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Review

Tumor biology and multidisciplinary strategies of oligometastasis in gastrointestinal cancers

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ABSTRACT

More than 70% of gastrointestinal (GI) cancers are diagnosed with metastases, leading to poor prognosis. For some cancer patients with limited sites of metastatic tumors, the term oligometastatic disease (OMD) has been coined as opposed to systemic polymetastasis (PMD) disease. Stephan Paget first described an organ-specific pattern of metastasis in 1889, now known as the "seed and soil" theory where distinct cancer types are found to metastasize to different tumor-specific sites. Our understanding of the biology of tumor metastasis and specifically the molecular mechanisms driving their formation are still limited, in particular, as it relates to the genesis of oligometastasis. In the following review, we discuss recent advances in general understanding of this metastatic behavior including the role of specific signaling pathways, various molecular features and biomarkers, as well as the interaction of carcinoma cells with their tissue microenvironments (both primary and metastatic niches). The unique features that underlie OMD provide potential targets for localized therapy. As it relates to clinical practice, OMD is emerging as treatable with surgical resection and/or other local therapy options. Strategies currently being applied in the clinical management of OMD will be discussed including surgical, radiation-based therapy, ablation procedures, and the results of emerging clinical trials involving immunotherapy.

1. Introduction

More than 70% of gastrointestinal (GI) cancers are diagnosed with manifest metastasis, either at the time of diagnosis (synchronous), or at later stages (metachronous) [1]. Whereas many primary tumors can be effectively controlled by local therapies (*e.g.* surgery, radiation or thermoablation), the effective treatment of metastatic disease represents an important clinical challenge. Given our aging populations worldwide, and the increasing incidence of GI cancers, the medical need to more effectively treat metastatic disease is urgent. In a subgroup of patients, metastasis can be limited to an individual lesion, or even a few foci, for a relatively long period of time and thus can be effectively treated using localized strategies for long term tumor control.

In 1995 Hellman and Weichselbaum proposed a new term for situations where limited tumor metastasis is seen that was termed "oligometastatic disease" or OMD. This has eventually led to a paradigm shift in our understanding and treatment of some metastatic diseases [2]. Importantly, current treatments for metastatic cancer are still largely based on the paradigm that metastatic spread beyond local lymph nodes is uniformly a systemic disease. This often results in non-selective, non-individualized systemic treatments which do not take into

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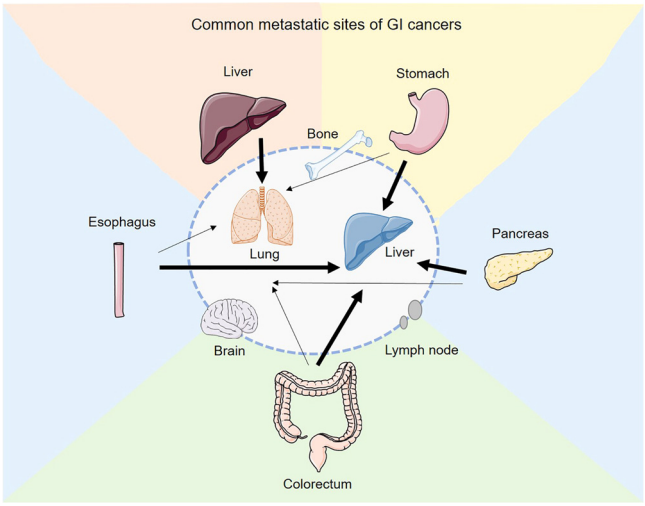

Fig. 1. Common sites of oligometastatic disease in GI cancers. For gastrointestinal cancers (including esophageal cancer, gastric cancer, liver cancer, pancreatic cancer, colorectal cancer *etc.*), liver and lung are relative common organs with localized spread of metastasis. It might be great benefit to achieve the control of oligometastatic disease. (Thickness of black arrows reflects the general frequencies of primary tumor metastasizes to the indicated distant organ site.).

consideration the substantial variability of potential clinical outcomes, and thus may exclude a subgroup to patients that could respond favorably to local or multimodal treatment regimens with a dramatic effect on disease outcome. In some instances of colorectal cancer (CRC), local as well as systemic treatments are currently being employed as a potential strategy for selected cases where single or few metastases are seen (Fig. 1). This treatment is still based largely on clinical experience rather than on scientific evidence. Importantly, systemic therapies are often associated with substantial adverse effects and a significant risk of inducing therapeutic resistance ultimately leading to uncontrollable tumor progression.

The identification of an oligometastatic state as a separate clinical entity suggests that a subgroup of patients could be effectively cured by a combination of local (surgery, radiotherapy, local ablative treatment) and systemic therapeutic strategies. The treatment success of multimodal approaches for OMD is dependent on effective diagnosis, clinical tolerability and optimized therapeutic algorithms. The integration of emerging genetic, epigenetic and environmental analyses, and the application of new therapeutic options such as immunotherapy and molecular targeted therapy may impact oligometastatic disease and thus represents an important emerging field in cancer research.

In the following sections we will discuss a series of biologically distinct mechanisms that can lead either to oligo- or polymetastases of gastrointestinal cancer [comprising mainly colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), and esophageal adenocarcinoma (EAC)]. A better understanding of the pathophysiology of these clinically distinct settings can enhance clinical practice by providing a set of therapy decision points based on biological, immunological and anatomical characteristics. Recent advances detailing the mechanisms and emerging biomarkers for the metastatic behavior of GI cancers will be highlighted, as well as new strategies that are being applied for the clinical management of OMD.

2. Definition and clinical significance of oligometastases

Weinberg et al. described the biologic characteristics of active invasion and metastasis, with the reseeding and colonization of some tumor cells with "metastatic signatures" in specific tissues, as central hallmarks of cancer [3]. The metastatic capacity of primary tumors can be defined based in part on the size and volume of the tumor, as well as the resident organ. The observation of oliogometastasis, and the related phenomenon of oligorecurrence (relapsed oligometastatic disease), suggests that local cancer treatments may be largely curative in a subpopulation of patients with metastases/recurrence [1]. The spectrum model for oligometastases has been described as a "cancer diaspora in cancer demography". It includes the passive migration from the primary lesion with mild hypoxia and unlimited nutrients that does not lead to evolutionary clonal pressure, with the homing of the cancer to a new niche. The origin of this cancer is known and only limited metastases are observed. The immune system has not addressed the potential threat, and reduced inflammation leads to fewer leukocytes within the tumor [4,5]. At one side of the spectrum, some cancers remain a local disease and do not metastasize. At the other extreme, the cancers are widely metastatic. Then there are cancers that exhibit a behavior intermediate between these two states, with clonal evolution conferring varying degrees of metastatic potential [6]. The intermediate phase is considered the oligometastatic state, where patients develop a limited number of metastases, and the disease does not quickly progress to a widespread distribution of cancer [2]. Niibe et al. further subclassified OMD into synchronous oligometastasis (a clinical scenario in which oligometastatic disease is detected at the time of diagnosis of the primary tumour [1]) and metachronous oligometastasis (the development of oligometastatic disease after treatment of the primary tumor). However the time interval for classification of metachronous versus synchronous has not been standardized [1]. A search in PubMed:MEDLINE in early 2011 returned 46 titles containing < oligometast* > [7]. Applying the same search terms today yields 1413 articles, with 416 reviews. This increased interest in OMD has emerged following advances in early diagnosis of metastatic disease, expanded techniques in multidisciplinary tumor management, and new directions in metastatic research. The oligometastatic state can now be seen as an important therapeutic opportunity that involves collaboration between surgical, radiotherapy and oncology perspectives [8]. To date, little is understood about the molecular basis of oligometastatic tumors, their interactions with the surrounding microenvironment, or the signaling pathways regulating polymetastatic versus oligometastatic spread. A better understanding of this biology will help in the development of more effective therapeutic strategies for this disease “phenotype”.

3. Hallmarks of tumor biology of oligometastatic disease

3.1. Cancer metabolism in OMD

It has been suggested that the metastatic cascade of a primary tumor is associated with "metabolic rewiring" where the environment dictates metabolic changes in secondary tumors [9]. A sugar diet has shown to promote breast cancer growth and metastasis with increased expression of 12-lipoxygenase and its metabolite contributing to lung metastasis [10]. A robust oxidation of glucose rather than glutamine in the citric acid cycle is seen in glioblastomas and brain metastases that can be correlated with the expression of acetyl-CoA synthetase enzyme 2 [11]. Similarly, aerobic glycolysis remodeling in breast cancer induces methylglyoxal (MG) formation and sustains YAP nuclear localization promoting tumor metastasis [12]. The Warburg pathway associated enzyme PFKFB4 couples glycoses and stimulates Steroid receptor coactive-3 (SRC-3) that helps promote metastasis formation [13]. The metabolic reprogramming of cancer cells can be evidenced by the presence of varied glycolysis or Oxidative phosphorylation (OXPHOS) balance in metastatic sites. Breast cancer cells with a high liver metastatic potential have been found to show increased expression of pyruvate dehydrogenase kinase-1 and an increased metastatic potential [14]. Inhibition of the glycolytic enzyme pyruvate kinase M2 can revert this metabolic switch from OXPHOS to glycosis and subsequently reduce lung metastasis in breast cancer [15]. In GI cancer studies, a pancreatic cancer model that displayed distant metastatic clones

showed increased glucose uptake and the secretion of lactate linked to the pentose phosphate pathway in concert with epigenetic reprogramming during pancreatic cancer progression [16]. PDAC cells can take up more glucose via increased expression of PON2 which contributes to the GLUT1 transport mechanism [17]. In colorectal cancer metastatic site formation is influenced by liver microenvironmental effects that can lead to an upregulation of ALDOB (a fructose metabolic enzyme) in tumor cells; Fructose metabolites can help fuel cancer cell metabolism. Targeting ALDOB, or reducing dietary fructose, can diminish liver metastasis in CRC [18].

Obesity is associated with local or distant metastasis formation. In ovarian cancer, obesity can promote lipogenesis in tumor cells and intraperitoneal metastasis [19]. Aberrant plasma free fatty acids (FFA) present in obesity can enhance TGF-β-induced nuclear USP9x-SMAD4 interaction that can promote lymph node metastasis of breast cancer [20]. In cervical cancer, the reprogramming of fatty acid metabolism induced by the long non-coding RNA LNMICC results in increased lymph node metastasis [21]. A high fat diet can promote lipid accumulation through SREBP, the sterol regulatory element binding protein-dependent lipogenesis that can occur in prostate cancer with PML gene loss leading to metastasis formation [22]. Under hypoxia and acidosis, glioblastoma cells were found to express more heparan sulfate proteoglycans (HSPG) resulting in the enhanced internalization of lipoproteins and a lipid-storage phenotype associated with increased lung metastasis [23]. Altered lipid metabolic patterns are detectable in a variety of cancers. Triple-negative breast cancer cells can utilize lipid droplets via fatty acid oxidation that is triggered by CUB-domain containing protein 1, or Src pathway modification, resulting in increased metastasis [24,25]. In lung metastases, cancer cells can possess increased pyruvate carboxylase anaplerosis leading to increased pyruvate facilitation in mitochondria [26]. In addition, prostate cancer cells have been shown to reprogram their glutamine metabolism and promote lipogenesis thus better supporting prostate cancer metastasis via the SRC-2 pathway [27]. Sounni et al. have found that tumors can undergo a metabolic shift toward carbohydrate and lipid metabolism after VEGF blockade using sunitinib or sorafenib, resulting in tumor regression. Lipogenesis inhibition can inhibit tumor regrowth and organ specific metastasis as evidenced via CRC and breast cancer models [28]. Metabolic microenvironments can influence the tumor stroma and further affect metastatic spread. In diabetes patients, hyperglycemia can impair tumor growth in early stages via attenuation of angiogenesis, however this biology can also enhance metastatic seeding through neutrophil impairment with reduced production of G-CSF [29]. 27-hydroxycholesterol is a cholesterol metabolite that appears in high fat diets and has been found to increase infiltration of polymorphonuclear neutrophils and γδT cells in pre-metastatic sites [30]. Tumor endothelial cells have been shown to undergo a hyperglycolytic metabolic shift resulting in increased VE-cadherin endocytosis, and a further loosening the EC barrier after activation of pericytes. By targeting the glycolytic activator PFKFB3, the accompanying metabolic shift was found to block tumor metastasis and to improve perfusion during chemotherapy [31]. A reprogrammed of choline metabolism induced by estrogen receptor α in breast cancer was reported to upregulate phosphatidylcholine synthesis and facilitate early stage breast cancer metastasis [32]. A controversial role of PGC-1α has been suggested in certain types of cancer. Breast cancer cells enriched in PGC-1α show a more global bioenergetic capacity with increased metastatic capacity to lung and bone [33]. However, PGC-1α can also function as a protective factor in prostate cancer by inhibiting polyamine synthesis via c-MYC suppression and reducing metastasis formation [34]. An amino acid metabolic transcriptome shift has been described in brain metastases moderated by glutamate decarboxylase 1 following epigenetic changes that enhance glutamate metabolism [35]. Increased expression of proline dehydrogenase as well as proline catabolism are increased in metastases as compared to primary breast cancer [36]. To date, the data and resources needed to better understand the metabolic mechanisms surrounding OMD in GI cancers are lacking. However, the recent advances in our understanding of cancer metabolism and metastasis in other types of cancer, suggest potential directions for enhancing the therapy of GI tumors by using metabolic inhibitors.

3.2. The tumor microenvironment in OMD - the role of cancer associated fibroblasts

Fibroblasts are the most abundant cells within connective tissues where they produce the components making up the extracellular matrix (ECM) and help maintain tissue homeostasis. Cancer associated fibroblasts (CAFs) represent a heterogeneous population of stromal cells strongly linked to cancer growth and progression. CAFs were described to secrete TGF-α that in turn helps promote peritoneal metastasis in ovarian cancer through activation of EGFR [37]. In breast cancer, the chemokines CXCL12 and CXCL14 produced by CAFs, have been shown to promote lung metastasis in mice, and their expression has been subsequently correlated with poor prognosis in patients [38,39]. For this reason, they represent potential targets for cancer stromal therapy [40,41]. A sub-population of CAFs showing low expression of p85alpha were shown to release exosomes enriched in Wnt10b that could subsequently promote breast cancer cell metastasis [42]. WNT2 derived from CAFs was shown to enhance liver metastasis formation in an experimental mouse model of colorectal cancer (CRC), and to correlate with poor survival in CRC patients [43]. The Wnt signaling antagonist sFRP2 released by aging fibroblasts was shown to augment the metastasis of melanoma [44]. Depletion of annexin A6 in fibroblasts was found to limit liver metastasis in an orthotopic PDAC mouse model [45].

High endoglin-expressing fibroblasts are thought to promote liver infiltration of CRCs while endoglin expression by fibroblasts at the tumor margin has been correlated with decreased disease free survival [46]. Neutralizing endoglin in the tumor microenvironment was found to benefit control of CRC disease progression [47]. Targeting of prolyl hydroxylase domain protein 2 (PHD2) expressed in CAFs was shown to destabilize HIF-1α and lead to less lung and liver metastasis in breast cancer [48]. Other sub-types of CAFs may play alternative roles in cancer metastasis. An elevated level of asporin (a TGF-β1 Inhibitor) expression in the tumor stroma is correlated with a good prognosis in breast cancer. Asporin may help constrain metastasis formation of breast cancer in mouse models [49]. In addition, asporin has also been shown to alter the tumor microenvironment and potentially drive metastasis in prostate cancer [50]. The expression and the role of asporin in GI cancers needs to be further explored. Recently, Wang et al. reported that asporin expressed in pancreatic stellate cells promoted pancreatic cancer cell invasion and migration by regulating their epithelial-to-mesenchymal transition through both autocrine and paracrine mechanisms [51].

CAFs may also contribute to tumor metastasis via induction of metabolic reprogramming in the cancer cells. Activation of p38 s/MAPK in CAFs can lead to an increased secretion of IL-6, CCL5, and CXCL10, that was linked to glycolysis and the utilization of glycogen that could further promote cancer invasion and metastasis [52]. Stromal expression of the metabolic regulator methyltransferase nicotinamide N-methyltransferase (NNMT), was shown to influence the CAF phenotype by regulating cytokine secretion and oncogenic matrix formation. Stromal NNMT overexpression was further shown to promote metastasis in a mouse model of ovarian cancer [53].

Through their interplay with cancer stem cells (CSC), CAFs can modulate organ specific tumor metastasis. In breast cancer, autophagic CAFs were shown to release high-mobility group box 1 (HMGB1) that acts as a ligand for TLR4-activation, and was in turn associated with the maintenance of tumor stemness and progression [54]. In a second study, the secretion of Netrin-1 by CAFs was shown to enhance cancer plasticity, while Netrin-1 neutralization was found to inhibit tumor growth of both colon and lung cancers [55]. In addition, CAFs have

been proposed to circulate together with circulating tumor cells (CTCs) to help support cancer metastasis. The presence of CAFs in the peripheral blood of breast cancer patients has been linked to metastatic disease and suggested the potential of using circulating CAFs as a promising biomarker for metastasis [56]. Serum levels of the TGF-β/BMP family member GDF15 (MIC-1) that is secreted by CAFs is thought to help stimulate tumor growth at distant sites in prostate cancer [57]. CAFs have been reported to recruit integrin α5 ^{high} ascitic tumor cells that act as "metastatic units" of ovarian cancer that in turn guide peritoneal invasion and promote transcoelomic metastasis [58].

The interaction between fibroblasts and immune cells can strongly influence cancer progression. CCL19 expression by fibroblasts in the tumor microenvironment of lung carcinoma can enhance the recruitment and activation of anti-tumor CD8 + T cells and thereby help restrict cancer progression through an enhanced immune response [59]. Similarly, deletion of aSMA + myofibroblasts in pancreatic cancer leads to reduced immune surveillance and increased levels of CD4 + Foxp3 + regulatory T cells (Tregs) [60]. Other CAF subtypes were shown to promote an immunosuppressive microenvironment that can accelerate cancer progression. Chitinase 3-like 1(Chi3L1) releasing fibroblasts are highly enriched in the microenvironments surrounding primary and pulmonary metastases of breast cancer. The deletion of Chi3L1 in fibroblasts was found to attenuate tumor growth and metastases, which was associated with an increased filtration of CD8 + and CD4 + T cells and decreased macrophage M2 reprogramming [61]. These findings highlight the importance of tumor stromal CAFs in the modulation of tumor metastasis. Although direct evidence relating to similar phenomenon in GI cancers is currently lacking, the results from breast cancer, prostate and ovarian cancer studies provide clues as to how organ-specific metastatic progression may be controlled in gastrointestinal cancers.

3.3. The tumor microenvironments linked to OMD - the role of exosomes in oligometastasis

Primary tumors can promote pre-metastatic niche formation in target organs in advance of the metastatic cancer cells [62]. We have emphasized the importance of preventing the formation of metastatic niche concerning modern strategies targeting metastasis previously [63]. The potential interaction between a primary tumor and distant sites may play an important role in the development of oligometastasis in gastrointestinal cancers. Various cellular and molecular mechanisms have been linked to the formation of the pre-metastatic niche. To this end, exosomes have been found to act as important mediators of intercellular communication [64]. Exosomes are extracellular vesicles produced by both tumor cells and CAFs that contain proteins, nucleic acids and lipids that reflect the biology of the parental cell [65]. Costa-Silva et al. found that pancreatic cancer-derived-exosomes induce a fibrotic microenvironment and help recruit bone marrow-derived macrophages for the development of liver metastasis [66]. Shao et al. reported that exosomes derived from colorectal cancer cells can induce macrophage polarization and establish an inflammatory pre-metastatic niche in the liver [67]. Interruption of exosome release, or their uptake, may affect the biological behavior of tumors and interfere with formation of the pre-metastatic niche. The role of exosomes in pre-metastatic niche formation in oligometastatic gastrointestinal cancers is at present unclear. However, several studies have revealed remarkable genetic and epigenetic heterogeneity between the primary tumors and metastatic sites linked to exosome biology [68,69]. Kim et al. discovered distinct patterns of exosome proteome expression and tyrosine kinase activities in different metastatic sites of pancreatic cancer, including liver, lung, and peritoneum [70]. Yu et al. compared the proteomic profiling of exosomes derived from weakly metastatic murine pancreatic cancer cells (Panc02), and highly metastatic subline-Panc02-H7 cells. They found that highly enriched proteins in the Panc02-H7-derived exosomes could be strongly associated with tumor growth, invasion, and metastasis [71]. Our group has established a highly metastatic pancreatic cancer cell line L3.6 pl after several cycles of *in vivo* selection. The L3.6 pl cells exhibit a higher incidence of liver metastases than the parental cells [72]. Recently, based on studies using this cell line model, we reported an immunosuppressive role of pancreatic cancer-derived EVs on NK cell dysfunction as it relates to pre-metastatic niche formation of PDAC [73]. A better understanding of the biology of exosomes will make impact on how the treatment of systematic metastatic disease is addressed in future.

3.4. Molecular features of oligometastatic disease

Patients with oligometastatic disease appear to benefit from localized therapy, however the molecular characteristics that distinguish oligo- from polymetastasis need to be better defined [74,75]. It has been suggested that oligo- or poly-metastasis may either originate from different clones, or may be part a sequential development with oligometastasis representing a transient state in the metastatic process [76]. Currently, the selection of oligometastatic patients is largely based on the number of metastases present, and the length of the disease-free interval [8,77]. The transition of the metastatic state from oligo- to polymetastasis has been observed in mouse models [78]. A better understanding of the molecular features, expression signatures or other hallmarks that help distinguish between oligo- and polymetastasis would clearly allow a more reliable selection of patients who could benefit from the OMD-guided therapy [8,77,79]. While information in this regard is still quite limited, initial transcriptional expression profiling based signatures have been proposed to help distinguish oligo-from polymetastasis. Lussier et al. reported that oligo- and polymetastasis could be clustered and characterized by prioritized microRNA (miRNA) signatures [77], including analysis of the miRNA-200 family, widely reported to be involved in metastasis [80]. In addition, high expression of miR-200c in metastatic tumor was shown to predict progression towards polymetastasis through regulation of epithelial-mesenchymal transition (EMT)-related pathways. Sun et al. reported a similar role of miR-200c in the transition from oligo- to polymetastasis through the target gene Sec23a, which appears to suppress oligo- to poly-metastatic progression by modifying the tumor microenvironment [81]. Subsequently, Lussier et al. described a larger and more homogenous group of patients with lung-derived metastases. In this study, a set of miRNAs were identified that were down-regulated in a high progression (HRP) group, as compared to a low rate of progression (LRP) group [82]. The presence of these miRNAs could be used to distinguish HRP from LRP. Wang et al. identified a panel of 10 miRNAs that could distinguish the oligo- from polymetastatic lung cancer [83]. In patients with oligometastatic liver disease, Fromme et al. reported that over-expression of FGFR3 in oligometastatic colorectal cancers was significantly associated with shorter overall survival. They suggested that FGFR3 overexpression could define a clinical subgroup with poor outcome and may thus represent a potential therapeutic target [84].

The molecular signatures proposed from the studies described above suggest that it should be able to further optimize and better distinguish oligo- from polymetastatic disease in GI cancers. To date, only a few genes and miRNAs have been found to overlap between GI tumors and the signatures detailed above [78,82,83]. It has been proposed that analysis of shared pathways, and pathway-based approaches may help overcome some of the inconsistency among individual gene based analysis. A re-analysis of the published miRNA datasets by Uppal et al. identified a series of Kyoto Encyclopedia of Genes and Genomes (KEGG)-derived pathways that are targeted by relevant miRNAs in oligometastasis [85]. Further enrichment of this dataset have identified three distinct functional pathway groups for; adhesion, invasion, and mobility (AIM); intracellular signaling pathways (ICS); and cancer-specific signaling pathways (CSS) group, that could be linked to specific cancer metastatic patterns. Wang et al. also discussed three pathways of axon guidance, cancer metastasis, and proteoglycan biology believed to

contribute to the lung cancer with OMD and PMD phenotypes via miRNA effects [83].

Pitroda et al. proposed a consensus molecular subtype for limited CRC liver metastases based on the integrated transcriptional analysis of both mRNA and miRNA. Three molecular subtypes were identified: 1.) canonical subtype, 2.) immune subtype and 3.) a stromal subtype [79]. Notably, the immune subtype 2-related metastases showed significantly over-expressed innate and adaptive immune genes as compared to the subtype 1 and subtype 3-type metastases, showed a robust immune infiltration in the original metastatic lesions. The patients with subtype 2 metastases showed a lower recurrence rate, and longer survival after hepatic resection of their metastatic lesions as compared to subtype 1 or subtype 3 metastases. By contrast, the poor-survival subtype 1 and 3 metastases showed an enrichment of expression patterns associated with stromal infiltration, presence of EMT, extracellular matrix remodeling, and angiogenesis. Integration of the resultant molecular subtypes with clinical risk stratification yielded three prognostic risk groups: low-risk, intermediate-risk, and high-risk. The integrated low-risk group showed significantly longer distant metastasis-free survival and overall survival, and was largely represented the oligometastatic phenotype. By targeting the subset of patients with predicted oligometastatic phenotype, the molecular signatures alone, or in combination with clinical risk score, may provide a rational strategy for the establishment of criteria for enhancing curative local therapies.

3.5. Tumor genomics and oligometastasis

To date, there are relatively few studies that have exclusively explored the potential gene mutations found between primary GI cancers and their metastatic disease. Zehir et al. compared data from advanced or metastatic cancers to primary tumors from TCGA [86]. The results from a metastatic cancer study were consistent with the TCGA findings. They identified major differences between the two cohorts. First, TP53 mutations were more frequent in metastatic gastric cancer, second; TP53 mutations were also found to be present in primary gastric cancer, and finally; the PIK3CA mutation was less frequent in metastatic gastric cancer than in primary cancer. In support of this observation, Ikari et al. also found that the TP53 mutation rate was significantly higher in gastric cancer patients with liver metastasis, as compared to those without metastasis [87]. In addition, the status of TP53 mutations in the liver metastatic group was linked to lymph node stage and venous invasion. Pectasides *et al.* found that PIK3CA mutations and amplification of EGFR, ERBB2, CKD4/6 and MET were frequently found to be different between primary gastric cancers and their metastatic lesions. Inconsistent gene mutations between the primary and matched metastatic gastric cancer tumors was found to occur in 45% patents [88]. Zhang et al. identified mutations in GPI, JAK3, PRSS8 and IDH3G that were more common in gastric cancer patients without peritoneal metastasis, than in peritoneal metastatic patients. Four mutations (PRDM1, c.950 G > A; XPC, c.1315 G > C; CD68, c.554A > C; ACVR1B, c.1345C > A) were only seen in peritoneal metastasis patients [89]. In one gastric adenocarcinoma with peritoneal metastasis, 23 somatic mutations were found in the primary tumor, while 12 somatic variants were associated with metastatic cancer . Four somatic variations (RP1L1, PRB1, HS6ST3 and DCTN1) were found to simultaneously occur in both primary and peritoneal metastatic cancer. Genomic profiling has been used for predicting lymph node metastasis in patients with gastric cancer, which may prove useful for the identification of patients for extended lymph node resection [90,91].

Intratumoral heterogeneity (ITH) is an important topic in cancer genomics, suggesting that a single tumor consists of different cell subpopulations [92]. APC, TP53, and KRAS mutations frequently occur in heterogeneous colorectal cancers which could be used to predict a high potential for liver metastasis [93]. Gene mutation and methylation events are observed in different disease stages of colorectal cancers. Compared to the corresponding lymph node metastases, KRAS mutations and p16INK4a methylation were found to be significantly lower in stage III CRCs, while in stage IV CRC KRAS, CDH1, and p16INK4a mutations were decreased, but did not reach significance. A comparison between stage IV primary tumors and their corresponding liver metastases showed an increase in RASSF1a methylation and a decrease in p16INK4a methylation. In lymph node metastases from stage III and IV CRCs, KRAS, BRAF and p53 mutations tend to increase. KRAS and p16IN4a mutations, as well as RASSF1a methylation were found to be higher in liver metastases than in lymph node metastases originating from stage IV CRC [94]. Comprehensive analysis of tumor genomics should provide unique signatures that could be used to classify OMD with more biological and genetic relevance.

3.6. Other biomarkers associated with the characterization of oligometastases

3.6.1. Alteration of ctDNAs in oligo- and polymetastasis

Circulating tumor DNA (ctDNA), the double-stranded DNA fragments released from tumor cells into the circulation during apoptosis or the necrotic process, represents an important target for current applications of liquid biopsy. Although the half-life of ctDNA is rather short, ctDNA levels and the degree of tumor burden remain consistent. CtDNAs also carry important genomic information regarding the tumor including copy number variation (CNV), genomic integrity, mutation burden, and gene methylation status. The genomic information from ctDNA may be seen to accurately reflect dynamic changes that occur in tumors with the context of metastatic tumor progression. The overall analysis of ctDNA may thus help to assess the genetic alterations of tumor burden and the presence of tumor heterogeneity that could be of benefit for precise cancer treatment [95].

Mutant allele frequencies (MAFs) of many cancer hot spot mutation genes (TP53, RET, FGFR3, and APC) have been shown to increase significantly in patients with metastasis as compared to patients with single malignant lesion [96]. The detection of KRAS mutations in ctDNA samples has shown potential application in pancreatic cancer oligometastasis. Bernard et al. used ctDNA analysis of pancreatic ductal adenocarcinoma (PDAC) patients to show that patients from the metastatic group carry higher levels of KRAS MAF than do patients with localized disease. KRAS MAF levels as detected by ctDNA analysis showed an association with poor progression-free survival (PFS) and overall survival (OS) based on univariate analysis [97]. In a study of metastatic colorectal cancer (mCRC), analysis of ctDNA pattern from patients with high tumor burden (> 1 metastasis) showed that RAS, BRAF, and ERBB2 alterations were detected in 84.6% cases, which was concordant with direct analysis of the tumor tissue [98]. A further analysis of ctDNA for presence of the gene RAS mutation has shown a high level of sensitivity (93.3%) and specificity (100%). Additional changes in ctDNA levels provided predictive information much earlier than changes of CEA and CA19-9 levels could be detected [99].

Alternations in methylation patterns in specific genes can be assessed by using ctDNA analysis that provide important information for metastasis associated studies. Methylation of the MT1M and MT1G promoters was found at a higher incidence in patients with lymph node metastasis or extrahepatic metastasis [100]. With identification of a link between DNA epigenetic modifications and cancer progression, the detection of 5-Hydroxymethylcytosine (5hmC) an important DNA modification factor, can be measured via ctDNA analysis for clinical relevance. Loss of 5hmc in tumor DNA has been observed with stage-dependent variations in lung cancer as they progress from early stage to late stage disease with metastasis. In this study, the number of 5hmC-enriched regions (5hMR) was found to be decreased in lung cancer patients with metastasis as compared to non-metastatic patients, or healthy individuals [101].

The limitations of ctDNA profiling are also important. Strickler, et al. found that in nearly 15% of metastatic colorectal cancer cases genomic alterations in ctDNA could not be detected, presumably

because of the low tumor burden leading to reduced levels of ctDNA [102]. Based on the trend of ctDNA application in various tumors types, ctDNA analysis could represent an important tool for distinguishing oligo- from polymetastasis following more detailed study.

3.6.2. Aneuploid CTCs in oligo- and polymetastasis

Circulating tumor cells (CTCs) are carcinoma cells shed from primary or metastatic solid tumors into the peripheral blood, whereas circulating endothelial cells (CECs) are derived from endothelial cells (ECs) which make up the blood vessels. Clinical relevance of CTCs in the context of cancer metastases/prognosis [103,104], and CECs with respect to assessing tumor angiogenesis, have been well detailed elsewhere [105]. CTC is now accepted as a breast cancer biomarker by the American Society of Clinical Oncology (ASCO) [106]. In the past decade, the detection of CTCs has been used to evaluate cancer patient prognosis [107], therapeutic efficacy [108,109], and to monitor post-surgical cancer relapse [110,111], as well as drug resistance in carcinoma patients [112,113] as well as in metastatic "patient-derived xenograft tumor mouse models" (mPDX) [114]. Aneuploidy (ap) is a hallmark of malignant cells [115,116]. The existence of aneuploid CTCs (apCTCs) can be detected in the peripheral circulation [117]. Recently, a comprehensive breast cancer study demonstrated that $EpCAM^+$ apCTCs and aneuploid disseminated tumor cells (apDTCs) in bone marrow are able to guide oligometastasis to lung in breast carcinoma patients [118].

In addition to aneuploid carcinoma cells, some aneuploid tumor endothelial cells (TECs) in neoplastic tissues [119] express inhibitory molecules such as PD-L1, that can attenuate the anti-cancer immune response mediated by $CD8^+$ T lymphocytes [120]. A recent study combining anti-angiogeneic agents and anti-PD-1 checkpoint blockade immunotherapy demonstrated a durable synergetic clinical response to malignant cancer cells [121]. The significance of TEC analysis suggests that analysis of circulating tumor endothelial cells (CTECs) may also show utility in clinical utilities [122,123]. Recent studies using SE-iFISH analysis [124] of specimens from various carcinoma patients indicated that in addition to PD-L1, several other tumor biomarkers are expressed by aneuploid CTECs (Fig. 2). The analysis of apCTECs could provide additional information regarding potential invasive cancer growth, metastasis and disease progression [122,123].

Recent results suggest that as a counterpart to 'nucleotide circulating tumor biomarker' ctDNA data, non-hematologic aneuploid CTCs, and CTECs may constitute important targets as 'cellular circulating tumor biomarkers' [125]. apCTCs and apCTECs possess distinct clinical significance and will provide insight for the evaluation of cancer metastases and therapeutic efficacy in carcinoma patients.

4. Multidisciplinary management of oligometastatic disease

Metastasis represents the main cause of treatment failure in tumor management. The concept of oligometastasis revealed an important potential disease process and therapeutic state that has changed our understanding of advanced malignant tumors and the choice of treatments [2,126]. There is still controversy regarding the definition of oligometastatic disease. Most clinical trial protocols and clinicians accept a definition of 1–3 or 1–5 metastatic lesions [8,127,128]. At this relatively early stage in cancer progression, the bio-invasiveness of the tumor is still relatively low reflected by a limited number of organs involved with few metastatic numbers [129,130]. As discussed, the better detection of oligometastatic patients can provide an important therapeutic window.

While cancer patients with oligometastasis can have a relatively good prognosis [131,132], the diagnosis of oligometastasis can be difficult in older patients where efficient diagnosis can be complicated by the presence of other diseases. A multidisciplinary team (MDT) approach can help integrate diverse sets of information regarding the physical conditions of the patients, pathological features of tumors, imaging, staging, *etc*. to provide optimal diagnosis and treatment for patients with OMD [4,133]. As at present, there is no specific set of uniform standards for MDT diagnosis of GI cancer OMD, a team approach can help with identification and management of the disease. The present data and guidelines support systemic therapy, or a multi-disciplinary, multi-therapeutic approach involving surgery as the main treatment option [127,134,135]. Surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy *etc*., are central to effective MDT [129,136].

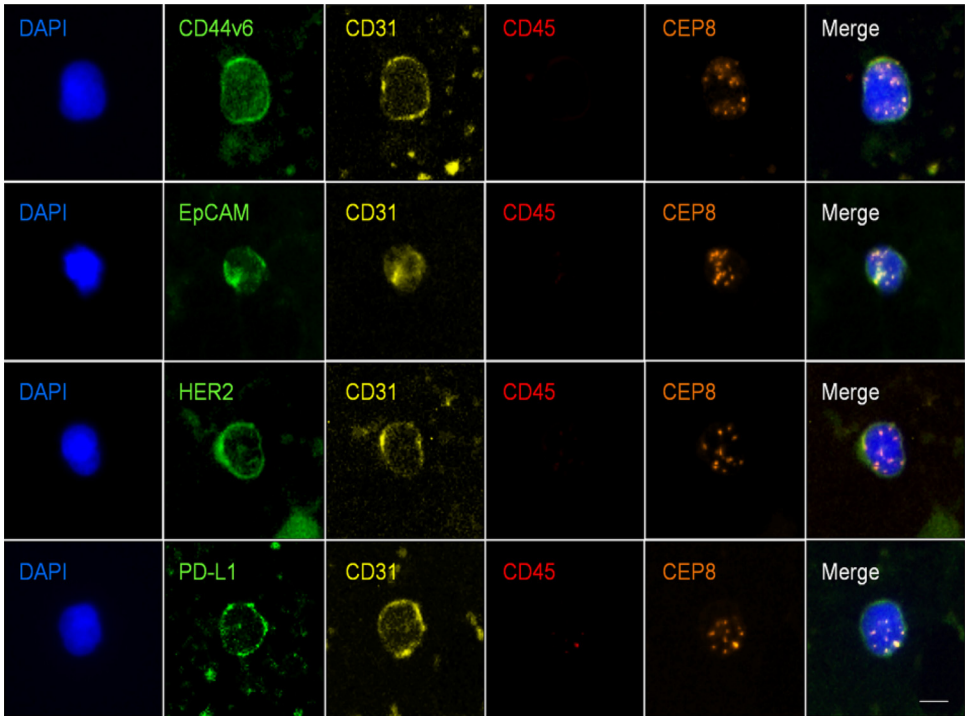

Fig. 2. *In situ* phenotypic and karyotypic characterization of aneuploid CTECs expressing tumor biomarkers. Following subtraction enrichment (SE) of non-hematologic circulating rare cells from variety of carcinoma patients, specimens are subjected to comprehensive characterization performed by immunofluorescence staining-FISH (iFISH) strategy. Several tumor biomarkers, including the stemness marker CD44v6, EpCAM, HER2 and PD-L1, are respectively expressed on the aneuploid CTECs ($CD31^+$/ $CD45^-$, ≥trisomy 8).

4.1. Surgical treatment of OMD

Surgery is an important treatment option for GI cancers with OMD. Liver is a common site of solid tumor metastasis, especially metastasis from colorectal cancer. The resection of liver metastases from colorectal cancer has improved its prognosis. The median survival time of untreated liver metastases was previously only 6.9 months, and the 5-year survival rate of patients who could not be surgically treated was less than 5%. The median survival time of patients with completely resected liver metastases or no evidence of metastatic disease is now around 35 months, and the 5-year survival rate can reach 30–57% [137–139]. Complete surgical resection of liver metastases is still probably the best option to cure GI cancer liver metastases [127,140–142]. A retrospective analysis by Sinn et al. has found that patients with advanced pancreatic cancer (locally advanced or locally resectable with hepatic oligometastasis) can benefit from pancreatoduodenectomy followed by gemcitabine-based chemotherapy [143].

4.2. Non-surgical treatment of OMD

For the treatment of colorectal cancer liver metastases, the European 2016 ESMO mCRC consensus has also highlighted the importance of surgical resection, but has also recommended other non-surgical treatments, including ablation procedures (RF, microwave, cryoablation, *etc.*), stereotactic body radiotherapy (SBRT), and selective internal radiation therapy (SIRT). All locally destructive treatments are classified as the "toolbox of local ablative treatment" (Fig. 3), which can be combined with surgery to expand therapeutic efficacy towards achieving no evidence of disease (NED) [127].

Retrospective studies from North America, Europe and Asia show that the application of SBRT for the treatment of oligometastatic disease can reach or exceed 90% of local tumor control [129,144,145]. Phase 3 studies are currently underway and show excellent preliminary results. Ongoing trials in the USA (eg, NCT02759783, NCT02089100, NCT02364557, NC01446744, NCT02893332 and NCT02417662), in conjunction with international studies should help inform as to which OMD patients will benefit the most from local intervention [135,146]. Although many short-term studies have suggested that SBRT is an appropriate strategy for OMD patients, the optimal dose and segmentation method for SBRT is still not well defined [126,147]. More prospective studies are clearly needed to help clarify the overall value and application of SBRT in the treatment of OMD in GI cancers.

In addition, the emerging breakthrough therapy approach of immune modulation has been assessed in the context of SBRT. The potential immunomodulatory effects of SBRT when used in conjunction with checkpoint inhibitors represents an important step in the clinical control of OMD [148,149]. Work to date suggests that SBRT can be exploited to benefit the immune response to cancer [4,150]. "ISABR" (Immunotherapy and stereotactic ablative radiotherapy) represents a combination of the two techniques - immunotherapy and SABR for cancer therapies [151]. These new therapeutic strategies combining radiotherapy with immunotherapy have already yielded significant effects in a variety of tumor models [152]. Early clinical trials have shown that this combined therapeutic approach can achieve promising results for metastatic solid tumors, especially in metastatic kidney and lung cancer patients [153]. Results of a series of ongoing clinical trials (eg, NCT02444741, NCT02298946, NCT02239900, NC01497808, NCT01769222 and NCT01401062) should help establish better clinical administration protocols for immunotherapy and radiotherapy approaches.

Radiofrequency ablation (RFA) technology is increasingly being used in the field of OMD management [77,154]. Radiofrequency ablation has its own unique advantages as a local treatment technique. RFA shows less trauma to patients and can be combined with surgery, or applied in postoperative recurrence, even in multiple relapses after treatment [152,155]. The combination RFA for liver metastases with immune checkpoint inhibitor therapies may help enhance antitumor immunity in a manner that mirrors that seen with ISABR [156]. Local chemotherapy including hepatic arterial infusion (HAI) therapy, is often used to treat hepatic metastases from CRC in both the resectable and non-resectable settings [157]. A prospective, multicenter, randomized, phase III trial of the RENAISSANCE (AIO-FLOT5) initiated by the AIO/CAO-V/CAOGI group in Germany was registered in October 2015 (NCT02578368). The aim of this trial is to investigate the

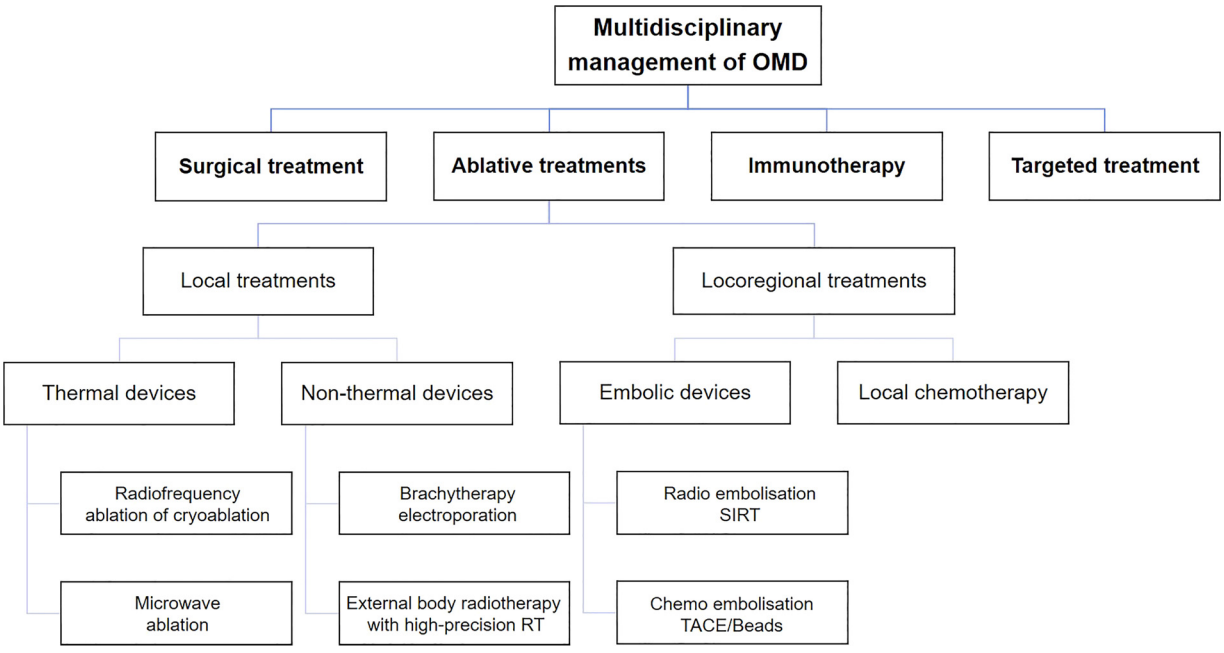

Fig. 3. Multidisciplinary management of OMD in GI cancers. Multidisciplinary mangement of OMD mainly involves surgical treatment, ablative treatments, chemotherapy, immunotherapy and targeted treatment. Appropriate treatment should be selected according to the patient's specific conditions, either alone or in combination, requiring careful MDT assessment. OMD, oligometastatic disease; RT, radiation therapy; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolization.

therapeutic effect of chemotherapy alone *vs*. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic gastric and gastroesophageal junction cancer [158]. The results of this study should be forthcoming.

Surgical options should be actively considered for the treatment of OMD. Local ablative treatment can be helpful as adjuvant therapies. Their use as a stand-alone approach can reduce their therapeutic significance. However, non-surgical treatment may still be an appropriate approach for patients with limited surgical options, or for patients unable or unwilling to undergo surgery due to complications. Although we are at present limited by a lack of large prospective randomized controlled trials, retrospective analysis has demonstrated that local treatment can substantially improve the prognosis of patients with oligometastatic disease from different GI cancer entities. To help identify the best option forward for complex clinical situations such as the effective treatment of patients in old age with confounding issues, an interdisciplinary approach using the expertise of surgeons, physiotherapists, social workers, psychologists and geriatricians will be expected to improve outcome effectively [159].

5. Conclusion

In this review, we have summarized recent advances and established knowledge regarding tumor biology and multidisciplinary therapeutic strategies of OMD especially in GI Cancers. Further knowledge with respect to cancer metabolism, tumor microenvironment, molecular signaling pathways and tumor genomics will help to better understand the process of OMD development, and will facilitate to distinguish OMD in GI cancer from polymetastatic disease. Since a majority of all GI cancers progress to a metastatic state, individualized therapy according to the underlying metastases should ideally be performed before therapy initiation. Therefore, treatment of metastatic GI cancer should be based on the molecular and cellular traits of the cancer cells in context with alterations of their local environment in the direction of precision medicine differentiating between oligo- and polymetastatic disease in GI cancer. Except for surgery, new targeted and individualized OMD treatment methods have emerged, including various radiotherapy, immunotherapy combined with radiotherapy, *etc*. Some therapeutic strategies have achieved initial success, but need to be expanded and validated in diverse settings.

Finally, it is important to note that current OMD diagnosis and treatment still face various challenges in the clinic including a lack of specific and unified standards for clinical practice. The most critical issue remains how to diagnose patients with OMD in GI cancer. However, with increasing knowledge of the underlying biology, it is expected that clinicians and researchers will pay more attention to the diversity of metastatic cancer diseases and will be able to develop comprehensive, tailored treatment strategies to maximize the therapeutic benefits and improve the quality of life for patients with metastatic GI cancer.

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Disclosures

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