher detection rate and better prediction of prognosis). Here, we provide an overview of CTCs in portal venous blood in the clinical context and future perspectives to enhance the role of portal CTCs as a valid biomarker in pancreatic cancer.

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INTRODUCTION

In recent decades, improvements in screening methods, surgical techniques, and the development of novel chemotherapeutic drugs have improved the prognosis of various cancers. However, clinical outcomes of pancreatic cancer (PC) remain dismal, with a 5-year survival rate of approximately 8% in the United States[1]. Several factors, including the absence of symptoms in the early stages and notoriously aggressive cancer biology, act as hurdles for the early diagnosis of PC[2,3]. Therefore, at the time of diagnosis, only 20% or fewer patients with PC are eligible for surgical resection[4]. Furthermore, the lack of a standardized assessment of perioperative recurrence risk and treatment strategies also contributes to the decreased survival rate. In a retrospective study of 957 patients with PC undergoing curative resection, 51.5% reported recurrence within one year after surgery[5]. This result suggests the presence of undetectable micrometastases in resectable PC before surgery despite extensive evaluation. Several randomized controlled trials have evaluated the effectiveness of neoadjuvant chemotherapy in patients with resectable PC; however, its efficacy has been inconsistent between studies[4]. Therefore, there is a need to discover biomarkers that may enable more precise stratification for recurrence after surgery or to determine which patients will benefit from neoadjuvant chemotherapy. However, biomarkers to identify these patients are not currently available.

Serum carbohydrate antigen 19-9 is the most commonly utilized biomarker of PC. Its value for PC is usually confined to treatment response rather than early detection or prognosis prediction because the sensitivity (80%) and specificity (75%) are not sufficient to meet the needs of clinicians[6]. Circulating tumor cells (CTCs), as part of the liquid biopsy family, are regarded as precursors of metastases[7]. CTCs have been evaluated as minimally invasive biomarkers for assessing prognostic indicators, such as progression-free survival (PFS) and overall survival (OS) in various solid tumors[8-11]. However, detecting CTCs in peripheral blood is challenging because approximately one CTC exists per billion blood cells in patients with PC[12]. Particularly in the non-metastatic status, peripheral blood specimens may have a yield too low for clinical value. A previous study revealed that CTCs have dynamic, spatiotemporal localization according to the location of the tumor; therefore, specific targeting of vascular compartments may increase the yield of CTCs[13]. Because blood drainage bypasses the liver first *via* the portal system in PC, the portal vein may be the most suitable blood vessel for CTC evaluation. The aim of this review was to describe the clinical implications and perspectives of portal venous CTCs in patients with PC.

EFFICACY AND LIMITATIONS OF CTCS IN PERIPHERAL BLOOD

CTCs are shed from the primary tumor site and can enter the vascular system, ultimately leading to metastasis in distant organs. Various methods and technologies have been introduced for CTC enrichment, isolation, and identification[2,14,15]. These techniques use the unique properties of CTCs, which have different sizes, densities, and electrical charges compared with normal blood cells[16]. Among them, the CellSearch® system (Menarini Silicon Biosystems, Huntingdon Valley, PA, United States) is the only Food and Drug Administration (FDA) approved assay method for CTC detection[2]. It relies on capturing CTCs immunomagnetically using antibodies against epithelial cell adhesion molecules, which are commonly expressed in malignant epithelial cells.

Detecting CTCs in cancerous diseases allows for the identification of high-risk patients who may require more intensive surveillance and treatment. Specifically, CTCs could be a potential prognostic indicator of chemoradiotherapy in gastrointestinal malignancies[17,18]. As with many other solid tumors, the clinical usefulness of a prognostic predictor in PC has been demonstrated in previous studies. In a recent meta-analysis of 19 studies of over 1300 patients with PC, the presence of CTCs in

the peripheral venous blood was associated with worse PFS and OS[19]. However, the paucity of CTCs in the peripheral blood considerably limits their use in various clinical settings. PC is one of the malignancies with the least number of CTCs detected by the CellSearch® method in comparison with other tumor entities[20]. Its detection rate was as low as 7%-48% at various stages of PC[2]. A recent study showed that the median number of CTCs was only 4 per milliliter in the peripheral blood of 46 patients with PC[21]. This low value has been attributed to the biophysical characteristics of CTCs and the venous drainage system of the pancreas. The average diameter of CTCs is approximately 25 μm, which is too large to allow them to enter capillary beds (8 μm in diameter)[20]. Furthermore, CTCs shed from the pancreas flow *via* the portal vein into the liver, and subsequent hepatic filtration could make the detection of CTCs in the peripheral blood very challenging[22,23]. Therefore, there is a need to discover blood sources that are abundant in CTCs theoretically.

ENDOSCOPIC ULTRASOUND-GUIDED PORTAL VEIN BLOOD SAMPLING

During surgery, portal venous blood can be collected by direct puncture of the extrahepatic portal vein with a syringe. However, non-surgical access to the portal vein is needed for individual risk stratification decision-making before neoadjuvant chemotherapy or surgery. Endoscopic ultrasonography (EUS) was initially introduced as a diagnostic imaging modality. However, the development of a linear echoendoscope in the early 1990s changed the landscape of EUS from a diagnostic to a therapeutic tool [24]. With the development of devices and accessories fit for echoendoscopes, various techniques for abdominal organs were introduced with minimal invasiveness, *e.g.*, EUS-guided fine needle aspiration (FNA), transmural drainage of pancreatic pseudocysts, EUS-guided bile duct and gallbladder drainage, EUS-guided gastrojejunostomy, and EUS-guided celiac plexus/neurolysis[25]. Furthermore, applications of EUS are not limited to visceral organs, but have also been extended to the field of vascular interventions[26]. Owing to its unique proximity and accessibility to the portal vein, various applications for EUS-guided portal vein interventions have been introduced, including EUS-guided FNA of portal vein thrombosis in hepatocellular carcinoma, portal injection chemotherapy, and measurement of portal vein pressure[27]. Importantly, the role of EUS-guided portal venous blood sampling in the detection of CTCs has recently drawn attention. Catenacci *et al*[22] first reported the feasibility and safety of EUS-guided acquisition of portal venous CTCs in patients with pancreaticobiliary cancer. After verifying the blood flow signal using Doppler ultrasound, the EUS-FNA needle was advanced transhepatically into the portal vein and blood was aspirated safely (Figure 1). It is necessary to pay close attention to the hepatic artery and bile ducts because these structures course together and can potentially lead to complications or inaccurate sampling. It is recommended to use a wide bore needle, such as a 19-G needle, for EUS-guided portal venous sampling to prevent blood clotting and CTC damage[28]. The amount of blood required for CTC isolation and identification is generally between 5 and 10 mL.

CLINICAL UTILITY OF PORTAL VENOUS CTCS

Higher detection rate and number compared to peripheral blood

The portal vein is the main drainage vessel of the pancreas, and the blood in the portal vein does not undergo hepatic filtration. Therefore, sampling from the portal vein might yield higher concentrations of CTCs than sampling from peripheral blood. Catenacci *et al*[22] first reported the feasibility and safety of EUS-guided acquisition of portal venous CTCs in 18 patients with pancreaticobiliary cancer. CTCs were detected in all portal vein samples (100%) but only 22% of peripheral blood samples. The median number of CTCs was significantly higher in samples from the portal vein than the peripheral blood (118.4 CTCs/7.5 mL *vs* 0.8 CTCs/7.5 mL, $P < 0.01$). These findings were validated in subsequent studies. In 41 patients with PC, the detection rate (58.5% *vs* 39.0%, $P = 0.02$) and number of CTCs (mean count, 313.4/3 mL *vs* 92.9/mL, $P < 0.01$) were significantly higher in samples from the portal vein than the peripheral blood[29]. Liu *et al*[23] also evaluated the detection rate and number of CTCs in the portal vein and peripheral blood of 29 patients with advanced or metastatic PC. CTCs were detected in all portal vein blood samples (100%), whereas CTCs were found in only 54% of peripheral blood samples. Furthermore, the mean count of CTCs in the portal venous blood was approximately 10 times higher than that in the peripheral blood (282.0/7.5 mL *vs* 21.0/7.5 mL, $P < 0.01$). Similar results were reported by Chapman *et al*[30]; portal venous blood demonstrated superior outcomes in both the detection rate (100% *vs* 23.5%) and enumeration (mean count, 118/7.5 mL *vs* 0.67/7.5 mL) in 17 patients with pancreaticobiliary cancers. Zhang *et al*[31] and Choi *et al*[32] reported that the number of CTCs in the portal venous blood was higher than that in the peripheral blood, whereas the detection rates were comparable between the portal and peripheral blood. In a meta-analysis by Pang *et al*[33] which included five studies that indicated patient-level data[22,23,34-36], the yield of CTCs was 7.7-fold (95%CI: 1.35-43.9) higher in the portal venous blood than in the peripheral blood.

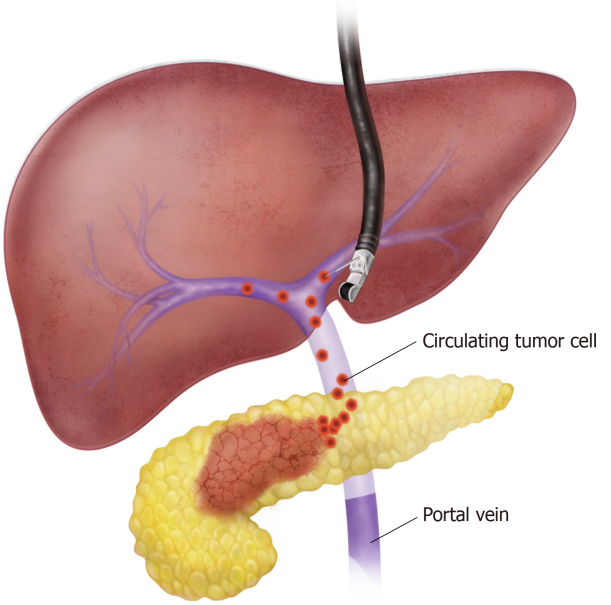

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Figure 1 Illustrated view of portal vein sampling with an endoscopic ultrasonography-fine needle aspiration needle. Circulating tumor cells (CTCs) from pancreatic cancer are released in the portal vein; portal blood sampling before passage in the liver can allow for improvement of the CTC recovery rate. The endoscopic ultrasonography-fine needle aspiration needle is advanced transhepatically into the portal vein and portal venous blood can be aspirated safely.

Some studies, however, have presented contradictory results to those of previous studies. In a study of 32 patients with resectable PC, there was no difference in the detection rate between the portal and peripheral veins (62.5% *vs* 68.8%)[37]. The number of CTCs also did not differ between the two sampling sites in this study. A study by Padillo-Ruiz *et al*[38] also reported no differences between the portal and peripheral blood in terms of the detection rate (100% *vs* 100%) and number of CTCs (median 310 *vs* 405.7, $P = 0.239$). A comparison of the CTC detection rate and number between the portal vein and peripheral blood in patients with PC is summarized in Table 1.

Correlation with tumor staging and histology

The correlation between the number of CTCs in the peripheral blood and tumor burden has been well established in various solid cancers[39]. However, only limited data are available on the correlation between portal CTCs and PC stages. Zhang *et al*[31] reported that the number of portal venous CTCs, especially the mesenchymal subtype, is positively correlated with advanced PC stages, including stages III and IV. In another study by Choi *et al*[32], a higher number of CTCs in the portal vein (≥ 3/7.5 mL) is positively correlated with advanced stages and lymph node metastasis. The association between CTCs and tumor differentiation was evaluated by Padillo-Ruiz *et al*[38] in 35 patients with resectable PC. Patients with poorly differentiated carcinoma had a larger number of CTC clusters than those with well or moderately differentiated types (median 41.0 *vs* 14.0), although the difference was not significant ($P = 0.107$).

Association with liver metastasis

Several studies have investigated the association between portal venous CTCs and liver metastasis in patients with PC. In a study by Bissolati *et al*[36] which included 20 patients who underwent surgery for PC, a greater risk of liver metastasis was observed in patients with CTCs in the portal venous blood than in those without CTCs (53% *vs* 8%, $P = 0.038$). Tien *et al*[29] reported a similar result; identification of CTCs in the portal venous blood was the only significant factor for the development of liver metastasis within 6 mo after surgery in 41 patients with resectable PC. A comparable result was also reported in a study that included locally advanced or metastatic PC[23]; patients with liver metastases demonstrated a higher mean number of CTCs than those without metastases (449.0/7.5 mL *vs* 126.0/7.5 mL, $P < 0.01$).

Correlation with PFS and OS

The role of portal venous CTCs as prognostic markers for PC has also been evaluated. According to a study by Liu *et al*[23] which included 29 patients with locally advanced or metastatic PC, OS was significantly shorter in patients with a CTC count ≥ 150/7.5 mL in portal venous blood compared to those with a CTC count ≤ 150/7.5 mL (median OS 9.2 wk *vs* 19.8 wk, $P < 0.01$). A similar result was reported by Chapman *et al*[30]; specifically, patients with portal venous CTCs ≥ 185/7.5 mL had significantly shorter PFS than patients with CTCs < 185/7.5 mL (mean PFS, 12.8 wk *vs* 43.3 wk, $P <$

Table 1 Comparison of the circulating tumor cell detection rate and number between peripheral and portal venous blood in patients with pancreatic cancer

Ref.	Patients, *N*	Cancer stage	Blood source	PoV sample	CTC isolation method	Detection rate, % (*n*/*N*)	Number of CTCs (mean ± SD)	Main findings
Catenacci *et al*[22], 2015	18	All	PoV, PV	EUS-guided	CellSearch	PoV: 100 (18/18), PV: 22.2 (4/18)	PoV: 118.4 ± 36.8/7.5 mL, PV: 0.8 ± 0.4/7.5 mL	Both the detection rate and number of CTCs were higher in the PoV than in the PV
Tien *et al* [29], 2016	41	Resectable	PoV, PV	Intraoperative	CMx platform	PoV: 58.5 (24/41), PV: 39.0 (16/41)	PoV: 313.4/3 mL, PV: 92.9/3 mL	Both the detection rate and number of CTCs were higher in the PoV than in the PV
Liu *et al*[23], 2018	29	Locally advanced, metastatic	PoV, PV	Transabdominal US-guided	ClearCell FX system	PoV: 100 (29/29), PV: 54 (8/14)	PoV: 282.0/7.5 mL, PV: 21.0/7.5 mL	Both the detection rate and number of CTCs were higher in the PoV than in the PV
Chapman *et al*[30], 2020	17[1]	All	PoV, PV	EUS-guided	CellSearch	PoV: 100 (17/17), PV: 23.5 (4/17)	PoV: 118.4 (1-516)/7.5 mL[2], PV: 0.67 (0-7)/7.5 mL[2]	Both the detection rate and number of CTCs were higher in the PoV than in the PV
Song *et al* [37], 2020	32	Resectable	PoV, PV	Intraoperative	Microfabricated Filter	PoV: 62.5 (20/32), PV: 68.8 (22/32)	Not shown	No differences in detection rate and number of CTCs between the PoV and PV
Padillo-Ruiz *et al*[38], 2021	35	Resectable	PoV, CV	Intraoperative	IsoFlux™	PoV: 100 (35/35), CV: 100 (35/35)	PoV: 310 (132.1-446.0)/mL[3], CV: 405.7 (130.7-533.8)/mL[3]	No differences in detection rate and number of CTCs between the PoV and CV
White *et al* [40], 2021	34	Resectable	PoV, PV	Intraoperative	CellSearch	PoV: 71 (22/31), PV: 50 (11/22)	Not shown	No differences in detection rate and number of CTCs between the PoV and PV
Zhang *et al* [31], 2021	31	All	PoV, PV	EUS-guided	Cyttel detection kit	PoV: 97 (31/30), PV: 87 (27/31)	PoV: 10/5 mL[4], PV: 6/5 mL[4]	Number of CTCs was higher in the PoV than in the PV
Choi *et al* [32], 2022	33	All	PoV, PV	Intraoperative	SMART BIOPSY™	PoV: 75.8 (25/33), PB: 92.1 (23/28)	PoV: 2.5/7.5 mL[4], PV: 1/7.5 mL[4]	Number of CTCs was higher in the PoV than in the PV

[1]Included two patients with cholangiocarcinoma and one with ampullary cancer.
[2]Expressed as mean (range).
[3]Expressed as median (range).
[4]Expressed as median.
PoV: Portal vein; PV: Peripheral vein; PB: Peripheral blood; CV: Central vein; CTCs: Circulating tumor cells; EUS: Endoscopic ultrasound; US: Ultrasound.

0.01). OS was also unfavorable in patients with higher counts of CTCs; however, the difference was not significant (mean OS, 29.5 wk *vs* 75.4 wk, $P = 0.07$). Moreover, a Cox-proportional hazards regression model demonstrated that every 10-cell increase in CTCs in the portal venous blood was associated with an increased likelihood of progression ($P = 0.03$) and death ($P = 0.01$) by 5% and 4%, respectively. White *et al*[40] reported the superiority of portal venous CTCs over peripheral blood for predicting survival. Thirty-one and 22 samples from the portal and peripheral veins, respectively, were collected during PC operation in 34 patients. Patients with ≥ 1 portal venous CTC/7.5 mL had an OS rate of 70% at 18 mo, whereas no deaths were reported in the absence of portal venous CTCs ($P < 0.01$). However, no correlation was observed between CTCs in the peripheral blood and OS. Similar results were validated by Choi *et al*[32]: CTCs in the portal vein, but not CTCs in peripheral blood, were a significant predictor of shorter PFS and OS. Zhang *et al*[31] also reported the prognostic value of portal venous CTCs, indicating that patients with a higher number of CTCs in the portal vein had poorer OS. The studies that analyzed the impact of portal venous CTCs on prognosis of patients with PC are summarized in Table 2.

Table 2 Clinical impact of portal venous circulating tumor cells on prognosis in patients with pancreatic cancer

Ref.	Patients, *N*	Cancer stage	Blood source	PoV sample	CTC isolation method	OS, median (95%CI)	PFS, median (95%CI)	Main findings
Bissolati *et al*[36], 2015	20	Resectable	PoV, PV	Intraoperative	CellSearch	CTCs (-): 23.1 (15.1-31.1) mo, CTCs (+): 26.2 (18.7-33.8) mo	CTCs (-): 19.4 (10.9-27.8) mo, CTCs (+): 18.9 (10.4-27.3) mo	PoV CTC-positive patients had a higher rate of liver metastases than CTC-negative patients.
Tien *et al* [29], 2016	41	Resectable	PoV, PV	Intraoperative	CMx platform	Not shown	Not shown	Number of CTCs in the PoV was the only significant risk factor of liver metastases within 6 mo after surgery.
Liu *et al* [23], 2018	29	Locally advanced, metastatic	PoV, PV	Transabdominal US-guided	ClearCell FX system	CTCs < 150/7.5 mL: 19.8 (16.8-25.4) wk, CTCs ≥ 150/7.5 mL: 9.2 (7.8-11.8) wk	Not shown	Higher CTC count in the PoV was associated with liver metastases and shorter OS.
Chapman *et al*[30], 2020	14	All	PoV, PV	EUS-guided	CellSearch	CTCs < 185/7.5 mL: 40.0 wk, CTCs ≥ 185/7.5 mL: 12.8 wk	CTCs < 185/7.5 mL: 75.4 wk, CTCs ≥ 185/7.5 mL: 29.5 wk	Every 10 CTC increase in the PoV was associated with a 5% and 4% increase in the likelihood of progression and death, respectively.
Padillo-Ruiz *et al* [38], 2021	35	Resectable	PoV, CV	Intraoperative	IsoFlux™	CTCs < 185/mL: 24.5 (19.6-29.4) mo, CTCs ≥ 185/mL: 10.0 (7.4-12.5) mo	Not shown	Higher number of CTCs in the PoV was associated with poorly differentiated cancer and shorter OS.
Pan *et al* [48], 2021	32	Resectable	PoV, PV	Intraoperative	CanPatrol™	Not shown	Not shown	Mesenchymal CTCs in the PoV ≥ 1/5 mL was a significant risk factor for metastasis, PFS, and OS.
White *et al* [40], 2021	34	Resectable	PoV, PV	Intraoperative	CellSearch	Not shown	Not shown	Patients with undetectable PoV CTCs showed a higher 18-mo survival rate (100%).
Zhang *et al* [31], 2021	31	All	PoV, PV	EUS-guided	Cyttel detection kit	Not shown	Not shown	The number of PoV CTCs, especially mesenchymal CTCs, was positively correlated with the advanced stage.
Choi *et al* [32], 2022	33	All	PoV, PV	Intraoperative	SMART BIOPSY™	CTCs < 3/7.5 mL: NA, CTCs ≥ 3/7.5 mL: 16.5 mo	CTCs < 3/7.5 mL: 13.4 mo, CTCs ≥ 3/7.5 mL: 7.5 mo	Higher number of PoV CTCs was associated with higher stage, lymph node metastasis, and poorer PFS and OS.
Song *et al* [37], 2020	32	Resectable	PoV, PV	Intraoperative	Microfabricated Filter	CTCs < 1/10 mL: 40.0 mo, CTCs ≥ 1/10 mL: 17.6 mo	Not shown	CTC count in the PoV was not significantly associated with OS.

CTCs: Circulating tumor cells; PoV: Portal vein; PV: Peripheral vein; OS: Overall survival; PFS: Progression free survival; US: Ultrasound; EUS: Endoscopic ultrasound; NA: Not achieved.

RECENT TRENDS IN PORTAL VENOUS CTC STUDIES

Phenotype analysis

There are various circulating biomarkers for liquid biopsy, including CTCs, circulating tumor deoxyribonucleic acid (ctDNA), ribonucleic acid, and extracellular vesicles[41]. The major advantage of CTCs over other circulating markers is the ability to detect whole tumor cells; this enables the identification of markers associated with prognosis beyond the enumeration of CTCs. The concept of epithelial-mesenchymal transition (EMT) is one of the most important elements in CTC phenotyping. This refers to the process by which tumor cells attached to the basement membrane gain mesenchymal properties, which finally leads to vessel invasion and induces metastasis[42]. Based on this concept, CTCs can be classified into three subpopulations with distinct properties: epithelial CTCs, mesenchymal CTCs (M-CTCs), and epithelial-mesenchymal transition CTCs (EMT-CTCs)[43] (Figure 2). Correlations between disease progression and M-CTCs in solid tumors have been reported previously[44,45]. Zhao *et al*[46] analyzed the phenotype of CTCs in the peripheral blood of 107 patients with PC. Advanced stage

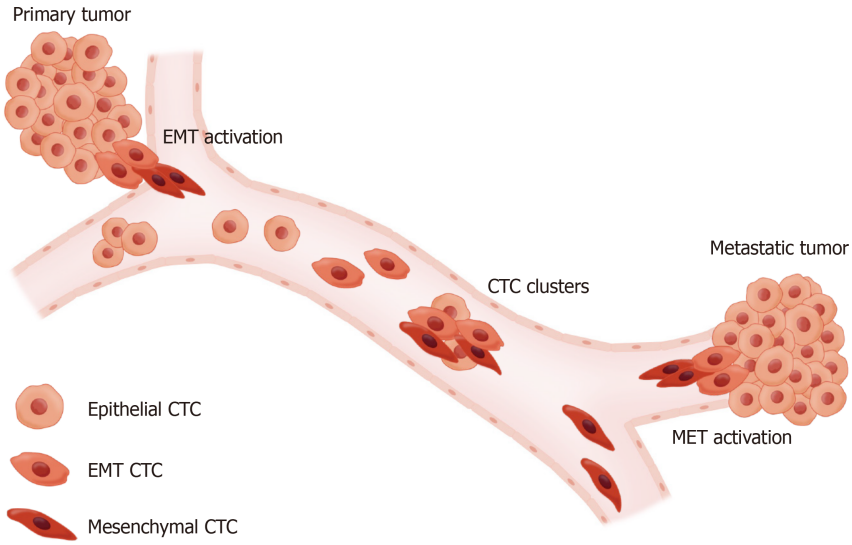

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Figure 2 Characteristic stages of circulating tumor cells during metastasis. Cells from the primary tumor undergo epithelial-mesenchymal transition, which enables them to disseminate to blood vessels. Cancer cells travel as various phenotypes of circulating tumor cells (CTCs) and extravasate the vascular system after undergoing mesenchymal-epithelial transition. This reverse process allows CTCs to escape from blood vessels into distant organs to form a metastatic tumor. CTC: Circulating tumor cell; EMT: Epithelial-mesenchymal transition; MET: Mesenchymal-epithelial transition.

and the presence of distant metastases were significantly associated with M-CTCs. Another study by Semaan *et al*[47] showed that prognostic variables, such as PFS and OS, were correlated with EMT-CTCs in peripheral blood but not with total CTC counts. Studies on the phenotype of CTCs have also been conducted using portal venous blood samples. According to a study by Pan *et al*[48] with 32 patients with resectable PC, M-CTCs in the portal vein were found to be a significant risk factor for metastasis-free survival and OS. Similar results were reported by Zhang *et al*[31]; in 31 patients with PC, a higher count of M-CTCs from portal venous blood was associated with advanced stage, lymph node, and distant metastases. However, this pattern was not observed in a study by Choi *et al*[32], in which no associations were observed between the phenotype of CTCs from the portal vein and prognosis. Since the abundance of CTCs in portal venous blood has been validated in previous studies, it is expected to be advantageous for phenotyping CTCs from portal venous blood. Further prospective studies with larger numbers of patients are warranted to evaluate the clinical efficacy of CTC phenotyping using portal venous samples.

Genotype analysis

Genotyping tumors for the identification of genetic mutations has become a routine practice for evaluating patients with certain solid-type cancers[49,50]. However, genotyping from primary tumor tissue has inherent limitations in that single tissue collection has a risk of selection bias from tumor heterogeneity, and acquiring tissue is not always feasible[51]. Therefore, genotypic analysis of CTCs has been conducted to reflect the genomics of primary tumors. In patients with PC, concordance of *KRAS* mutations in CTCs, which presents in over 90% of PC cases, has been reported repeatedly compared to primary pancreatic tumors[22,37,52]. However, a discordant rate of 42% for *KRAS* mutations between CTCs and primary tumors was also reported in 59 patients with PC[53]. These conflicting results may represent the natural evolution of metastatic tumors triggered by genomic instability and heterogeneity within the primary tumor[54]. Therefore, testing for other genetic mutations, such as *TP53, SMAD4,* and *P16,* which are commonly observed in PC, might be needed to confirm tumor identity[55]. Although the utility of ctDNA for tailored therapies or predicting response has been explored in many studies[56], only limited data regarding genotyping with CTCs for personalized medicine in PC are available to date. Yu *et al*[57] reported that an increase in *SMAD4* expression levels in CTCs was associated with longer PFS and favorable treatment response in 37 patients with PC treated with gemcitabine/nab-paclitaxel. Recently, the FDA approved high-throughput next-generation sequencing-based multigene biopsy that can detect genomic mutations and polymerase chain reaction-based single-gene or multigene assays[58]. Further studies are needed to validate the clinical efficacy of the newly developed genotyping techniques for tailored therapy in patients with PC.

FUTURE PERSPECTIVES

Several unmet needs, including early detection, preoperative risk stratification, and the development of effective and personalized chemotherapeutic agents, should be addressed to improve the prognosis of PC. Recently, the theory of a "three-step procedure" for pancreatic carcinogenesis has been widely adapted to the clinical field, giving rise to the opportunity for early diagnosis and intervention over a long period of time[14]. PC screening relies only on cross-sectional imaging or is accompanied by EUS-guided tissue acquisition in high-risk individuals[59]. To date, there have been no reports regarding the usefulness of CTCs for the early detection or screening of PC. CtDNA, another family of liquid biopsy, has been found to be useful for early PC detection with 64% sensitivity and 99% specificity when combined with well-selected plasma proteins[60]. A relevant study by Cohen *et al*[60]. to explore the role of CTCs in the early diagnosis of PC is registered and ongoing (ClinicalTrials.gov, NCT0207616). Further studies with larger numbers of patients are warranted to evaluate the clinical efficacy of CTCs in this field. The high number of CTCs in the peripheral blood of patients with lung and breast cancer makes CTC-guided tailored therapy more feasible to study[61-64]. By contrast, the small number of CTCs in peripheral blood is a concern for further studies on CTCs in PC. Therefore, the abundance of CTCs in portal venous blood may play a crucial role in resolving various clinical issues in the future.

Another noteworthy point is the method used to sample CTCs from the portal vein. As described in Tables 1 and 2, intraoperative sampling of portal venous blood rather than the EUS-guided approach has been more dominant. This may mean that patients who undergo portal vein sampling intraoperatively lose the opportunity to be assessed for risk of recurrence before surgery. In the future, EUS-guided portal vein CTC sampling, which preserves the patient's normal anatomy, should be performed more widely. Standardization of CTC isolation techniques and the development of new assays that can provide clinicians with comprehensive insight into CTC heterogeneity should be investigated further.

CONCLUSION

CTCs have emerged as a new biomarker for various solid cancers over the past decade. However, their role, especially in the peripheral blood, has been limited in PC. Previous midsize studies demonstrated promising results of CTCs from the portal venous blood with a higher detection rate and better prognosis prediction than those by conventional CTC research from the peripheral blood. In the future, studies with larger numbers of patients are needed to establish the role of CTCs from the portal venous blood in early detection, risk stratification of postoperative recurrence, prediction of treatment resistance, and identification of tumor-specific biomarkers for developing targeted chemotherapeutic agents.

FOOTNOTES

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