



Thermal ablation and systemic therapies in the metastatic liver: time for a “glocal” approach

Andrea Veltri¹ · Marco Calandri¹

Received: 19 May 2019 / Revised: 19 May 2019 / Accepted: 28 May 2019 / Published online: 17 June 2019
© European Society of Radiology 2019

The local scenario

Minami et al [1] highlighted the relative high rate of local tumor progression (LTP) after radiofrequency ablation (RFA) for unresectable colorectal liver metastases (CRLM), ranging from 8.8 to 40%. Furthermore, the phase II CLOCC trial (NCT00043004) results demonstrated a significant improvement in disease-free survival (DFS) and overall survival (OS) in case of a combined approach compared with chemotherapy alone [2]. Thus, low LTP rate is desirable since it ultimately impacts on OS; an effective and complete local therapy with subsequent low LTP rate is the primary and prominent goal for interventional radiologists. For this purpose, both technical skills (improved by technological advancements such as ablation confirmation software development) and oncological expertise are required. Indeed, LTP rates are affected by adequate ablation margins (required margins of at least 5 mm in CRC metastases [3]) and patients' selection considering tumor biological characteristics [4].

Apparently, with this approach, the local interventions do not seem to be different from a surgical technique (with the goal of free resection margin and careful selection of surgical candidates).

However, ablation therapy is relevantly different from surgical resection; ablation therapies leave tumor debris in situ which potentially has a huge impact on short- and long-term outcomes. Actually, on the one hand, it has been demonstrated that ablation may induce extra-target tumor growth and local recurrence with a more aggressive tumor phenotype [5]. On

the other hand, as it has been underlined in the review article by Minami et al [1], several studies revealed that the ablation therapy positively stimulates the innate and adaptive immune system locally and globally. The understanding of interaction between the tumor debris left by the ablation and the immune system and the possible presence of minimal residual disease is a key point for further investigation in interventional oncological procedures.

The systemic scenario

In a systemic scenario, in the last two decades, target therapies have revolutionized cancer management [6]. Furthermore, in recent years, immunotherapy represented the major breakthrough in clinical cancer care with significant improvement in OS in many advanced-stage cancers (lung, melanoma, bladder, renal cell carcinoma, etc.). With the term immunotherapy, we include a wide range of treatments: cytokines, immune checkpoint inhibitors (ICIs), cancer vaccines, and cell-based immunotherapy (infusion of ex vivo-activated tumor-specific T cells). ICIs are both target therapies and a type of immunotherapy; they act by stopping the tumor immune suppression and can be considered today the most used and effective immunotherapeutic agents in clinical practice. Indeed, PD1, PD-L1, and anti CTLA4 inhibitors showed promising clinical outcomes and have been approved for many cancer treatments [7].

The “glocal” approach

In the future, one of the major challenges for interventional radiologists will be obtaining a comprehensive knowledge regarding the potential synergistic effect between interventional local treatments and systemic, global treatments and translating it into clinical practice.

This comment refers to the article available at <https://doi.org/10.1007/s00330-019-06189-6>.

✉ Andrea Veltri
andrea.veltri@unito.it

¹ Radiology Unit, Department of Oncology, San Luigi Gonzaga Hospital, University of Torino, Regione Gonzole 10, 10043 Orbassano, Turin, Italy

The term “glocal” is a linguistic blend of two words, global and local, and it has had a large spread in social and economic spheres in recent years. It means, by definition, to reflect or to be characterized by both local and global considerations and analyze the bi-directional influences between local and global systems [8].

Similarly, in a clinical oncological scenario, the term “glocal” can be used to define the research field concerning interactions between local and systemic therapies. As well as in economical sciences, interactions between local interventions and systemic oncological treatments can be bi-directional and beneficial for both fields.

Seminal studies (recently summarized in a white paper from the Society of Interventional Oncology [9]) have already demonstrated that this bi-directional interaction exists and should be better investigated by larger preclinical and clinical studies. Indeed, local interventions may boost the efficacy of systemic therapies by increasing the activation of tumor-specific T cells in combination with anti-CTLA4 therapies; vice versa, systemic therapies will be a useful aid to local therapies in case of persistence of minimal residual disease after ablation.

Future developments

Future researches will require to focus on the beneficial treatments for patients such as particular interventions or combined treatments and also to discover the correct timing of sequential treatments.

In the near future, three major research fields can be outlined:

1. “From bench to bedside” research on immune tumor micro-environment: several data are already present in the literature; however, it requires more effort by the interventional community to better understand the molecular mechanisms behind residual disease and immune system stimulation of ablation treatments;
2. The detection of minimal residual disease: the development of biomarkers to early predict recurrence before conventional cross-sectional imaging will pave the way to a correct selection of patients in case of combined treatments with systemic therapies. Development of liquid biopsy tools (early detection of circulating tumor materials with sensitive technologies) and radiomics analysis of tumors and ablation area will be of great value in this regard;
3. Timing of sequential treatments: after comprehension of the molecular mechanisms and selection of the correct

patients through sensitive technologies, trials should be designed to validate the best “glocal” approach for the right patient.

In conclusion, today more than ever, the linguistic expression “think globally, act locally” (often been used within the context of “glocalization”) perfectly suits the urgent actions that interventional radiologists should take in order to integrate the local interventions within the systemic clinical scenario.

Interventional radiologists are asked to act in this multidisciplinary setting (together with medical oncologists, radiation oncologists, and surgical oncologists) as interventional oncologists, with a strong clinical background and patient-oriented mentality. This is the only way in which interventional oncology will truly grow up and will be fully recognized as the fourth pillar of oncology.

Acknowledgments Authors thank Dr. Fatemeh Darvizeh, MD, for the language editing.

Funding The authors state that this work has not received any funding.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Andrea Veltri.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was not required for this Editorial Comment.

References

1. Minami Y, Nishida N, Kudo M (2019) Radiofrequency ablation of liver metastasis: potential impact on immune checkpoint inhibitor therapy. *Eur Radiol*. <https://doi.org/10.1007/s00330-019-06189-6>
2. Ruers T, Van Coevorden F, Punt CJ et al (2017) Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. *J Natl Cancer Inst* 109(9). <https://doi.org/10.1093/jnci/djx015>
3. Shady W, Petre EN, Gonen M et al (2016) Percutaneous radiofrequency ablation of colorectal cancer liver metastases: factors affecting outcomes—a 10-year experience at a single center. *Radiology* 278(2):601–611
4. Calandri M, Yamashita S, Gazzera C et al (2018) Ablation of colorectal liver metastasis: interaction of ablation margins and RAS

- mutation profiling on local tumour progression-free survival. *Eur Radiol* 28:2727–2734
5. Rozenblum N, Zeira E, Scaiewicz V et al (2015) Oncogenesis: an "off-target" effect of radiofrequency ablation. *Radiology* 276(2): 426–432. <https://doi.org/10.1148/radiol.2015141695>
 6. Van Cutsem E, Cervantes A, Adam R et al (2016) ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 27:1386–1422
 7. Wei SC, Duffy CR, Allison JP (2018) Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov* 8(9):1069–1086
 8. Oxford English Dictionary, Available at <https://www.oed.com/view/Entry/276090?redirectedFrom=global#eid>. Accessed 10 May 2019
 9. Erinjeri JP, Fine GC, Adema GJ et al (2019) Immunotherapy and the interventional oncologist: challenges and opportunities—a society of interventional oncology white paper. *Radiology*. <https://doi.org/10.1148/radiol.2019182326>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.