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Capecitabine maintenance after radiofrequency ablation: A preventive strategy for lung oligometastases from colorectal cancer

Giangregorio F. Preventing CRC lung oligometastases recurrence

Abstract

Preventing the recurrence of lung oligometastases after local therapy in patients with colorectal cancer is an area requiring investigation. A recent article demonstrated that adding capecitabine maintenance therapy after radiofrequency ablation improved the 5-year overall survival (88.7% vs 69.1%) and reduced local tumor progression (22.7% vs 49.0%) compared with radiofrequency ablation alone. Although progression-free survival did not differ significantly between the two treatments, multivariate analysis confirmed a robust survival benefit. These findings support the use of systemic maintenance to eradicate micrometastases after locoregional control and warrant validation in prospective randomized trials.

Key Words: Colorectal cancer; Lung oligometastases; Radiofrequency ablation; Capecitabine; Maintenance therapy; Recurrence prevention

Giangregorio F. Capecitabine maintenance after radiofrequency ablation: A preventive strategy for lung oligometastases from colorectal cancer. *World J Gastroenterol* 2025; In press

Core Tip: Preventing the recurrence of lung oligometastases from colorectal cancer after local therapy is crucial. Recent evidence demonstrated that capecitabine maintenance after radiofrequency ablation significantly increased 5-year overall survival and reduced 5-year local tumor progression rates compared with radiofrequency ablation alone. This synergistic approach proactively targets micrometastatic disease. Despite the retrospective nature of the study, its robust results support the confirmation of systemic maintenance with local ablation in prospective randomized controlled trials.

TO THE EDITOR

The recent article by Li *et al*[1], titled “Radiofrequency ablation with or without capecitabine maintenance therapy for lung oligometastases from colorectal cancer”, was

read with great interest. The study aimed to determine whether adding capecitabine maintenance therapy after radiofrequency ablation (RFA) improves outcomes for patients with lung oligometastases from colorectal cancer (CRC) compared with RFA alone. It was a multicenter retrospective study (2016-2023) analyzing 247 patients from two cancer centers, comparing overall survival, progression-free survival, and local tumor progression between RFA + capecitabine and RFA-only groups.

CRC is the third most diagnosed cancer and the third-leading cause of cancer-related deaths in both males and females in the United States[2]. Oligometastatic disease (OMD) is a newly recognized distinct intermediate state between localized disease and widespread metastasis on the spectrum of CRC[3]. OMD is primarily defined by clinical characteristics, particularly the number of lesions detected by imaging[4]. It is increasingly evident that OMD has a distinct biological behavior that is potentially characterized by a less aggressive genomic profile and responsiveness to metastasis-directed therapy[5].

While the reported clinical incidence of OMD has been low (1.1%) in some surgical series[6], real-world data suggest a higher prevalence. A recent Finnish population-based study of 1671 patients found that 18% of patients presented with synchronous metastases at diagnosis[7]. Furthermore, 255 (19.6%) of 1302 patients with resected stage I-III tumors developed metachronous metastases [94 patients (7.2%) with early metastases and 161 patients (12.4%) with late metastases]. Another recent Norwegian population-based study of 7950 patients with CRC detected 1843 (23.2%) synchronous metastases and 1117 (20.1%) metachronous metastases[8].

Oligometastatic CRC is described as an intermediate state between localized and disseminated disease[9]. Aggressive local therapy may yield long-term survival with surgical resection as the benchmark treatment. However, minimally invasive alternatives such as RFA and stereotactic ablative radiotherapy (SABR) are increasingly used in patients who have contraindications for surgery[10,11].

Therefore, Li *et al*[1] conducted a multicenter retrospective analysis of 247 patients who received either RFA + capecitabine or RFA alone. They demonstrated that RFA +

capecitabine maintenance achieved a superior 5-year overall survival compared with RFA alone (88.7% vs 69.1%, $P = 0.011$) and markedly reduced local tumor progression (22.7% vs 49.0%, $P < 0.001$). Progression-free survival did not differ significantly but multivariate analysis confirmed the survival benefit [hazard ratio (HR) = 0.31, 95% confidence interval: 0.12-0.79]. Capecitabine may eliminate proliferating micrometastases that persist after RFA[12].

Furthermore, experimental evidence suggests that thermal ablation releases tumor antigens and induces local immune modulation (an *in situ* vaccine effect), synergizing with chemotherapies that exhibit immunomodulatory properties and potentially creating a hostile environment for residual disease[13]. This mechanism explains the observation of improvement in overall survival but no significant change in progression-free survival[14].

The central goal in treating oligometastatic CRC is to achieve complete eradication of all metastatic deposits with the intent of cure. This strategy relies heavily on highly targeted local therapies directed at the metastatic sites. Li *et al*[1] provided pivotal evidence that combining a locoregional treatment (*i.e.* RFA) with systemic chemotherapy (*i.e.* capecitabine maintenance) significantly enhanced patient outcomes. To appreciate the clinical importance of this retrospective, multicenter study, it is essential to note that surgical resection is still the most established and effective treatment. However, for patients who are not surgical candidates or for patients who prefer a less invasive approach, alternative treatments must exist.

RFA and SABR, among others, offer minimally invasive yet highly precise tumor ablation and have been successful in carefully selected patients[15]. The 2016 European Society for Medical Oncology (ESMO) consensus guidelines recommend RFA as a viable therapeutic option alongside surgical resection and SABR for managing lung metastases[16]. This recommendation was subsequently endorsed by Asian oncologic societies in 2018[17].

The Table 1 provides details on key international studies exploring the integration of capecitabine or other systemic approaches with locoregional treatments (such as

surgery, RFA, and SABR) in oligometastatic CRC. Within this body of evidence, randomized controlled trials such as the EORTC 40983 study and the SABR-COMET trial stand out as the highest level of evidence, demonstrating the potential survival benefit of combining locoregional with systemic therapies[11,18]. Large retrospective cohorts, including the recent work of Li *et al*[1] and the multicenter series reported by de Baère *et al*[10], illustrate the real-world feasibility of RFA with or without capecitabine and provide long-term outcome data.

Smaller prospective or observational studies from Geng *et al*[19] and Kim *et al*[20] further support the tolerability and clinical applicability of capecitabine as a maintenance or salvage treatment. A systematic reviews and meta-analyses (such as the work of Sonbol *et al*[21]) and clinical guidelines, including the ESMO recommendations[9], underscore the rationale for multimodal treatment in metastatic CRC. Finally, mechanistic insights provided by Chu and Dupuy[13] and the narrative review by Delpla *et al*[22] contributed important biological and clinical context and reinforced the plausibility of systemic therapy after ablation.

Delpla *et al*[22] evaluated RFA for the treatment of CRC lung metastases and reported local control rates between 62% and 91%. Key predictors of successful local control included metastasis size < 2 cm, sufficient distance from major bronchi or vessels, and ablation margins > 5 mm. Their review ultimately indicated that thermal ablation is a safe and effective minimally invasive treatment for a carefully selected subset of patients. Furthermore, Kim *et al*[20] demonstrated that capecitabine monotherapy provided moderate disease control and a tolerable toxicity profile as a third-line or fourth-line treatment for metastatic CRC in patients who were refractory to standard chemotherapy.

Li *et al*[1] established a robust survival benefit for capecitabine (HR = 0.31, 95% confidence interval: 0.12-0.79). The data compellingly suggest that capecitabine is effective in preferentially eradicating residual micrometastases following RFA. Unfortunately, no significant improvement was detected in progression-free survival. This dissociation suggests that capecitabine maintenance may not prevent new

metastatic occurrences but could alter the biology of subsequent recurrences, making them more treatable and prolonging overall survival. This modification of the disease trajectory is a key potential benefit of maintenance therapy that deserves emphasis and further study.

There are several limitations in this study that should be considered. Its retrospective nature introduces the potential for significant selection bias. The patients selected for RFA + capecitabine by the multidisciplinary tumor boards may have been systematically different from patients in the RFA-alone group. For instance, they may have had a better performance status, fewer comorbidities, or more indolent disease biology (factors not fully captured by multivariate analysis). Furthermore, the lack of randomization leads to unmeasured confounders that could influence the observed survival benefit.

Another similar limitation was that the patient categorization into the RFA + capecitabine group ($n = 148$) or RFA-alone group ($n = 99$) was based on individualized therapeutic decisions by multidisciplinary tumor boards at both institutions (a practice that is appropriate and accepted). The number of lesions as well as controlled/treated primary, limited-burden OMD (commonly $\leq 3-5$ Lesions in $\leq 1-3$ organs), good performance status, and objective response or stable disease after induction/local ablation were the primary factors for choosing candidates[23]. Modern consensus guidelines also emphasize the disease-free interval, the possibility of achieving local control of all sites, and the molecular profile (*e.g.*, rat sarcoma viral oncogene homolog or B-RAF proto-oncogene serine/threonine kinase mutation status) of the tumor. These factors are increasingly recognized as predictors of outcomes in OMD[24].

Another limitation was the duration of capecitabine treatment. Li *et al*[1] used capecitabine for 4 weeks while most groups start induction systemic therapy after completion of metastasis-directed treatment (*e.g.*, RFA) with continuous low-dose capecitabine until radiologic progression or unacceptable toxicity occurs. Trials and guideline summaries recommend maintenance beginning 3-6 months after initial therapy and continuing until no longer tolerated[25].

Capecitabine toxicity may have been a limitation. It can determine patient management as 92% of patients treated with capecitabine experience ³ some degree of toxicity. Grade 3-4 toxicity occurred in 30% of patients receiving monotherapy and in 47% with combination therapy[26]. Patients over the age of 70 years are more susceptible to significant treatment-related toxicities. While the difference in the incidence of hand-foot syndrome between older and younger patients approached statistical significance, a pronounced disparity was observed in rates of diarrhea with older patients experiencing this adverse event at nearly twice the rate of their younger counterparts. Heightened vigilance and adapted supportive care strategies should be developed for treating elderly patients[27]. Toxicities (hand-foot syndrome, diarrhea, cytopenia, rare cardiotoxicity) must be managed with protocolized dose reductions, treatment breaks, and symptomatic/supportive care. Because severe fluoropyrimidine toxicity can be life-threatening, dihydropyrimidine dehydrogenase/dihydropyrimidine dehydrogenase gene testing or careful clinical screening is recommended per regulatory and oncology society guidance[28].

The final limitation was that the trial was performed at only two tertiary centers in China. Its outcomes may not be fully generalizable to populations with different molecular profiles (such as varying rates ⁴ of Kirsten rat sarcoma viral oncogene homolog, neuroblastoma rat sarcoma viral oncogene homolog, or B-RAF proto-oncogene serine/threonine kinase mutations) or to healthcare settings with different structures and/or resources[29-32].

Despite these limitations this compelling evidence obliges the scientific community to initiate prospective trials, specifically those powered to confirm a true overall survival benefit. The findings from Li *et al*[1] are consistent with a recent meta-analysis[33], indicating that the most effective strategy for improving survival involves a multimodal approach combining surgery, locoregional treatments (*i.e.* RFA, SABR), and chemotherapy. This comprehensive strategy demonstrated a significantly lower HR (0.22), representing the strongest survival benefit compared with any single modality. While image-guided thermoablation (HR = 0.53) and surgery alone (HR = 0.57) were

highly effective, they were not statistically significant in this analysis. The meta-regression confirmed that combination therapy consistently yielded the best survival outcomes. The optimal strategy, however, is highly dependent on the extent of metastatic disease. Surgery provides the most substantial incremental survival gain (HR = 0.26) for patients with limited, isolated pulmonary metastases.

CONCLUSION

Collectively, the study from Li *et al*[1] and the studies presented in Table 1 suggest that capecitabine maintenance after locoregional treatment is feasible, biologically grounded, and promising for survival benefits. Nevertheless, these studies require additional confirmation through prospective randomized trials. These trials must be designed to confirm the survival benefit as well as identify the patient subgroups (based on clinical, radiological, and molecular characteristics) that derive the most benefit from this intensive, preventative strategy. Integrating multiple therapeutic modalities is paramount for maximizing overall survival in oligometastatic CRC.

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