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Combination of endoscopic ultrasound-guided radiofrequency ablation and adaptive radiation therapy for the treatment of lymph node metastases from colon adenocarcinoma: A case report

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ABSTRACT

Oligometastatic colorectal cancer (CRC) is a clinically relevant entity, and surgery is the gold standard therapeutic option. Current guidelines recommend evaluating other local ablative treatments (LATs) in patients not eligible for surgery. Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) and stereotactic body radiation therapy (SBRT) are emerging as highly beneficial less-invasive LATs in alternative to surgery. In our paper, we report the first case in literature of lymph node metastases from CRC treated sequentially with EUS-RFA and SBRT, providing evidence of their efficacy and safety. LATs combined with systemic chemotherapy might be included in a multimodal therapeutic approach to oligometastatic disease.

Introduction

Surgery is the gold standard treatment for oligometastatic colorectal cancer (CRC), being the only potentially curative option. When surgery can not be pursued, other local ablative treatments (LATs), in combination with systemic chemotherapy (CT), may contribute to achieve long-term disease control, potentially increasing overall survival (OS) (Yoshino et al., 2018; Kovács et al., 2022). Radiofrequency ablation (RFA) and stereotactic body radiation therapy (SBRT) are widely accepted less-invasive alternative treatments to surgical resection for local control of secondary neoplastic lesions (Yu et al., 2021).

We herein report the first case of a patient with unresectable mesenteric lymph node metastases of CRC treated with endoscopic ultrasound-guided RFA (EUS-RFA) combined with subsequent SBRT session.

Case and methods

In 2019 a 40-years-old female underwent laparoscopic proctocolectomy with ileal pouch-anal anastomosis for a longstanding ulcerative colitis complicated by locally advanced transverse colon cancer. The pathological examination found a poorly differentiated mucinous adenocarcinoma with signet-ring cells. Pathological TNM staging was pT4aN2bM0. Eight cycles of adjuvant CT with capecitabin and oxaliplatin were administered from January to June 2020. At the end of treatment, carcinoembryonic antigen (CEA) and CA 19.9 serum levels were within normal range. Contrast-enhanced (CE)-CT scan of chest and abdomen did not show metastases.

Subsequent follow up did not report any evidence of disease relapse until February 2021, when CEA serum level increased to 109.81 ng/ml. CE-CT scan showed confluent mesenteric lymphadenopathies located adjacent to the superior mesenteric vein suggestive for disease recurrence (Fig. 1a). A first line treatment with 11 cycles of FOLFIRI and bevacizumab was therefore administered. During treatment course CEA

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serum level progressively dropped to 6.7 ng/ml. CE-CT scans performed on May 2021 and September 2021 documented a stable disease according to RECIST criteria 1.1[4], and signs of partial morphologic response to treatment according to Choi criteria due to decreased tumor enhancement (Thian et al., 2014).

After multidisciplinary team assessment, the disease was judged surgically unresectable due to the high risk to damage the superior mesenteric vessels. Hence, we considered other LAT options. Both EUS-guided RFA and SBRT where available at our Institution. We decided to sequentially combine both LATs in order to overcome limits of either technique. Specifically, given the volume of lymph node metastases, SBRT alone might have determined either a poorer peripheral control or severe toxicity. Besides, performing EUS-guided RFA prior to SBRT might have allowed to increase SBRT efficacy by exploiting a higher amount of necrosis, and to treat peripheral boundaries of lymphadenopathies.

In October 2021 the patient underwent EUS-RFA under deep sedation with propofol with a linear EUS endoscope (GF-UCT180, Olympus, Tokyo, Japan). Prophylactic intravenous antibiotic was administered prior to the procedure. Between the gastric antrum and the pancreatic body, the lymph node metastases were detected as a single group of confluent hypoechogenic nodules measuring 46 × 16 mm. Contrast-enhanced harmonic EUS (CH-EUS) with intravenous injection of SonoVue (Bracco Imaging, Milan, Italy) showed intralesional low vascular enhancement. EUS-guided RFA was performed by using a 19 Gauge monopolar RFA needle (EUSRA™ EUS-Guided RFA, TaeWoong Medical, Gyeonggi-do, South Korea) with a 15-mm active tip, and a dedicated RFA current generator system (VIVA Combo, STARmed). This system is equipped with an inner cooling system of the probe which prevents tissue charring and increases ablation accuracy. RFA needle was inserted into the cranial part of the target lymphadenopathies under EUS guidance and ablation was started (Fig. 2). In total, 10 RFA applications at a power setting of 30 W were performed for an average time of 10 s. After 2 weeks, EUS-RFA was repeated in order to treat the caudal section of the target malignant lymph nodes. 7 RFA applications at a power setting of 30 W were performed for an average time of 15 s. Patient well tolerated both procedures, and no peri- neither post-operative complications were observed.

Subsequently, the patient was referred for magnetic resonance (MR)-guided radiotherapy (MRgRT) for consolidation purposes on a 0.35 T MR Linac unit (MRIdian, Viewray Inc, Mountain View, CA, USA). The gross tumor volume (GTV) consisted of the lymph nodes present at the root of the mesentery. From 16 to 22 December 2021, the patient underwent 5 consecutive fractions of stereotactic MRgRT for a total dose of 30 Gy prescribed at 80% isodose normalization. Fig. 3 shows the dose distribution of the stereotactic MRgRT treatment. To ensure adequate daily target coverage and to avoid unnecessary dose to surrounding healthy organs, daily sessions were delivered using an online adaptive MRgRT technique. With this approach, the treatment plan is re-optimised daily. To minimize therapy volumes and increase accuracy, treatment was delivered in inspiratory breath hold mode. Intra-fraction motion was managed by applying a gating approach based on real-time acquisition on a sagittal cine MRI during the whole time of the radiation fraction. The treatment was well tolerated, with no acute toxicities of any type reported.

A 1-month follow-up contrast-enhanced CT scan of chest and abdomen showed a larger hypodense area within the lymphadenopathies suggestive for a complete necrosis, demonstrating a good response to EUS-RFA treatment combined with SBRT (Fig. 1b).

Discussion

Oligometastatic disease (OMD) has been proposed as a specific intermediate scenario between localized and systemic metastatic disease (Hellman, 1995).

According to international guidelines, in the setting of oligometastatic CRC, despite systemic therapy remains the standard of care, surgery, or alternatively LATs, should be considered whenever possible (Yoshino et al., 2018; Kovács et al., 2022). Indeed, when CRC is confined to a single or few organs, surgery is the standard treatment, being the only potentially curative option. Whenever surgery cannot be pursued, integrating a metastasis-directed LAT to systemic therapy represents the best treatment strategy.

Despite being included and recommended in international guidelines, evidence supporting this strategy is weak. Few randomized, phase II trials have shown that addition of LATs to standard systemic treatment for oligometastatic CRC allows to achieve a survival benefit. Specifically, Ruers *et al.* demonstrated that combination of systemic treatment and aggressive local treatment (RFA+/-surgery) prolongs OS of 5.1 months in patients with unresectable colorectal liver metastases, when compared with patients treated with systemic therapy alone (HR 0.58, 95%CI 0.38–0.88, $p = 0.01$) (Ruers et al., 2017). More recently, the randomized prospective phase II trial SABR-COMET showed a survival benefit from addition of stereotactic ablative radiotherapy to palliative standard systemic treatment in patients with tumor-agnostic OMD (Palma et al., 2020). Moreover, combination treatment was not associated to increased toxicity neither to decreased quality of life.

Based on available evidence, treatment algorithm for OMD CRC starts from best systemic treatment, in order to achieve disease control. At the time of best response, LATs should be considered. The choice of the best LAT relies on both patient and tumor features, and on the expertise of treating Institution. Available options include local thermal

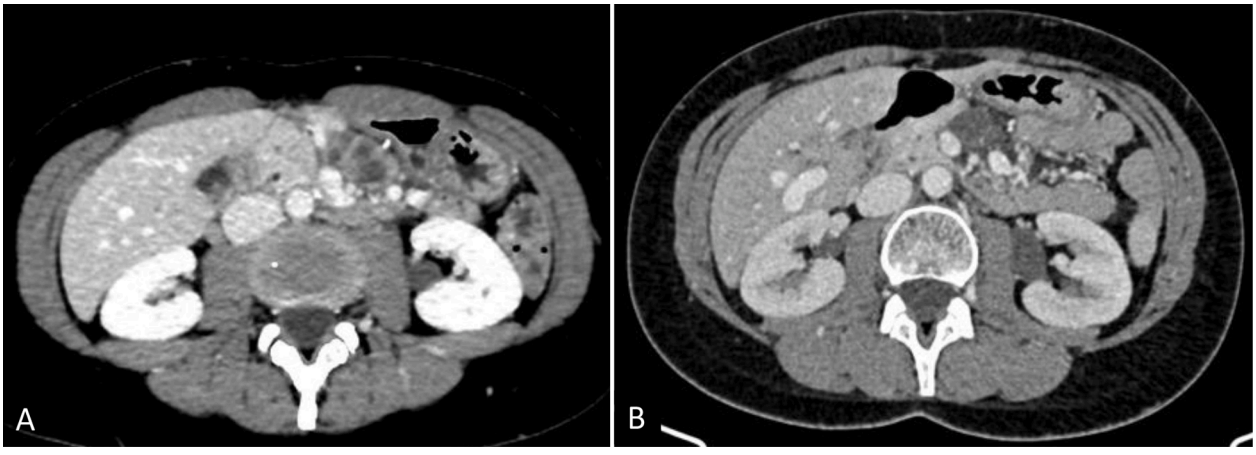

Fig. 1. (A) Axial contrast-enhanced computed tomography (CE-CT) image shows confluent lymphadenopathies with mixed peripheral enhancement and focal central necrosis in the root of mesentery. *B)* Axial CE-CT image shows the same lymphadenopathies completely necrotic one month after the end of treatment.

Fig. 2. Endoscopic ultrasound (EUS)-guided radiofrequency ablation. The needle is seen within the confluent hypoechogenic mesenteric nodules.

Fig. 3. Dose distribution of stereotactic magnetic resonance imaging (MRI)-guided radiotherapy treatment. The planning target volume (PTV) is shown in blue, obtained by adding 3 mm isotropic margins to the gross tumor volume (GTV). In orange colourwash is shown the 80% prescription dose of 30 Gy at the 80% isodose and in green the 50% isodose.

ablations, conformal radiation and embolization.

In this case report, during follow up for stage III CRC, a disease relapse with involvement of a single lymph node station was observed, configuring a *de novo* metachronous oligorecurrence according to the dynamic oligometastatic state model (Guckenberger et al., 2020).

First line treatment allowed to achieve tumor control, with best response being stable disease according to RECIST 1.1 criteria and partial response according to Choi criteria (Eisenhauer et al., 2009; Thian et al., 2014). In the current case, imaging assessment was limited to CT scan. Whereas, Fluorodeoxyglucose PET/CT scan is usually recommended in order to confirm OMD (deSouza et al., 2018). Indeed, by identification of small metastases, it allows to discriminate between true OMD and pseudoOMD in case of early polymetastatic disease, improving patients' selection and avoiding unnecessary LATs in case of widespread disease (Samim et al., 2017). However, in the current case, PET scan was waived due to mucinous histology of primary tumor and the subsequent risk of false negative. Oligometastatic disease may represent an unique biologic entity with favourable prognosis (Time to Debunk an Urban Myth? The 8 June 2022). Thus, besides imaging, further attempts are being made in order to molecularly select patient harboring disease with biological characteristics of OMD (Time to Debunk an Urban Myth? The 8 June 2022). Indeed, a low tumor burden at imaging might be observed in different settings, ranging from true OMD to early phase of polymetastatic systemic disease. Up to now, no biomarker predictive of benefit from LATs has been identified for selection of OMD.

Having achieved the best response, we decided to consolidate disease control with local ablation. A sequential combination of two LATs available at our Institution was chosen in order to exploit benefits and overcome at the same time limits from both techniques, and consequentially achieve a synergic activity. We chose to perform RFA prior to SBRT, given the target volume, because SBRT alone might have determined either a poorer peripheral control or severe toxicity according to administered dose. Moreover, EUS-RFA could guarantee to treat peripheral margins of lymphadenopathies. Subsequently, we exploited the effect of the steep dose gradients obtained from SBRT, both through direct killing of hypoxic tumor cells, and indirectly through the release of anti-tumor antigens derived from the stimulation of the anti-tumor immune system to increase indirect tumor cell death (Song et al.,

2021; Ms et al., 2015).

This case report fits within the growing evidence supporting the role of LATs in achieving improved long-term outcomes in patients with OMD.

Conclusion

In conclusion, our case provides evidence, for the first time to our knowledge, of safety and feasibility of combined treatment with EUS-RFA and SBRT for colorectal lymph node metastases. LATs should always be embedded in combination with systemic therapy as part of a multimodal therapy approach, following a careful patients' selection within a detailed multidisciplinary team discussion and assessment.

Patient consent statement

The authors received written, informed consent from the patient to publish this case.

Authors contribution

The authors confirm contribution to the paper as follows: Fabia Attili and Luigi Sofo conceived of the main idea. Federica Borrelli de Andreis, Maria Alessandra Calegari, and Angela Romano drafted the manuscript. All the Authors provided critical feedback and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

deSouza, N.M., Liu, Y., Chiti, A., et al., 2018. Strategies and technical challenges for imaging oligometastatic disease: recommendations from the European Organisation for Research and Treatment of Cancer imaging group. Eur. J. Cancer 91, 153–163.

Eisenhauer, E.A., Therasse, P., Bogaerts, J., et al., 2009. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur. J. Cancer 45, 228–247.

Guckenberger, M., Lievens, Y., Bouma, A.B., et al., 2020. Characterisation and classification of oligometastatic disease: a European society for radiotherapy and oncology and European organisation for research and treatment of cancer consensus recommendation. Lancet Oncol. 21, e18–e28.

Hellman, S., 1995. Weichselbaum RR. Oligometastases. J. Clin. Oncol. 13, 8–10.

Kovács, A., Bischoff, P., Haddad, H., et al., 2022. Long-term comparative study on the local tumour control of different ablation technologies in primary and secondary liver malignancies. J. Pers. Med. 12, 430.

Ms, K., Kim, W., Ih, P., et al., 2015. Radiobiological mechanisms of stereotactic body radiation therapy and stereotactic radiation surgery. Radiat. Oncol. J. 33 https://doi.org/10.3857/roj.2015.33.4.265. Epub ahead of print December.

Palma, D.A., Olson, R., Harrow, S., et al., 2020. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. J. Clin. Oncol. 38, 2830–2838.

Ruers, T., Van Coevorden, F., Punt, C.J.A., et al., 2017. Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. J. Natl. Cancer Inst. 109 https://doi.org/10.1093/jnci/djx015. Epub ahead of print 1 September.

Samim, M., Molenaar, I.Q., Seesing, M.F.J., et al., 2017. The diagnostic performance of 18F-FDG PET/CT, CT and MRI in the treatment evaluation of ablation therapy for colorectal liver metastases: a systematic review and meta-analysis. Surg. Oncol. 26, 37–45.

Song, C.W., Glatstein, E., Marks, L.B., et al., 2021. Biological principles of stereotactic body radiation therapy (SBRT) and stereotactic radiation surgery (SRS): indirect cell death. Int. J. Radiat. Oncol. Biol. Phys. 110, 21–34.

Thian, Y., Gutzeit, A., Koh, M., et al., 2014. Revised Choi imaging criteria correlate with clinical outcomes in patients with metastatic renal cell carcinoma treated with sunitinib. Radiology 273, 452–461.

Time to Debunk an Urban Myth? The, 2022a. Abscopal Effect" With Radiation and Anti–PD-1. J. Clin. Oncol. https://ascopubs.org/doi/full/10.1200/JCO.20.02046 accessed 8 June.

Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis. Nat. Commun., 2022 https://www.nature.com/articles/s41467-018-04278-6 accessed 8 June.

Yoshino, T., Arnold, D., Taniguchi, H., et al., 2018. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann. Oncol. 29, 44–70.

Yu J., Kim D.H., Lee J., et al. Radiofrequency ablation versus stereotactic body radiation therapy in the treatment of colorectal cancer liver metastases. Cancer Res. Treat.. Epub ahead of print 13 October 2021. DOI: 10.4143/crt.2021.674.