



SDI Review Form 1.6

Journal Name:	Journal of Cancer and Tumor International
Manuscript Number:	Ms_JCTI_27710
Title of the Manuscript:	Evolutionary Basis of Cancer Metastasis and its Implication to a Lasting Cure
Type of the Article	Review paper

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
<u>Compulsory</u> REVISION comments	This review paper focuses on describing the tumour progression as an evolutionary Darwinian progress were many mutations emerging randomly and stochastically generating functional gains (oncogenes) and functional losses (tumour suppressor genes) and a lot of nonsense mutations that might be reserves for upcoming situations. These genome alterations occur by natural selection and different clones emerge in the same tumour causing various growth advantages depending on the microenvironments inside or around the tumour. There is also a fighting between tumour cells within the tumour mass were some cells are kicked out (losers). And the winners stay left. The looser are suggested to include capability as potential metastatic cells. A minority of mutations are driving the tumour growth forward. But many other mutations found are postulated to describe the whole tumour history from the original mutation causing the transformation. This is suggested by the authors to be of importance for the understanding of tumour progression in general. This type of describing tumour progression is interesting and didactic but could be called a two-dimensional theory. Having an enough large tissue dish the clonal development generating the tumour genomic diversification could be followed on the two-dimensional bottom of that dish using a microscope, if	



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	the nutritional and oxygen milieu could be simulated. However, there are more global three - dimensional positions that drastically alter the genome from one division to the next. The authors refer to alteration of the whole genome once as a side issue (line 39-40). However there is a huge literature focusing on tetraploidization in tumour cells as an important intermediate position between tumours with a diploid DNA content being subsequently transformed to a triploid (aneuploid) DNA content. The point is that the tumours with gains of oncogenes, losses of tumour suppressor genes and knock out of mitotic figure regulating genes will cause an additional huge genomic alteration by passing an octaploid unstable mitotic figure and generate daughter cells drastically altered very rapidly from one generation to the next. Furthermore there is a relatively new knowledge describing the Darwinian evolutionary tree to have Polyploidizations appeared before many cleavages in the evolutionary tree and might have given extra genomic hardware favouring natural selection. 1. I want the authors to include some publications discussing tetraploidization to play a role in transforming more stable diploid tumours to tumours in the triploid DNA region. There are many publications. 2. Tumours growing and generating a three-dimensional tumour mass will reach problem with anoxia due to lack of blood vessels. This anoxia drives tumours to the tetraploid stage. Several reports describe this. Please add one publication about that. 3. Tetraploidization preceding cleavages in the evolutionary Darwinian tree is described by Yves Van de Peer, Steven Maere and Axel Meyer. Title: The evolutionary significance of	
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	ancient genome duplication. Nature Review Genetics. 2009. Furthermore, teraploidization occurs in the human body as a reaction to various stress factors. These data add a three – dimensional powerful contribution to the whole genome alteration like an earthquake and should be mentioned in a review of evolutionary development of human tumours by natural selection. If we have a future as the authors state about a global burden of disease caused by cancers to be doubled in the two decades from 2010 to 2030 we need all aspects of knowledge gathered about tumour behaviour. The evolutionary aspect on cancer will be complete by adding the new knowledge of polyploidization before cleavages of during Mother evolution.	
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<u>Minor</u> REVISION comments	On line 239 and line 309 the authors write “as summarized by [48]” and “as inferred by [59]” In these cases it would be better to use one name of the of the referred authors and et.al instead of using the brackets as a person. To describe tumours as having an evolutionary history the authors denote as a paradigm shift in the understanding of tumour progression. If possible it would be interesting to point out in the Conclusion in what way this knowledge in the future will increase tumour survival as compared to early detection by mammography screening and screening by tumour markers in proteomics or helping people stop smoking. What part of the new knowledge will first give us tools to improve treatments of the tumours. Methods to killing winner cells or looser cells? The treatments postulated in the Conclusion are general and not specific related to the paradigm shift. There is a risk of enthusiastically highlight our gene-technical progress in methods without putting them in a pipeline for creating the new methods needed. Here the authors may use some fantasy	
<u>Optional/General</u> comments	A review in cancer with a postulated worse outcome in the next two decades and at the same time describe a positive great paradigm shift need to point out some future strategies leading to a stronger fight against cancer	

Reviewer Details:

Name:	<i>Roland Sennerstam</i>
Department, University & Country	<i>Department of Oncology and Pathology Karolinska Hospital and Karolinska Institute , Sweden</i>