



The debate for thermal ablation of colorectal cancer pulmonary metastases is heating up

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Colorectal cancer (CRC) is the third most common cancer worldwide and the fourth most common cause of cancer death. The number of deaths is expected to rise in all countries until 2035, for both colon and rectal cancer by 60% and 71% respectively, mainly due to population growth and ageing (1). The highest CRC incidence rates are in Australia, New Zealand, Europe, and North America, and the lowest rates are found in Africa and South-Central Asia. These geographic differences appear to be attributable to differences in socioeconomic status, and to dietary and environmental exposures imposed upon a background of genetically determined susceptibility (2).

Death from CRC is usually a result of metastatic spread. Lung is the second most common site for metachronous CRC metastatic spread, liver being the first. About 20% of patients present with synchronous metastases, most commonly in the liver, and up to 60% of the remaining patients develop metastases within 5 years (3). Rectal cancer and left-sided colon cancer are associated with significantly higher rates of lung-only metastases, seen in 10–20% of patients (4,5). The prognosis of untreated stage IV disease is poor, with an average lifespan of 5–6 months (4). There is extensive data showing survival benefit for metastasectomy for CRC lung metastases,

favourable factors being a maximum of 3 metastases, unilateral lesions, lack of thoracic nodal involvement, long disease-free interval (DFI) and no elevated carcinoembryonic antigen (CEA) pre thoracotomy (6). A history of resected liver metastases did not reach statistical significance for poorer outcome, provided there was no evidence of hepatic metastatic involvement at the time of pulmonary metastasectomy (6).

Disease recurrence is common after pulmonary metastasectomy—with 69% of patients showing new metastases in lung, liver or both; repeat resection carries a better survival than other treatments or palliative care (7,8). The addition of targeted therapy to conventional chemotherapy has been a recent valuable adjunct to the neoadjuvant or adjuvant treatment of the primary colorectal site. However, pulmonary metastases do not respond well to chemotherapy (9).

Recent data on stereotactic body radiation therapy (SBRT) of pulmonary oligometastatic disease shows a significantly lower local control rate for CRC primaries compared to other primary sites with 24-month cumulative incidence rates of local failure above 40% (10-12).

Heat based thermal ablation for both primary and secondary lung malignancies has been performed since

the early 2000s, with most publications considering radiofrequency ablation (RFA). A later development is microwave ablation (MWA), used on a wider scale in the clinical setting for the past 10 years. No significant difference in the outcome of CRC metastases treated with RFA compared to MWA has been reported in early publications, with promising 3-year overall survival rates of 58% and 64% respectively, and comparable complication rates (13). However, more recent publications show statistically significant better local tumor control for MWA compared with RFA and laser-induced thermotherapy (LITT) (14). Complications after lung thermal ablation are usually self-limiting. Grade 3 or 4 adverse events are reported to occur in less than 10% of patients and include aseptic pleuritis, pneumonia, abscess, bleeding requiring blood transfusion, pneumothorax, broncho-pleural fistula requiring pleurodesis, thermal injury of nerves and diaphragm, tumor seeding, and pseudoaneurysm formation (15). The incidence of pneumothorax requiring a chest drain appears to be linked to the number of treated lesions and the length of the procedure (16). The incidence of pneumonia and abscess lies below 2% and is more prone in patients with older age and pre-existing inflammatory lung disease and in patients who have received prior radiotherapy (15).

The long-term follow-up of a large patient group (157 patients) with RFA of their CRC lung metastases (434 lesions) shows very promising results of 20% 5-year survival, especially on the background of 3/4 of the patient cohort having had liver and/or peritoneal resection prior to their lung RFA. Interestingly, opposed to many other studies, neither lesion size, nor lesion number, nor pre-ablation CEA were prognostic factors (17).

The largest report on RFA of lung metastases included 566 consecutive patients with 1037 lung metastases from colon (34%), rectum (18%), renal (12%), soft-tissue sarcoma (9%) and other miscellaneous origins (28%). A poorer overall survival (OS) occurred when the size exceeded 2 cm and the number of metastases 3. A very encouraging 91.6% local control rate at 3 years for metastases not exceeding 3cm was reported (18). When looking at the subpopulation of 293 CRC lung metastases, the 1-, 3-, and 5-year OSs were 92.9%, 76.1%, and 56.0%. These results are within the range of the best results achieved by surgery—a 5-year OS of 53.5% reported in a multi-center registry of lung metastasectomy for CRC (19); a 5-year OS of 32.7–56% in a literature review looking at 11 publications with 1307 patients, with a 39.1–67.8% 5-year OS if only R0 resection was considered (20). For those patients eligible for lung

metastasectomy, surgical management of recurrences is limited given the technical difficulties inherent to repeat thoracotomy and loss of lung volume.

The first prospective multicentre trial by Hasegawa *et al.* (21) evaluating the long-term efficacy of percutaneous RFA of CRC lung metastases parallels and even exceeds the best reported local control rate, with a primary 91% local control rate, secondary 3-year local control rate of 98% with successful re-ablation in 5 of 6 patients with local recurrence and a very favourable 3-year OS rate of 84%. Careful selection of patients—metastases smaller than 3 cm in maximum diameter, 70% of patients with single lung metastasis, 83% of the metastases in peripheral location, and stringent exclusion criteria (concomitant liver metastasis, nodal metastasis, location of target lesion adjacent to hilum or major organs, and previous radiotherapy) contributed to this promising outcome. This very favourable 3-year OS compared to the 35–72% reported in a recent systematic review on percutaneous RFA in CRC lung metastases (22) is likely a result of careful selection of patients in Hasegawa *et al.*'s study, possibly aided to a certain extent by the low rate of pathologic confirmation of the treated lesions of only 7%, raising the possibility that some of the lesions may not have represented colorectal metastases. It is however common practice to favour gestalt reasoning and waive tissue diagnosis in the typical scenario of advanced CRC with new and or enlarging spherical peripheral lung nodule(s). Of note that there was one (of 88 RFA sessions) grade 5 adverse event with no grade 3 or 4 events in Hasegawa *et al.*'s study (21), with an even lower mortality rate of 1/610 and major complications reported between 0–8% in the mentioned systematic review (22).

Opposed to RF heating which is limited in areas of low electrical conductivity resulting in tissues being adequately heated only immediately adjacent to the RF electrode, MW heating occurs via dielectric hysteresis by forcing polar molecules—primarily H₂O—to increase their kinetic energy by continuously realigning with the oscillating field. Microwaves are capable of propagating through tissues with low electrical and thermal conductivity and high impedance, such as the lung, also penetrating through charred and desiccated tissue building up around heat-based ablation applicators. MWA produces faster and more homogeneous lethal heating of larger tissue volumes with little susceptibility to heat-sink effects and without the need of grounding pads or other ancillary components (23). By virtue of its direct heating and more predictable heat profile, MWA is expected to produce more favourable outcomes than RFA, with quicker

procedures, lower local recurrence rates and the option of successfully targeting larger lesions (24-28).

There is enough evidence to support the belief that thermal ablation of CRC lung metastases not only prolongs survival, but even provides cure in a select sub-population with favourable parameters. It carries less morbidity than surgery, is superior to SBRT, is cost-effective, has minimal impact on pulmonary function and quality of life, and, above all, is repeatable.

Complications of percutaneous lung ablations are usually minor and self-limiting; in skilled hands, many major complications can be circumvented, i.e., by creating an artificial pneumothorax or injecting fluid to displace the ablation area from critical structures and by avoiding unfavourable trajectories—potentially aided by computer-assisted navigation of antenna insertion, as already successfully performed in the liver (29).

The combination of thermal ablation of CRC lung metastases with immune-modulating treatment, either injected into the target lesion or systemically administered, is an exciting avenue worth exploring (30).

The hope for prospective randomized controlled trials directly comparing the local treatment options of CRC lung metastases is rather bleak. The number needed to treat is way too high to reach statistical significance, even if aiming for non-inferiority, there are too many different ablation systems on the market with different antennae and ablation protocols. Well-designed studies in similar scenarios such as STARS and ROSEL, comparing local treatment of early stage primary lung cancer, had to be prematurely discontinued due to poor accrual numbers (31).

Hasegawa *et al.*'s well designed prospective multicentre observational study on long-term outcome of RFA in CRC pulmonary metastases adds to the myriad of retrospective studies, meta-analyses, and review articles showing the efficacy of heat-based percutaneous thermal ablation of CRC lung metastases.

In an era of limited resources, an aging population and an increasing incidence of CRC in the industrialised world, 'choosing wisely' is paramount—offering select patients effective, efficient, affordable and repeatable local treatment options for their CRC pulmonary metastases with minimal impact on quality of life. This is a task CT-guided thermal ablation can deliver.

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Footnote

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