Recent advances and future directions in locoregional therapy for colorectal cancer with liver metastasis

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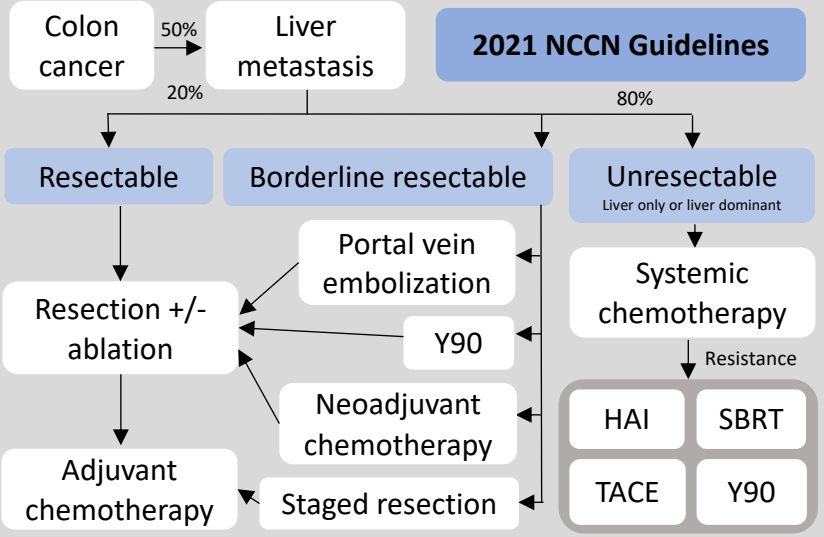
Introduction

Colorectal liver metastasis (CRLM) occurs in up to 50% of patients with colorectal cancer and is both the leading site of metastasis and the leading cause of death in this group.[1] Locoregional therapies including ablation, transarterial chemoembolization (TACE), and transarterial radioembolization (TARE) play an important role in the management of CRLM.

Ablation refers to radiofrequency (RFA) or microwave ablation (MWA), in which probes inserted percutaneously into the tumor use thermal energy to induce cellular necrosis. TACE refers to the catheter-directed intraarterial delivery of chemotherapy, usually irinotecan drug-eluting beads (DEBIRI) in the setting of CRLM. TARE refers to the catheter-directed intraarterial delivery of the radioactive isotope yttrium (Y90).



HAI = hepatic artery infusion (implantable chemotherapy pump); SBRT = stereotactic body radiation therapy; TACE = transarterial chemoembolization; Y90 = Yttrium-90, here synonymous with transarterial radioembolization (TARE)

Transarterial chemoembolization

Martin 2015 trial: Improved downstaging for resection using DEBIRI plus FOLFOX vs FOLFOX first line.[3]

Fiorentini 2012 trial: Improved OS for DEBIRI vs third- or fourth-line FOLFIRI.[2]

PARAGON II: Resection after neoadjuvant DEBIRI has comparable tumor response and OS to chemotherapy.[4]

In 2012, a randomized controlled trial (RCT)[2] showed that treatment with DEBIRI compared to systemic chemotherapy (FOLFIRI) improved overall survival (OS), progression free survival (PFS), and quality of life (QOL) in patients with CRLM previously treated with 2-3 lines of systemic chemotherapy. As first line, DEBIRI plus FOLFOX is superior to FOLFOX in downstaging to resection.[3] DEBIRI has been shown to confer a similar survival benefit as a neoadjuvant vs systemic chemotherapy.[4]

Transarterial radioembolization

SIRFLOX, FOXFIRE, FOXFIRE Global trials: Y90 + systemic chemo vs systemic chemo does not improve OS.[5]

Y90 can be used as salvage therapy in unresectable CRLM or to induce lobar necrosis and contralateral lobe hypertrophy in patients who are borderline resectable due to an inadequate liver remnant.[1] As a first line therapy for unresectable CRLM, Y90 combined with systemic chemotherapy increased PFS in the liver but failed to improve OS in three large RCTs.[5] As second line therapy, Y90 improves PFS in patients refractory to one line of chemotherapy.[6,7]

MORE study: Y90 improves OS in chemorefractory tumors.[6]

EPOCH trial: Y90 + second line chemo improves PFS after failure of first line chemotherapy.[7]

Ablation

EORTC-CLOCC trial: RFA+ systemic chemo improves OS vs systemic chemo (35.9% vs 8.9% survival at 8 years).[9]

COLLISON trial: RFA vs resection for tumors <3 cm .[8]

Current guidelines suggest ablation in conjunction with surgery as the first line for resectable CRLM. The ongoing COLLISON trial[8] directly compares ablation to resection in tumors less than 3 cm. Results of the EORTC-CLOCC trial demonstrate improved OS for ablation in conjunction with systemic therapy for first line treatment of unresectable disease.[9] Compared to RFA, MWA achieves better local tumor control for CRLM in multiple retrospective studies,[10] likely due to its resistance to heat sink effects.

Future directions

The future wave of clinical trials further clarify the roles of locoregional therapy in treatment guidelines. One exciting group of trials pair locoregional therapies with new immunomodulators, including:

- ILOC: Immunotherapy + ablation
- iRE-C: Immunotherapy + Y90
- SIRTCI: Immunotherapy + Y90

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