INVITED COMMENTARY

Development of a Research Agenda for the Management of Metastatic Colorectal Cancer: Proceedings from a Multidisciplinary Research Consensus Panel

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ABBREVIATIONS

AHRQ = Agency for Healthcare Research and Quality, CLM = colorectal liver metastases, CRC = colorectal cancer, DEBIRI = drug-eluting beads loaded with irinotecan, FLR = future liver remnant, FOLFIRI = folinic acid/5-fluorouracil/irinotecan [systemic chemotherapy regimen], FOLFOX = folinic acid, fluorouracil, and oxaliplatin [systemic chemotherapy regimen], HAI = hepatic arterial infusion, IO = interventional oncology, mCRC = metastatic colorectal cancer, NCCN = National Comprehensive Cancer Network, PVE = portal vein embolization, RCP = Research Consensus Panel, RECIST = response evaluation criteria in solid tumors, RF = radiofrequency, RILD = radiation-induced liver disease, RT = radiation therapy, 3D = three-dimensional, TTP = time to progression, VEGF = anti-vascular endothelial growth factor

INTRODUCTION

Colorectal cancer (CRC), the second leading cause of cancer death in the United States, occurs in an estimated more than 145,000 patients annually, with almost 50,000 deaths each year. Metastatic liver disease is the cause of death in the majority of them (1,2). Liver-only metastases affect up to one half of patients with CRC (1,2), with approximately 15% (range, 8%–26%) presenting synchronously (3,4) and an additional 15% found metachronously during the next 5 years (3). Colorectal liver metastases (CLMs) are resectable in 20%–25% of patients only; some of the remaining 75%–

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Table 1. United States Agency for Healthcare Research and Quality Classification of Levels of Evidence (11)

Level	Description
I	Evidence from randomized controlled trial(s)
II-1	Evidence from controlled trial(s) without randomization
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one center or research group
II-3	Evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments could be included here
III	Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees

Note.—Modified from Owens et al (11).

80% may benefit from "downsizing" therapy, which can result in 10%–20% more patients becoming resectable. Overall survival rates in patients with either primarily or secondarily resectable CLMs can be as high as 58% at 5 years and 15% at 10 years (5,6). Current front-line treatments available to improve downsizing and resectability include systemic therapies (chemotherapy with or without bevacizumab or cetuximab) and pre-operative portal vein embolization (PVE). Other approaches include local ablation therapies, regional intraarterial therapies with embolization (transcatheter arterial chemoembolization, or radioembolization by selective internal radiation therapy with Yttrium 90-loaded microspheres) or infusion (ie, hepatic arterial infusion [HAI] pump chemotherapy), and external beam radiation therapy (RT). The role of these liver-targeted therapies to promote conversion from unresectable to resectable liver disease remains an evaluation in progress. For the majority of patients with unresectable CRC liver metastases, standard of care is first- and second-line triplet chemotherapy, which is associated with a median survival of 18–24 months (7–10). Multiple single-institution retrospective reports suggest the potential for improvement in survival time by the addition of liver-directed therapies such as chemoembolization, HAI, or radioembolization. This has not been prospectively evaluated in controlled trials, but could potentially represent a major development in Interventional Oncology (IO). The Society of Interventional Radiology (SIR) Foundation has identified the management of metastatic CRC (mCRC) as an emerging interventional radiologic research priority and convened a Research Consensus Panel (RCP) Meeting on October 3, 2011 to establish a prioritized research agenda. This article reports the proceedings from this meeting.

METHODS

Panel Membership

In April 2011, the SIR Foundation sent to the SIR membership an invitation to submit applications to lead the RCP Meeting. A lead investigator was selected, who invited, in cooperation with the SIR Foundation, (i) a multidisciplinary group of expert panelists, (ii) representatives from governmental agencies, and (iii) representatives from industries involved in the IO field. The 13 expert panelists included eight interventional radiologists, two medical oncologists, two surgical oncologists, and one radiation oncologist, all with demonstrated relevant experience. Government agencies included the Food and Drug Administration (FDA; four representatives from the Center for Devices and Radiological Health and one from the Center for Drug Evaluation and Research) and the Agency for Healthcare Research and Quality (AHRQ; one representative from the Center for Outcomes and Evidence). Industry representatives came from major companies involved in the production and/or distribution in the United States of products for local or regional liver-directed therapies.

Agenda Methodology

The stated objective of the RCP was to define a prioritized research agenda for the management of mCRC, including topics amenable to basic science/technology research, pilot clinical research, and multicenter clinical trials. The process involved several steps. First, each panelist gave a 10-minute presentation on an assigned topic in their field of expertise providing an updated review of current knowledge on the outcomes of relevant therapies, using the AHRQ classification of levels of evidence (**Table 1**) (11). Panelists were also asked to include in their presentations descriptions of gaps in the current knowledge base, and recommendations for basic science and clinical research questions or projects that need further study. Specifically, panelists were asked to (i) define the most important clinical questions that could realistically be answered through pivotal multi-institutional clinical trials or registries, (ii) describe the most promising future directions that merit preclinical or early clinical exploration in the management of mCRC, and (iii) outline the critical alliances that must be developed to advance the prioritized research and how the SIR Foundation can best support these initiatives. A total of 12 presentations were given (11 individual and one joint). Afterwards, a round-robin discussion was held to examine important research questions, potential opportunities for future research studies, and consolidate similar or redundant ideas into succinct titles of research projects that deserved prioritization. Thereafter, invited comments from government and industry representatives were heard. This step resulted in a consolidated list of research projects being voted on anonymously by each

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