Peer Review File

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Comment 1: The aspect of metabolism is discussed very superficial; the effect of different metabolites should be presented more in detail; the effect of glucose is not the same as fructose, and in this respect the impact of diabetes is usually a negative predictor.

Reply 1: Thank you for the comment. We agree with your suggestion. This paragraph was edited and expanded as requested.

Changes in the text: “Contrary to normal cells most cancer cells depend on aerobic glycolysis instead of mitochondrial oxidative phosphorylation as the energy source, and thus cancer cells have increased glucose uptake and glycolysis utilization leading to lactate production which is also known as the “Warburg effect” (41). Fructose derived from the sucrose was found to be responsible for the development of lung metastases through induction of 12-LOX signalling (37). Conversely, a decrease in fructose consumption limits metastatic potential (42). Obesity has also shown to promote metastasis through increased lipogenesis, increased vascularity and decreased M1/M2 macrophage ratios which accounts for enhanced tumorigenicity (39).

Under hypoxia and acidosis, cancer cells exhibit increased metastatic potential and that is mediated by proteoglycan-dependent endocytosis (43).”

Comment 2: In bone the cells responsible for the preparation of the metastatic niche are called osteoclasts - these are modified macrophages; the exosome paragraph is very superficial; either expand this or delete it completely; there are now several studies on the function of exosomes in lung cancer available, which have not been discussed.

Reply 2: The paragraph discussing Exosomes has been deleted.

Comment 3: MRNA: Focus on those reports which deal with lung cancer; and discuss the findings of Lussier and Wang, name the examples for lung cancer, and explain the function, at least a few examples.

Reply 3: We agree with your suggestion. The paragraph has been edited to reflect the requested changes as below.

Changes in the text: "Lussier and colleagues analyzed the microRNA patterns in samples taken from lung metastasectomies from patients with oligometastatic cancers and found that a specific set of miRNAs that are known to be associated with tumor-suppression functions were down-regulated in a group of patients with a high rate of progression (24). They also investigated microRNA profiles and expression patterns in primary and metastatic samples from cancer patients and found that high expression of miR-200c in metastatic tumors resulted in a significant increase in the metastatic burden and was shown to predict progression towards polymetastasis through regulation of EMT-related pathways (55).

In addition to predicting patient survival and tumor relapse, patients with NSCLC with and without metastasis, exhibit different miRNA profiles (56, 57). Specific miRNAs have been found to control certain functional pathways and thus believed to contribute to the lung cancer metastatic potential: hsa-let-7a (Inhibits cell proliferation through suppression of RAS and repression of the HMGA2 oncogene and associated with prolonged survival in NSCLC), hsa-miR-221 (inhibits angiogenesis in lung cancer), hsa-miR-137 (promotes lung cancer invasion), hsa-miR-372 (promotes tumor proliferation), and hsa-miR-182 (promotes lung cancer invasion) (56) (Table 4). Wang et al. identified a panel of 10 miRNAs that could distinguish the oligo- from polymetastatic lung cancer (58). MiR-654-5p, miR-485-3p, miR-329, -miR-655, miR-431, miR-891a, -miR-887, were associated with oligometastatic disease. MiR-205, -miR-216b, miR-506 were associated with polymetastatic disease."

Comment 4: The paragraph on cytokines is very superficial despite there exist several reports on the function of cytokines; moreover, several cytokines act as ligands for tyrosine receptor

kinases and are functioning in lung cancer.

Reply 4: We thank you for this comment. We agree that this paragraph needs expansion. The paragraph has been edited as below.

Changes in the text: “Several proangiogenic cytokines are also present at the tumor site such as: PDGF, FGF-2, FGF-6, IL-6, IL-8, VEGF and angiopoietin which are responsible for promoting tumor growth and increasing tumor blood vessel density (77). NSCLC tumor cells secretes interleukin-17 which in turn attracts tumor associated macrophages. Tumor associated macrophages secretes cyclogenase-2 (COX2), Matrix metalloproteinase-9 (MMP9), PDGF-B, VEGFA, HGF, Cathepsin-k to increase tumor invasiveness (78). Adenocarcinoma-associated CAFs also secrete immunomodulatory cytokines such as TGF-b and VEGF inducing Forkhead box P3 expressing regulatory T-cells that are correlated with a poor outcome in lung adenocarcinoma (79).”

Comment 5: Circulating tumor cells: Here an association of tumor cells with platelets and neutrophils have been reported, the former acting as protectors for the tumor cells, the latter depending of either N1 or N2 cells can also protect the tumor cells within the circulation.

Reply 5: We agree with this valuable comment. The paragraph has been edited as below.

Changes in the text: “A strong reciprocal interaction between the CTCs and the blood microenvironment including the platelets and the neutrophils has been reported. The CTCs activate and educate the platelets, while the platelets protect the CTCs (88). The ATP released through CTC-induced platelet aggregation binds to the P2Y2 receptor, stimulating intravasation and metastases development (89). Furthermore, the adherence of platelets at the surface of CTCs protects the CTCs from being recognized by the immune cells thereby promotes CTCs survival (90). Blocking this interaction using P2Y12 inhibitor (ticagrelor) or aspirin, has been studied as a tool to reduce metastases (91, 92). Another important interaction is between the neutrophils and the CTCs. The neutrophils generate neutrophil extracellular traps by secreting their chromatin content (93). While this process was initially

thought to be a mechanism to kill bacteria, recent reports show that this mechanism promotes metastases though increased migration and proliferation of CTCs (94)."

Comment 6: Genomic alterations in primary and secondary tumor cells: there exist several reports on this issue; in contrast to many other tumors in the lung a preferred mode is a trunk mutation which is kept in mets, and secondary mutations later induced in mets; there are also other forms, especially clonal evolution; however, this should be clearly separated and discussed. It should be clearly stated, if the authors discuss mutations or posttranslational modifications, such as silencing, expression, etc.

Reply 6: The paragraph has been edited to reflect the requested changes as below.
Changes in the text: "In lung cancer, driver mutations are classified into trunk (initiating) mutations and branching mutations (95, 96). While trunk driver mutations initiate the formation of the primary tumor, branching driver mutations lead to subclonal evolution of the malignancy. Most activating mutations in the EGFR, BRAF, KRAS, MET, RET, ROS1 and ALK are trunk drivers (96) and are highly concordant in primary and metastatic tumors. However, many reports have shown discordant trunk mutations between paired primary and metastatic lung cancer specimens suggesting the presence of tumor heterogeneity (97)".

Comment 7: The paper summarizes a lot of data surrounding the topic of metastasis/disease progression in solid tumors and touches on NSCLC, but does not convey a clear takeaway for the readers. Some of the sentences are contradictory. For example, the first three sentences of conclusion ('The current approach to identifying oligometastatic disease incorporates baseline imaging characteristics and early clinical behavior, such as reserving aggressive, local treatment of both primary and oligometastatic site(s) until after 6–12 months of systemic therapy. Designed to allow the natural history of disease to declare itself, such approaches are far from ideal.') appear to be directly contradicting the statement made in the preceding paragraph ('It appears reasonable to Identifying the patients who remain in the oligometastatic state after a period of observation and do not bloom with multiple sites of

metastatic disease allows for the better selection of patients with a more favorable underlying biology who will likely gain the most benefit from aggressive surgical resection.').

Reply 7: Thank you for your comment. The conclusion has been edited to reflect the requested changes as below.

Changes in the text: "The current approach to identifying oligometastatic disease incorporates baseline imaging characteristics and clinical behavior, while reserving aggressive, local treatment of both primary and oligometastatic site(s) until after 6–12 months of systemic therapy designed to allow the natural history of disease to declare itself, such approaches are far from ideal.

Earlier understanding of a true oligometastatic state, through Integration of molecular prognostic classifiers such as SNFs, Ct DNA, CTCs, and cytokines along with other clinical features, might allow earlier and more effective use of local therapies."

Comment 8: The section titled - The approach to molecularly targetable oligometastatic NSCLC - does not provide an insight into authors' take on treatment approach. Additionally, paper does not outline the authors' interpretation of the available literature and in-depth discussion on what the future direction of research may look like specifically for oligometastatic NSCLC.

Reply 8: Thank you for the comment. We agree that the approach was not clear. The paragraph edited to clearly show that treating oligoprogression after tissue retrieval from the progressive sites in molecularly targeted lung cancer is the authors' approach.

Changes in the text:

Treating oligoprogression in molecularly targetable oligometastatic NSCLC:

Although patients with NSCLC harboring driver mutations have high rates of response to tyrosine kinase inhibitors (TKIs), depending on the molecular target resistance generally develops after 10-20 months of treatment, even with use of state-of-the-art third generation TKIs such as Osimertinib (108). One of the frequently seen situations when treating these

patients is the progression of a single or few clinically detectable metastatic lesions while other metastases respond to treatment. This represents the “escape” of a resistant subclone that drives progression. This suggests that future diagnostic and therapeutic decision-making will need to be based on tissue retrieved directly from metastatic tissue rather than inferred from previously resected primary tumor. Several studies have shown that aggressive localized management of these resistant subclones may preserve the efficacy of a relatively nontoxic systemic treatment and leave the patient with more options over time (109, 110).

Comment 9: Genomic alterations in primary and secondary tumor cells: there exist several reports on this issue; in contrast to many other tumors in the lung a preferred mode is a trunk mutation which is kept in mets, and secondary mutations later induced in mets; there are also other forms, especially clonal evolution; however, this should be clearly separated and discussed. It should be clearly stated, if the authors discuss mutations or posttranslational modifications, such as silencing, expression, etc.

Reply 9: The paragraph has been edited to reflect the requested changes as below.

Changes in the text: “In lung cancer, driver mutations are classified into trunk (initiating) mutations and branching mutations (95, 96). While trunk driver mutations initiate the formation of the primary tumor, branching driver mutations lead to subclonal evolution of the malignancy. Most activating mutations in the EGFR, BRAF, KRAS, MET, RET, ROS1 and ALK are trunk drivers (96) and are highly concordant in primary and metastatic tumors. However, many reports have shown discordant trunk mutations between paired primary and metastatic lung cancer specimens suggesting the presence of tumor heterogeneity (97)”.