



Perspective on therapeutic application of selective internal radiotherapy in colorectal cancer liver metastasis

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Comment on: van Hazel GA, Heinemann V, Sharma NK, *et al.* SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients With Metastatic Colorectal Cancer. *J Clin Oncol* 2016;34:1723-31.

Abstract: The liver is a predominant site of metastasis from a wide variety of neoplasms, and 60–80% of patients from colorectal cancer (CRC). Minority of liver metastasis are resectable which mandate an alternative option to take place in order to achieve good quality of life and improve overall survival. Selective internal radiation therapy (SIRT), has been evolving in various liver tumors, particularly hepatocellular carcinoma (HCC) and liver metastasis from colorectal cancer (CRC). The main principle of SIRT technology is in its delivery and of its radiation treatment rather than embolization. It allows distal trap of yttrium-90 resin microspheres at the arteriolar end of feeding vessel. Which make it precise in targeting tumor cell and thus normal tissue could be spared that otherwise may sacrifice. SIRT has accomplished great success in the field of HCC and been administered recently along with chemotherapy in liver metastasis from different primaries and showed efficient improvement in term of disease free survival and quality of life. Hence then, SIRT is a valid surrogated option for liver metastasis draws surgeon attention for a serious consideration in the future. Therefore, we believe that SIRT is a well designed treatment modality for CRCLM with promising results that deserve to take part in a well randomized trial for further analysis.

Keywords: Liver metastasis; colorectal cancer; selective internal radiotherapy; FOLFOX

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Incidence and definition of colorectal cancer with liver metastasis

Locally advanced rectal cancer is challenging with lots of debate still the current time. MCRC, however, is a serious issue to consider, which accounted for relatively higher percentage in CRC. Moreover, MCRC could be a worse scenario when presented with multiple live involvement combined with locally advanced tumor, make surgery is impossible and began to look for alternative intervention. Short course radiotherapy (SCRT) and internal radiotherapy (IRT) are on top of various type of regimen that will be addressed in our point of you.

Interestingly, issue to consider before going further in

our discussion is intent of curability in colorectal cancer liver metastasis (CRCLM) is significantly less often in synchronous metastases than for metachronous metastases (6.3% *vs.* 16.9%, respectively) (1). Also, 5-year survival rates were shorter in synchronous than metachronous CRCLM (3.3% *vs.* 6.1%, respectively). Unfortunately, percentage of synchronous CRCLM is steadily increasing compared to metachronous metastases, which may reflect high quality radiological image, and promoting national screening program and could be unexplained fast tumor growth (2). Moreover, treatment strategies are different among them. However both entities have poorly defined in the literature that ads further confusion and difficulty to determine treatment approach.

Therefore, discriminate between synchronous and metachronous liver metastasis is warranted, still definitions are uncertain among studies. Detection at or before diagnosis of the primary tumor (3), if metastases detected up to 3 (4), 4 (5) or 6 months (6,7) following diagnosis. In order to emphasize patient safety, we should be well oriented about patient diagnosis and tumor stage to avoid over or under treatment.

Current radiotherapy approach in CRCLM

In order to achieve appropriate tumor down staging, potentiate the dose and pathway of RT therapy to target tumor cells. Delivery of RT therapy has been proposed among studies, however RT dose and pathway were varies among the studies and standardization is lacking. Recently, interesting trial addressed novel approach in treating CRCLM. SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) *vs.* mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients with Metastatic Colorectal Cancer. This trial published in the *Journal of Clinical Oncology*, described unique way to deliver SIRT to CRCLM in order to achieve appropriate control. SIRT is a new radio-embolization technique that has recently been approved by the FDA for treatment of patients with non-resectable CRCLM. SIRT is yttrium-90 resins microspheres given into hepatic artery to achieve high doses of radiation targeted liver tumors, regardless of their number or position. On top of that, smaller diameter of microspheres has attributed in effective radio-embolization within microvasculature of the tumor without damaging adjacent normal liver tissue and that because, liver tumors derived blood supply from hepatic artery while liver parenchyma is predominated by portal vein (8). However SIRT has drawn serious attention for investigation, still consideration of technical demanding part and delicate precaution as well as the need of invasive preoperative studies to rule out arterio-venous shunt or existing anatomical variations, add an obstacle in decision plan, at which weight the risk and benefit of certain procedure before planning liver metastasis management. The technique of SIRT, dosing has been described previously (9). In addition, Systemic chemotherapy has tremendous investigation in the field of CRCLM, however still results are unsatisfactory till current time (10). Therefore, seeking for an alternative option should be considered to potentiate chemotherapy effect.

Currently, SIRT is a new modality of treatment that attains great success in the patients with hepatocellular carcinoma (HCC) (11). Therein, application of SIRT has extrapolated from HCC that keep evolving in CRCLM. Till then, SIRT have studied and examined in different primaries colonizing liver that indeed showing early success in their initial series (12,13). In a recent meta-analysis, SIRT has accounted for the first line therapy in unresectable CRCLM in 90% of the time (14).

Interestingly, treatment with SIRT has promising results in patients with advanced unresectable CRCLM as initial therapy or after failure of frequent chemotherapy regimens trial (12). Van Hazel *et al.* (15) conducted a randomized clinical trial to assess SIRT technique plus fluorouracil/leucovorin *vs.* Chemotherapy only in 11 patients diagnosed with untreated advanced CRCLM. The time to progression disease was in favor of SIRT arm (18.6 *vs.* 3.6 months, $P < 0.0005$). Median survival was significantly longer for patients received SIRT (29.4 *vs.* 12.8 months, $P = 0.02$) respectively. SIRT has initiated and progressed well in the section of CRCLM with acceptable toxicity. Recently, SIRFLOX trial conducted by van Hazel *et al.* (16), invented a novel clinical trial, they aimed to compare efficacy of combination therapy of SIRT plus mFOLFOX6 plus or minus bevacizumab *vs.* mfolfox6 in unresectable CRCLM. They investigated 530 patients deemed to be unresectable CRCLM, gathered from 87 centers in Australia, Europe, Israel, New Zealand, and the United States. A total of 263 were assigned to control and 267 were assigned to SIRT arm. They demonstrated SIRT plus FOLFOX-based first-line chemotherapy did not improve progression free survival (PFS) at any site (10.2 *vs.* 10.7 months) however it is significantly delayed disease progression in liver only (12.6 *vs.* 20.5 months).

Apparently, there were several reports delineate positive feedback of SIRT utilization in CRCLM since initial series (17), however it is at early milestone and comprehensive outcome still uncertain. Therefore, SIRFLOX trial accounted for the fundamental start of SIRT technology in CRCLM that delivered valuable information through this trial. Interestingly, complete response rate had been achieved up to 6% in SIRT arm compared to 1.9% in control group, $P = 0.020$. In this trial, SIRT directed to take care of liver metastasis, which represented a new entity of RT utilization. Often time, the use of radiotherapy directed toward rectum in metastasis CRC in form of CRT or SCRT, aiming to achieve down staging and then facilitate R0 resection. Nevertheless,

Table 1 Outcome of selective internal radiotherapy in CRCLM

| Authors | Year | No | Patients | Methods | Outcome | Toxicity |
|------------------------------|------|----|---------------|---|--|---------------|
| van Hazel <i>et al.</i> (15) | 2004 | 11 | RCT | SIRT +5FU/L vs. 5FU/L | Response rate (91% vs. 0%)—time to progression (15.6 vs. 4.7 months) | Mild toxicity |
| Murthy <i>et al.</i> (12) | 2005 | 12 | Retrospective | SIRT in uCRCLM failed to response to CTx | Tumor response MS 24.6 months | |
| Welsh <i>et al.</i> (13) | 2006 | – | Animal study | SIRT in CRCLM | LR improved | Mild toxicity |
| Kucuk <i>et al.</i> (21) | 2011 | 78 | Retrospective | SIRT in Liver Mets from different primaries | 55% responder—improve PFS | |
| Turkmen <i>et al.</i> (22) | 2013 | 61 | Retrospective | SIRT in Liver Mets from different primaries | OS responder vs. nonresponder (32.0±5.6 vs. 11.4±2.1 months) (P=0.054) | |

CRCLM, colorectal liver metastasis; CTx, chemotherapy; RFA, radiofrequency ablation; OS, overall survival; MS, median survival; uCRCLM, unresectable colorectal liver metastasis; SIRT, selective internal radiotherapy.

in current trial, he deviated from the standard way and invented new approach at which oxaliplatin take care of both local and distant metastasis along with additional management directed to serve liver metastasis (SIRT). Indeed, FOLFOX regimen could accomplish mild local control insufficient to achieve appropriate downsizing in locally advanced rectal cancer. Therefore, this approach will raise another inquiry; in how to achieve R0 resection in those with margin threatening or borderline respectability without radiotherapy directed toward rectum and pelvic? Answer could be yes for liver only metastasis but would be questionable if rectum was unresectable. Then, would it be suitable to consider SCRT on top of SIRT treatment? This is a new era of debates which has to be clarified in the future. Nevertheless, additional information is required to estimate recurrent rate and overall survival in those patients group. SIRT is a promising cut off technology in the field of radio-oncology, however it is technical demanding and awareness of technical preparation is a must to avoid unintended complication. Moreover, assessing tumor response is another debates issue to consider, however PET/CT has shown superiority among conventional imaging methods after SIRT treatment (18,19). Lastly, SIRT is a new modality of treatment that serves most patients with unresectable CRCLM in a resectable primary lesion with limitation to liver only metastasis. GERCOR database patients with unresectable disease, the response rate is higher in patients with liver-limited metastases than in those with non-liver-limited metastases (20). Several subset studies published in regards of clinical impact of using SIRT technology in CRCLM illustrated in *Table 1*.

In counterpart, Radiofrequency ablation (RFA) is a localized thermal treatment induce tumor necrosis and then cell destruction by rising tissue temperatures up to 50–100 C for 10–30 minutes (23,24). RFA has shown its superiority among others, which been validated in a recent phase II randomized trial. This trial is an extension of EORTC intergroup randomized study 40004 (CLOCC) (4). This trial evaluated the benefit of combining FOLFOX chemotherapy plus RFA *vs.* FOLFOX in 119 patients with unresectable CRCLM. They designed RFA indication very well for a max of nine liver lesions without extra-hepatic involvement. They illustrated 30-months overall survival rate 61.7% *vs.* 57.6% in RFA and control group respectively. In addition, they stated median overall survival was 45.6 *vs.* 40.5 months, P<0.01, respectively. In a systemic review (25) assessing RFA in CRCLM. Clearly declared paucity of data in RFA as well and proved EORTC intergroup randomized study randomized trial is accounting for a single well designed trial along with other small studies (26-30). They showed promising results of RFA in CRCLM as illustrated in *Table 2*.

Nevertheless, the effectiveness of RFA is limited to tumor size (<3 cm) and localization (1 cm or more deep to the liver parenchyma), and close to major vessels, ≥2 cm from large liver veins (24). Berber *et al.* (29), suggested predicted criteria to estimate poor response to RFA approach. More than three liver metastases, CEA level greater than 200 ng/mL, the presence of extra-hepatic disease, and liver metastasis larger than 5 cm could estimate poor response to RFA alongside with higher rate of procedure related complication. Hence then, RFA is good enough with certain restrictions that mandate modification or alternative

Table 2 Results of Radiofrequency Ablation Trials in CRCLM

| Authors | Year | No | Patient | Study design | Methods | Outcome |
|---------------------------|------|-----------------|---------|--------------------------|-------------------------|---|
| Elias <i>et al.</i> (31) | 2004 | 88 | CRCLM | Retrospective | RFA vs. liver resection | RFA = resection in small lesion |
| Berber <i>et al.</i> (29) | 2005 | 135 | uCRCLM | Prospective | CTx (80%) + RFA | MS 28.9 months MS better in <3 cm lesion |
| Mulier <i>et al.</i> (32) | 2008 | Review | CRCLM | Review | RFA vs. liver resection | LR (RFA = resection) if (T<3 cm) But higher in (>3 cm) |
| Ruers <i>et al.</i> (4) | 2012 | 119 (60 vs. 59) | uCRCLM | Randomized control trial | RFA + FOFOX vs. FOLFOX | MS 45.6 vs. 40.5 months, P<0.0 |
| Yoon <i>et al.</i> (33) | 2016 | 50 | CRCLM | Retrospective | RFA | PFS longer, 13.6% CR |

CRCLM, colorectal liver metastasis; CTx, chemotherapy; CR, complete response; RFA, radiofrequency ablation; MS, median survival; uCRCLM, unresectable colorectal liver metastasis; PFS, progression free survival.

method to deal with extensive form of CRCLM.

In the current era of debates, when and how SIRT or RFA is indicated in CRCLM? Yet, has to investigate several parameters to weight the risk and benefit of each pathway. Indeed, RFA picture is clearer than SIRT in term of predicting response and their impact in the overall survival. Whereas in SIRT, is a valid technique with a history of success literally, yet prognostic factors and indication as well as impact on overall survival has to be addressed in the future. In SIRFLOX trial (16), had few limitation that in our opinion might be important. From our point of you, liver metastasis might be stratified according to the number and size of the tumor involved in liver or other any site. Other era of debates is whether any way possible to modify SIRT dose or pathway for lesser extent of SIRT related liver toxicity. SIRT is in its infancy stage and required further analysis in order to validate its application and feasibility in the field of CRCLM.

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Footnote

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